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•Review•

Approved drugs and natural products at clinical stages for treating Alzheimer's disease

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[ABSTRACT] Alzheimer's disease (AD) remains the foremost cause of dementia and represents a significant unmet healthcare need globally. The complex pathogenesis of AD, characterized by various pathological and physiological events, has historically challenged the development of anti-AD drugs. However, recent breakthroughs in AD drug development, including the approvals of aducanumab, lecanemab, and sodium oligomannate (GV-971), have ended a nearly two-decade hiatus in the introduction of new AD drugs. These developments have addressed long-standing challenges in AD drug development, marking a substantial shift in the therapeutic landscape of AD. Moreover, natural products (NPs) have shown promise in AD drug research, with several currently under clinical investigation. Their distinct properties and mechanisms of action offer new avenues to complement and enhance existing AD treatment approaches. This review article aims to provide an overview of the recent advancements and prospects in AD therapeutics, focusing on both NPs and approved drugs.

[KEY WORDS] Alzheimer's disease; amyloid-beta; Natural products; Clinical trials; Cognition
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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder impacting the central nervous system (CNS) and is predominantly linked to age-related dementia. It is characterized by notable histopathological changes in brain tissue and behavioral alterations [1]. Clinically, AD presents with a gradual onset, eventually leading to symptoms such as memory loss, abnormal behaviors, cognitive deficits, and social dysfunction [2, 3]. The disease progresses relentlessly, culminating in a significant loss of independence among patients. This progression poses a severe threat to human health and contributes to various social challenges, including economic burdens, caregiving demands, and increased healthcare needs. With the rising aging population, AD has escalated into a critical public health issue, underscoring the imperative for effective treatments. Hence, the pursuit of safe and effective interventions for AD has become a pivotal area of medical research [4-6].

Understanding AD's complex neuropathological features is essential for developing targeted therapies. The disease is marked by the accumulation of amyloid plaques, primarily composed of amyloid-beta (Aβ) peptides, and the formation of neurofibrillary tangles, predominantly made of hyperphosphorylated tau protein [2, 3]. Additionally, cholinergic dysfunction and neurotransmitter imbalances in AD have been key targets for therapy. The disease is thought to be influenced by various factors, including genetics, aging, immune dysfunction, hormonal levels, mitochondrial abnormalities, neuronal loss, inflammation, and environmental factors. Several hypotheses have been proposed to explain its etiology, such as the cholinergic hypothesis, oxidative stress,

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Aβ deposition, tau protein hyperphosphorylation, and genetic mutations (Fig. 1) [7, 8].

Based on the pathogenesis hypothesis of AD, numerous efforts have been undertaken to develop effective therapeutic approaches. Among the approved anti-AD drugs, acetylcholinesterase (AChE) inhibitors have been extensively used to increase the availability of acetylcholine in the brain (Fig. 2). Drugs such as donepezil, rivastigmine, and galantamine have shown efficacy in alleviating cognitive decline and enhancing behavioral symptoms in AD patients. Additionally, memantine, a *N*-methyl-D-aspartate (NMDA) receptor antagonist (Fig. 2), has been approved for treating moderate to severe AD, offering an alternative mechanism of action by modulating glutamatergic signaling [9]. The complex pathogenesis of AD has posed significant hurdles in the development of new drugs, resulting in a notable scarcity of new approvals over the past two decades [10]. However, recent research breakthroughs have led to the approval of innovative drugs such as aducanumab, leqembi, and sodium oligomannate (GV-971). These medications target specific pathological aspects of AD, including the clearance of Aβ aggregates and modulation of mechanisms related to gut microbiota [11, 12], thereby opening new pathways for AD treatment.

The potential of natural products (NPs) in the treatment of AD has garnered significant interest. Notably, huperzine A, derived from the Chinese herb *Huperzia serrata*, and galantamine, extracted from the bulbs of certain daffodil species, have proven their clinical efficacy in enhancing cognitive and memory functions, as well as daily living activities of AD patients. Natural compounds sourced from plants and other origins have demonstrated promising effects in clinical studies or early-stage clinical trials, sparking extensive research into their effectiveness for AD therapy. Furthermore, natural compounds possess the capacity to influence multiple molecular mechanisms involved in AD pathogenesis. These include reducing inflammation, alleviating oxidative stress, preventing Aβ aggregation, and inhibiting tau neurofibrillary tangles (NFTs). By targeting these pathological mechanisms, NPs offer a comprehensive approach to combat AD or prevent disease progression [13, 14].

The current study aims to provide a comprehensive analysis of approved anti-AD drugs, detailing their mechanisms of action, clinical evidence, safety profiles, and potential adverse effects. Additionally, this study will highlight naturally occurring compounds that are currently under clinical evaluation for their therapeutic potential in AD, illuminating the innovative approaches being pursued in AD research and treatment. Furthermore, a significant aspect of novelty in AD treatment is represented by recent breakthroughs that have broadened the treatment landscape and introduced new opportunities for managing the disease. The approval of drugs

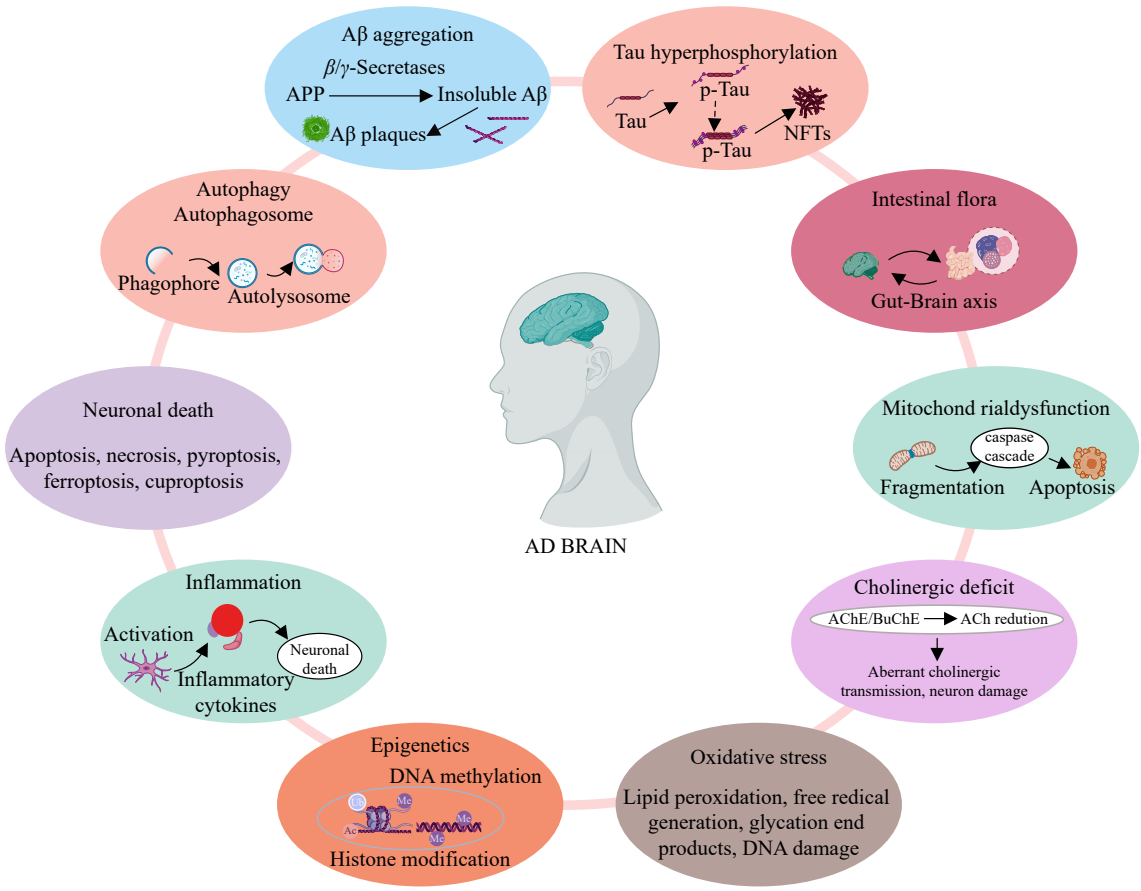

Fig. 1 Overview of the major pathophysiology of AD.

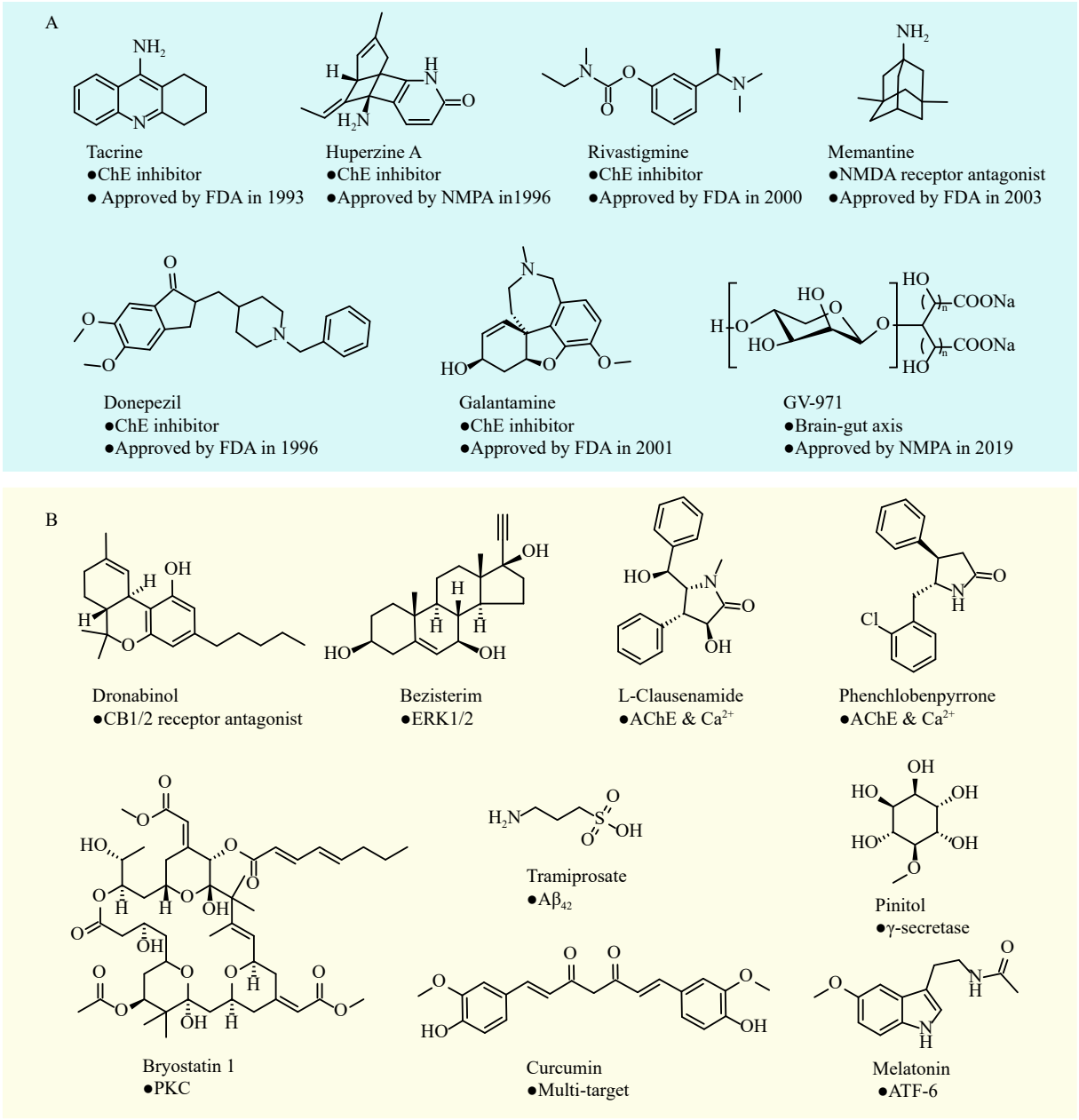

Fig. 2 Chemical structures and targets of approved anti-AD drugs (A) and NPs in clinical trials (B).

such as aducanumab, leqembi, and GV-971 marks significant milestones in AD therapeutics, offering novel mechanisms of action and potential benefits for patients. By showcasing these innovative therapies, this study aims to highlight the latest advancements in AD research and emphasize the importance of exploring new treatment modalities to address the evolving needs of individuals affected by AD.

Overview of AD Pathology

AD is marked by distinct neuropathological characteristics that lead to progressive cognitive decline and functional impairment. The two primary pathological hallmarks of AD are the accumulation of amyloid plaques and the formation of neurofibrillary tangles.

Amyloid plaques are primarily composed of aggregated Aβ peptides, derived from the proteolytic processing of amyloid precursor protein (APP) [15]. These peptides, in specific conformations, aggregate into insoluble fibrils that deposit in the brain's extracellular spaces. This deposition disrupts normal neuronal signaling, contributing to synaptic dysfunction and neuronal loss. Conversely, neurofibrillary tangles consist mainly of hyperphosphorylated tau protein. Tau is a microtubule-associated protein that stabilizes microtubules in neurons [16]. In AD, abnormal hyperphosphorylation causes tau protein to aggregate, forming intracellular tangles. This accumulation disrupts the neuronal cytoskeleton and impairs the transport of essential molecules within neurons, leading to

neuronal dysfunction and death. Cholinergic dysfunction and neurotransmitter imbalances also play critical roles in AD pathology [17]. Cholinergic neurons, located primarily in the basal forebrain, are integral to learning, memory, and cognitive functions. In AD, the degeneration of these neurons leads to a significant reduction in acetylcholine levels, contributing to the cognitive impairments observed in the disease. The decline in cholinergic transmission contributes to cognitive impairments observed in AD. Furthermore, there is growing evidence suggesting the involvement of other neurotransmitters in AD. Dysfunction of the glutamatergic system, characterized by an imbalance between excitatory and inhibitory neurotransmission, has also been implicated in AD pathology [18]. Excessive activation of NMDA receptors, which bind to the neurotransmitter glutamate, can lead to excitotoxicity and neuronal damage. Hence, aberrant glutamatergic signaling and altered NMDA receptor activity contribute to AD-related neurotoxicity [19].

Understanding these complex neuropathological features is crucial for developing targeted therapeutic strategies. These pathological insights have guided the development of numerous therapeutic approaches aimed at targeting amyloid plaque accumulation, neurofibrillary tangle formation, and related mechanisms to potentially slow or halt disease progression. While these hypotheses have provided a valuable framework for research and drug development, their complete role in AD pathophysiology continues to be a topic of ongoing investigation and debate within the scientific community. Ongoing research into the complexities of AD pathogenesis, including the interplay between amyloid, tau, and other pathological processes, is essential for advancing our understanding of the disease and developing more effective treatments. By critically evaluating and refining these popular hypotheses in light of emerging evidence, researchers can uncover new insights into the underlying mechanisms of AD and identify novel therapeutic targets for intervention. The subsequent sections will explore the approved anti-AD drugs, their mechanisms of action, clinical evidence, safety profiles, and potential adverse effects.

Approved Anti-AD Drugs

Cholinesterase inhibitors

AChE inhibitors are a class of drugs extensively utilized in the clinical management of AD. They function by inhibiting the activity of acetylcholinesterase, an enzyme that breaks down acetylcholine in the brain. By increasing acetylcholine levels, these drugs aim to enhance cholinergic neurotransmission and improve cognitive function in patients with AD.

Tacrine

Tacrine was the first cholinesterase inhibitor approved for the treatment of AD in 1993. As a first-generation AChE inhibitor, tacrine works by reversibly inhibiting acetylcholinesterase, which increases acetylcholine levels in the brain. This inhibitory action occurs in both plasma and tissues and is accompanied by the stimulation of M and N receptors, thereby facilitating acetylcholine release and enhancing glucose utilization in brain tissue [20]. Early studies demonstrated the efficacy of tacrine in improving cognitive function and atypical behavior in patients with mild to moderate AD. However, despite its therapeutic benefits, the use of tacrine has been limited due to its association with hepatotoxicity, significant peripheral side effects, and elevated serum levels of alanine transaminase and aspartate transaminase. Research has shown that the primary amine group within the tacrine molecule can undergo metabolism by the liver's CYP450 enzyme family, resulting in the generation of nitrogen oxides and high concentrations of superoxide radicals, contributing to its toxic side effects [21].

Nevertheless, tacrine's structural features, such as its small molecular weight, high lipid solubility, and ability to penetrate the blood-brain barrier, make it an attractive scaffold for drug design [22]. These attributes offer significant opportunities for rational modifications, particularly to the amino group of tacrine's scaffold. Modifications to the amino group can reduce tacrine's toxicity by enabling covalent attachment to various bioactive chemical fragments or pharmacophores, potentially providing synergistic effects and enhanced anti-AD activity. Therefore, the field of tacrine-based drug design remains active, with numerous medicinal chemistry efforts focused on exploring the potential of tacrine derivatives in the treatment of AD [23].

Donepezil

Donepezil, a member of the hexahydropyridine derivative class, was approved by the Food and Drug Administration (FDA) in 1996 for the clinical treatment of AD. As a second-generation, selective, and reversible central AChE inhibitor, donepezil exhibits minimal activity on peripheral AChE. By inhibiting AChE activity, donepezil slows the breakdown of acetylcholine in synaptic clefts, thereby increasing acetylcholine levels and enhancing cognitive function in AD patients. Donepezil is widely used in the treatment of mild to moderate AD and vascular dementia, as it can improve cognitive and overall brain function. In clinical practice, oral administration of 10 $mg \cdot kg^{-1}$ results in a dose-dependent inhibition of brain AChE activity. The common adverse reactions associated with donepezil primarily include nausea, vomiting, diarrhea, fatigue, muscle spasms, and anorexia [24]. These symptoms are typically mild and tend to improve with continued use of the medication.

Donepezil is primarily metabolized by hepatic enzymes, and research has identified its 6-oxo derivative (6-ODD) as the major active metabolite, which exhibits comparable inhibitory activity on AChE [25]. Due to its high lipid solubility, donepezil can readily penetrate the blood-brain barrier and demonstrates strong affinity for AChE. It specifically binds to AChE in the cerebral cortex, thereby providing high therapeutic effects with minimal side effects [26]. Furthermore, donepezil has a chiral center, existing as a pair of enantiomers: *R*-donepezil and *S*-donepezil. The binding affinity of

S-donepezil to AChE is 2.2 times higher than that of *R*-donepezil. Clinically, the racemic mixture of donepezil is administered [27].

The structure of donepezil includes a benzylic portion that interacts with the catalytic anionic site (CAS) and a dimethoxy indanone part that targets the peripheral anionic site (PAS) of the AChE enzyme. Given the complex nature of AD, drugs that interact with a single receptor or enzyme are often inadequate for effective treatment. Consequently, structural modifications of donepezil have been extensively explored to enhance its anti-AD capabilities. These modifications primarily focus on replacing the benzylpiperidine moiety with various heterocyclic rings, attaching donepezil to natural compounds, and combining it with condensed heterocyclic rings. Such medicinal chemistry efforts have led to improved activities of donepezil derivatives, establishing it as a significant scaffold for designing novel drugs targeting AD [28].

Rivastigmine

Rivastigmine was approved by the FDA in 2000 for the treatment of AD and is an orally active carbamate compound with dual inhibitory activity against AChE and butyrylcholinesterase (BChE) [29]. It is highly penetrable through the blood-brain barrier. Unlike some other AD drugs, rivastigmine can be administered not only orally but also *via* a transdermal patch, allowing the drug to enter the bloodstream through the skin and thereby increase acetylcholine levels in the brain. Rivastigmine acts as a pseudo-parasympathomimetic and cholinergic agent, enhancing excitatory neural transmission in the brain, which contributes to improved cognitive functions [29]. Rivastigmine is primarily used for treating mild to moderate dementia caused by AD or Parkinson's disease. Clinical evidence indicates that rivastigmine is safe and well-tolerated, with no severe liver impairment associated with its use. However, long-term administration of rivastigmine is commonly associated with side effects such as nausea, vomiting, and diarrhea.

Furthermore, studies have shown that rivastigmine, beyond its inhibition of AChE, can also influence the processing of APP by directing it towards *α*-secretase rather than beta-site APP-cleaving enzyme 1 (BACE1) and dose-dependently enhance *α*-secretase activity. This discovery suggests that rivastigmine not only mitigates symptoms of AD but may also intervene in the disease's progression [30]. Additionally, medicinal research has identified the carbamate moiety as the key pharmacophore responsible for rivastigmine's therapeutic effects. By incorporating this moiety into other synthetic small molecules and natural compounds, a variety of structurally novel chemical entities with multi-target potential have been developed. Thus, rivastigmine-based drug design represents a significant research direction and is a prominent topic in the field of anti-AD drug research [31, 32].

Huperzine A

Huperzine A has been traditionally used in Chinese medicine for memory enhancement and the treatment of fever and inflammation. In 1996, it was approved by China's National Medical Products Administration (NMPA) as a second-class new drug for the treatment of AD, classifying it within the second generation of AChE inhibitors. Derived from the Chinese herb *Huperzia serrata*, huperzine A is a natural sesquiterpene alkaloid characterized by low toxicity and high efficacy in clinical use. Compared with other AChE inhibitors, such as donepezil and rivastigmine, huperzine A exhibits greater penetration across the blood-brain barrier and a longer duration of action. It has been shown to improve memory and cognitive impairments in AD patients with a low incidence of adverse reactions, demonstrating good clinical safety [33]. Additionally, huperzine A is small in size and highly lipid-soluble. Upon entering the CNS, it predominantly distributes to brain regions closely associated with learning and memory functions, such as the frontal lobe, temporal lobe, and hippocampus [34]. At low doses, huperzine A exerts a potent inhibitory effect on AChE in the synaptic cleft, significantly increasing the concentration of acetylcholine in its distribution area. This enhances neuronal excitatory conduction, strengthens excitatory effects in learning and memory-related brain regions, and thereby improves cognitive function and memory retention.

Beyond its role in inhibiting acetylcholinesterase activity, huperzine A also counteracts oxidative stress and cell apoptosis induced by neurotoxic substances such as Aβ and hydrogen peroxide. It activates the protein kinase C (PKC) signaling pathway to promote the non-amyloidogenic degradation of APP, leading to the production of soluble APP alpha (sAPPα) and reducing Aβ-mediated toxicity. In turn, sAPPα promotes cell proliferation and axonal growth and protects neurons [35, 36]. In addition to its use in treating AD, huperzine A is also commonly used in clinical practice to treat vascular dementia, enhancing memory and cognitive functions in patients.

Galantamine

Launched in 2001, galantamine is a phenanthrene alkaloid derived from plants in the Amaryllidaceae family. It functions as a selective, reversible, and competitive AChE inhibitor [37]. In addition to inhibiting AChE, galantamine enhances the intrinsic action of acetylcholine by binding to allosteric sites on nicotinic receptors, thereby facilitating nicotinic neurotransmission and improving cognitive function in mild to moderate AD [38, 39]. Galantamine also plays a role in inhibiting the aggregation and cytotoxicity of Aβ peptides and preventing oxidative damage induced by Aβ. Clinically, galantamine is administered orally and is generally well-tolerated, with minimal side effects. The most common adverse reactions, primarily nausea and vomiting, usually occur during the initial phase of treatment. Additionally, galantamine is used in the treatment of myasthenia gravis, cerebral palsy, radiculitis, and traumatic sensorimotor disorders in children [38, 40].

Galantamine is rapidly absorbed when taken orally, boasting a bioavailability of up to 90%, with an elimination

half-life of approximately 7 h. It is primarily metabolized in the liver to desmethyl galantamine, which retains one-third of the parent compound's AChE inhibitory activity [37]. Pharmacological studies have demonstrated that galantamine can improve memory impairment and spatial orientation in rats, enhance the excitatory effects of the CNS, and facilitate the formation of conditioned reflexes [41]. Clinical research indicates that galantamine significantly improves patients' emotional states and their ability to perform daily activities, showing greater efficacy in memory enhancement compared with other drugs.

NMDA receptor antagonist

The excitatory neurotransmitter glutamate plays a crucial role in both the pathological and physiological processes of AD, with approximately 70% of excitatory synapses in the CNS being activated by glutamate. Dysfunction in this process, primarily mediated by NMDA receptors, can lead to excessive and prolonged excitatory effects, resulting in the degeneration and death of cortical and subcortical neurons [42].

Memantine, approved in 2003 for the treatment of moderate to severe AD, is the only drug specifically indicated for this stage of the disease [43, 44]. It is a voltage-dependent, moderate-affinity, noncompetitive antagonist of NMDA receptors, able to block the NMDA receptor-gated cation channel with strong voltage dependence and rapid blocking/unblocking kinetics [45]. By acting on NMDA receptors, memantine improves neural signal transmission and delays the release of glutamate, thereby exhibiting neuroprotective effects by preventing excessive calcium ion entry into neurons [46].

Clinical studies have demonstrated that memantine does not cause significant liver adverse effects, whether administered alone or in combination with cholinesterase inhibitors [10, 11]. Targeting different receptors compared with the other four approved drugs, memantine has minimal adverse effects, making it suitable for combination therapy or multi-target treatment. In 2014, the FDA approved a combination formulation of memantine and donepezil for the treatment of AD. Clinical studies have shown that this combination provides superior therapeutic efficacy in improving patients' cognitive abilities, overall condition, and behavior compared with the use of donepezil alone [47].

Other approved drugs

In addition to cholinesterase inhibitors and NMDA receptor antagonists, recent advancements in AD treatment have led to the approval of several other drugs that offer novel therapeutic approaches and target different aspects of AD pathology. These developments reflect an expanding understanding of the disease's multifactorial nature and the necessity for diverse treatment strategies.

Aducanumab

In 2021, aducanumab, a drug based on the Aβ hypothesis, was approved by the FDA for the treatment of AD. Aducanumab specifically binds to Aβ peptides and facilitates the clearance of Aβ accumulations in the brains of AD patients. As a monoclonal antibody, aducanumab targets various stages of the $A\beta_{42}$ pathology, including its monomeric, oligomeric, and plaque forms, as well as its extracellular deposition in neurons. This targeted action ultimately leads to a significant reduction in Aβ deposition (Fig. 3) [48]. This approval marks a pivotal moment in AD treatment, reflecting a shift towards therapies that directly intervene in the disease's molecular pathogenesis.

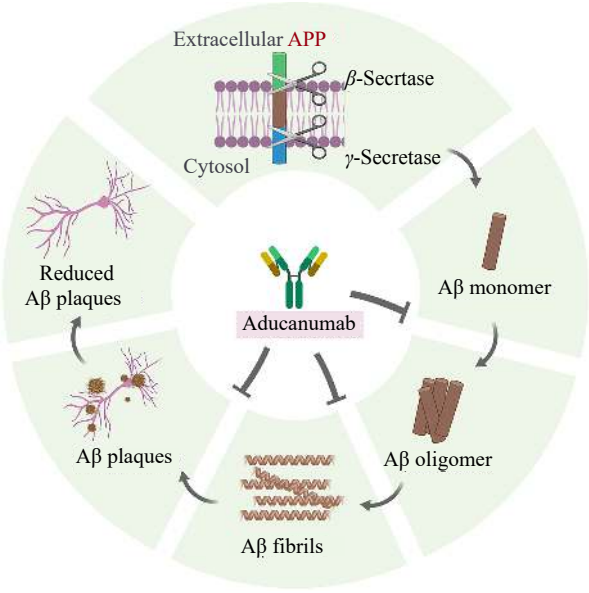

Fig. 3 Schematic diagram of Aβ reduction by aducanumab involving multiple processes.

Since the approval of memantine in 2003, the field of AD treatment has experienced a nearly two-decade hiatus without the introduction of significantly effective novel drugs that directly target the disease's progression. Existing medications and cognitive behavioral therapies have primarily focused on symptom management rather than altering the underlying disease process. Aducanumab, however, is anticipated to potentially impact the progression of AD. This drug is a high-affinity IgG1 monoclonal antibody that selectively recognizes conformational epitopes of Aβ [49]. It binds to Aβ deposits in the brain, activating the immune system to clear these protein accumulations. Nevertheless, the approval of aducanumab has sparked considerable debate within the scientific community. Its initial approval by regulatory agencies was granted under accelerated conditions based on the surrogate endpoint of plaque reduction [50, 51]. The EMERGE trial (NCT02484547), which evaluated the efficacy of aducanumab in mitigating cognitive and functional decline, reported a significant average baseline change in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at 78 weeks in the high-dose (10 $mg \cdot kg^{-1}$) aducanumab group compared with the placebo group ($P = 0.012$). Secondary endpoints also favored the high-dose group. Additionally, a sub-study indicated notable reductions in baseline PET SUVR and biomarker levels in both aducanumab treatment arms compared with the placebo group. Conversely, the ENGAGE trial (NCT

02477800) did not demonstrate a significant difference in CDR-SB scores at 78 weeks between the aducanumab treatment and placebo groups, which may have been influenced by limited blood-brain barrier penetration and selectivity for amyloid plaques [52]. Ongoing studies continue to investigate the clinical relevance and long-term effectiveness of aducanumab in AD. Despite these challenges, the approval of aducanumab marks a significant milestone as it represents a novel strategy for AD treatment. It offers new possibilities for disease management with potential disease-modifying effects, underscoring a pivotal advancement in the therapeutic landscape for AD.

Leqembi

Leqembi was granted accelerated approval by the FDA in 2023, marking it as the second monoclonal antibody targeting Aβ approved for the treatment of AD. The pivotal Phase III clinical trial, CLARITY AD, evaluated the drug in 1795 patients exhibiting symptoms of mild dementia due to early-stage AD. Results from this trial demonstrated that after 18 months of treatment, the rate of decline in cognitive and memory function was reduced by 27% in participants receiving Leqembi compared with those given a placebo [53]. Common adverse effects associated with Leqembi primarily include flu-like symptoms, nausea, vomiting, headache, and amyloid-related imaging abnormalities (ARIA). ARIA represents a known side effect observed with antibody therapies targeting amyloid, characterized by temporary swelling in certain brain regions or small bleeding points. This side effect can indicate potential intracranial hemorrhage and is a serious risk associated with this class of antibody drugs [54].

The safety and efficacy of Leqembi for AD patients at other stages remain unexplored. As an emerging therapy, further research is crucial to fully understand the efficacy, safety, and long-term effects of Leqembi. Data from ongoing studies will be essential to assess the broader implications and potential limitations of this therapy, potentially guiding its application across more diverse patient groups and stages of the disease.

GV-971 (Sodium oligomannate)

In 2019, GV-971 received conditional approval in China as a treatment designed to improve cognitive function in patients with mild to moderate AD. This drug represents the first novel therapeutic targeting the brain-gut axis specifically for AD management. Derived from marine brown algae extract, sodium oligomannate is prepared as a low molecular-weight acid oligosaccharide compound. It functions by reshaping the gut microbiota, maintaining intestinal flora balance, and reducing the activation of microglia and astrocytes. This, in turn, alleviates neuroinflammation in the brain, which consequently decreases Aβ accumulation and tau protein hyperphosphorylation (Fig. 4) [55]. This innovative approach highlights the increasing recognition of the gut-brain axis's role in neurodegenerative diseases and opens new avenues for the development of AD treatments.

The brain-gut axis hypothesis suggests that the CNS can influence the gastrointestinal (GI) system and vice versa; disruptions in the GI system can also affect the CNS. Disturbances in brain-gut interactions can lead to inflammation and promote the accumulation of Aβ and tau protein in the gut, blood, and brain, contributing to the development and progression of AD [56, 57]. Research by GENG *et al*. has shown that dysbiosis in the gut microbiota can lead to abnormal increases in peripheral phenylalanine and isoleucine levels, which in turn induces the differentiation and proliferation of pro-inflammatory Th1 cells. This promotes their infiltration into the brain, where they activate M1 microglia, triggering inflammation associated with AD. Sodium oligomannate has been shown to remodel the gut microbiota, reducing the concentrations of phenylalanine and isoleucine and thereby decreasing the infiltration of Th1 cells into the brain. This modulation of the gut microbiota by sodium oligomannate ultimately alleviates neuroinflammation and leads to improvements in cognitive functions [55]. Additionally, research indicates that gut microbiota dysbiosis occurs in the preclinical stages of AD, before the appearance of neurodegenerative symptoms, and these changes are closely related to the formation of Aβ and tau hyperphosphorylation [58].

These newly approved drugs, including sodium oligomannate, represent innovative approaches to AD treatment, targeting various mechanisms and pathological processes. Despite the promising preliminary outcomes, it is crucial to recognize that further research is needed to fully understand their long-term efficacy, safety profiles, and clinical relevance. Ongoing research and rigorous clinical trials are essential to determine the true therapeutic potential of these drugs and to ensure they provide optimal benefits for patients with AD.

NPs Undergoing Clinical Trials for AD Treatment

The exploration of NPs for AD treatment is a vital and promising avenue in therapeutic development. Derived from plants, marine organisms, and various other sources, these NPs have historically been foundational to traditional medicine and have demonstrated potential across numerous diseases, including AD [59, 60]. Traditionally, these substances have been utilized to alleviate symptoms and enhance overall well-being. In the context of AD, NPs offer a diverse spectrum of bioactive compounds with potential neuroprotective and cognitive-enhancing properties. Two notable examples are huperzine A and galantamine, both derived from natural sources and clinically proven to be effective in managing AD symptoms. Beyond these clinically used drugs, a multitude of other NPs have shown promising potential for AD treatment. These act through various mechanisms, including antioxidant and anti-inflammatory effects, inhibition of Aβ aggregation, and the promotion of neurogenesis and synaptic plasticity. While the progress of NPs in AD treatment has been extensively reviewed, this section will not delve into those details. Instead, it will focus on several NPs currently in

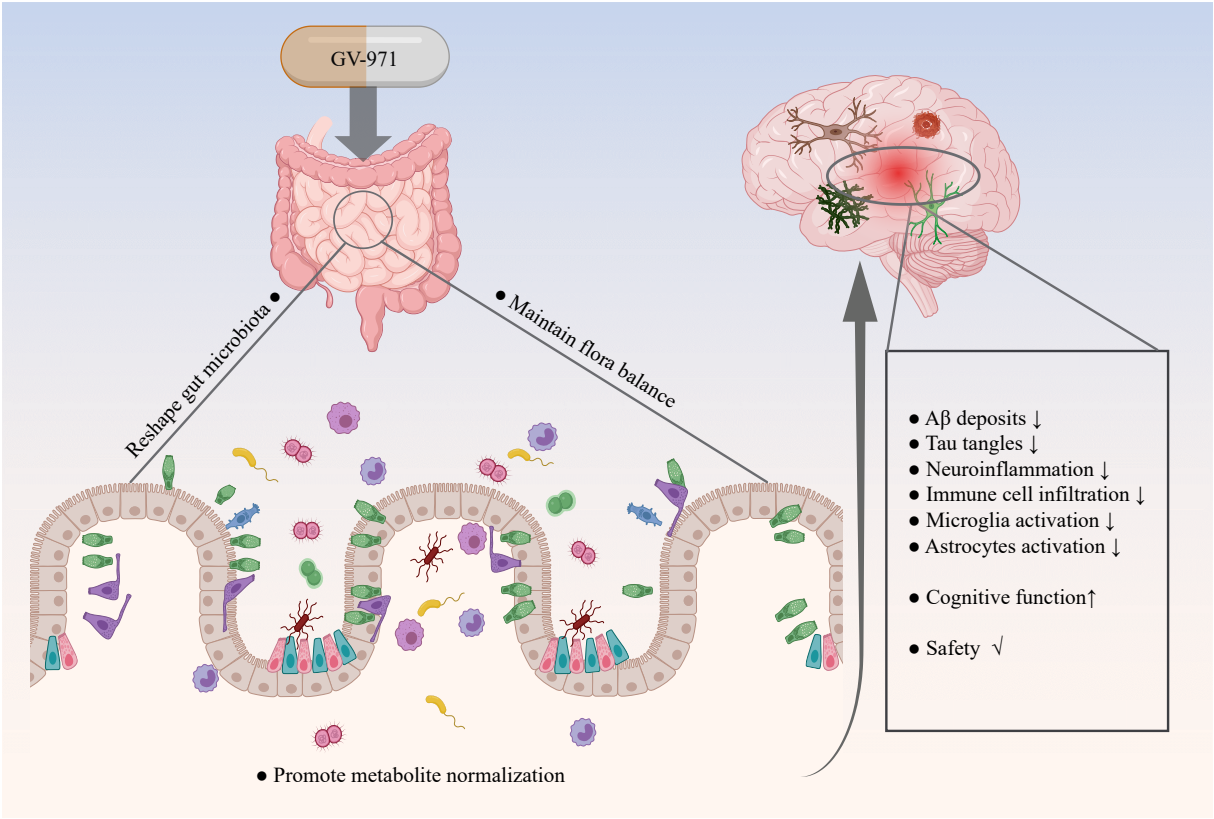

Fig. 4 Schematic diagram of aducanumab alleviating AD pathology by acting on the brain-gut axis.

the clinical trial phase. Their chemical structures and relevant clinical information are summarized in Fig. 2 and Table 1.

L-clausenamide, a bioactive ingredient extracted from the leaves of *Melia azedarach*, exhibits properties that inhibit Aβ production and improve cognitive function. It is currently used clinically to treat cognitive impairments in elderly patients with dementia and is undergoing phase II clinical trials in China [61]. Additionally, phenchlobenpyrrone, a derivative of clausenamide, is a highly selective, blood-brain barrier penetrable neuronal calcium antagonist that has shown potential to improve memory impairments and is also in clinical trials. Tramiprosate, a natural amino acid derived from seaweed, works by maintaining soluble Aβ peptides in a non-fibrillar, freely aggregated state, thus reducing the formation of fibrillar fibers and decreasing neurotoxicity. Tramiprosate has progressed to phase III clinical trials for the treatment of AD [62]. Moreover, the prodrug of tramiprosate, ALZ-801, is an investigational oral small-molecule drug that has shown long-term efficacy and good safety profiles in AD patients, particularly those carrying the APOE4 gene—a major genetic risk factor for AD. ALZ-801 is currently in phase III clinical trials (NCT04770220) [63, 64].

Pinitol, a cyclic sugar alcohol found in soybeans and fruits, acts as an insulin sensitizer and has been shown to reduce the production of Aβ by regulating γ-secretase activity. It has undergone Phase II studies aimed at assessing its safety and efficacy in treating cognitive decline in AD. In these studies, subjects received escalating doses ranging from 1500 to 5000 mg daily to determine the optimal dosage for balancing efficacy and safety outcomes. The positive results, including good tolerability, cognitive stabilization, and interference with Aβ accumulation, support pinitol's potential as a promising therapeutic intervention for AD [65]. Melatonin, a natural hormone secreted by the pineal gland and also produced by various organisms, including bacteria and eukaryotes, has been validated as a novel selective activating transcription factor 6 (ATF-6) inhibitor [66]. It has been shown to reverse lysosomal signaling pathways, promote phagocytic activity of microglia cells, and regulate mitochondrial energy metabolism, thereby improving Aβ pathology and cognition [67]. Bezisterim, a derivative of the natural anti-inflammatory steroid β-AET, is an orally active NF-κB inhibitor. It has been shown to protect neurons by reducing inflammation and improving glucose utilization, thereby promoting brain health. Clinical results have demonstrated that bezisterim can improve cognition and biomarker levels in AD patients and is currently in phase III clinical trials [68]. Resveratrol, a polyphenol compound rich in red grapes, is known for its multiple pharmacological activities and is clinically safe and well-tolerated in individuals with mild-to-moderate AD. Clinical trials have revealed that it can stabilize the decrease in Aβ levels and attenuate functional decline. However, due to the limited assessment of clinical benefits, further research in larger studies is needed to determine its therapeutic efficacy for AD treatment [69].

Dronabinol, a non-addictive cannabinoid derived from

Table 1 Natural compounds in clinic trials for AD treatment

Compound name	Origin	Trial number	Phase	Initiation time	Target	Mechanism	Status	Regulatory authority
Dronabinol	Cannabis	NCT02792257	2	2017	CB1 and/or CB2 receptor agonist	Inhibition of glutamatergic, dopaminergic and other neurotransmitter release, anti-inflammation	Recruiting	FDA
		NCT05239390	2	2021			Not recruiting	
		NCT05612711	2	2023			Recruiting	
		NCT05543681	2	2022			Recruiting	
Bryostatin 1	Bryozoan	NCT04538066	2	2020	Protein kinase C	Anti-inflammation, anti-oxidative stress, synaptogenesis promotion	Completed	FDA
		NCT02431468	2	2015			Completed	
		NCT03560245	2	2018			Completed	
Bezisterim	Adrenal sterol metabolite	NCT04669028	3	2021	ERK1/2	Anti-inflammation and insulin sensitizing actions	Completed	FDA
		NCT05227820	2	2022			Completed	
Melatonin	Bacteria, eukaryotes	NCT04522960	Unknown	2020	ATF-6	Alleviation of neurotoxicity, anti-inflammation, mitophagy improvement	Recruiting	FDA
		NCT00544791	2	2007			Unknown	
		NCT00940589	2	2009			Completed	
L-Clausenamide	Melia azedarach	CTR20131933	2	2016	Ca^{2+} channel, AChE	Inhibition of Aβ aggregation and tau protein hyperphosphorylation	Recruiting	NMPA
Phenchlobenpyrrone		CTR20130336	2	2014			Recruiting	
Curcumin	Curcuma	NCT01811381	2	2014	Multiple pathways	Anti-inflammation, anti-amyloid, and antioxidation	Unknown	FDA
Pinitol	Soybeans and fruits	NCT00470418	2	2007	Insulin signaling, γ-secretase	Inhibition of Aβ production, spare the cleavage of Notch	Completed	FDA
		NCT01928420	2	2007				
Tramiprosate	Seaweed	NCT00314912	3	2006	$Aβ_{42}$	Inhibition of Aβ oligomer formation	Unknown	FDA
Resveratrol	Grapes, peanuts	NCT00678431	3	2008	Multiple pathways	Anti-inflammation, antioxidation, and epigenetic modulation	Completed	FDA
		NCT01504854	2	2012			Completed	

cannabis, acts as an agonist at both cannabinoid (CB) 1 and 2 receptors. It has been shown to reduce the production and deposition of Aβ peptides. Additionally, dronabinol can enhance mitochondrial function, facilitating energy supply and signal transmission, and is currently being evaluated in multiple phase II clinical trials [70]. This dual mechanism of action—both neuroprotective and supportive of cellular energy processes —positions dronabinol as a potentially valuable therapeutic agent in AD. Bryostatin 1, a macrocyclic lactone compound isolated from the marine bryozoan Bugula neritina, acts as a potent CNS penetrant modulator of PKC. It has shown promising therapeutic effects in the treatment of AD in multiple phase II clinical trials [71]. However, a recent phase II trial (NCT04538066) assessing the long-term effectiveness of Bryostatin 1 in treating moderate to severe AD indicated mixed results. The Severe Impairment Battery (SIB) scores improved by 1.4 points in the experimental group compared with a 0.6-point increase in the placebo group. Unfortunately, these results did not meet the primary endpoint of the study, highlighting the challenges and variability inherent in AD drug development [11, 72].

Perspectives and Conclusions

AD continues to be a formidable challenge in healthcare due to the complexity of its pathogenesis and the limited availability of effective treatments. In this review, we have explored the underlying mechanisms of AD, evaluated clinical medications, discussed natural compounds in clinical trials, and reviewed recently approved drugs. Understanding the pathogenesis of AD is essential for developing effective therapeutics. The accumulation of Aβ plaques and NFTs, along with neuroinflammation, synaptic dysfunction, and oxidative stress, contribute to the progressive cognitive decline and neuronal loss characteristic of AD. Targeting these mechanisms has been central to the development of new drugs. While currently used AD medications, such as cholinesterase inhibitors and NMDA antagonists, provide symptomatic relief and modest cognitive benefits, they do not halt disease progression. Recent years have witnessed significant advancements in the development of antibody-based drugs targeting Aβ clearance, which have shown promise in clinical practice. Additionally, GV-971, which acts by modulating the gut microbiota composition, has demonstrated cognitive improvements and favorable clinical outcomes. Despite the accelerated approval of these new drugs, further studies are necessary to understand their mechanisms of action and to validate their efficacy in diverse populations. Moreover, this review has highlighted the importance of exploring NPs as potential sources of AD treatments. NPs, exemplified by huperzine A and galantamine, have shown efficacy in improving cognitive function by reducing Aβ aggregation, enhancing synaptic plasticity, and modulating inflammatory pathways. The multifaceted mechanisms of action and potentially fewer side effects of NPs make them an intriguing avenue for further investigation.

This review has illuminated the exploration of innovative therapeutic strategies in AD treatment, yet it also underscores the inherent challenges present. Further research endeavors must navigate the complexities of translating preclinical discoveries into clinical applications, address the variability in individual treatment responses, and ensure robust clinical validation of novel therapies. Looking ahead, promising avenues for advancing AD research include personalized medicine approaches tailored to individual patient characteristics. This strategy emphasizes the importance of understanding genetic, biochemical, and environmental factors that influence disease progression and response to treatment. Leveraging cutting-edge technologies such as artificial intelligence (AI) for drug discovery also holds significant potential. AI can analyze vast datasets to identify new drug targets, predict drug efficacy, and optimize clinical trial designs, potentially accelerating the development of effective therapies. Additionally, exploring synergistic combination therapies that target the multifaceted nature of AD pathology could improve treatment outcomes. Such approaches would address various aspects of the disease simultaneously, such as Aβ and tau pathologies, inflammation, and neurodegeneration, offering a more comprehensive treatment strategy. By embracing these opportunities, the field of AD therapeutics can advance toward more effective and tailored treatments for individuals affected by this complex neurodegenerative condition.

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