Pharmacological Targets and Therapeutic Strategies in Alzheimer's Disease: Mechanistic Insights and Emerging Drug Approaches

Deepak Mewada, Muskan Tomar and Manoj Goyal

ABSTRACT

Alzheimer's disease, a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and neuronal death, has multiple inter-connected mechanisms that contribute to its pathogenesis (the largest factor being amyloid beta accumulation; however, other factors such as hyperphosphorylated tau protein accumulation, oxidative stress, mitochondrial dysfunction, and inflammatory response are also involved). Currently available drug treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, relieve symptoms but do not significantly influence the progression of the disease itself. Increased knowledge regarding the relevant molecular pathways involved in the pathogenesis of the disease has led to the recent development of additional potential pharmaceutical targets that may be used to create more effective therapies aimed at delaying or preventing Alzheimer's Disease. New strategies are emerging for the development of treatment approaches that include anti-amyloid and anti-tau treatment approaches, inhibition of kinases, neuroprotective agents, and modulation of inflammatory signaling pathways. Overall, this review covers the major pharmacological targets that have been identified in Alzheimer's disease as well as the current treatments available for the disease, discusses the limitations of those treatments, and presents recent advances in the development of therapeutics to modify the pathological processes associated with Alzheimer's disease. Understanding these pharmacological strategies will ultimately improve the ability to develop therapeutics for delaying or halting the progression of Alzheimer's disease.

Keywords: Amyloid pathology, Cognitive impairment, Disease-modifying therapy, Neurodegeneration, Neuroinflammation, Oxidative stress, Pharmacotherapy, Tau aggregation

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Introduction

Alzheimer's Disease (AD) is the most prevalent type of dementia and is one of the most significant global health concerns due to its progressive nature and increasing incidence with older age. The loss of cognitive function, memory problems, behavioral changes, and a loss of independence from anyone's assistance are considered to be the clinical symptoms of AD. While there has been considerable effort to study AD, there is still no cure or disease-modifying therapy for AD; therefore, patients will only be provided with symptomatic management.[1] There is an increased need to understand the underlying molecular and pharmacological pathology of AD because of the increasing socioeconomic burden associated with the disease.[2] Alzheimer's disease is caused by numerous different pathological processes that contribute together to form the complex pathogenesis of the disease as follows: the accumulation of amyloid beta peptide, which leads to the development of an extracellular plaque; the abnormal hyperphosphorylation of tau protein resulting in the development of neurofibrillary tangles; oxidative stress; mitochondrial dysfunction; synaptic loss and chronic neuroinflammation all result in neuronal degeneration; and provide important therapeutic insights regarding possible pharmacological targets for the treatment of the disease.[3] There is increasing evidence to suggest that targeting a single pathway is likely not enough to treat the disease and therefore will require a multi-target pharmacological approach to treatment. The current treatment for Alzheimer's is primarily treating Alzheimer's Disease using cholinergic inhibitors and NMDA receptor antagonists that act by improving the balance of neurotransmitters or decreasing excitotoxicity. To make progress, therefore there is an urgent need to develop drugs that modify the progression of the disease as opposed to being simply symptomatic. Advances in Molecular Pharmacology and Drug Discovery are opening the door for new treatment of Alzheimer's by developing new therapeutic methods focused on eliminating amyloid plaques, developing methods for modulating tau protein concentrations, using anti-inflammatory processes, and providing neuroprotective strategies.[4] In this review article, we will present an overview of all pharmacological targets or pathways that may be involved in Alzheimer's disease, describe currently available treatments, and describe new drug development approaches that may modify the course of Alzheimer's disease. Finally, this review provides an overview of mechanistic information that can lead to the discovery of more effective pharmacological agents to treat Alzheimer's disease.[5]

Methodology

Literature Search Strategy

A comprehensive literature review of scientific literature on pharmacological targets and treatment strategies for Alzheimer's disease was conducted. The search included international databases that allow access to peer-reviewed scientific literature on biomedical and pharmacological studies, as well as clinical studies (i.e., PubMed, Scopus, Web of Science, and Google Scholar). Volume and time-period criteria were established to include older and newer literature, thus ensuring that studies from both foundation and newer

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studies of Alzheimer's pharmacotherapy between the years 2005 and 2025 were included. To obtain search results, a search strategy was developed using combinations of keywords and Medical Subject Headings (MeSH terms) such as "Alzheimer's disease," "pharmacological targets," "amyloid beta," "tau protein," "neuroinflammation," "oxidative stress," "cholinesterase inhibitors," "NMDA antagonist," and "emerging Alzheimer's therapies," along with Boolean operators (AND and OR) for purposes of refining search results to improve on relevance of results. Furthermore, through a manual search of the references from review articles and clinical studies found in literature databases, additional relevant articles were identified.[6]

Inclusion and Exclusion Criteria

The studies that were included in this review were chosen based on their meeting pre-established inclusion and exclusion criteria regarding their scientific relevance and consistency of methodologies. Studies that included a focus on pharmacological mechanisms, drug targets, methods of treatment, or clinical pharmacotherapy related to Alzheimer's disease were eligible for inclusion in this review. Eligible studies included original research articles, review papers, clinical trials, and meta-analyses published in peer-reviewed journals that are indexed by the major scientific databases. Studies that did not meet the following inclusion/exclusion criteria were excluded from this review: (1) the article was not in the English language; (2) the study did not have a full-text version available; (3) the article was an abstract only; or (4) the study did not have a pharmacologic or mechanistic relationship with Alzheimer's disease. During the screening phase, duplicates of study records that were found across multiple databases were eliminated.

Study Selection and Data Extraction

This article presents a narrative review of published literature on pharmacological targets and therapeutic strategies in Alzheimer's disease. Relevant articles were identified from databases including PubMed, Scopus, Web of Science, and Google Scholar published between 2005 and 2025. Keywords such as "Alzheimer's disease," "pharmacological targets," "amyloid beta," "tau protein," "neuroinflammation," "oxidative stress," and "emerging therapies" were used. Articles were selected based on relevance to the topic and were thematically organized into mechanistic and therapeutic categories.

Data Analysis and Synthesis

A qualitative analysis of the literature was completed to improve understanding of the pharmacological mechanisms and therapeutic progress in Alzheimer's disease. Mechanistic interpretation, pharmacological importance, and possible application (i.e., translational) of the therapeutic mechanisms were considered when drawing conclusions regarding the findings of the different studies reviewed. The studies were synthesized and related to reveal factual evidence for the common trends and limitations associated with the development of new drugs to treat Alzheimer's disease. The goal of the synthesis approach was to combine pertinent information from molecular pharmacology, preclinical, and clinical studies to give current and future information on pharmacotherapy for Alzheimer's disease.

Epidemiology and Clinical Burden of Alzheimer's disease

Alzheimer's disease remains the leading cause of dementia worldwide and represents a growing public health challenge. According to recent global burden estimates, more than 55 million people are currently living with dementia globally, with Alzheimer's disease accounting for approximately 60%–70% of cases.[7] Projections suggest that this number may exceed 139 million by 2050 due to population aging. The Global Burden of Disease (GBD) studies indicate a substantial increase in disability-adjusted life years and socioeconomic burden associated with Alzheimer's disease.[8] Low- and middle-income countries are expected to experience the largest increase in prevalence, highlighting disparities in diagnosis and treatment access.[9] These trends emphasize the urgent need for improved preventive strategies, early diagnosis, and scalable therapeutic interventions.

Health-System Readiness for Disease-Modifying Therapies

The introduction of anti-amyloid immunotherapies presents new challenges for healthcare systems. These treatments require intravenous infusion infrastructure, repeated dosing schedules, and access to magnetic resonance imaging (MRI) for monitoring amyloid-related imaging abnormalities (ARIA). Limited infusion capacity, availability of trained personnel, and imaging resources may restrict widespread implementation, particularly in resource-limited settings. Health systems must therefore strengthen diagnostic pathways, biomarker testing availability, and monitoring protocols to support safe and equitable delivery of disease-modifying therapies for Alzheimer's disease.

Pathophysiology of Alzheimer's Disease

Progressive neurological degeneration is the hallmark of Alzheimer's Disease. There are many biochemical and cellular processes that result in devastating brain damage in Alzheimer's. The pathological processes underlying Alzheimer's include abnormal protein aggregation, neurotransmitter imbalance, oxidative injury, mitochondrial dysfunction, and chronic neuroinflammation. Together, these factors culminate in synaptic loss, neuronal loss, and eventually progressive cognitive decline. Understanding the molecular pathogenic mechanisms that result in the pathology of the Alzheimer's disease is critical for developing drug targets and therapeutic strategies aimed at modifying the underlying disease process.[10] These main pathological mechanisms of Alzheimer's disease and therapeutic targets are illustrated in Figure 1.

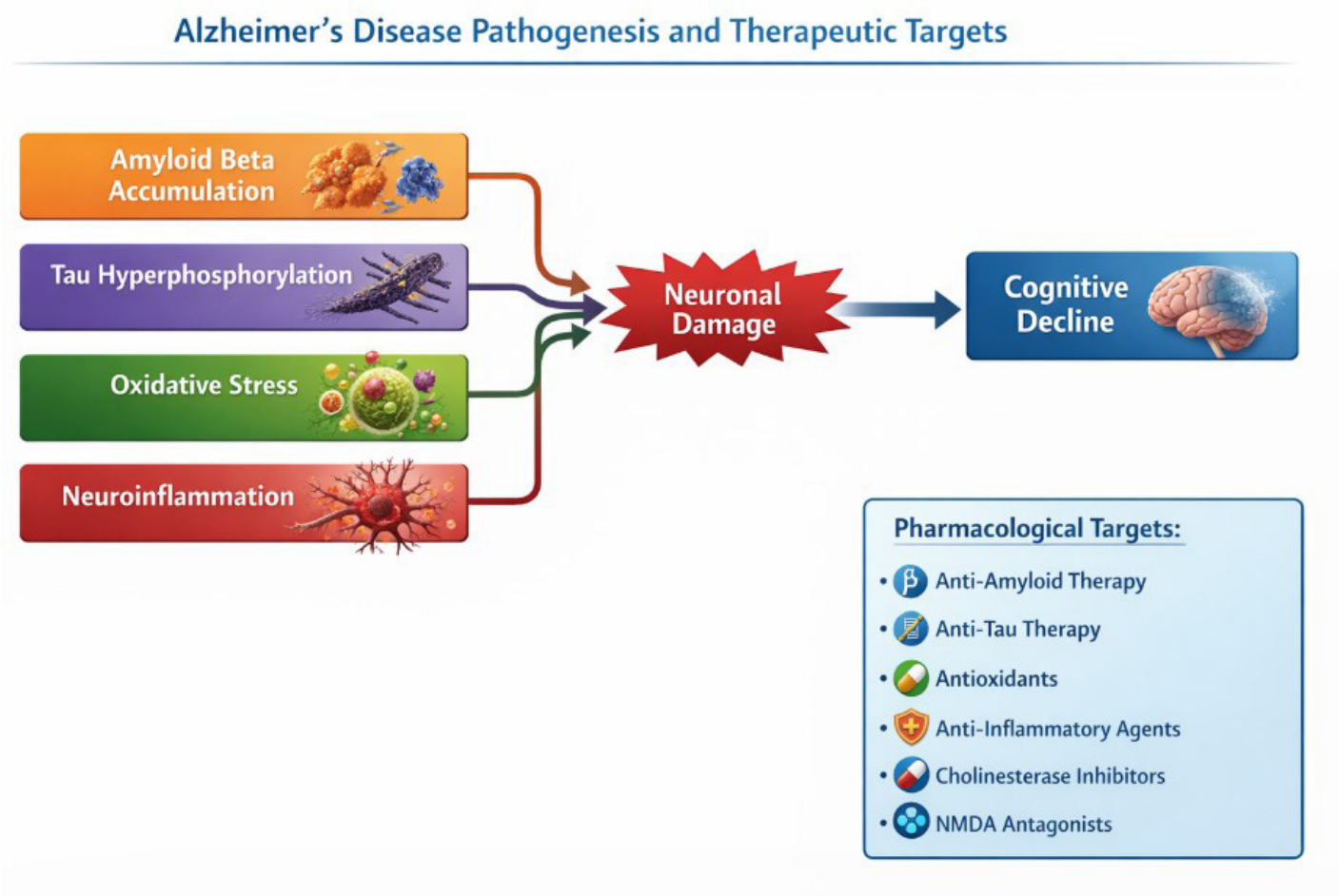

Fig 1 | Overview of Alzheimer's disease pathogenesis and pharmacological intervention targets

The figure illustrates major pathological mechanisms, including amyloid beta accumulation, tau hyperphosphorylation, oxidative stress, and neuroinflammation, leading to neuronal damage and cognitive decline. The diagram also highlights pharmacological intervention strategies such as anti-amyloid therapy, anti-tau therapy, antioxidants, anti-inflammatory agents, cholinesterase inhibitors, and NMDA receptor antagonists.

Amyloid Beta Cascade Hypothesis

One of the most widely recognized pathways that explains how Alzheimer's disease develops is the amyloid beta cascade. The process begins with an incorrect processing of amyloid precursor protein (APP) via the actions of β-secretase and γ-secretase, leading to the creation of amyloid beta (Aβ) peptides, with Aβ42 being a particularly strong aggregator.[11] The aggregation of Aβ is known to create oligomers and amyloid plaques in the extracellular space, which creates synaptic disruption and induces cell death. Aggregated amyloid beta (Aβ) interferes with normal neuronal signaling and causes oxidative stress, which further increases neuronal degeneration through an inflammatory response. There is also evidence to suggest that the build-up of amyloid plaques is associated with mitochondrial dysfunction as well as abnormalities in calcium homeostasis. The main focus of pharmacological interventions targeting this cascade involves the use of β-secretase inhibitors, γ-secretase modulators, and monoclonal antibodies to increase the clearance of amyloid.[12] The pathways associated with the production and aggregation of amyloid beta are outlined in Figure 2.

The figure illustrates the processing of amyloid precursor protein (APP) through β-secretase and γ-secretase pathways, leading to the formation of amyloid beta peptides (Aβ40 and Aβ42). Subsequent aggregation into oligomers, protofibrils, and amyloid plaques contributes to synaptic dysfunction, oxidative stress, neuroinflammation, and neuronal damage. The diagram also highlights potential pharmacological intervention strategies, including β-secretase inhibitors, γ-secretase inhibitors, and anti-aggregation therapeutic approaches.

Tau Protein Hyperphosphorylation

The Tau Protein is a microtubule-associated protein that is responsible for the maintenance of cytoskeletal stability and axonal transport of neurons. The abnormal activation of kinases like Glycogen Synthase Kinase 3 beta (GSK3β) and Cyclin Dependent Kinase

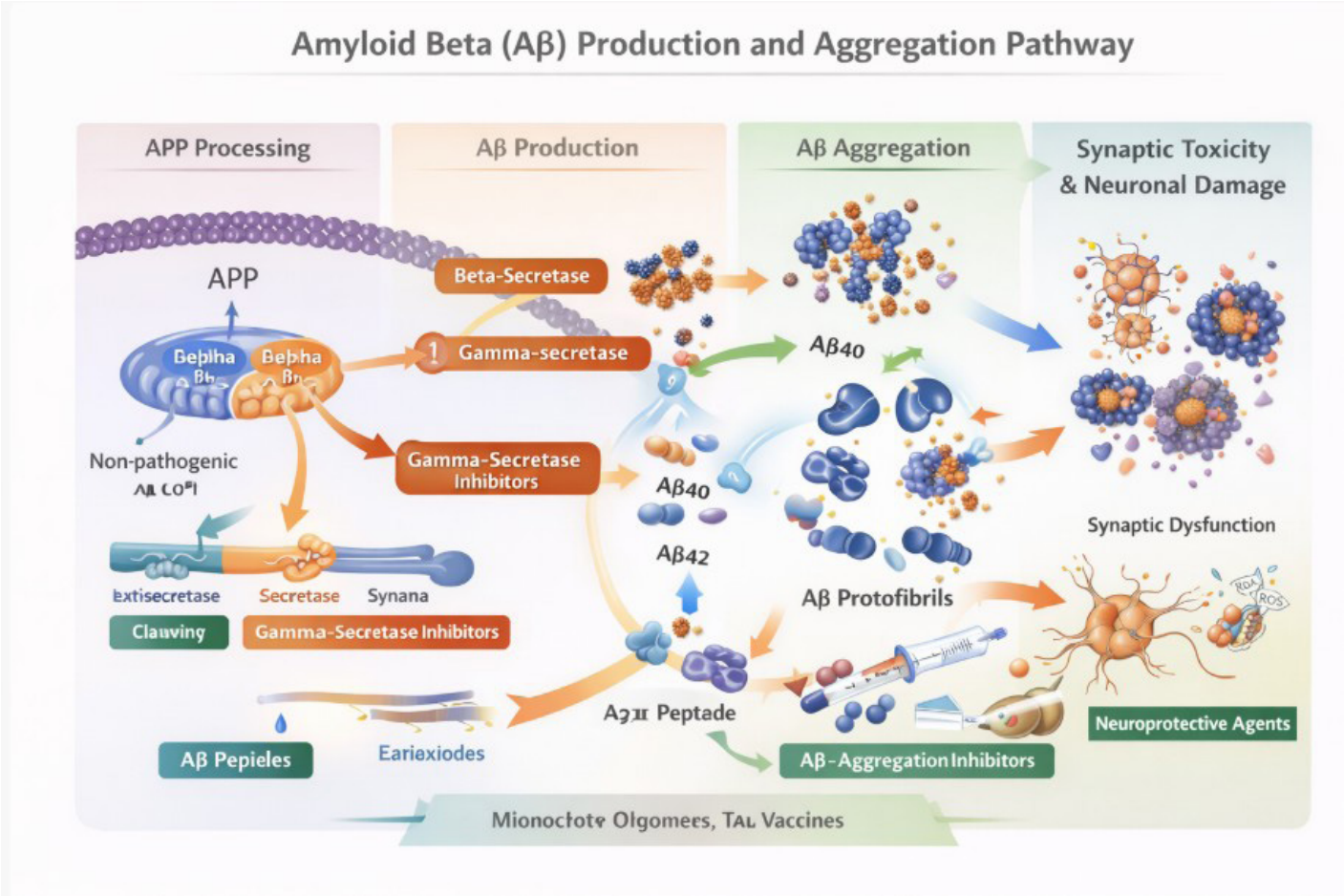

Fig 2 | Amyloid beta (Aβ) production and aggregation pathway in Alzheimer's disease

5 (CDK5) can cause tau protein to become hyperphosphorylated.[13] When tau is hyperphosphorylated, tau loses its ability to stabilize microtubules and form intracellular neurofibrillary tangles. Neurofibrillary tangle formation disrupts axonal transport, inhibits the mediation of synaptic communication, and leads to neuronal degeneration, ultimately contributing to cognitive decline and the severity of the disease as measured by neurofibrillary tangles versus amyloid deposition.[14] Tau pathology correlates with the severity of the disease and cognitive decline more closely than amyloid deposits. There are pharmacological strategies to treat tau pathology, including kinase inhibitors, tau aggregation inhibitors, and tau-directed immunotherapies.[15] Figure 3 illustrates how tau is hyperphosphorylated and its role in neurodegeneration.

The figure illustrates the abnormal phosphorylation of tau protein mediated by kinases, such as CDK5, GSK3β, and MAPK pathways, leading to tau aggregation and formation of neurofibrillary tangles. These pathological changes result in microtubule destabilization, cytoskeletal disruption, synaptic dysfunction, and neuronal degeneration. The diagram also highlights potential pharmacological intervention strategies, including tau aggregation inhibitors, kinase inhibitors, and tau-targeted immunotherapy.

Cholinergic dysfunction

One of the first neurochemical changes noticed in patients with Alzheimer's disease is a deficiency in cholinergic activity. The death of cholinergic neurons in the basal forebrain leads to the loss of production and release of the neurotransmitter acetylcholine, which is necessary for learning and memory processes.[16] Neuroanatomical studies have shown that limitations in the function of cholinergic neurons are highly correlated with the deterioration of cognition and the development of behavioral issues associated with the disease.[17] Evidence related to low levels of acetylcholine provides the basis for pharmacological interventions, such as acetylcholinesterase inhibitors, which work by increasing the amount of acetylcholine in the synapse by inhibiting the degradation of acetylcholine by acetylcholinesterase.[18] Acetylcholinesterase inhibitors will ameliorate cognitive symptoms, but they do not slow down the progression of the disease, suggesting that cholinergic dysfunction is only one of the many abnormalities involved in the complex pathology of Alzheimer's disease.[19]

Oxidative Stress and Mitochondrial Dysfunction

Alzheimer's disease is advanced in part by oxidative stress with an excess of reactive oxygen species (ROS) and poor function of antioxidants. Oxidative stress

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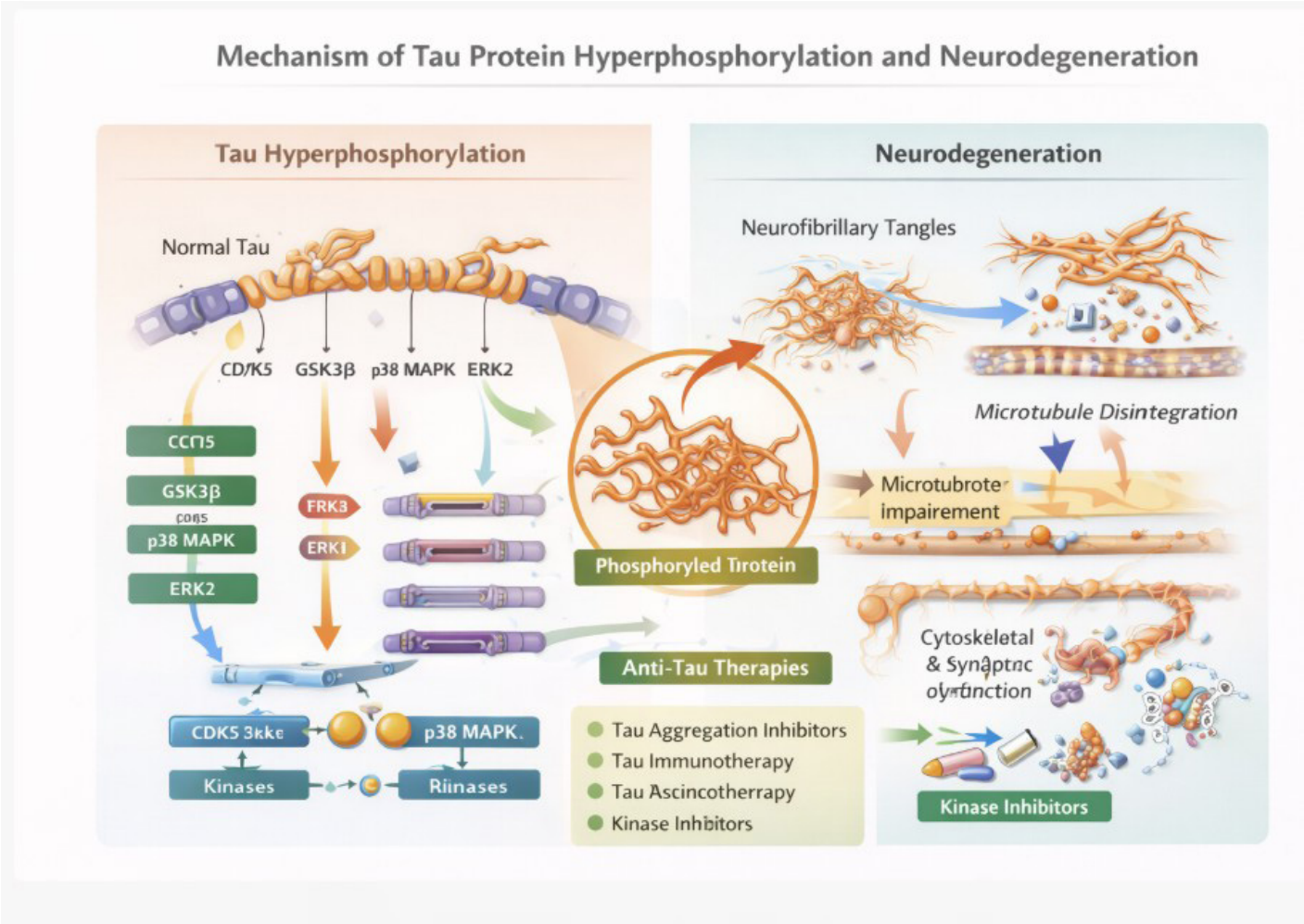

Fig 3 | Mechanism of tau protein hyperphosphorylation and neurodegeneration in Alzheimer's disease

can lead to lipid peroxidation, protein oxidation, and DNA damage which can ultimately cause neuronal injury.[20] In addition to oxidative damage, mitochondrial dysfunction can worsen mitochondrial damage with effects on cellular energy metabolism, leading to increased expression of apoptotic (programmed cell death) pathways. Mitochondrial dysfunction is enhanced by the accumulation of amyloid β and tau in a vicious cycle of increased oxidative damage and neuronal degeneration. There are many pharmacological strategies that target oxidative stress, including the use of antioxidants, mitochondrial protectants, or anything that will enhance energy metabolism in neurons.[21]

Neuroinflammation and Microglial Activation

Neuroinflammation is becoming more widely accepted as one of many factors in increasing the rate of disease progression in Alzheimer's. Neuroinflammation occurs when microglia and astrocytes activate in response to a buildup of Amyloid beta, as well as injury to the neurons. This activation causes the release of several pro-inflammatory cytokines (e.g. interleukin-1 beta, tumor necrosis factor alpha, and interleukin-6). Chronically activated inflammatory signaling via pathways such as nuclear factor (NF)-kappaB (NF-κB) pathway and the NLRP3 inflammasome leads to chronic neuronal damage and reduced function of synapses over time. Acute activation of microglial cells may provide an initial protective function (e.g., clearing amyloid), but chronic activation can lead to neurotoxic effects that contribute to the progression of Alzheimer's disease.[22] There are pharmacological interventions to manage neuroinflammation associated with Alzheimer's, including anti-inflammatories, modulators of microglial cells, and inhibitors of inflammatory signaling pathways. The mechanisms of neuroinflammation in the pathology of Alzheimer's disease are illustrated in Figure 4.

The figure illustrates the role of amyloid beta accumulation and pathological tau in activating microglia and astrocytes, resulting in oxidative stress and neuroinflammatory responses. Activation of signaling pathways such as NLRP3 inflammasome, NF-κB, and JAK/STAT leads to the release of pro-inflammatory cytokines, including IL-1β and TNF-α, contributing to neuronal damage and disease progression. The diagram also highlights potential pharmacological intervention strategies, including anti-inflammatory agents, NLRP3 inhibitors, NF-κB inhibitors, JAK/STAT pathway inhibitors, and microglial modulators.

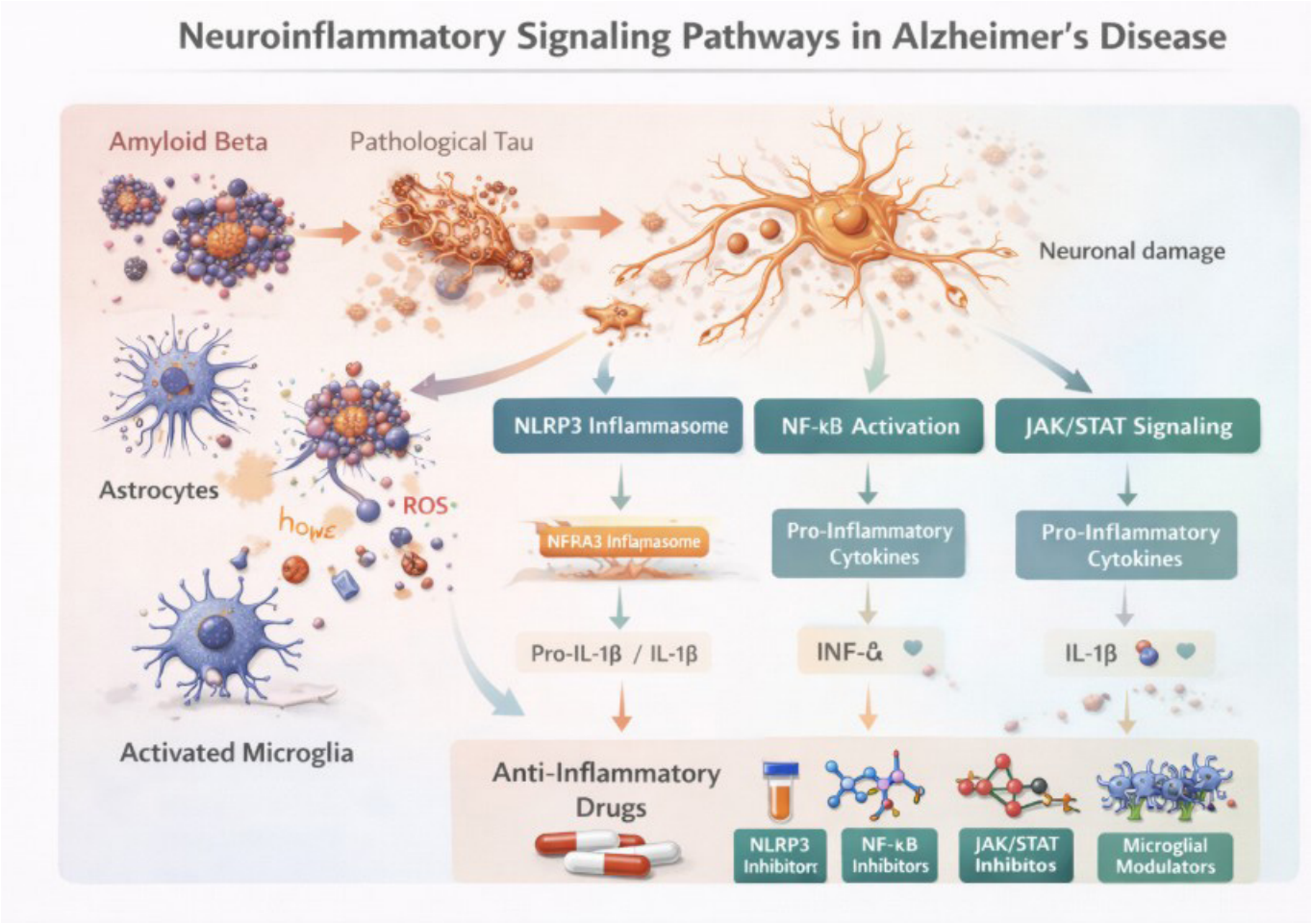

Fig 4 | Neuroinflammatory signaling pathways and pharmacological intervention targets in Alzheimer's disease

Pharmacological Targets in Alzheimer's Disease

Alzheimer's disease is multifactorial in a systemically defined manner; therefore, there are many identified pharmacologic targets, which include improving neurotransmission, decreasing pathogenic (pathological) protein aggregate formation, and stopping neurodegeneration. There are multiple pharmacologic routes of intervention, predominantly through molecular pathways that have been identified throughout the process of progression related to Alzheimer's. The primary pharmacological targets of Alzheimer's and their potential therapeutic effects are provided in Table 1.

Acetylcholinesterase Enzyme as a Drug Target

One of the earliest pharmacological treatments of Alzheimer's disease is based on the cholinergic hypothesis. The loss of cholinergic neurons causes a decline in the availability of acetylcholine in the synapse, which negatively impacts memory and cognitive abilities. Therefore, the enzyme that causes the breakdown of acetylcholine (i.e., acetylcholinesterase [AChE]) has been identified as the major pharmacological target.[26] The inhibition of AChE leads to an increase in acetylcholine at the synaptic junction, which enhances neurotransmission and cognitive function. Medications such as donepezil, rivastigmine, and galantamine exert their effects by this mechanism and are used extensively for treating the symptoms of mild to moderate Alzheimer's disease. Although these drugs are useful clinically, they do not have any effect on the underlying disease process; thus, there will be a need for alternative pharmacological approaches that may slow down or stop the disease process from continuing to advance.

NMDA Receptor Modulation

One of the main causes of brain cell damage caused by Alzheimer's disease is glutamate-induced excitotoxicity. Overstimulation of the NMDA (N-methyl-D-aspartate) receptor, which creates a large amount of calcium and marks oxidative stress, the breakdown of the mitochondria, and the death of neurons in the brain. Therefore, changing the activity of the NMDA receptor has become a pharmacological strategy to treat Alzheimer's disease. Memantine is an NMDA antagonist that reduces the pathological impact of glutamate without impacting normal synaptic transmission. By doing this, memantine prevents the damage caused by the death of neurons due to excitotoxicity and improves cognition and function in people with moderate-to-severe Alzheimer's disease. However, like the cholinesterase inhibitors, NMDA antagonists provide symptomatic benefit and not a cure or disease-modifying effect.

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Table 1 | Pathophysiological mechanisms and pharmacological targets in Alzheimer's disease[23–25]

Pathophysiological mechanism	Key molecular events	Pharmacological targets	Therapeutic strategy	Representative agents	Development stage	Key risks
Amyloid beta accumulation	APP cleavage, Aβ40/Aβ42 aggregation, plaque formation	β-secretase, γ-secretase	Secretase inhibitors, anti-amyloid therapies	Lecanemab, Donanemab	Phase III/ Approved	ARIA, edema
Tau hyper-phosphorylation	Kinase activation (GSK3β, CDK5), neurofibrillary tangles	Tau protein, kinases	Tau aggregation inhibitors, kinase inhibitors	Tideglusib	Phase II	Hepatotoxicity
Cholinergic dysfunction	Reduced acetylcholine levels	Acetylcholinesterase enzyme	Cholinesterase inhibitors	Donepezil	Approved	GI upset
Oxidative stress	ROS generation, mitochondrial dysfunction	Antioxidant pathways	Antioxidants, mitochondrial protectors	Vitamin E	Clinical	Limited efficacy
Neuroinflammation	Microglial activation, cytokine release	NLRP3, NF-κB, JAK/STAT pathways	Anti-inflammatory agents, microglial modulators	Minocycline	Experimental	Immuno-suppression

Anti-Amyloid Therapeutic Targets

Alzheimer's disease is predominantly caused by the accumulation of amyloid beta; thus, significant attention has been given to this pathology in terms of pharmacological research and development. There are different therapeutic approaches for amyloid pathology, which include reducing the amount of amyloid that is produced, preventing amyloid from aggregating into insoluble clumps, or enhancing the removal (i.e., clearance) of amyloid deposits. Pharmacological targets for amyloid-targeting therapies include two enzymes that are part of the normal process for producing amyloid beta, β-secretase (BACE1) and γ-secretase. Monoclonal antibodies that have been developed specifically to increase the clearance of amyloid from the brain are one of the most recent types of therapies developed. While some anti-amyloid therapies can effectively reduce the amount of amyloid present in the brain, their effects on clinical outcomes vary and indicate that both the stage of the disease and when the intervention is implemented are important predictors of therapeutic success. Ongoing research continues to focus on developing therapies that improve the overall effectiveness of amyloid-targeting approaches, but that also minimize the potential for adverse effects associated with these therapies.

Anti-Tau Therapeutic Strategies

Tau pathology has received increasing interest as a pharmacological target. It is associated with the severity of the disease and cognitive decline. Hyperphosphorylation and aggregation of tau proteins contributes to the disruption of the neuronal cytoskeleton, impacting axonal transport. The pharmacological approaches to targeting tau pathology focus on the prevention of tau hyperphosphorylation, inhibition of tau aggregation, or increasing the clearance of dysfunctional tau protein. Kinase inhibitors that target enzymes such as GSK3β and CDK5 have been examined as a method of reducing tau hyperphosphorylation. Furthermore, tau aggregation inhibitors, as well as nutritional and immunotherapy approaches to modifying intracellular tau accumulation, have also been assessed.[27] While there are many ongoing clinical trials for these anti-tau therapies, there continues to be considerable potential to provide a medicinal disease-modifying approach for pharmacotherapy of Alzheimer's disease.

Anti-Inflammatory and Antioxidant Targets

The development of Alzheimer's disease is characterized by neuroinflammation and oxidative stress as significant components in neuronal injury and progression of the overall disease. Microglia and astrocyte activation exhibit protracted release of inflammation-inducing substances, resulting in synapse impairment and death of neurons. Therefore, it is a viable therapeutic option to focus on pharmacological modulation of inflammatory signaling pathways (specifically NF-κB pathways and NLRP3 inflammasome pathways). Additionally, the antioxidants' properties are based on their ability to remove reactive oxygen species and prevent oxidative-cellular damage to neuronal cells. Current investigation into the slowing of neurodegeneration is achieved through the use of substances targeting mitochondrial function as well as inflammatory mediators.[28] In view of the fact that oxidative stress and inflammation are closely related to both amyloid and tau pathology, the combined use of anti-inflammatory and antioxidant pharmacological agents may offer promise for future therapeutic strategies.

Currently Approved Pharmacological Therapies

Currently available pharmaceutical treatments for Alzheimer's disease do not provide disease modification despite studies on disease-modifying therapies. These treatments are symptomatic in nature, aiming to improve neurotransmitter balance and decrease neuronal damage related to excitotoxicity. The primary targets for these treatments are cholinergic dysfunction and excitatory glutamatergic pathways, both of which have been correlated with cognitive decline. Table 2 provides details regarding the pharmacological profile, mechanism of action, and effects of the presently

Table 2 | Currently approved drugs for Alzheimer's disease and their mechanisms of action[30–32]

Drug	Drug class	Mechanism of action	Therapeutic effects	Limitations	Dose (mg/day)	Adverse effects
Donepezil	Cholinesterase inhibitor	Inhibits acetylcholinesterase, increases acetylcholine	Improves cognitive symptoms	Symptomatic relief only	5–10	Symptomatic only
Rivastigmine	Cholinesterase inhibitor	Inhibits AChE and BuChE	Cognitive improvement	GI side effects	3–12	GI effects
Galantamine	Cholinesterase inhibitor	AChE inhibition and nicotinic receptor modulation	Memory improvement	Limited disease modification	8–24	Limited efficacy
Memantine	NMDA receptor antagonist	Reduces glutamate excitotoxicity	Slows symptom progression	Moderate efficacy	10–20	Moderate benefit

available pharmacological agents for the treatment of Alzheimer's Disease, and Figure 5 depicts the respective mechanisms of action.[29]

Cholinesterase Inhibitors

The first-line treatment for mild to moderate Alzheimer's disease (AD) consists of a class of medications called cholinesterase inhibitors. Cholinesterase inhibitors increase the level of acetylcholine by inhibiting the degrading action of only one particular enzyme (acetylcholinesterase) found in the synaptic cleft (the space between two neurons). The increase in the availability of acetylcholine improves the transmission of information between cholinergic neurons (neurons that use acetylcholine) and results in temporary improvements in cognitive function, memory, and behavioral symptoms. Donepezil, rivastigmine, and galantamine are the three commonly used cholinesterase inhibitors. Donepezil specifically inhibits acetylcholinesterase; rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase (another enzyme that breaks down acetylcholine); and galantamine acts as an inhibitor of acetylcholinesterase and a modulator of nicotinic receptors, thereby enhancing cholinergic

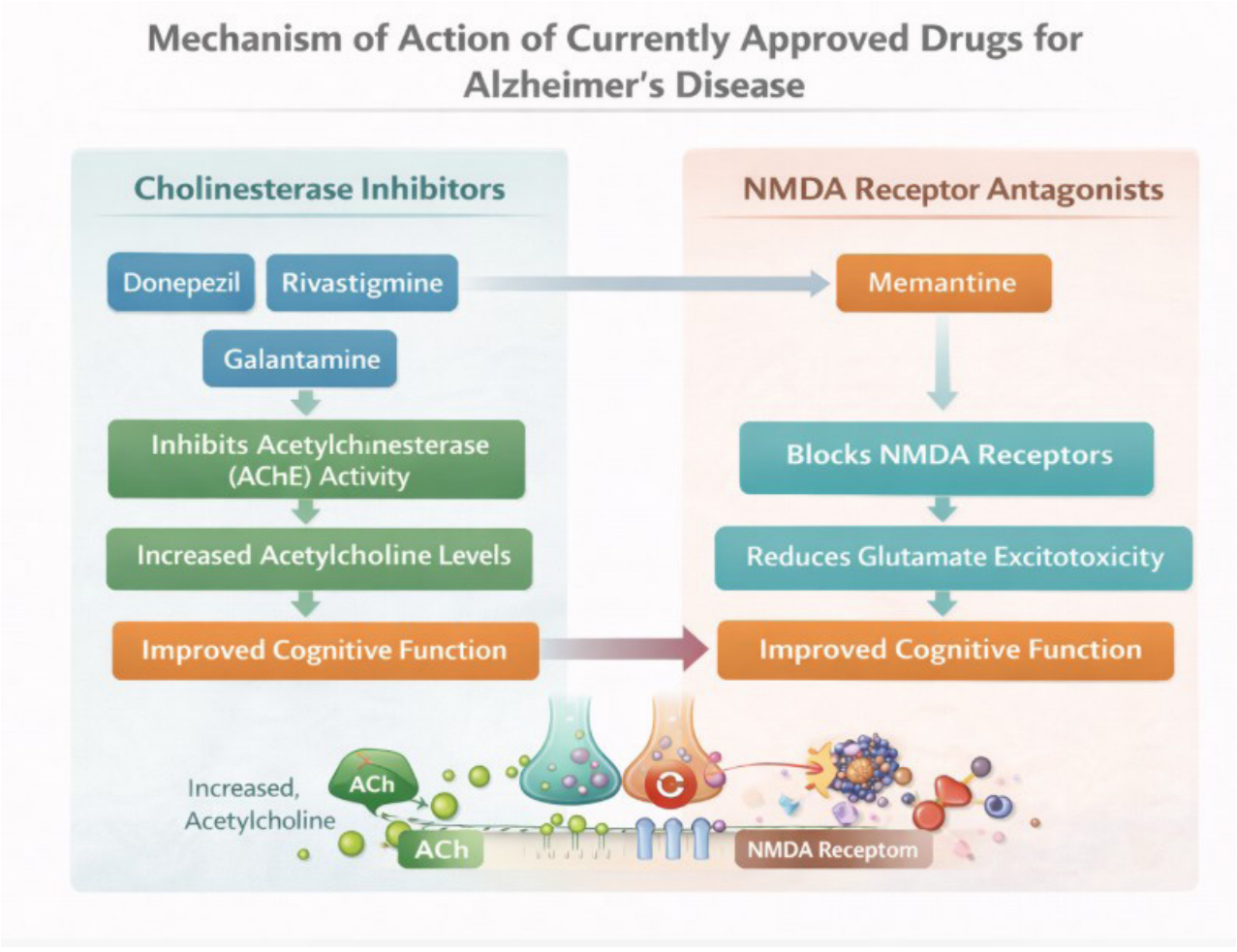

Fig 5 | Flowchart illustrating the mechanism of action of currently approved drugs for Alzheimer's disease

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transmission even further. While cholinesterase inhibitors provide symptomatic relief, they offer modest relief and do not change or prevent the progression of neurodegeneration. Currently approved pharmacological agents for Alzheimer's disease and their mechanisms of action are summarized in Table 2.

NMDA Receptor Antagonists

In cases of moderate-to-severe Alzheimer's Disease, the excitotoxicity of glutamate is thought to be a major mechanism of neuronal injury. Overstimulation of NMDA receptors results in an increase of intracellular calcium through the excessive excitation of the receptors, which in turn causes the release of oxidative stress and consequently neuronal cell death.[33] There is evidence that the use of NMDA receptor antagonists can stop the pathological activity of glutamate, but they do not affect normal synaptic signaling. The only approved NMDA receptor antagonist for the treatment of Alzheimer's Disease is Memantine. Memantine works by blocking the effects of too much activation of NMDA receptors, which reduces the amount of excitotoxicity and helps improve cognitive and functional outcomes for the patient. Memantine is commonly used alone or in combination with cholinesterase inhibitors to further increase the symptomatic benefit of therapy for patients with moderate-to-severe Alzheimer's Disease.[34] The pharmacological actions of all of the approved treatments are shown in Figure 5.

The figure demonstrates the pharmacological mechanisms of currently approved therapies, including cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which inhibit acetylcholinesterase activity and increase acetylcholine levels, and NMDA receptor antagonists (memantine), which reduce glutamate-mediated excitotoxicity. These mechanisms contribute to symptomatic improvement and stabilization of cognitive function in patients with Alzheimer's disease.

Limitations of Existing Pharmacotherapy

Currently authorized pharmacological therapies provide symptomatic relief. However, they have many limitations that prevent them from having long-term effectiveness. Many of them do not address the underlying pathophysiological mechanisms of amyloid deposition, tau aggregates, and chronic neuroinflammation. Therefore, there is no stopping the progression of the disease with the use of these drugs. In addition to patient variability with respect to response to drug treatment, there is also limited efficacy of these drugs when utilized at later disease stages, and there is also the presence of adverse effects such as gastrointestinal disturbances, dizziness, and confusion, among others. All of these limitations create an increased demand for disease-modifying pharmacological therapies that have the capacity to slow or prevent neurodegeneration. As a consequence, current research appears to be increasingly focused on the identification of new therapeutic targets to change the course of the disease and not just on managing the symptoms of neurodegeneration.[35]

Anti-Amyloid Monoclonal Antibodies and Disease-Modifying Therapies

Recent advances in Alzheimer's disease pharmacotherapy include anti-amyloid monoclonal antibodies targeting amyloid beta aggregates. Lecanemab demonstrated clinical benefit in the phase 3 CLARITY-AD trial, showing a significant slowing of cognitive decline in patients with early Alzheimer's disease. Donanemab also showed positive results in phase 3 TRAILBLAZER-ALZ-2, with a reduction in clinical decline and amyloid burden. These therapies represent disease-modifying approaches but require careful patient selection and monitoring. Aducanumab, previously approved under accelerated approval, was later withdrawn due to limited clinical benefit and commercial considerations. These developments highlight both progress and ongoing challenges in disease-modifying therapy.

Safety Considerations and ARIA Monitoring

Anti-amyloid monoclonal antibodies are associated with amyloid-related imaging abnormalities (ARIA), including ARIA-E (edema) and ARIA-H (microhemorrhage). These events are more common in APOE ε4 carriers and during early treatment phases. Therefore, MRI monitoring before and during treatment is recommended. Most ARIA events are asymptomatic; however, careful dose titration and monitoring protocols are necessary to ensure patient safety in clinical practice.

Biomarker-Guided Patient Selection

The use of disease-modifying therapies requires confirmation of amyloid pathology prior to treatment initiation. Biomarker-guided patient selection using amyloid PET imaging or cerebrospinal fluid biomarkers improves treatment precision and reduces unnecessary exposure to therapy. Emerging blood-based biomarkers are also being investigated to support early diagnosis and treatment decision-making.

Emerging Drug Approaches and Novel Therapeutic Targets

The ineffectiveness of present medications for Alzheimer's disease has led to an emphasis on finding ways to change the course of this disorder through treatments that will target the fundamental cause of the disorder rather than just help symptoms. Advances in molecular pharmacology and neurobiology have allowed for the identification of many new targets for pharmacologic treatment that would aim to delay or prevent further neurodegeneration rather than merely providing symptomatic benefit. Novel pharmacotherapeutic agents and treatment strategies currently being studied are outlined in Table 3, and future pharmacotherapeutic targets are depicted in Figure 6.

The figure illustrates novel and emerging pharmacological targets involved in Alzheimer's disease management, including anti-amyloid therapies, tau-targeted interventions, kinase inhibitors, neuroprotective agents, microglial modulators, and combination therapeutic approaches. These strategies aim to modify disease progression by targeting multiple pathological

Table 3 | Emerging pharmacological agents under investigation for Alzheimer's disease[36,37]

Drug/Strategy	Target	Mechanism	Example agent	Stage	Key risks
BACE inhibitors	β-secretase	Reduces amyloid beta production	Verubecestat	Clinical	Cognitive worsening
Anti-amyloid monoclonal antibodies	Amyloid plaques	Enhances amyloid clearance	Lecanemab	Approved	ARIA
Anti-tau therapies	Tau protein	Prevents tau aggregation	Gosuranemab	Phase II	Limited efficacy
Kinase inhibitors	GSK3β, CDK5	Reduces tau phosphorylation	Tideglusib	Clinical	Liver toxicity
GLP-1 receptor agonists	Neuroprotection	Reduces inflammation and oxidative stress	Liraglutide	Clinical	GI effects
Microglial Modulators	Neuroinflammation	Regulates the inflammatory response	TREM2 agonist	Experimental	Unknown Safety

pathways such as amyloid accumulation, tau pathology, oxidative stress, and neuroinflammation, highlighting future directions in Alzheimer's pharmacotherapy.

Disease-Modifying Therapies

DMTs are drugs that change the underlying cause(s) of the disease, as opposed to merely treating the symptoms of the disease. DMTs are considered to be the "future of treatment" for individuals with Alzheimer's disease, because they may change the course of the disease by preventing (1) the formation/aggregation of amyloid-beta; (2) the aggregation of tau; and (3) the inflammation caused by tau or amyloid-beta. Several DMTs that target amyloid production and/or aggregation have been developed over the last several years, including β-secretase inhibitors and monoclonal antibodies. Some agents have shown promise in their ability to reduce amyloid burden; however, clinical results

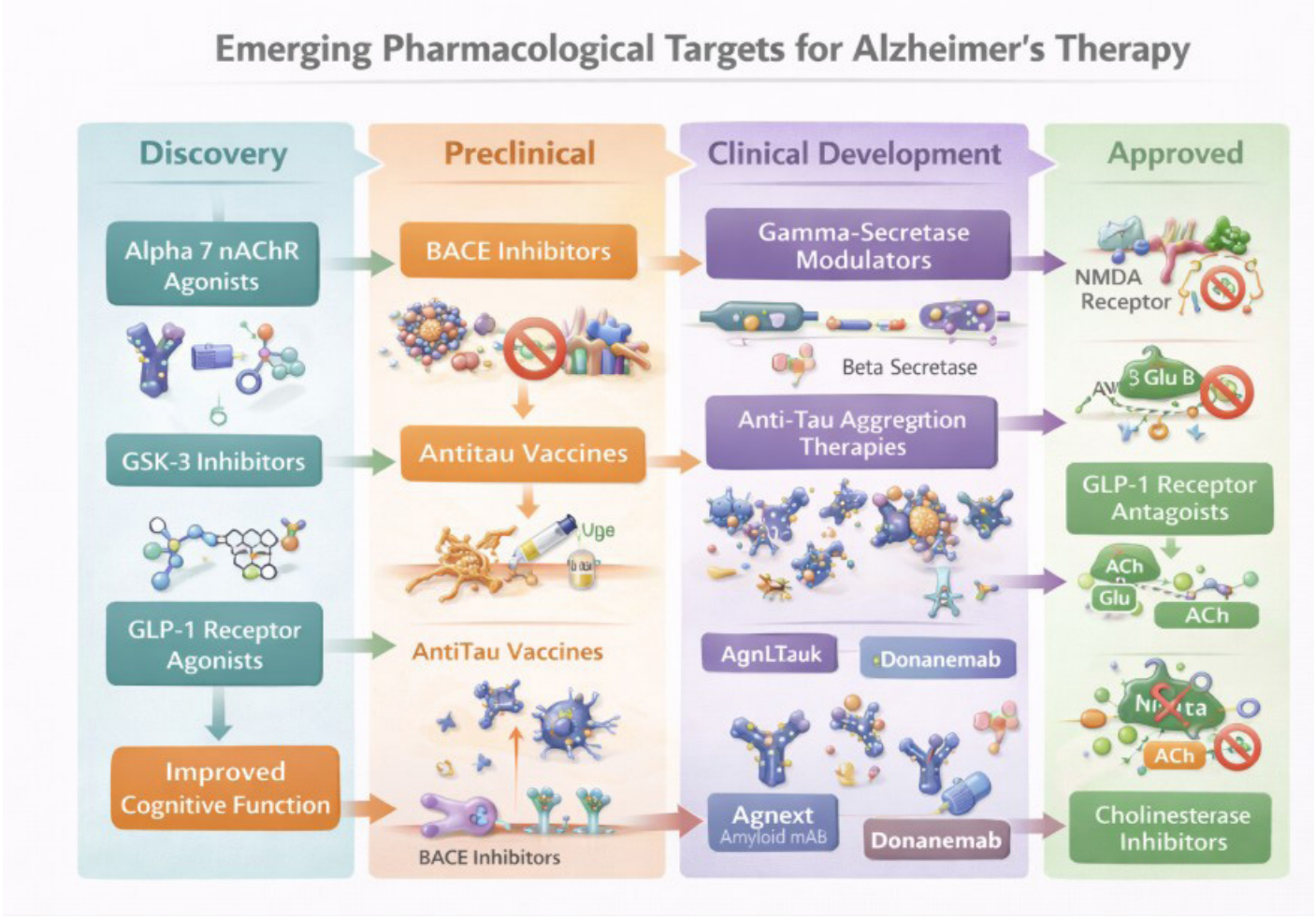

Fig 6 | Emerging pharmacological targets and future therapeutic strategies in Alzheimer's disease

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with these agents have been inconsistent. These inconsistencies may be due to an inconsistency in the timing of treatment; therefore, current studies are focused on identifying biomarkers for the earliest possible diagnosis of Alzheimer's disease to allow for treatment in a timely manner and ultimately to improve clinical outcomes.

Immunotherapy-Based Approaches

Immunotherapy is a novel pharmacotherapy option for Alzheimer's disease that is continuing to be investigated. Attempts have been made to use both active and passive immunization to remove pathogenic proteins from the brain. With passive immunotherapy, the patient receives a monoclonal antibody against amyloid beta or tau protein, which will then be removed by immune mechanisms (e.g., phagocytosis). Immunotherapy targeting tau has also been examined, since tau pathologies have been correlated with the severity of the disease. While the use of immunotherapy to reduce the accumulation of any one of these proteins has shown promising results in terms of accelerating their clearance from the brain, there are still major obstacles to safety, penetration of the blood–brain barrier, and variability of response to immunotherapy products that will continue to be evaluated.

Multi-Target Directed Ligands

Alzheimer's disease is a multifactorial illness, which means that there are many factors that can cause it; therefore, single-target therapies have had limited ability to modify the course of the disease. In order to target the multiple mechanisms of pathology simultaneously, there has been much interest in the development of a newly identified class of drugs called multi-target directed ligands (MTDLs). The goal of MTDLs is to produce drugs that have a combined effect: the ability to both inhibit cholinesterase and cause antioxidant, anti-inflammatory, and anti-amyloid actions.The rationale for MTDLs is that they allow for the simultaneous modification of related causal pathways that lead to Alzheimer's disease; thereby, improving the effectiveness of medications and decreasing the number of medications required to treat the disease, which can lead to adverse drug reactions. Therefore, the MTDL approach is receiving increased interest and is seen as a potential avenue for future drug development for Alzheimer's disease.

Neuroprotective Pharmacological Strategies

Neuroprotective strategies are designed to help retain the ability of neurons to maintain both their structure and function by: (1) reducing oxidative stress; (2) increasing mitochondrial function; and (3) preventing the loss of synapses throughout the course of neurodegeneration. Many pharmacological agents that target oxidative damage, mitochondrial dysfunction, and inflammatory signaling pathways are currently being studied for their ability to halt or slow down the rate of neurodegeneration. Many neuroprotective compounds have been discovered through preclinical studies that exhibit properties of being an antioxidant, stabilizing mitochondria, and/or modulating the neurotrophic signaling pathway, showing a large amount of promise as potential neuroprotective agents. Such neuroprotective approaches seek to maintain the survival and functional integrity of neurons through means other than just limiting the aggregation of proteins.[38] The combination of neuroprotective strategies with disease-modifying therapies may provide an effective avenue for future advancement of pharmacotherapy in Alzheimer's disease.

BACE Inhibitors: Clinical Trial Discontinuations

Although β-secretase (BACE) inhibitors were initially promising for reducing amyloid production, several large clinical trials were discontinued due to lack of efficacy and safety concerns, including cognitive worsening. These findings suggest that complete inhibition of amyloid production may not be a viable therapeutic strategy, and research focus has shifted toward earlier intervention and alternative targets.

Anti-Tau and Microglial-Targeted Therapies

Anti-tau therapeutic approaches, including tau aggregation inhibitors and anti-tau monoclonal antibodies, are currently under clinical investigation, though clinical efficacy remains limited. Microglial modulation strategies, particularly targeting TREM2 signaling, represent emerging therapeutic approaches aimed at enhancing amyloid clearance and reducing neuroinflammation. These strategies remain in early clinical development but show promise for multi-pathway disease modification.

Comparative Clinical Efficacy and Safety

Recent phase 3 trials of anti-amyloid monoclonal antibodies have demonstrated modest but clinically meaningful slowing of cognitive decline. Lecanemab showed approximately 27% slowing in clinical decline in early Alzheimer's disease, while donanemab demonstrated similar reductions depending on tau burden. However, these benefits must be balanced against safety concerns, particularly amyloid-related imaging abnormalities (ARIA). ARIA-E has been reported in approximately 12%–25% of treated patients, with a higher incidence among APOE ε4 carriers. Most events are asymptomatic but require MRI monitoring. These findings highlight the need to balance efficacy with individualized safety risk assessment.

Sequencing and Combination Therapeutic Strategies

Given the multifactorial nature of Alzheimer's disease, sequential and combination therapeutic approaches are being explored. Anti-amyloid therapies may be most effective in early disease stages to reduce amyloid burden, followed by anti-tau therapies targeting downstream neurodegeneration. Combination strategies involving anti-amyloid agents with anti-inflammatory or neuroprotective drugs may enhance therapeutic benefit. Future treatment paradigms may involve

stage-specific therapy where disease-modifying therapies are initiated early, followed by symptomatic and neuroprotective treatments during later stages.

Biomarker-Driven Framework for Therapy Selection

Biomarker-guided treatment selection is increasingly important for precision medicine in Alzheimer's disease. The AT(N) framework categorizes patients based on amyloid (A), tau (T), and neurodegeneration (N) biomarkers. Plasma biomarkers such as p-tau217, Aβ42/40 ratio, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) provide minimally invasive tools for early detection and staging. Patients with positive amyloid biomarkers may benefit from anti-amyloid monoclonal antibodies, whereas elevated tau biomarkers may support inclusion in anti-tau therapeutic trials. Neurodegeneration markers such as NfL may guide supportive and neuroprotective treatment strategies. This biomarker-driven approach enables personalized therapy selection and improved clinical outcomes.

Challenges in Alzheimer's Drug Development

Drug development for Alzheimer's disease has proved to be very difficult, in spite of improved understanding of how the molecular mechanisms work for the disease. This is primarily due to the fact that there is no single process that causes the relevant changes we observe when someone has Alzheimer's; instead, there are multiple processes that all interact with one another: (1) accumulation of beta-amyloid; (2) tau protein accumulation; (3) oxidative stress; (4) problems with mitochondrial function; and (5) inflammation within the brain. If we focus on developing drugs to treat only one of these processes, our likelihood of successfully developing safe and effective drugs is low, due to the fact that each of these processes affects the others, thus making the progression of disease extremely complex, and therefore necessitating the use of a drug to impact all five processes. Another major barrier to the development of Alzheimer's drugs occurs because of the diagnosis of the disease, since diagnosis tends to occur much later in the course of the disease, with significant damage done to the brain, which makes treatment likely to be less effective than treatment earlier in the course of the disease. In fact, there are many disease-modifying therapies that have demonstrated efficacy/benefit in preclinical studies but fail to show efficacy/benefit in phase III clinical trials due to treatment beginning too late or inability to appropriately select patients. There continues to be a great need for identifying biomarkers that accurately identify early-stage Alzheimer's disease, so that we may be able to improve the chances of patients having a favorable response to existing or new treatments. One of the significant limitations of Alzheimer's pharmacotherapy is the delivery of drugs to the central nervous system (CNS). The blood–brain barrier (BBB) is one of the physiological barriers to drug delivery that limits access of many pharmacological agents to the brain and reduces bioavailability at the target site. Achieving an effective therapeutic concentration of a drug without causing systemic toxicity is one of the major challenges for drug developers. Moreover, differences in patient responses due to variability in genetics and the progression of Alzheimer's are also responsible for the inconsistent clinical success of the treatments available today. Compounding these issues is the existence of adverse events associated with specific therapies, particularly with the immunotherapy approach, making the translation of these types of therapies into clinical practice very difficult. High rates of failure in late-stage clinical trials have also increased the economic and risk burden of developing drugs to treat Alzheimer's. Table 4 summarizes the advantages and disadvantages of existing and new therapeutic strategies. In order to overcome the challenges related to the delivery of pharmacological interventions to the CNS in Alzheimer's disease, researchers must improve their understanding of the pathophysiology of the disease, develop new multi-targeted pharmacological agents, develop new early diagnostic methods, and develop innovative methods to deliver drugs to the CNS.

Future Perspectives in Alzheimer's Pharmacology

Researchers have developed a much greater understanding of the cellular and molecular processes associated with Alzheimer's disease, thereby influencing pharmacology and drug-based medical research in the future. Moving away from traditional treatment methods aimed only at alleviating symptoms, future treatment options will focus on preventing or slowing further development of Alzheimer's disease. As a result, the effects of future pharmacological approaches will tend to include strong use of early diagnosis and treatment strategies based on multiple sites of action. Effective future treatment options for Alzheimer's disease will require therapeutic compounds capable of acting

Table 4 | Advantages and limitations of current and emerging therapeutic strategies[39,40]

Therapeutic approach	Advantages	Limitations	Evidence level	Future prospectives
Cholinesterase inhibitors	Symptomatic improvement	No disease modification	High	Combination therapy
NMDA Antagonist	Reduces excitotoxicity	Limited efficacy	High	Adjunct therapy
Anti-amyloid therapy	Targets disease pathology	Variable clinical outcomes	Moderate	Early stage intervention
Anti-tau therapy	Addresses neurodegeneration	Under investigation	Low	Disease-modifying potential
Anti-inflammatory strategies	Reduces neuroinflammation	Target specificity issues	Low	Precision pharmacology
Multi-target drugs	Acts on multiple pathways	Complex development	Experimental	Future therapeutic approach

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on multiple pathophysiologic processes simultaneously, as opposed to just one pathophysiologic target. The reason for this is due to the interaction and influence on each other of the four pathologic processes associated with Alzheimer's disease: amyloid accumulation, tauopathy, oxidative stress, and neuroinflammation. Together, these processes represent a more-complex treatment target, with multisite therapy or multi-targeted approaches theoretically providing superior treatment efficacy as compared with a monotherapy approach. In addition to multi-targeted approaches to treatment, a second major area of pharmacological research for Alzheimer's disease involves the discovery of reliable early-detection and early-treatment biomarkers. Studies have shown that early intervention through pharmacotherapy prior to the development of severe neuronal damage represents the most effective approach for treating the disease. Advances in neuroimaging, cerebrospinal fluid, and blood-borne biomarkers are expected to provide the basis for early detection and more targeted pharmacotherapy interventions in people with Alzheimer's disease. New forms of drug delivery may have great potential to advance Alzheimer's treatments. Nanoparticle-delivered drugs and other drug delivery systems that specifically deliver drugs to the brain through the blood–brain barrier could allow for improved bioavailability, greater therapeutic efficacy, and fewer side effects.[41] Additionally, there has been an increasing focus on neuroprotective and preventive approaches that promote the health of the brain and reduce risk factors that increase the likelihood of developing Alzheimer's disease. A combination of pharmacological therapies with lifestyle and metabolic treatment modalities may enhance long-term success. Ongoing collaborations among molecular pharmacology, clinical research, and translational medicine will be required to develop effective disease-modifying treatments for patients with Alzheimer's disease.

Conclusion

Alzheimer's Disease is among the hardest to treat degenerative diseases due to its complex and multi-causal origins, which include the buildup of beta-amyloid protein, problems with tau proteins, oxidative stress, problems with mitochondrial function, and long-term inflammation of the brain. Although FDA-approved medications have been developed that relieve symptoms of Alzheimer's via changes in the function of cholinergic and glutamatergic neurotransmitters, none of them can stop the progression of Alzheimer's, so alternative treatments must be developed. Molecular pharmacology is yielding results related to our understanding of the underlying mechanisms of Alzheimer's and has led to the identification of new pharmacological targets. As a result, new types of therapies are emerging as treatment options, including disease modification and immunotherapy, multi-target ligands, and neuroprotective agents. However, problems with early diagnosis, drug crossing the blood–brain barrier, and variations in treatment outcomes continue to present difficulties with treating AD patients. Integrated approaches will be necessary in the future to treat Alzheimer's with effective pharmacotherapies, which include early diagnosis, multi-target pharmacological treatments, and innovative drug delivery methods. Continued research exploring the underlying mechanisms of diseases and practical applications of this knowledge will help produce effective ways to reduce the progression of Alzheimer's disease and improve the quality of life of individuals living with the disease.

List of Abbreviations

Aβ: Amyloid Beta
ACh: Acetylcholine
AChE: Acetylcholinesterase
AD: Alzheimer's Disease
APOE: Apolipoprotein E
APP: Amyloid Precursor Protein
BACE1: Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1
BBB: Blood–Brain Barrier
BuChE: Butyrylcholinesterase
CDK5: Cyclin-Dependent Kinase 5
CNS: Central Nervous System
DMTs: Disease-Modifying Therapies
GLP-1: Glucagon-Like Peptide-1
GSK3β: Glycogen Synthase Kinase 3 Beta
IL: Interleukin
IL-1β: Interleukin-1 Beta
IL-6: Interleukin-6
JAK: Janus Kinase
MAPK: Mitogen-Activated Protein Kinase
MTDLs: Multi-Target Directed Ligands
NF-κB: Nuclear Factor Kappa B
NLRP3: NOD-like Receptor Family Pyrin Domain Containing 3
NMDA: N-Methyl-D-Aspartate
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSEN1: Presenilin-1
PSEN2: Presenilin-2
ROS: Reactive Oxygen Species
STAT: Signal Transducer and Activator of Transcription
TNF-α: Tumor Necrosis Factor Alpha

Limitations

The present review has several limitations that should be considered while interpreting the findings. First, the review is based on previously published literature, and therefore, the conclusions depend on the quality, availability, and methodological variations of the included studies. Differences in study design, experimental models, and clinical trial outcomes may influence the consistency of reported findings. Second, although extensive literature databases were searched, the possibility of publication bias cannot be completely excluded, as studies reporting positive outcomes are more likely to be published than those with negative or inconclusive results. In addition, Alzheimer's disease is a multifactorial disorder involving complex and interrelated pathological mechanisms, which makes it challenging to comprehensively address all potential therapeutic targets within a single review. Emerging

pharmacological strategies discussed in this review are still under investigation, and their long-term clinical efficacy and safety remain to be fully established. Therefore, further well-designed clinical studies and translational research are required to validate the therapeutic potential of emerging pharmacological approaches in Alzheimer's disease.

Transparency Statement

The authors declare that this review article was conducted using publicly available scientific literature obtained from recognized academic databases, including PubMed, Scopus, Web of Science, and Google Scholar Transparency Statement. This review was conducted using publicly available literature from recognized academic databases. The article represents a narrative synthesis of available evidence. No new experimental data were generated. No new experimental data involving human participants or animals were generated for this study. The author confirms that the manuscript represents an unbiased synthesis of available literature and that no financial or commercial interests influenced the preparation of this review. All sources of information have been appropriately acknowledged through citation of original research articles and review papers.

AI Tool Usage

AI tools were used only for linguistic editing and formatting assistance under human supervision, consistent with journal transparency policies.

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