Biomedical Research and Therapy 2025, 12(9):7708-7722

Open Access Full Text Article

Review

Amyloid Beta and Tau Aggregation: The Etiology and Potential Pharmaceutical Approaches for Alzheimer's Disease

Pushpendra Soni, Syed Misbahul Hasan, Shom Prakash Kushwaha*, Kuldeep Singh, Arun Kumar, Abdul Hafeez, Suvaiv , Samman , Salman Khan

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized primarily by the accumulation of amyloid-β (Aβ) peptide and hyperphosphorylated, cleaved forms of the microtubule-associated protein tau. The probability of developing AD increases with age, mainly because the burdens of Aβ and tau pathology grow over time. Aβ plaques are composed of amyloid-β generated when β- and γ-secretases cleave the amyloid precursor protein (APP); these extracellular deposits disrupt neuronal homeostasis and ultimately trigger cell death. Neurofibrillary tangles formed by hyperphosphorylated tau compromise neuronal architecture and impair intracellular transport. This article discusses the formation of Aβ plaques and tau tangles as well as their potential modulation or clearance through interventions targeting molecules such as glycogen synthase kinase-3 (GSK-3) and fragment crystallizable receptors (FcRs). We also review the structures, mechanisms of action, neuropathological consequences, and synergistic effects of Aβ accumulation and tau phosphorylation. Monoclonal antibodies, including aducanumab and lecanemab, can slow plaque formation, neutralize Aβ toxicity, stimulate immune-mediated clearance, and remove existing aggregates. Tau-directed antibodies such as semorinemab and tilavonemab are currently in clinical trials and aim to lessen tau aggregation, stabilize microtubules, and inhibit pathogenic kinase activity. Advanced drug-delivery systems (*e.g.*, exosome-loaded or peptide-conjugated nanoparticles) may facilitate the development of more precise, safer, and more potent therapeutics for AD.

Key words: Alzheimer's disease, Amyloid β plaque, Neurotoxicity, Monoclonal antibody, Tau tangles, Neuroinflammation

Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh, 226026, India

Correspondence

Shom Prakash Kushwaha, Faculty of Pharmacy, Integral University, Dasauli, Kursi Road, Lucknow, Uttar Pradesh, 226026, India

Email: shompk@iul.ac.in

History

- Received: 12-12-2024
- Accepted: 13-5-2025
- Published Online: 30-9-2025

DOI : 10.15419/rjv09v43

Check for updates

INTRODUCTION

Alzheimer's disease is a neurodegenerative condition characterized by progressive forgetfulness, cognitive decline, impaired physical function, and ultimately death resulting from widespread neuronal loss[1]. Alzheimer's disease (AD) is named after Dr. Alois Alzheimer, a German physician and pathologist who reported the first patient with the disorder in 1906[2]. Alzheimer's disease is one of the greatest medical challenges of this century and the leading cause of dementia[3]. Globally, approximately 40 million people are estimated to have dementia, a figure projected to double roughly every two decades and to exceed 80 million by 2050[4]. The prevalence of AD rises with age, increasing from about 27.6 % among individuals aged 65–74 years to roughly 36.4 % in those over 80 years[5]. AD pathology is characterized primarily by the formation of amyloid-β (Aβ) plaques and neurofibrillary tau tangles resulting from the accumulation of hyper-phosphorylated tau protein in the brain[6]. Aβ plaques are insoluble fibrillar structures composed of aggregated Aβ peptides in the extracellular space, whereas tau tangles are intracellular aggregates of abnormally phosphorylated tau protein that destabilize microtubules[7,8]. The interplay between these lesions is believed to drive the symptomatic progression of AD. Alzheimer's disease typically begins insidiously with difficulty remembering recent events and progresses gradually over time[9]. Acetylcholine (ACh), a neurotransmitter first isolated in 1867 and responsible for transmitting impulses between neurons as well as to voluntary and involuntary muscle cells, is found at reduced concentrations in the brains of individuals with AD[10].

METHODS

The present review utilized a range of scholarly search engines—Google Scholar, Semantic Scholar, ScienceOpen, and PubMed—as well as journal databases to identify recent primary and review articles. The search combined the keywords "Alzheimer's disease," "amyloid-β plaques," "neurotoxicity," "monoclonal antibodies," "tau tangles,"

Cite this article : Soni P, Hasan S M, Kushwaha S P, Singh K, Kumar A, Hafeez A, S, S, Khan S. **Amyloid Beta and Tau Aggregation: The Etiology and Potential Pharmaceutical Approaches for Alzheimer's Disease**. *Biomed. Res. Ther.* 2025; 12(9):7708-7722.

"clinical trials," and "neuroinflammation." Inclusion criteria were English-language, peer-reviewed studies that addressed pathophysiology, pharmacological clinical trials, or drug-delivery advancements. In total, 138 articles published between 2011 and 2025 were selected for this review.

AMYLOID β PLAQUES AND TAU TANGLES: THE CORE PATHOLOGY

Aβ plaques and tau tangles are now more thoroughly understood as pathologies of Alzheimer's disease (AD). Both tau tangles and Aβ plaques are implicated in neurotoxic effects (**Figure 1** [11,12]). The interactions between Aβ and tau are major drivers of neurotoxicity, suggesting that these two AD pathological components synergistically increase neuronal damage. New phosphorylation sites of tau have been identified, and an understanding of tau seeding and spreading has deepened insight into tau pathology. These findings explain how tau spreads throughout neuronal networks and causes axonal degeneration in mammals [13].

Aβ Plaques

Formation and Accumulation

Alzheimer's disease is characterized by extracellular Aβ plaques whose precise pathogenesis remains incompletely understood. These plaques develop from the amyloid precursor protein (APP), which is cleaved by β- and γ-secretases. The resulting Aβ peptides are deposited in the brain, form insoluble plaques, impair cellular function, and ultimately drive neurodegeneration [11].

Proteolytic Processing of APP

The processing of APP, a transmembrane glycoprotein expressed mainly in neurons, generates Aβ peptides [14]. APP can follow either a non-amyloidogenic or an amyloidogenic pathway.

- Cleavage by β-Secretase (BACE1): APP is first cleaved by β-secretase, an aspartyl protease, in its extracellular domain. This cleavage produces two fragments: soluble APPβ (sAPPβ), which is released extracellularly, and the membrane-tethered C99 (β-CTF). C99 is the critical substrate for γ-secretase [15].
- Cleavage by γ-Secretase: The multi-protein γ-secretase complex processes C99 within its transmembrane region, releasing Aβ peptides into the extracellular space and an intracellular APP domain (AICD). The most abundant isoforms are Aβ40 and Aβ42 [16]. Aβ42 is highly aggregation-prone and constitutes the principal building block of amyloid plaques [17].

Oligomerization of Aβ

Aβ peptides self-associate; Aβ42 aggregates more readily than Aβ40 because of its hydrophobic C-terminal end [18]. Aggregation proceeds from soluble monomers to toxic oligomers that disrupt neuronal signaling and synaptic plasticity, then to protofibrils, and finally to mature fibrils and plaques [19].

Formation of Amyloid Fibrils

Protofibrils assemble into insoluble amyloid fibrils that form the structural core of plaques [20]. These fibrils adopt a characteristic cross-β-sheet conformation, conferring high stability and resistance to degradation [21,22].

Deposition and Plaque Development

Amyloid fibrils coalesce into extracellular deposits that constitute amyloid plaques, which are surrounded by dystrophic neurites, activated astrocytes and microglia, and extracellular matrix components such as apolipoprotein E (ApoE) [23,24].

Genetic mutations in APP, presenilin-1, or presenilin-2 (components of γ-secretase) increase Aβ42 production. The ApoE ε4 allele promotes aggregation and inhibits clearance. Impaired activity of Aβ-degrading enzymes (*e.g.*, neprilysin) or reduced transport across the blood–brain barrier further enhances accumulation [25].

Tau Tangles

Tau Phosphorylation and Aggregation

Tau is a microtubule-associated protein (MAP) that stabilizes microtubules in neurons. Hyperphosphorylated tau detaches from microtubules, aggregates, impairs axonal transport, and ultimately causes neuronal death [13].

Formation and Function of Tau Protein

Tau is encoded by the MAPT gene on chromosome 17, which generates six isoforms via alternative splicing differing in their microtubule-binding repeats (3R vs. 4R) and N-terminal inserts. Native tau is intrinsically disordered, enabling dynamic interaction with microtubules [26].

Pathological Transition of Tau

Under pathological conditions tau becomes hyperphosphorylated by kinases such as GSK-3β and CDK5 [27]. Detached tau undergoes conformational

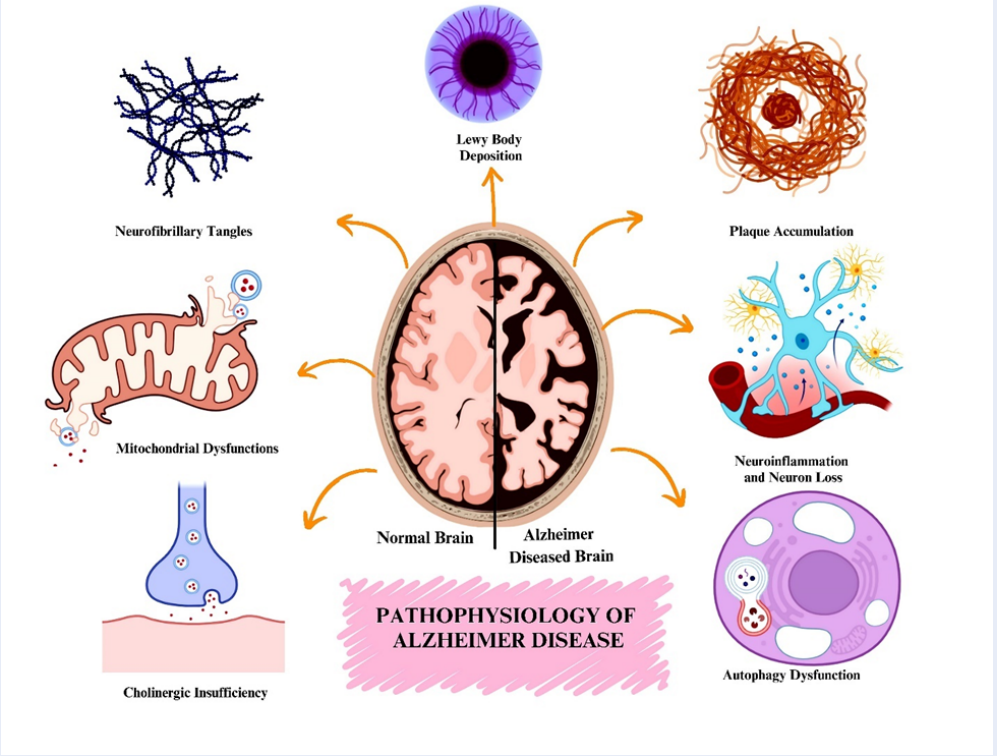

Figure 1: **Pathophysiology of Alzheimer's Disease**.

changes, forms soluble toxic oligomers, and then paired helical filaments (PHFs) and straight filaments (SFs). These filaments aggregate into neurofibrillary tangles (NFTs) that can propagate in a prion-like manner[28].

Post-Translational Modifications (PTMs)

PTMs profoundly influence tau behavior. Hyperphosphorylation drives mislocalization and aggregation; acetylation hinders degradation; ubiquitination can target tau for proteasomal clearance or stabilize aggregates; truncation yields highly aggregation-prone fragments; and glycation further enhances aggregation propensity[29].

Pathological tau disrupts microtubule integrity, axonal transport, synaptic plasticity, and mitochondrial function, and it induces neuroinflammation, all of which culminate in neuronal death[30].

Tau pathology is promoted by MAPT mutations (e.g., P301L and the H1 haplotype)[31], PTMs[29], oxidative stress and neuroinflammation[32], and an imbalance between kinases (e.g., GSK-3β) and phosphatases (e.g., PP2A)[33].

Combined Impact on Cognitive Decline

The connection between Aβ and tau pathologies is robust. Whereas Aβ plaques contribute to early synaptic impairment and prodromal clinical symptoms, tau tangles correlate directly with neuronal loss and the severity of cognitive decline[34].

Synergistic Effects

Aβ and tau pathologies are not independent; they interact sequentially and synergistically. Aβ plaques are thought to appear first, triggering cascades that lead to tau hyperphosphorylation and aggregation[35].

MECHANISM OF ACTION OF Aβ AND TAU TARGETING DRUG

Aβ Targeting

Monoclonal antibodies (mAbs) are lab-engineered, Y-shaped protein structures[36] composed of two heavy and two light chains. The variable region (Fab) at the ends binds to the target antigen[37], while the constant region (Fc) interacts with immune-cell receptors[38]. The binding of mAbs to Aβ—in

its soluble or plaque form—activates immune processes such as phagocytosis via Fc receptors on microglia, thereby facilitating plaque removal. Complement receptors also enhance clearance through the complement cascade[39,40]. Although effective in promoting Aβ clearance, mAbs may induce inflammation through activation of Toll-like receptors (TLRs)[41,42]. Drugs such as aducanumab exploit this mechanism to target Aβ and trigger microglial activation for plaque clearance, though their effects can be complex and require careful management[43]. Amyloid-related imaging abnormalities are serious side-effects of anti-Aβ antibodies (e.g., aducanumab, lecanemab, gantenerumab). Edema (ARIA-E) and hemosiderin-related hemorrhages (ARIA-H) are associated with disruption of the blood–brain barrier following amyloid clearance from cerebral vessels[44]. APOE-ε4 carriers face an increased risk. Symptoms include headaches, confusion, and seizures. Regular MRI monitoring is required for early detection, and dose adjustments may be necessary in severe cases[45].

Aducanumab

Aducanumab is a monoclonal antibody that targets Aβ and reduces plaque accumulation in patients with Alzheimer's disease (AD) (**Table 1**)[46]. Several clinical studies show that aducanumab can slow cognitive decline in patients at an early stage of AD[52]. The aducanumab controversy was sparked by conflicting Phase 3 trial results (ENGAGE vs. EMERGE) and differing FDA-review interpretations. ENGAGE did not reach its primary endpoint, whereas EMERGE showed a modest slowing of cognitive decline[53].

Lecanemab

Lecanemab is a monoclonal antibody directed against soluble Aβ protofibrils; it decreases amyloid plaques and clinical manifestations in early AD[54]. By neutralizing protofibrils, lecanemab reduces new-plaque formation and maintains a lower amyloid burden[47]. Collectively, trial data indicate that lecanemab delays both cognitive and functional decline. Study NCT03887455 (**Table 2**) showed that lecanemab significantly slowed clinical decline in early AD (CDR-SB; $p < 0.0001$)[55].

Gantenerumab

Gantenerumab is an antibody that binds aggregated Aβ and facilitates its removal from the brain[48]. Emerging studies suggest that gantenerumab reduces amyloid plaques and improves cognition. Although its mechanism resembles that of aducanumab, gantenerumab is delivered subcutaneously, a route that may enhance treatment adherence if approved[12,64]. Ongoing trials are evaluating its efficacy, safety, and potential to slow early AD progression.

Tau-Targeting

Therapies that target tau tangles modulate several receptors and molecular partners. One key target is the microtubule-associated protein tau[65]. Glycogen synthase kinase-3 (GSK-3) inhibitors and mitogen-activated protein kinase (MAPK) inhibitors both reduce tau phosphorylation[66]. Because MAPKs mediate stress- and inflammation-related signaling, their down-regulation lessens phosphorylation and inflammation. These interactions decrease tau aggregation, stabilize microtubules, and reduce tau-induced neurotoxicity, thereby helping to maintain neuronal function and limiting tau's prion-like propagation[67].

Tau antisense oligonucleotides (ASOs)

Tau ASOs are short synthetic single-stranded RNAs or DNAs designed to bind a specific sequence within tau (MAPT) mRNA, thereby reducing tau translation[68].

Mechanism of Action: Tau ASOs hybridize via Watson–Crick base pairing with tau mRNA, forming an RNA–DNA duplex that recruits RNase H, which cleaves the RNA strand[69]. RNase H–mediated cleavage is catalytic, so multiple mRNAs can be degraded. Lower tau levels limit formation of hyperphosphorylated tau, paired helical filaments, and neurofibrillary tangles[70]. Reduced aggregates lessen axonal transport disruption and neuronal dysfunction[71]. IONIS-MAPTRx, delivered intrathecally, has shown significant reductions in cerebrospinal-fluid tau levels in early trials[72].

Anti-tau antibodies

Anti-tau antibodies are therapeutic mAbs that bind pathological tau conformations in AD[48]. They are in various clinical and preclinical stages[73].

Biomarker validation in AD still faces challenges of specificity, sensitivity, and clinical utility. Reliable biomarkers (Aβ, tau, NfL) must distinguish AD from other neurodegenerative disorders and track disease progression. Blood biomarkers are less invasive than CSF or PET but currently offer lower specificity. Translating biomarker findings into clinical practice therefore remains difficult[11,27].

Table 1: Mechanism of action

Aspect	Aducanumab	Lecanemab	Gantenerumab
Target	Aggregated Aβ (Aβ) plaques and soluble oligomers	Soluble Aβ (Aβ) protofibrils	Aggregated Aβ (Aβ) plaques
Mechanism of Action	**1**. Binds aggregated Aβ plaques and oligomers. **2**. Fc region activates microglia for plaque clearance. **3**. Reduces amyloid burden, neuroinflammation, and slows cognitive decline.[46]	**1**. Binds soluble Aβ protofibrils to prevent plaque formation. **2**. Activates microglia to clear protofibrils and plaques. **3**. Slows cognitive decline by reducing amyloid burden.[47]	**1**. Binds aggregated Aβ plaques. **2**. Disaggregates plaques and activates microglia for clearance. **3**. Reduces amyloid burden and inhibits new plaque formation.[48]
Efficacy	Reduces amyloid burden and slows cognitive decline in early AD.[49]	Delays cognitive and functional decline, with positive results in early AD.[50]	Reduces amyloid plaques, but clinical efficacy in cognitive decline is still under study.
Adverse Effects	Amyloid related imaging abnormalities (ARIA), including brain swelling (ARIA-E) and microhemorrhages (ARIA-H).[46]	ARIA was observed but at a lower incidence compared to Aducanumab.[51]	ARIA-E and ARIA-H, but typically at a lower incidence than Aducanumab.[48]
Novelty	Focused on plaque clearance in early-stage AD.[52]	Targets protofibrils, a neurotoxic intermediate form of Aβ.[50]	Subcutaneous delivery, potentially improving patient compliance.[12]

Mechanism of Action: Anti-tau antibodies bind hyperphosphorylated, oligomeric, or aggregated tau, preventing its detachment from microtubules and subsequent destabilization[74]. They block aggregation of tau monomers/oligomers into paired helical filaments (PHFs) and neurofibrillary tangles (NFTs)[75]. Fc-receptor engagement on microglia promotes phagocytosis of antibody–tau complexes, followed by lysosomal degradation, thereby reducing intra- and extracellular tau[74]. Restored tau homeostasis stabilizes microtubules, maintains axonal transport, and attenuates glia-mediated inflammation[76]. Anti-tau antibodies also preserve neuronal-membrane integrity by neutralizing toxic tau oligomers that disturb calcium balance and synaptic function[75].

Examples under investigation

- Semorinemab (Genentech/Roche) has shown mixed results; initial trials were inconclusive, but later studies suggest modest neuroprotective effects[77–79].
- Zagotenemab (LY3303560, Eli Lilly) demonstrated tau reduction and memory improvement in animals, yet early-stage human data remain inconclusive[80,81].
- Tilavonemab (ABBV-8E12, AbbVie), an IgG1-λ antibody, lowered tau pathology and showed encouraging safety/biomarker signals in Phase 1-2 studies[82,83]. Trial M15-562 (**Table 3**) is a Phase 2, double-blind, placebo-controlled study evaluating low- and high-dose tilavonemab.[84–87]

Table 2: Clinical trial results with duration limitation and controversy

Drug	NCT Number	Trial Phase / Duration	Limitations	Controversies	Statistical Outcomes
Aducanumab	NCT01397539 [56]	Phase 1 (2011–2013) 53 participants	Small sample, single-dose, short follow-up; efficacy assessment not possible.	ARIA-E (100% in 60 mg/kg group); early safety concern but limited controversy due to phase and size.	Dose-dependent ARIA-E (100% at 60 mg/kg); linear PK up to 30 mg/kg; cognition not statistically significant.
	NCT01677572 [57]	Phase 1b (2012–2019) 197 participants	Small sample; short follow-up; focused on amyloid reduction not efficacy.	Mild concern; no major controversy.	Significant ($p < 0.05$) dose-dependent plaque reduction on PET; ARIA incidence increased with dose.
	NCT02477800 (EMERGE) [58,59]	Phase 3 (2015–2019) ~1,600 participants	Early termination; inconsistent outcomes; post-hoc analysis; potential unblinding due to ARIA.	FDA approval despite advisory panel rejection; EMERGE positive, ENGAGE negative; resignations from FDA board.	22% decline reduction (CDR-SB −0.39; $p = 0.012$); ARIA-E in 35% of APOE ε4+ patients.
	NCT02484547 (ENGAGE) [58,59]	Phase 3 (2015–2019) ~1,600 participants	Same as EMERGE; dose modification; no significant effect.	Same as EMERGE;	No significant effect; inconsistent with EMERGE.
	NCT04241068 [60]	Phase 3 Extension (2020–2023) 2,400 participants	No control group; limited to 10 mg/kg; single dose reporting; unclear participant number.	Continued ARIA concern; treatment discontinuations due to adverse events; ADA positivity raised tolerability issues.	Detailed statistical outcomes not available due to study termination.
Lecanemab	NCT03887455 [54,61]	Phase 3 (Clarity AD, 2019–2022) 1,795 participants	Targeted only early AD; amyloid confirmation required; generalizability limited. [62]	Debate over clinical significance of small CDR-SB change (0.45); ARIA-E (12.6%), ARIA-H (17.3%) despite mild severity.	Highly significant ($p < 0.0001$); slowed clinical decline; improved CDR-SB, ADAS-Cog14, iADL, MMSE; PET confirmed amyloid reduction.
Gantenerumab	NCT03444870 [63]	Phase 3 (GRADUATE I/II, 2018–2023) 1,053 participants	Failed primary endpoint (CDR-SB); no significant cognitive benefit; modest trends in secondary outcomes.	Focused on amyloid reduction despite failed cognitive outcomes; subcutaneous route praised for compliance but raised concerns.	Non-significant CDR-SB difference (−0.31; 95% CI: −0.66 to 0.05); significant amyloid reduction; ARIA-E observed in notable proportion.

Table 3: Clinical trial results with duration limitation and controversy

Compound	Trial (NCT No. / Phase)	Trial Details (Phase / Duration / Participants)	Limitations	Controversy	Statistical Results
Semorinemab	NCT03289143 (Phase 2 – Tauriel) [88,89]	Phase 2 / 73 weeks / 457 patients with mild AD	No significant benefit on secondary cognitive/functional measures; limited sample size	Targeting tau at symptomatic stage questioned; no dose-dependent efficacy	Failed primary endpoint (CDR-SB, p=0.37); no significant change in ADAS-Cog13, ADCS-ADL; ADAS-cog11 showed 42.2% reduction vs baseline (not statistically confirmed) [90]
Zagotenemab	NCT02754830 (Phase 1) [91]	Phase 1 / 2016–2018 / 110 mixed participants (healthy + MCI + AD)	Small sample size; short duration; focus on safety, not efficacy	Increase in tau not clinically significant; unclear target engagement	Linear pharmacokinetics; dose-dependent increase in plasma tau; no PET amyloid or MRI changes. [92]
	NCT03019536 (Phase 1) [93]	Phase 1 / 2017–2019 / 24 MCI-AD & mild AD patients	Small size; short 16-week period; no efficacy data	Debate continues due to Phase 2 failures	Safe; linear PK; no significant biomarker changes; no clinical efficacy
	NCT03518073 (Phase 2) [81,94]	Phase 2 / 2018–2021 / 285 early AD patients	No clinical/biomarker benefit; insufficient dose response	Plasma tau increased but not linked to outcome; tau-targeting still under debate	iADRS ratio > 1 for both doses; no significant changes in PET tau, MRI, NfL
Tilavonemab	M15-562 (Phase 2 – PSP) [95,96]	Phase 2 / 2016–2019 / 377 PSP patients aged 49–86	No improvement on clinical or quality-of-life measures	Efficacy of tau-targeting in PSP questioned; halted for inefficacy	No significant difference in PSPRS; 87.5% reported AEs, 25.5% had severe AEs; study terminated early
AADvac1	NCT01850238 (Phase 1) [97]	Phase 1 / 2013–2015 / Mild to moderate AD patients	Short duration; small sample; not designed for efficacy	Active tau immunotherapy strategy under scrutiny	Safe; immunogenic; antibody response observed; exploratory biomarker trends
	NCT02579252 (Phase 2 – ADAMANT) [97]	Phase 2 / 2016–2019 / Mild AD patients	No significant cognitive/functional benefits; limited efficacy evidence	Modest post-hoc subgroup findings require further confirmation	>0.05 for clinical endpoints; safe and immunogenic; no significant efficacy
ACI-35	NCT04445831 (Phase 1b/2a) [45,98]	Phase 1b/2a / 2019–2023 / 57 MCI/mild AD patients (age 50–75)	Final results pending; short-duration, individual-level data undisclosed	Link between antibody response and clinical benefit remains unproven	Interim: significant increase in anti-pTau IgG titers; no efficacy stats available; strong immunogenicity

• AADvac1 is an active vaccine developing a self-immune response against pathological tau; Phase 1-2 studies revealed robust immunogenicity and tau reduction. Phase 3 is ongoing [84,85] (NCT01850238; NCT02579252).

• ACI-35, a liposome-based vaccine, elicited selective anti-tau immunity in Phase 1 and is now in Phase 2 for efficacy evaluation [86,87].

Combination Therapies and Novel Approaches

• Tau-aggregation inhibitor TRx0237 (LMTX) dissolves existing tangles and may halt or reverse dementia progression [99].

• Neuroinflammation modulators such as sargramostim reduce immune dysregulation and may improve cognition; mefenamic acid is under study for similar effects [100].

• NLRP3-inflammasome inhibitors (e.g., MCC950, tetramethylpyrazine, kakonein) decrease neuroinflammation in preclinical AD models [101–103].

• β-Site amyloid precursor-protein cleaving enzyme-1 (BACE1) inhibitors (verubecestat, lanabecestat) lower Aβ synthesis by inhibiting β-secretase [104]. However, many agents (*e.g.*, NB-360) were halted owing to adverse effects such as hair depigmentation, anxiety, weight loss, falls, suicidality, and sleep disorders. Umibecestat (CNP520) advanced further because of higher selectivity and favorable pharmacokinetics, yet overall risks highlight the difficulty of targeting amyloid pathways [105,106].

DRUG DELIVERY SYSTEMS TARGETING Aβ PLAQUES AND TAU TANGLES

Nanoparticle-based delivery systems

Polymeric Nanoparticles: Polymeric nanoparticles have been found to be useful for penetrating the blood–brain barrier (BBB) and releasing drugs at the target, i.e., Aβ plaques [107,108]. Experiments have also shown that these nanoparticles can be functionalized with targeting ligands that increase their selectivity toward Aβ and therefore enhance the efficacy of drug delivery and decrease the amyloid load in the brain [109,110].

Lipid Nanoparticles: Lipid nanoparticles have potential in the encapsulation and distribution of therapeutic agents that deal with Aβ and tau aggregates [111,112]. These systems offer long-term stability and controlled release, can cross the BBB, and may reduce neurotoxicity while improving cognitive function [113].

Exosome-based delivery systems

Exosome Engineering: Small interfering RNAs and other small molecules can be incorporated into exosomes, naturally occurring vesicles 40–100 nm in size, to target neurons [114]. Exosomes can enter the brain and release their contents, specifically near Aβ plaques and tau tangles [115].

Exosome-Loaded Drug Carriers: Exosomes combined with other delivery systems and nanoparticles can increase the specificity and efficiency of drug delivery. Preclinical studies of exosome-loaded nanoparticles have shown their potential to target Aβ and tau tangles [116,117].

Peptide-based delivery systems

Peptide-Conjugated Nanoparticles: Nanoparticles can be functionalized with high-affinity peptides that specifically bind Aβ plaques and tau tangles, resulting in enhanced targeting efficiency [118]. For therapeutic applications, these peptide-conjugated nanoparticles can effectively transport active agents, including antibodies and small molecules, to pathological regions to improve treatment outcomes and minimize adverse effects [119,120].

Cell-Penetrating Peptides (CPPs): CPPs are used to carry therapeutically valuable agents across cell membranes [121]. CPPs can be coupled with a drug or genetic material to improve their uptake by neurons, thereby directly targeting Aβ and tau damage and possibly even altering the disease course [122].

Liposome-based delivery systems

Immunoliposomes: Immunoliposomes, which are liposomes linked with particular antibodies against Aβ or tau, have been created to enhance drug-delivery selectivity and effectiveness [123]. The BBB permits only regulated entry of substances, posing a major challenge to delivering Alzheimer's-disease therapeutics into the brain. For large molecules like monoclonal antibodies (*e.g.*, aducanumab), transport is restricted, and this requires an intravenous infusion or specialized methods of delivery. Small-molecule drugs generally have either low bioavailability or rapid clearance. Possible strategies include nanoparticle-based delivery, receptor-mediated transcytosis, and focused ultrasound for temporary opening of the BBB to maximize therapeutic effects and minimize systemic side effects. These systems can cross the BBB and thus provide ligands to affected regions; consequently, they have demonstrated their ability to reduce amyloid and tau accumulation in preclinical trials [124,125].

Multifunctional Liposomes: Liposomes with targeting ligands, imaging agents, and therapeutic agents are useful in the management of multiple aspects of this disease [126]. Liposomes can deliver and release drugs, monitor the response and effectiveness of treatment, and respond accurately to Aβ and tau tangles [127,128].

Limitations and Challenges in Drug-Delivery Systems

- **Blood–Brain Barrier (BBB) Permeability**: The BBB remains a major obstacle, limiting the ability of therapeutic agents (especially large molecules and biologics) to reach effective concentrations in the brain parenchyma. At the molecular level, this barrier limits transcytosis and receptor-mediated transport unless specific ligands or transport mechanisms are exploited [129].
- **Rapid Systemic Clearance**: Nanoparticles, liposomes, and other delivery vehicles are often rapidly cleared by the reticuloendothelial system (RES), leading to reduced circulation time and poor central nervous system (CNS) bioavailability. This clearance depends on molecular surface features such as charge and hydrophilicity, which can reduce systemic circulation and CNS accumulation [130].
- **Immunogenicity and Biocompatibility**: Synthetic carriers are recognized as foreign particles by the immune system, which may trigger inflammatory responses, immune clearance, or allergic reactions. Minor changes in surface chemistry at the molecular level (*e.g.*, terminal groups, PEG density) can dramatically affect immune recognition [131].
- **Inconsistent Physicochemical Properties**: Variability in nanoparticle synthesis can lead to differences in size, surface charge, and morphology, affecting drug-loading efficiency, release kinetics, and targeting accuracy. Batch-to-batch variability in nanoparticle synthesis (*e.g.*, inconsistent nucleation or polymerization rates) can alter critical parameters like zeta potential, hydrodynamic diameter, and surface-ligand density, which influence molecular interactions with the BBB and target cells [132].
- **Potential toxicity of carriers**: Some carrier materials or their degradation products (e.g., cationic polymers, metal-based NPs) may generate reactive oxygen species (ROS) or interfere with cellular organelles and enzymes, leading to molecular-level toxicity [133].
- **Enzymatic degradation of peptides**: Therapeutic peptides are highly susceptible to proteolytic enzymes (*e.g.*, peptidases, endopeptidases) in blood and tissues, leading to cleavage at specific amino-acid residues and a short systemic half-life. Structural modification (*e.g.*, D-amino acids, PEGylation) is often needed to enhance stability [134].
- **Cell-Penetrating Peptides**: CPPs like TAT allow drug entry via direct translocation or endocytosis, but they lack receptor specificity and are prone to enzymatic cleavage. Modifying CPPs with drugs can change their conformation, reducing efficiency and stability at the molecular level [135].
- **Exosome Production Challenges**: Exosomes—natural nanocarriers—are heterogeneous in composition (lipids, proteins, RNA). Isolating them in a reproducible, scalable, and clinical-grade manner requires controlling the molecular makeup, including tetraspanins (*e.g.*, CD63, CD81) and surface markers, which is technically difficult [136].

In addition to the points mentioned above, other challenges in drug delivery include cargo heterogeneity in exosomes, limited stability and shelf-life of formulations, weak correlation between pathology clearance and cognitive benefit, poor translational value of preclinical models, and uncertain long-term safety of novel delivery systems. Further research is required to overcome these challenges and enhance the efficacy of CNS-targeted therapies [137,138].

CONCLUSION

In conclusion, Alzheimer's-disease pathogenesis is associated with neuronal death, disruption of synaptic connections, and changes in cognitive ability. APP, upon degradation, produces Aβ, and these plaques cause oxidative stress and inflammation that affect neurons; they also interfere with normal neuronal function.

Research in AD has shown that there is a relationship between tau and Aβ pathologies, and these findings have revealed a significant contribution of these two proteins to the neurotoxicity that characterizes AD. Monoclonal antibodies such as aducanumab or lecanemab have shown potential in eradicating Aβ plaques efficiently. Because these antibodies can bind to aggregated forms of Aβ, enhance immunological processes, and activate microglia, they contribute to the removal of these aggregates. The main goals of tau-targeted therapy are to stop tau phosphorylation, diminish tau deposition, and stabilize microtubules via different ligands, such as epothilones and kinase inhibitors. Other immunotherapeutic techniques that promote the removal of tau proteins from the brain have also been developed and found useful. Similarly,

drug-delivery methods involving the encapsulation of peptides and nanoparticles or loading into exosomes make it possible to increase the activity and specificity of the aforementioned therapeutics.

Overall, the above discussion reveals that the association between tau and Aβ pathologies is complex, indicating that the development of AD therapeutics requires multiple, complementary interventions targeting several pathological factors. Subsequent work will have to continue investigating the molecular relationships between tau and Aβ to determine how to design drugs that can effectively target these pathways. Nevertheless, current and future research aims to help those affected by this chronic disease achieve a better prognosis and higher quality of life, owing to advanced knowledge of the disease's pathophysiology and the continuing refinement of therapeutic interventions.

ABBREVIATIONS

Aβ: Amyloid-β; **ACh**: Acetylcholine; **AD**: Alzheimer's Disease; **AICD**: APP Intracellular Domain; **ApoE**: Apolipoprotein E; **APP**: Amyloid Precursor Protein; **ARIA-E**: Amyloid-Related Imaging Abnormalities - Edema; **ARIA-H**: Amyloid-Related Imaging Abnormalities - Hemosiderin; **ASOs**: Antisense Oligonucleotides; **BACE1**: Beta-site APP Cleaving Enzyme 1; **BBB**: Blood-Brain Barrier; **β-CTF**: β-C-Terminal Fragment; **CDK5**: Cyclin-Dependent Kinase 5; **CDR-SB**: Clinical Dementia Rating-Sum of Boxes; **CNS**: Central Nervous System; **CPPs**: Cell-Penetrating Peptides; **CSF**: Cerebrospinal Fluid; **Fab**: Fragment, Antigen-Binding; **Fc**: Fragment Crystallizable; **FcRs**: Fragment Crystallizable Receptors; **FDA**: Food and Drug Administration; **GSK-3**: Glycogen Synthase Kinase-3; **IgG1**: Immunoglobulin G1; **mAbs**: Monoclonal Antibodies; **MAP**: Microtubule-Associated Protein; **MAPK**: Mitogen-Activated Protein Kinase; **MAPT**: Microtubule-Associated Protein Tau; **MRI**: Magnetic Resonance Imaging; **NFTs**: Neurofibrillary Tangles; **NfL**: Neurofilament Light Chain; **NLRP3**: NLR Family Pyrin Domain Containing 3; **PET**: Positron Emission Tomography; **PHFs**: Paired Helical Filaments; **PP2A**: Protein Phosphatase 2A; **PTMs**: Post-Translational Modifications; **RES**: Reticuloendothelial System; **RNA**: Ribonucleic Acid; **ROS**: Reactive Oxygen Species; **sAPPβ**: soluble APPβ; **SFs**: Straight Filaments; **TLRs**: Toll-like Receptors

ACKNOWLEDGMENTS

The authors are grateful to Integral University, Lucknow, for providing the amenities, space, and resources for this work. The authors express their sincere gratitude to the Dean, Research and Development for the kind support (manuscript communication number: IU/R&D/2025-MCN0003365).

AUTHOR'S CONTRIBUTIONS

All the authors contributed to the study concepts and design data. The collection and main manuscript writing were performed by Pushpendra Soni, Samman, and Salman Khan; the data analysis was performed by Kuldeep Singh, Arun Kumar, Abdul Hafeez, and Suvaiv; and the data were reviewed by Syed Misbahul Hasan and Shom Prakash Kushwaha. All the authors approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative AI (a type of artificial intelligence technology that can produce various types of content including text, imagery, audio and synthetic data. Examples include ChatGPT, NovelAI, Jasper AI, Rytr AI, DALL-E, *etc.*) and AI-assisted technologies in the writing process before submission.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Kumar A, Nisha CM, Silakari C, Sharma I, Anusha K, Gupta N. Current and novel therapeutic molecules and targets in Alzheimer's disease. Journal of the Formosan Medical Association. 2016;115(1):3–10. PMID: 26220908. Available from: https://doi.org/10.1016/j.jfma.2015.04.001.

2. Athar T, Balushi KA, Khan SA. Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. Molecular biology reports. 2021;48(7):5629–5645. Available from: https://doi.org/10.1007/s11033-021-06512-9.
3. Hanseeuw BJ, Betensky RA, Jacobs HI, Schultz AP, Sepulcre J, Becker JA. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. JAMA Neurology. 2019;76(8):915–24. PMID: 31157827. Available from: https://doi.org/10.1001/jamaneurol.2019.1424.
4. Khan M, Ahsan F, Ahmad U, Akhtar J. Badruddeen, Mujahid M. ALZHEIMER DISEASE: A REVIEW. World Journal of Pharmacy and Pharmaceutical Sciences. 2016;5:649–66.
5. Bentley M, Minstrell M, Bucher H, Morrissey M, Robinson A, Stirling C. A case study evaluation protocol to assess processes, effectiveness and impact of a nurse practitioner-led memory clinic. Health. 2014;6:748–756. Available from: https://doi.org/10.4236/health.2014.68096.
6. Rizvi SM, Shaikh S, Naaz D, Shakil S, Ahmad A, Haneef M. Kinetics and Molecular Docking Study of an Anti-diabetic Drug Glimepiride as Acetylcholinesterase Inhibitor: Implication for Alzheimer's Disease-Diabetes Dual Therapy. Neurochemical Research. 2016;41(6):1475–82. PMID: 26886763. Available from: https://doi.org/10.1007/s11064-016-1859-3.
7. Arendt T, Stieler JT, Holzer M. Tau and tauopathies. Brain Research Bulletin. 2016;126(Pt 3):238–92. PMID: 27615390. Available from: https://doi.org/10.1016/j.brainresbull.2016.08.018.
8. Jamal QM, Siddiqui MU, Alharbi AH, Albejaidi F, Akhtar S, Alzohairy MA. A Computational Study of Natural Compounds from Bacopa monnieri in the Treatment of Alzheimer's Disease. Current Pharmaceutical Design. 2020;26(7):790–800. PMID: 31894743. Available from: https://doi.org/10.2174/1381612826666200102142257.
9. Taqui R, Debnath M. Advances on plant extracts and phytocompounds with acetylcholinesterase inhibition activity for possible treatment of Alzheimer's disease. Phytomedicine plus. 2021;2(1):100184. Available from: https://doi.org/10.1016/j.phyplu.2021.100184.
10. Murray AP, Faraoni MB, Castro MJ, Alza NP, Cavallaro V. Natural AChE inhibitors from plants and their contribution to Alzheimer's disease therapy. Current neuropharmacology. 2013;11(4):388–413. Available from: https://doi.org/10.2174/1570159X11311040004.
11. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine. 2016;8(6):595–608. PMID: 27025652. Available from: https://doi.org/10.15252/emmm.201606210.
12. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH. The Amyloid-β Pathway in Alzheimer's Disease. Molecular Psychiatry. 2021;26(10):5481–503. PMID: 34456336. Available from: https://doi.org/10.1038/s41380-021-01249-0.
13. Wang Y, Mandelkow E. Tau in physiology and pathology. Nature Reviews Neuroscience. 2016;17(1):5–21. PMID: 26631930. Available from: https://doi.org/10.1038/nrn.2015.1.
14. Haass C, Kaether C, Thinakaran G, Sisodia S. Trafficking and proteolytic processing of APP. Cold Spring Harbor Perspectives in Medicine. 2012;2(5):a006270. PMID: 22553493. Available from: https://doi.org/10.1101/cshperspect.a006270.
15. Zhao J, Liu X, Xia W, Zhang Y, Wang C. Targeting amyloidogenic processing of APP in Alzheimer's disease. Frontiers in Molecular Neuroscience. 2020;13:137. PMID: 32848600. Available from: https://doi.org/10.3389/fnmol.2020.00137.
16. Hur JY. γ-Secretase in Alzheimer's disease. Experimental & Molecular Medicine. 2022;54(4):433–46. PMID: 35396575. Available from: https://doi.org/10.1038/s12276-022-00754-8.
17. Bhattarai A, Devkota S, Do HN, Wang J, Bhattarai S, Wolfe MS. Mechanism of tripeptide trimming of amyloid β-peptide 49 by γ-secretase. Journal of the American Chemical Society. 2022;144(14):6215–26. PMID: 35377629. Available from: https://doi.org/10.1021/jacs.1c10533.
18. Wells C, Brennan S, Keon M, Ooi L. The role of amyloid oligomers in neurodegenerative pathologies. International Journal of Biological Macromolecules. 2021;181:582–604. PMID: 33766600. Available from: https://doi.org/10.1016/j.ijbiomac.2021.03.113.
19. Madhu P, Mukhopadhyay S. Distinct types of amyloid-β oligomers displaying diverse neurotoxicity mechanisms in Alzheimer's disease. Journal of Cellular Biochemistry. 2021;122(11):1594–608. PMID: 34494298. Available from: https://doi.org/10.1002/jcb.30141.
20. van Dyck CH. Anti-amyloid-β monoclonal antibodies for Alzheimer's disease: pitfalls and promise. Biological Psychiatry. 2018;83(4):311–9. PMID: 28967385. Available from: https://doi.org/10.1016/j.biopsych.2017.08.010.
21. Brown MR, Radford SE, Hewitt EW. Modulation of β-amyloid fibril formation in Alzheimer's disease by microglia and infection. Frontiers in Molecular Neuroscience. 2020;13:609073. PMID: 33324164. Available from: https://doi.org/10.3389/fnmol.2020.609073.
22. Sedov I, Khaibrakhmanova D. Molecular mechanisms of inhibition of protein amyloid fibril formation: evidence and perspectives based on kinetic models. International Journal of Molecular Sciences. 2022;23(21):13428. PMID: 36362217. Available from: https://doi.org/10.3390/ijms232113428.
23. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. Signal Transduction and Targeted Therapy. 2024;9(1):211. PMID: 39174535. Available from: https://doi.org/10.1038/s41392-024-01911-3.
24. Wange NK, Khan I, Pinnamaneni R, Cheekati H, Prasad J, Vidhya R. β-amyloid deposition-based research on neurodegenerative disease and their relationship in elucidate the clear molecular mechanism. Multidisciplinary Science Journal. 2024;6(4):2024045–2024045. Available from: https://doi.org/10.31893/multiscience.2024045.
25. Depp C, Sun T, Sasmita AO, Spieth L, Berghoff SA, Nazarenko T. Myelin dysfunction drives amyloid-β deposition in models of Alzheimer's disease. Nature. 2023;618(7964):349–57. PMID: 37258678. Available from: https://doi.org/10.1038/s41586-023-06120-6.
26. Ramesh M, Gopinath P, Govindaraju T. Role of post-translational modifications in Alzheimer's disease. Chembiochem : A European Journal of Chemical Biology. 2020;21(8):1052–79. PMID: 31863723. Available from: https://doi.org/10.1002/cbic.201900573.
27. Mathieu C, Pappu RV, Taylor JP. Beyond aggregation: pathological phase transitions in neurodegenerative disease. Science. 2020;370(6512):56–60. PMID: 33004511. Available from: https://doi.org/10.1126/science.abb8032.
28. Sinsky J, Pichlerova K, Hanes J. Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies. International Journal of Molecular Sciences. 2021;22(17):9207. PMID: 34502116. Available from: https://doi.org/10.3390/ijms22179207.
29. Ye H, Han Y, Li P, Su Z, Huang Y. The role of post-translational modifications on the structure and function of tau protein. Journal of Molecular Neuroscience. 2022;72(8):1557–71. PMID: 35325356. Available from: https://doi.org/10.1007/s12031-022-02002-0.
30. Gibbons GS, Lee VM, Trojanowski JQ. Mechanisms of cell-to-cell transmission of pathological tau: a review. JAMA Neurology. 2019;76(1):101–8. PMID: 30193298. Available from: https://doi.org/10.1001/jamaneurol.2018.2505.
31. Pan L, Meng L, He M, Zhang Z. Tau in the pathophysiology of Parkinson's disease. Journal of Molecular Neuroscience. 2021;71(11):2179–91. PMID: 33459970. Available from: https://doi.org/10.1007/s12031-020-01776-5.
32. Sharifi-Rad J, Rapposelli S, Sestito S, Herrera-Bravo J, Arancibia-Diaz A, Salazar LA. Multi-target mechanisms of phytochemicals in Alzheimer's disease: effects on oxidative stress, neuroinflammation and protein aggregation. Journal of Personalized Medicine. 2022;12(9):1515. PMID: 36143299. Available from: https://doi.org/10.3390/jpm12091515.

33. Benítez MJ, Cuadros R, Jiménez JS. Phosphorylation and dephosphorylation of tau protein by the catalytic subunit of PKA, as probed by electrophoretic mobility retard. Journal of Alzheimer's Disease. 2021;79(3):1143–56. PMID: 33386804. Available from: https://doi.org/10.3233/JAD-201077.
34. Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, et al. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. Science translational medicine. 2016;8(338):338ra66–338ra66. Available from: https://doi.org/10.1126/scitranslmed.aaf23.
35. Musiek ES, Holtzman DM. Three dimensions of the amyloid hypothesis: time, space and 'wingmen'. Nature Neuroscience. 2015;18(6):800–6. PMID: 26007213. Available from: https://doi.org/10.1038/nn.4018.
36. Morgan BP. Complement in the pathogenesis of Alzheimer's disease. In: Seminars in immunopathology. Berlin/Heidelberg: Springer Berlin Heidelberg, 2018: 113-124.; 2018. Available from: https://doi.org/10.1007/s00281-017-0662-9.
37. Babrak L, McGarvey JA, Stanker LH, Hnasko R. Identification and verification of hybridoma-derived monoclonal antibody variable region sequences using recombinant DNA technology and mass spectrometry. Molecular Immunology. 2017;90:287–94. PMID: 28865256. Available from: https://doi.org/10.1016/j.molimm.2017.08.014.
38. Vlasak J, Ionescu R. Fragmentation of monoclonal antibodies. In: MAbs. Taylor & Francis, 2011. p. 253-263. 2011;Available from: https://doi.org/10.4161/mabs.3.3.15608.
39. Carrillo-Mora P, Luna R, Colín-Barenque L. Amyloid beta: multiple mechanisms of toxicity and only some protective effects? Oxidative Medicine and Cellular Longevity. 2014;2014(1):795375. PMID: 24683437. Available from: https://doi.org/10.1155/2014/795375.
40. Bolduc DM, Montagna DR, Seghers MC, Wolfe MS, Selkoe DJ. The amyloid-beta forming tripeptide cleavage mechanism of γ-secretase. eLife. 2016;5:e17578. PMID: 27580372. Available from: https://doi.org/10.7554/eLife.17578.
41. Walsh S, Merrick R, Milne R, Brayne C. Aducanumab for Alzheimer's disease? BMJ (Clinical Research Ed). 2021;374:n1682. PMID: 34226181. Available from: https://doi.org/10.1136/bmj.n1682.
42. Padda IS, Parmar M. Aducanumab. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Jul 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK573062/. Treasure Island (FL): StatPearls Publishing; 2024.
43. Calvo-Rodriguez M, García-Rodríguez C, Villalobos C, Núñez L. Role of toll like receptor 4 in Alzheimer's disease. Frontiers in Immunology. 2020;11:1588. PMID: 32983082. Available from: https://doi.org/10.3389/fimmu.2020.01588.
44. Haeberlein SB, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. The journal of prevention of Alzheimer's disease. 2022;9(2):197–210. PMID: 35542991. Available from: https://doi.org/10.14283/jpad.2022.30.
45. Beshir SA, Aadithsoorya AM, Parveen A, Goh SS, Hussain N, Menon VB. Aducanumab therapy to treat Alzheimer's disease: a narrative review. International journal of alzheimer's disease. 2022;2022(1):9343514. PMID: 35308835. Available from: https://doi.org/10.1155/2022/9343514.
46. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016;537(7618):50–6. PMID: 27582220. Available from: https://doi.org/10.1038/nature19323.
47. Loeffler DA. Antibody-mediated clearance of brain amyloid-β: mechanisms of action, effects of natural and monoclonal anti-Aβ antibodies, and downstream effects. Journal of Alzheimer's disease reports. 2023;7(1):873–899. Available from: https://doi.org/10.3233/ADR-230025.
48. Ostrowitzki S, Lasser RA, Dorflinger E, Scheltens P, Barkhof F, Nikolcheva T, et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimer's research & therapy. 2017;9(1):95. PMID: 29221491. Available from: https://doi.org/10.1186/s13195-017-0318-y.
49. Dickson SP, Hennessey S, Johnson JN, Knowlton N, Hendrix SB. Avoiding future controversies in the Alzheimer's disease space through understanding the aducanumab data and FDA review. Alzheimer's research & therapy. 2023;15(1):98. PMID: 37226162. Available from: https://doi.org/10.1186/s13195-023-01238-1.
50. Aisen P, Bateman RJ, Crowther D, Cummings J, Dwyer J, Iwatsubo T, et al. The case for regulatory approval of amyloid-lowering immunotherapies in Alzheimer's disease based on clearcut biomarker evidence. Alzheimer's & Dementia. 2025;21(1):e14342. PMID: 39535341. Available from: https://doi.org/10.1002/alz.14342.
51. Johannesson M, Söderberg L, Zachrisson O, Fritz N, Kylefjord H, Gkanatsiou E, et al. Lecanemab demonstrates highly selective binding to Aβ protofibrils isolated from Alzheimer's disease brains. Molecular and Cellular Neurosciences. 2024;130:103949. PMID: 38906341. Available from: https://doi.org/10.1016/j.mcn.2024.103949.
52. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: an analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's & Dementia. 2021;17(4):696–701. PMID: 33135381. Available from: https://doi.org/10.1002/alz.12213.
53. Park YH, Hodges A, Risacher SL, Lin K, Jang JW, Ahn S, et al. Dysregulated Fc gamma receptor-mediated phagocytosis pathway in Alzheimer's disease: network-based gene expression analysis. Neurobiology of Aging. 2020;88:24–32. PMID: 31901293. Available from: https://doi.org/10.1016/j.neurobiolaging.2019.12.001.
54. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RY, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimer's research & therapy. 2021;13(1):80. PMID: 33865446. Available from: https://doi.org/10.1186/s13195-021-00813-8.
55. Landhuis E. Researchers call for a major rethink of how Alzheimer's treatments are evaluated. Nature. 2024;627(8003):S18–S20. PMID: 38480971. Available from: https://doi.org/10.1038/d41586-024-00756-.
56. A Randomized, Blinded, Placebo-Controlled Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of BIIB037 in Subjects With Mild to Moderate Alzheimer's Disease [Internet]. 2011 [cited 2011 Jun 1]. Available from: https://clinicaltrials.gov/study/NCT01397539.
57. A Randomized, Double-Blinded, Placebo-Controlled Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB037 in Subjects With Prodromal or Mild Alzheimer's Disease [Internet]. 2012 [cited 2012 Oct 5]. Available from: https://clinicaltrials.gov/study/NCT01677572.
58. A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease [Internet]. 2015 [cited 2015 Aug 13]. Available from: https://clinicaltrials.gov/study/NCT02477800.
59. A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer's Disease [Internet]. 2015 [cited 2015 Sep 15]. Available from: https://clinicaltrials.gov/study/NCT02484547.
60. Phase 3b Open-Label, Multicenter, Safety Study of BIIB037 (Aducanumab) in Subjects With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205 [Internet]. 2020 [cited 2020 Mar 2]. Available from: https://clinicaltrials.gov/study/NCT04241068.

61. Cummings J, Osse AM, Cammann D, Powell J, Chen J. Anti-Amyloid Monoclonal Antibodies for the Treatment of Alzheimer's Disease. BioDrugs : Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy. 2024;38(1):5–22. PMID: 37955845. Available from: https://doi.org/10.1007/s40259-023-00633-2.
62. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. New England Journal of Medicine. 2023;388(1):9–21. Available from: https://doi.org/10.1056/NEJMoa2212948.
63. A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of Gantenerumab in Patients With Early (Prodromal to Mild) [Internet]. 2024 [cited 2025 Jan 31]. Available from: https://clinicaltrials.gov/study/NCT03444870.
64. Bayer V. An overview of monoclonal antibodies. In: Seminars in oncology nursing. WB Saunders, 2019. p. 150927; 2019. Available from: https://doi.org/10.1016/j.soncn.2019.08.006.
65. Barbier P, Zejneli O, Martinho M, Lasorsa A, Belle V, Smet-Nocca C. Role of tau as a microtubule-associated protein: structural and functional aspects. Frontiers in Aging Neuroscience. 2019;11:204. PMID: 31447664. Available from: https://doi.org/10.3389/fnagi.2019.00204.
66. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. Pharmacology & Therapeutics. 2015;148:114–31. PMID: 25435019. Available from: https://doi.org/10.1016/j.pharmthera.2014.11.016.
67. Lee JK, Kim NJ. Recent advances in the inhibition of p38 MAPK as a potential strategy for the treatment of Alzheimer's disease. Molecules (Basel, Switzerland). 2017;22(8):1287. PMID: 28767069. Available from: https://doi.org/10.3390/molecules22081287.
68. DeVos SL, Miller RL, Schoch KM, Holmes BB, Kebodeaux CS, Wegener AJ, et al. Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy. Science Translational Medicine. 2017;9(374):eaag0481. PMID: 28123067. Available from: https://doi.org/10.1126/scitranslmed.aag0481.
69. Kaur P, Khera A, Alajangi HK, Sharma A, Jaiswal PK, Singh G. Role of tau in various tauopathies, treatment approaches, and emerging role of nanotechnology in neurodegenerative disorders. Molecular Neurobiology. 2023;60(3):1690–720. PMID: 36562884. Available from: https://doi.org/10.1007/s12035-022-03164-z.
70. Mummery CJ, Börjesson-Hanson A, Blackburn DJ, Vijverberg EG, Deyn PPD, Ducharme S. Tau-targeting antisense oligonucleotide MAPTRx in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. Nature Medicine. 2023;29(6):1437–47. PMID: 37095250. Available from: https://doi.org/10.1038/s41591-023-02326-3.
71. Wang C, Terrigno M, Joenson L, Li M, Schroeter M, Nordbo B, et al. (CA)noligonucleotides correct RNA mis-splicing in TDP-43 pathology. bioRxiv. 2023;p. 2023.12.21.572777. Available from: https://doi.org/10.1101/2023.12.21.572777.
72. Easton A, Jensen ML, Wang C, Hagedorn PH, Li Y, Weed M. Identification and characterization of a MAPT-targeting locked nucleic acid antisense oligonucleotide therapeutic for tauopathies. Molecular Therapy Nucleic Acids. 2022;29:625–42. PMID: 36090761. Available from: https://doi.org/10.1016/j.omtn.2022.07.027.
73. Panza F, Lozupone M. The challenges of anti-tau therapeutics in Alzheimer disease. Nature Reviews Neurology. 2022;18(10):577–8. PMID: 35941199. Available from: https://doi.org/10.1038/s41582-022-00702-0.
74. Congdon EE, Pan R, Jiang Y, Sandusky-Beltran LA, Dodge A, Lin Y, et al. Single domain antibodies targeting pathological tau protein: influence of four IgG subclasses on efficacy and toxicity. EBioMedicine. 2022;84:104249. PMID: 36099813. Available from: https://doi.org/10.1016/j.ebiom.2022.104249.
75. Suzuki N, Hatta T, Ito M, Kusakabe KI. Kusakabe K ichi. Anti-amyloid-β antibodies and anti-tau therapies for Alzheimer's disease: recent advances and perspectives. Chemical & Pharmaceutical Bulletin. 2024;72(7):602–9. PMID: 38945936. Available from: https://doi.org/10.1248/cpb.c24-00069.
76. Sigurdsson EM. Tau Immunotherapies for Alzheimer's Disease and Related Tauopathies: Status of Trials and Insights from Preclinical Studies. Journal of Alzheimer's Disease. 2024;101(s1):S129–S140. Available from: https://doi.org/10.3233/JAD-231238.
77. Moreira SC, Jansen AK, Silva FM. Dietary interventions and cognition of Alzheimer's disease patients: a systematic review of randomized controlled trial. Dementia & Neuropsychologia. 2020;14(3):258–82. PMID: 32973980. Available from: https://doi.org/10.1590/1980-57642020dn14-030008.
78. Monteiro C, Toth B, Brunstein F, Bobbala A, Datta S, Ceniceros R, et al. Randomized phase II study of the safety and efficacy of semorinemab in participants with mild-to-moderate Alzheimer disease: lauriet. Neurology. 2023;101(14):e1391–401. PMID: 37643887. Available from: https://doi.org/10.1212/WNL.0000000000207663.
79. Abdel-Haleem AM, Casavant E, Toth B, Teng E, Monteiro C, Pandya NJ, et al. CSF proteomic analysis of semorinemab Ph2 trials in prodromal-to-mild (Tauriel) and mild-to-moderate (Lauriet) Alzheimers disease identifies distinct trial cell-type specific proteomic signatures. MedRxiv. 2024;p. 2024.04.11.24305670. Available from: https://doi.org/10.1101/2024.04.11.24305670.
80. Fleisher AS, Munsie LM, Perahia DG, Andersen SW, Higgins IA, Hauck PM, et al. Assessment of Efficacy and Safety of Zagotenemab: Results From PERISCOPE-ALZ, a Phase 2 Study in Early Symptomatic Alzheimer Disease. Neurology. 2024;102(5):e208061. PMID: 38386949. Available from: https://doi.org/10.1212/WNL.0000000000208061.
81. Abyadeh M, Gupta V, Gupta V, Chitranshi N, Wu Y, Amirkhani A. Comparative analysis of aducanumab, zagotenemab and pioglitazone as targeted treatment strategies for Alzheimer's disease. Aging and Disease. 2021;12(8):1964–76. PMID: 34881080. Available from: https://doi.org/10.14336/AD.2021.0719.
82. Florian H, Wang D, Arnold SE, Boada M, Guo Q, Jin Z. Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. Brain. 2023;146(6):2275–84. PMID: 36730056. Available from: https://doi.org/10.1093/brain/awad024.
83. Zhou X, Zou H, Lutz MW, Arbeev K, Akushevich I, Yashin A, et al. Assessing tilavonemab efficacy in early Alzheimer's disease via longitudinal item response theory modeling. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2024;10(2):e12471. PMID: 38835820. Available from: https://doi.org/10.1002/trc2.12471.
84. Novak P, Kovacech B, Katina S, Schmidt R, Scheltens P, Kontsekova E. ADAMANT: a placebo-controlled randomized phase 2 study of AADvac1, an active immunotherapy against pathological tau in Alzheimer's disease. Nature Aging. 2021;1(6):521–34. PMID: 37117834. Available from: https://doi.org/10.1038/s43587-021-00070-2.
85. Novak P, Zilka N, Zilkova M, Kovacech B, Skrabana R, Ondrus M, et al. AADvac1, an active immunotherapy for Alzheimer's disease and non Alzheimer tauopathies: an overview of preclinical and clinical development. The journal of prevention of Alzheimer's disease. 2019;6(1):63–9. PMID: 30569088. Available from: https://doi.org/10.14283/jpad.2018.45.
86. Akhani B. Advances in tau protein inhibitors for alzheimer's disease: a review. Nirma University Journal of Pharmaceutical Sciences. 2017;4(1):19–24.
87. Branca C, Oddo S. Paving the way for new clinical trials for Alzheimer's Disease. Biological Psychiatry. 2017;81(2):88–9. PMID: 27938878. Available from: https://doi.org/10.1016/j.biopsych.2016.10.016.
88. Thangwaritorn S, Lee C, Metchikoff E, Razdan V, Ghafary S, Rivera D, et al. A Review of Recent Advances in the Management of Alzheimer's Disease. Cureus. 2024;16(4):e58416. PMID: 38756263. Available from: https://doi.org/10.7759/

cureus.58416.
89. Guo X, Yan L, Zhang D, Zhao Y. Passive immunotherapy for Alzheimer's disease. Ageing Research Reviews. 2024;94:102192. PMID: 38219962. Available from: https://doi.org/10.1016/j.arr.2024.102192.
90. Ramakrishnan V, Bender B, Langenhorst J, Magnusson MO, Dolton M, Shim J, et al. Semorinemab Pharmacokinetics and The Effect on Plasma Total Tau Pharmacodynamics in Clinical Studies. The Journal of Prevention of Alzheimer's Disease. 2024;11(5):1241–50. PMID: 39350369. Available from: https://doi.org/10.14283/jpad.2024.146.
91. Single-Dose, Dose-Escalation Study With LY3303560 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Healthy Subjects and Patients With Mild Cognitive Impairment Due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease [Internet]. 2016 [cited 2016 Apr 25]. Available from: https://clinicaltrials.gov/study/NCT02754830.
92. Gu X, Qi L, Qi Q, Zhou J, Chen S, Wang L. Monoclonal antibody therapy for Alzheimer's disease focusing on intracerebral targets. Bioscience Trends. 2024;18(1):49–65. PMID: 38382942. Available from: https://doi.org/10.5582/bst.2023.01288.
93. Multiple-Dose, Dose-Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY3303560 in Patients With Mild Cognitive Impairment Due to Alzheimer's Disease or Mild to Moderate Alzheimer's Disease [Internet]. 2017 [cited 2017 Jan 31]. Available from: https://clinicaltrials.gov/study/NCT03019536.
94. Parums DV. Editorial: Targets for Disease-Modifying Therapies in Alzheimer's Disease, Including Amyloid β and Tau Protein. Medical Science Monitor. 2021;27:e934077–1. PMID: 34305135.
95. Clinical_Study_M15-562_English.pdf [Internet]. [cited 2025 Jan 31]. Available from: https://www.abbvie.com/content/dam/abbvie-dotcom/uploads/PDFs/results-summaries/Clinical_Study_M15-562_English.pdf.
96. Salunkhe J, Ugale R. Recent updates on immunotherapy in neurodegenerative diseases. Brain Research. 2024;1845:149205. PMID: 39197568. Available from: https://doi.org/10.1016/j.brainres.2024.149205.
97. Xiao D, Zhang C. Current therapeutics for Alzheimer ' s disease and clinical trials. Exploration of Neuroscience. 2024;3(3):255–71. Available from: https://doi.org/10.37349/en.2024.00048.
98. AC Immune SA. A Phase Ib/IIa Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of Different Doses, Regimens and Combinations of Tau Targeted Vaccines in Subjects With Early Alzheimer's Disease [Internet]. clinicaltrials.gov; 2024 Jul [cited 2025 Jan 31]. Report No.: NCT04445831. Available from: https://clinicaltrials.gov/study/NCT04445831.
99. Wischik CM, Harrington CR, Storey JM. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biochemical Pharmacology. 2014;88(4):529–39. PMID: 24361915. Available from: https://doi.org/10.1016/j.bcp.2013.12.008.
100. Blurton-Jones M, Spencer B, Michael S, Castello NA, Agazaryan AA, Davis JL, et al. Neural stem cells genetically-modified to express neprilysin reduce pathology in Alzheimer transgenic models. Stem Cell Research & Therapy. 2014;5(2):46. PMID: 25022790. Available from: https://doi.org/10.1186/scrt440.
101. Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. Nature Immunology. 2015;16(3):229–36. PMID: 25689443. Available from: https://doi.org/10.1038/ni.3102.
102. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013;493(7434):674–8. PMID: 23254930. Available from: https://doi.org/10.1038/nature11729.
103. Zhang X, Wang Z, Zheng Y, Yu Q, Zeng M, Bai L. Inhibitors of the NLRP3 inflammasome pathway as promising therapeutic candidates for inflammatory diseases (Review). International Journal of Molecular Medicine. 2023;51(4):1–21. PMID: 36960868. Available from: https://doi.org/10.3892/ijmm.2023.5238.
104. Egan MF, Kost J, Tariot PN, Aisen PS, Cummings JL, Vellas B. Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease. The New England Journal of Medicine. 2018;378(18):1691–703. PMID: 29719179. Available from: https://doi.org/10.1056/NEJMoa1706441.
105. Moussa-Pacha NM, Abdin SM, Omar HA, Alniss H, Al-Tel TH. BACE1 inhibitors: current status and future directions in treating Alzheimer's disease. Medicinal Research Reviews. 2020;40(1):339–84. PMID: 31347728. Available from: https://doi.org/10.1002/med.21622.
106. Ran FA, Hsu PD, Wright J, Agarwala V, Scott DA, Zhang F. Genome engineering using the CRISPR-Cas9 system. Nature Protocols. 2013;8(11):2281–308. PMID: 24157548. Available from: https://doi.org/10.1038/nprot.2013.143.
107. Elmahboub YS, Elkordy AA. Polymeric nanoparticles: A promising strategy for treatment of Alzheimer's disease. Journal of Taibah University Medical Sciences. 2024;19(3):549–65. PMID: 38736898. Available from: https://doi.org/10.1016/j.jtumed.2024.04.004.
108. Faiyaz M, Ganayee MA, Akhtar S, Krishnan S, Flora B, Dogra D. Nanomaterials in Alzheimer's disease treatment: a comprehensive review. Frontiers in Bioscience (Landmark Edition). 2021;26(10):851–65. PMID: 34719210. Available from: https://doi.org/10.52586/4992.
109. Pei J, Palanisamy CP, Natarajan PM, Umapathy VR, Roy JR, Srinivasan GP, et al. Curcumin-loaded polymeric nanomaterials as a novel therapeutic strategy for Alzheimer's disease: A comprehensive review. Ageing Research Reviews. 2024;99:102393. PMID: 38925479. Available from: https://doi.org/10.1016/j.arr.2024.102393.
110. Silva RO, Counil H, Rabanel JM, Haddad M, Zaouter C, Khedher MRB. Donepezil-Loaded Nanocarriers for the Treatment of Alzheimer's Disease: Superior Efficacy of Extracellular Vesicles Over Polymeric Nanoparticles. International Journal of Nanomedicine. 2024;19:1077–96. PMID: 38317848. Available from: https://doi.org/10.2147/IJN.S449227.
111. Andrade S, Pereira MC, Loureiro JA. Caffeic acid loaded into engineered lipid nanoparticles for Alzheimer's disease therapy. Colloids and Surfaces B, Biointerfaces. 2023;225:113270. PMID: 36996633. Available from: https://doi.org/10.1016/j.colsurfb.2023.113270.
112. Kendre PN, Pote A, Bhalke R, Prajapati BG, Jain SP, Kapoor D. Lipid nanoparticles in targeting Alzheimer's disease. In: Alzheimer's Disease and Advanced Drug Delivery Strategies. Academic Press, 2024. p. 283-295. Elsevier. Available from: https://doi.org/10.1016/B978-0-443-13205-6.00021-2.
113. Gao C, Liu Y, Zhang TL, Luo Y, Gao J, Chu JJ. Biomembrane-Derived Nanoparticles in Alzheimer's Disease Therapy: A Comprehensive Review of Synthetic Lipid Nanoparticles and Natural Cell-Derived Vesicles. International Journal of Nanomedicine. 2023;18:7441–68. PMID: 38090364. Available from: https://doi.org/10.2147/IJN.S436774.
114. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nature Biotechnology. 2011;29(4):341–5. PMID: 21423189. Available from: https://doi.org/10.1038/nbt.1807.
115. Koh HB, Kim HJ, Kang SW, Yoo TH. Exosome-Based Drug Delivery: Translation from Bench to Clinic. Pharmaceutics. 2023;15(8):2042. PMID: 37631256. Available from: https://doi.org/10.3390/pharmaceutics15082042.
116. Wang Z, Gao C, Zhang L, Sui R. Novel combination of Olesoxime/Resveratrol-encapsulated exosomes to improve cognitive function by targeting amyloid β-induced Alzheimer's disease: investigation on in vitro and in vivo

model. Inflammopharmacology. 2024;32(4):2613–28. PMID: 38753222. Available from: https://doi.org/10.1007/s10787-024-01476-1.

117. Kapoor D, Sharma D, Pathak Y, Prajapati BG, Satani B. Nanoformulations targeting Alzheimer's disease. In: Alzheimer's Disease and Advanced Drug Delivery Strategies. Academic Press, 2024. p. 265-282. Elsevier. Available from: https://doi.org/10.1016/B978-0-443-13205-6.00010-8.
118. Mal P, Rath SK, Halder T. Targeted Nano-based Drug Delivery in Alzheimer's Disease and Dementia. In: Nanomaterials for Drug Delivery and Neurological Diseases Management. Singapore: Springer Nature Singapore, 2024. p. 281-302.
119. Singh B, Day CM, Abdella S, Garg S. Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2024;367:402–24. PMID: 38286338. Available from: https://doi.org/10.1016/j.jconrel.2024.01.047.
120. Roghani AK, Garcia RI, Roghani A, Reddy A, Khemka S, Reddy RP, et al. Treating Alzheimer's disease using nanoparticle-mediated drug delivery strategies/systems. Ageing Research Reviews. 2024;97:102291. PMID: 38614367. Available from: https://doi.org/10.1016/j.arr.2024.102291.
121. Qian K, Yang P, Li Y, Meng R, Cheng Y, Zhou L, et al. Rational fusion design inspired by cell-penetrating peptide: SS31/S-14 G Humanin hybrid peptide with amplified multimodal efficacy and bio-permeability for the treatment of Alzheimer's disease. Asian Journal of Pharmaceutical Sciences. 2024;19(4):100938. PMID: 39253611. Available from: https://doi.org/10.1016/j.ajps.2024.100938.
122. Pirhaghi M, Mamashli F, Moosavi-Movahedi F, Arghavani P, Amiri A, Davaeil B. Cell-penetrating peptides: promising therapeutics and drug-delivery systems for neurodegenerative diseases. Molecular Pharmaceutics. 2024;21(5):2097–117. PMID: 38440998. Available from: https://doi.org/10.1021/acs.molpharmaceut.3c01167.
123. Ordóñez-Gutiérrez L, Posado-Fernández A, Ahmadvand D, Lettiero B, Wu L, Antón M. ImmunoPEGliposome-mediated reduction of blood and brain amyloid levels in a mouse model of Alzheimer's disease is restricted to aged animals. Biomaterials. 2017;112:141–52. PMID: 27760398. Available from: https://doi.org/10.1016/j.biomaterials.2016.07.027.
124. Loureiro JA, Gomes B, Coelho MA, do Carmo Pereira M, Rocha S. Immunoliposomes doubly targeted to transferrin receptor and to α-synuclein. Future Science OA. 2015;1(4):71. PMID: 28031922. Available from: https://doi.org/10.4155/fso.15.71.
125. Patel RJ, Patel AA, Trivedi N, Pandya V, Alexander A, Patel V, et al.. Liposomes as carrier for drug delivery in Alzheimer's disease. In: Alzheimer's Disease and Advanced Drug Delivery Strategies. Academic Press, 2024. p. 153-179. Available from: https://doi.org/10.1016/B978-0-443-13205-6.00008-X.
126. Ansari MA, Tripathi T, Venkidasamy B, Monziani A, Rajakumar G, Alomary MN. Multifunctional nanocarriers for Alzheimer's disease: befriending the barriers. Molecular Neurobiology. 2024;61(5):3042–89. PMID: 37966683. Available from: https://doi.org/10.1007/s12035-023-03730-z.
127. Senapati S, Tripathi K, Awad K, Rahimipour S. Multifunctional Liposomes Targeting Amyloid-β Oligomers for Early Diagnosis and Therapy of Alzheimer's Disease. Small. 2024;20(31):2311670. PMID: 38461531. Available from: https://doi.org/10.1002/smll.202311670.
128. Mancini S, Balducci C, Micotti E, Tolomeo D, Forloni G, Masserini M. Multifunctional liposomes delay phenotype progression and prevent memory impairment in a presymptomatic stage mouse model of Alzheimer disease. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2017;258:121–9. PMID: 28501671. Available from: https://doi.org/10.1016/j.jconrel.2017.05.013.
129. Ali S, Ali SA, Kumar M, Jahan I, Hak J. Emerging Strategies for Targeted Drug Delivery across the BloodBarrier in Neurological Disorder. Current Pharmaceutical Research. 2025;1(1):1–14. Available from: https://doi.org/10.63785/cpr.2025.1.1.114.
130. Banyal MM, Musarrat M, Raj MH, Joshi MA. A Review: Recent Advances in Novel Drug Delivery System for Intra-Nasal Drug Delivery & Clinical Applications . Goya Journal. 2025;18(1):87–106. Available from: https://doi.org/10.5281/zenodo.14623241.
131. Bai L, Yu L, Ran M, Zhong X, Sun M, Xu M. Harnessing the Potential of Exosomes in Therapeutic Interventions for Brain Disorders. International Journal of Molecular Sciences. 2025;26(6):2491. PMID: 40141135. Available from: https://doi.org/10.3390/ijms26062491.
132. Kömür M, KHT, Öztürk AA. Development of donepezil hydrochloride-loaded PLGA-based nanoparticles for Alzheimer's disease treatment. Scientific Reports. 2025;15(1):13184. PMID: 40240764. Available from: https://doi.org/10.1038/s41598-025-95792-3.
133. Abaidullah N, Muhammad K, Waheed Y. Delving into nanoparticle systems for enhanced drug delivery technologies. AAPS PharmSciTech. 2025;26(3):74. PMID: 40038143. Available from: https://doi.org/10.1208/s12249-025-03063-1.
134. Komal K, Ghosh R, Sil D, Sharma R, Kumar S, Pandey P. Advancements in nose-to-brain drug targeting for Alzheimer's disease: a review of nanocarriers and clinical insights. Inflammopharmacology. 2025;33(2):605–26. PMID: 39776027. Available from: https://doi.org/10.1007/s10787-024-01636-3.
135. Du JJ, Zhang RY, Jiang S, Xiao S, Liu Y, Niu Y, et al. Applications of cell penetrating peptide-based drug delivery system in immunotherapy. Frontiers in Immunology. 2025;16:1540192. PMID: 39911386. Available from: https://doi.org/10.3389/fimmu.2025.1540192.
136. Ma YN, Hu X, Karako K, Song P, Tang W, Xia Y. Exploring the multiple therapeutic mechanisms and challenges of mesenchymal stem cell-derived exosomes in Alzheimer's disease. Bioscience Trends. 2024;18(5):413–30. PMID: 39401895. Available from: https://doi.org/10.5582/bst.2024.01306.
137. Akhtar A, Andleeb A, Waris TS, Bazzar M, Moradi AR, Awan NR. Neurodegenerative diseases and effective drug delivery: A review of challenges and novel therapeutics. Journal of Controlled Release : Official Journal of the Controlled Release Society. 2021;330:1152–67. PMID: 33197487. Available from: https://doi.org/10.1016/j.jconrel.2020.11.021.
138. de la Torre C, Ceña V. The delivery challenge in neurodegenerative disorders: the nanoparticles role in Alzheimer's disease therapeutics and diagnostics. Pharmaceutics. 2018;10(4):190. PMID: 30336640. Available from: https://doi.org/10.3390/pharmaceutics10040190.