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Drug delivery strategies with lipid-based nanoparticles for Alzheimer's disease treatment

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Abstract

Alzheimer's disease (AD) is a distinctive form of dementia characterized by age-related cognitive decline and memory impairment. A key hallmark of AD is the irreversible overaccumulation of beta-amyloid (Aβ) in the brain, associated with neuroinflammation and neuronal death. Although Aβ clearance and immunoregulation have been the major therapeutic strategies for AD, highly selective transport across the blood–brain barrier (BBB) negatively affects the delivery efficacy of the drugs without the ability to cross the BBB. In this review, we discuss the potential of lipid-based nanoparticles (LBNs) as promising vehicles for drug delivery in AD treatment. LBNs, composed of phospholipid mono- or bilayer, have attracted attention due to their exceptional cellular penetration capabilities and drug loading capabilities, which also facilitate cargo transcytosis across the BBB. Recent advances in the development and engineering of LBNs overcome the existing limitations of the current clinical approaches for AD treatment by addressing off-target effects and low therapeutic efficacy. Here, we review the transport pathways across the BBB, as well as various types of LBNs for AD therapy, including exosomes, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), to elucidate their distinctive properties, preparation methodologies, and therapeutic efficacy, thereby offering innovative avenues for novel drug development for clinical translation in AD therapy.

Keywords Alzheimer's disease, Blood–brain barrier, Drug delivery, Exosomes, Lipid-based nanoparticles, Liposomes

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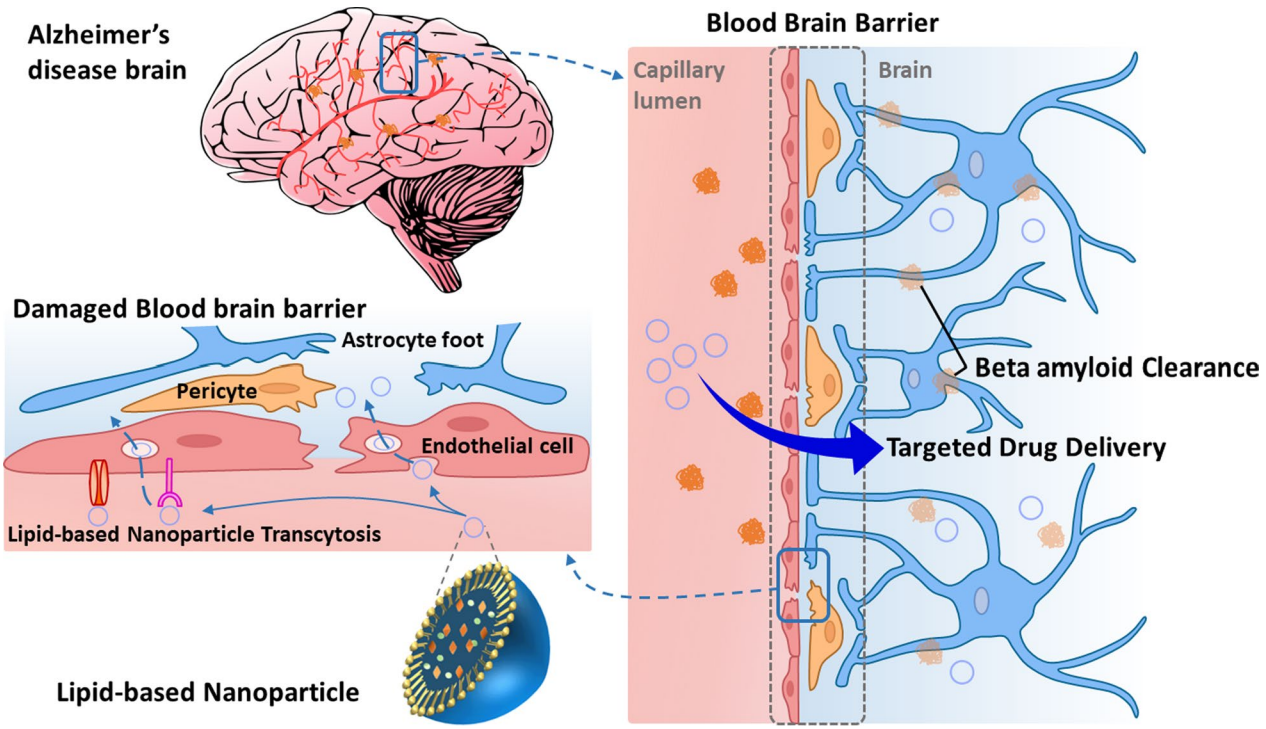
Graphical Abstract



Introduction

The increasing prevalence of central nervous system (CNS) disorders has largely been attributed to neurodegenerative processes, such as Alzheimer's disease (AD) [1]. AD is an irreversible, progressive neurodegenerative disorder that leads to cognitive decline marked by symptoms such as memory loss, linguistic difficulties, and agnosia, eventually leading to death. Although the etiology of AD remains a topic of ongoing debate, it is widely acknowledged that genetic and environmental factors contribute to its pathogenesis [2, 3]. Patients with AD share common features, notably the progressive accumulation of misfolded proteins, including beta-amyloid (Aβ) [4], tau, or α-synuclein [5, 6], concurrently occurring with neuronal death [7].

Several biomolecules, proposed as therapeutics, are currently approved by the US Food and Drug Administration (FDA) for treating AD, mostly through the regulation of neurotransmitters or enzymes, such as acetylcholinesterase (AChE) inhibitors[8], or by targeted inhibition of N-methyl-D-aspartate (NMDA) receptors [9]. However, these drugs are only capable of providing temporary relief from symptoms of cognitive decline and do not address the underlying root cause of neuronal death [9, 10]. Therefore, immunotherapies have recently been explored as alternative approaches for treating the early stages of AD by removing misfolded proteins. Unlike other therapeutics that stimulate neuronal functions, immunotherapeutic drugs consist of anti-Aβ antibodies that specifically bind to Aβ, preventing aggregation and promoting its removal from the brain [11]. However, it has been repeatedly reported that the risk of adverse effects, such as amyloid-related imaging abnormalities (ARIA), increases with immunotherapy [12–14], and improvements are required for greater brain-targeting efficiency and blood–brain barrier (BBB) penetration. The BBB usually acts as a highly selective physicochemical barrier to the systemic delivery of therapeutics [8, 15]. Consisting of pericytes, neurovascular endothelial cells, and astrocyte endfeet, the BBB protects the brain by maintaining homeostasis through the strict regulation of penetrating solutes that circulate in the blood [16, 17]. Thus, most therapeutic molecules with molecular weights greater than 400 Da cannot cross the BBB, highlighting the need for a functional moiety for efficient drug delivery. Among the systemic delivery systems, nanoparticles, liposomes, and exosomes are highlighted for their biocompatibility and ability to cross the BBB owing to their phospholipid bilayer [18, 19]. Therefore, these platforms have been utilized in recent studies as potential

therapeutics for drug delivery to the brain, especially in AD [20–23].

In this review, we explore the potential applications of lipid-based nanoparticles (LBNs) in the treatment of AD. Given the intricate nature of AD progression and the current uncertainties in treatment pathways, we propose hypotheses to elucidate the potential mechanisms underlying its development. In addition, we investigate the complexities of transporting biomolecules across the BBB, which is a crucial consideration when designing effective nanotherapeutics for the treatment of AD. Finally, we clarify both the definition and recent advancements in utilizing LBNs, either as carriers for drug delivery or as therapeutic agents themselves, enhancing their potential in AD treatment approaches.

Development of therapeutics for Alzheimer's disease

Hypotheses in Alzheimer's disease pathophysiology

Cholinergic hypothesis

The cholinergic hypothesis suggests that an insufficient number of neurotransmitters, particularly acetylcholine (Ach), in the brain causes AD. AD is characterized by the degeneration of cholinergic neurons, leading to decreased levels of Ach in the hippocampus, a cerebral region that participates in processing memory[24]. Ach is synthesized from acetyl-CoA and choline by Ach transferase (ChAT) in presynaptic neurons [25]. After extracellular secretion, Ach binds to muscarinic or nicotine receptors in the postsynaptic neurons, leading to ion influx [26]. Synaptic Ach homeostasis is maintained by AChE which degrades Ach [27]. In AD, low levels of Ach in the brain are caused by reduced ChAT activity or increased AChE [28] (Fig. 1A).

Glutamate excitotoxicity

During AD, glutamate, an excitatory neurotransmitter, accumulates and acts as a neurotoxin that may affect patient behavior, cognition, learning, and memory [29–31]. There are several events by which glutamate induces excitotoxicity via the NMDA receptors (Fig. 1B). First, extracellular sodium and chloride ion concentrations cause swelling of cells and dendrites, thereby inducing depolarization [32]. This is followed by a calcium ion (Ca^{2+}) influx, which leads to gradual neuronal degeneration [33]. NMDA receptors, in their physiological state, allow Ca^{2+} influx for neurotransmission. In AD, NMDA receptor activity is increased, which can prolong the opening of ion channels, leading to excessive Ca^{2+} influx, thereby inducing excitotoxicity and cell death [34].

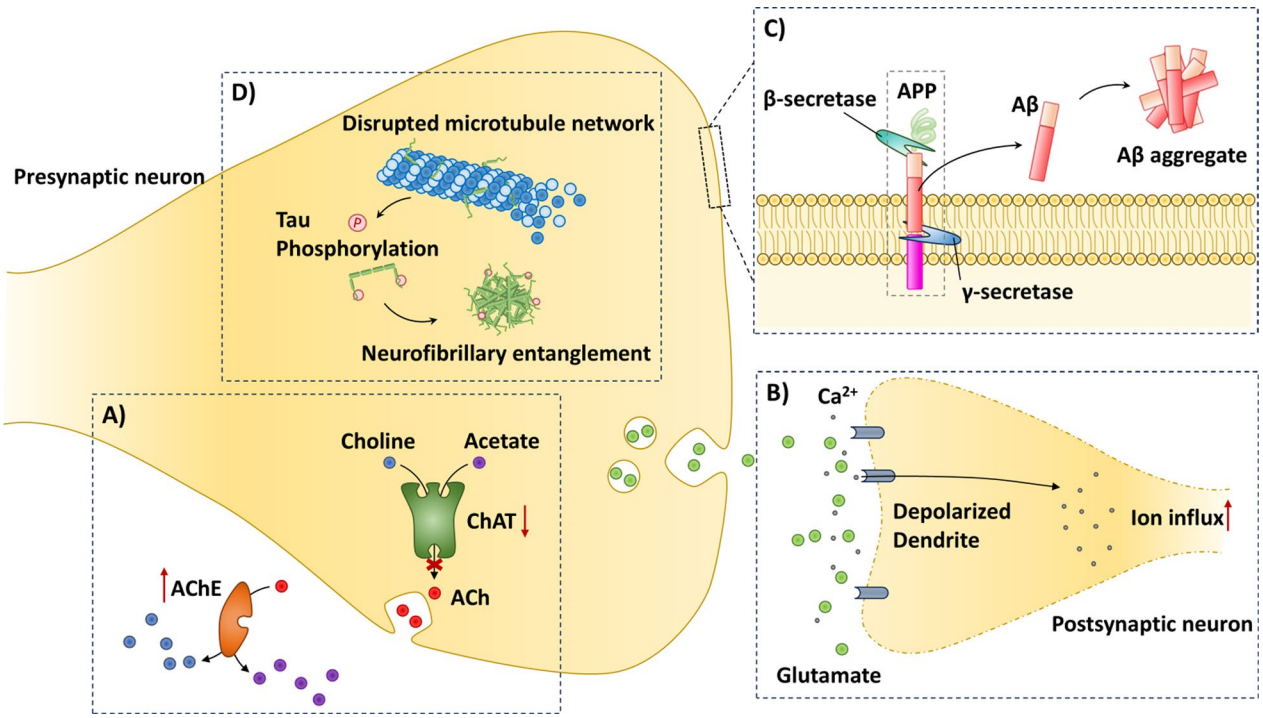


Fig. 1 Graphical illustration of Alzheimer's disease pathological development representing the **A** cholinergic hypothesis, **B** glutamate excitotoxicity, **C** amyloid cascade, and **D** tau protein aggregation. *ChAT* Acetylcholine transferase, *ACh* Acetylcholine, *AChE* Acetylcholinesterase, *Aβ* Beta-amyloid, *APP* Amyloid precursor protein

Amyloid cascade

Amyloid cascade refers to a process that includes production and accumulation of Aβ, consequently leading to AD. Since the formulation of the amyloid cascade hypothesis in 1992, most researchers have considered Aβ accumulation to be the major cause of neurodegeneration [35]. Aβ peptides are produced by sequential cleavage of the amyloid precursor protein (APP) by the α-, β- and γ-secretase enzyme complexes. Under normal conditions, APP is processed by α- and γ-secretases, producing non-aggregating Aβ [36]. However, in neuropathological conditions, the APP is catabolized by β- and γ-secretases forming insoluble Aβ, which is prone to aggregate [37] (Fig. 1C). Such Aβ plaques show neurotoxicity and cause neuronal death via cascades of intracellular neurofibrillary tangle formation, neuronal plasticity decline and synaptic dysfunction, finally leading to loss of cognitive functions [38, 39]. However, several lines of evidence from animal models and clinical studies have challenged the amyloid cascade hypothesis. Evidence has shown that aggregation of Aβ plaques in human brains is independent of cognitive impairment [40] and that, in animal models, dementia occurs prior to plaque deposition [41, 42]. These findings suggest that aggregated Aβ plaques may be a consequence, rather than a cause, of neurotoxicity. In addition, the precise molecular mechanisms underlying the correlation of Aβ accumulation and neurodegeneration remain unknown [9, 43].

Tau protein aggregation

Another pathological biomarker of AD is the tau protein. Tau protein was first recognized in 1991 by Braak et al. [44], but extensive investigations thereof have recently been launched [45, 46]. Tau proteins are soluble and abundant in axons and regulate the stabilization of microtubules. Hyperphosphorylation of tau leads to the loss of microtubule-binding capacity and formation of neurofibrillary tangles [25] (Fig. 1D). This disrupts the neuronal microtubule network and inhibits cell-to-cell communication, eventually leading to cytoskeletal dysfunction and neurodegeneration [25]. Although neurofibrillary entanglements are key pathophysiological states in AD, their isolated inhibition is difficult to achieve. Therefore, treatments targeting tau proteins are often multi-targeted, especially for amyloid plaques [47] (Table 1).

Alzheimer's disease therapeutics and their limitations

Pharmacological drugs in clinical use

Several medicines are used to relieve pain, attenuate symptoms, and improve mobility in patients with neurodegenerative disorders [7]. Cholinesterase inhibitors are FDA-approved drugs used to treat mild to moderate AD [48, 49]. Rivastigmine, galantamine, and donepezil are cholinesterase inhibitors that prevent AChE-mediated hydrolysis of Ach, a neurotransmitter associated with memory [50]. Thus, the synaptic levels of Ach are maintained, thereby postponing AD progression. The therapeutic effects of cholinergic drugs have been previously evaluated [49–51]. Furthermore, the FDA has approved transdermal patches of donepezil and rivastigmine to manage AD dementia [52, 53]. However, adverse effects such as diarrhea, nausea, and vomiting have been reported [54, 55].

FDA-approved memantine is an NMDA antagonist prescribed since 2003 for the treatment of moderate to severe AD [56]. Memantine binds noncompetitively to the NMDA receptor channel, thereby reducing excessive glutamate attachment, which lowers the influx of Ca^{2+} which induces neurotoxicity. Memantine treatment improves memory, cognition, and daily acting performance; however, the precise mechanism and degree of efficacy remain to be determined.

In addition, a fixed-dose combination of donepezil and memantine has been used to treat moderate-to-severe AD. Namzaric® (Allergan Inc., Dublin, Ireland), a capsule of donepezil hydrochloride and memantine hydrochloride extended-release, was approved by the FDA in 2014 for the treatment of moderate to severe AD [57]. It is prescribed to patients who have already taken donepezil and memantine together or donepezil alone [57]. Several

Table 1 Pathological hypotheses and their mechanisms leading to Alzheimer's disease

Pathological hypothesis	Major substance	Mechanism in Alzheimer's disease	References
Cholinergic dysfunction	Acetylcholine	A low level of acetylcholine is maintained due to either increased activity of acetylcholine esterase or decreased activity of acetylcholine transferase	[24, 28]
Glutamate excitotoxicity	Glutamate / Calcium ion	Increased level of glutamate induces overstimulation of NMDA receptors, leading to massive influx of calcium ions into neuronal cells	[32–34]
Amyloid cascade	Beta-amyloid	Abnormal catabolism of amyloid precursor protein by β- and γ-secretases produces insoluble beta amyloids which then aggregate and present toxicity	[37, 38]
Tau protein aggregation	Tau protein	Hyperphosphorylation of tau protein disrupts microtubules and induces neurofibrillary tangles, leading to dysfunction of cells	[25]

meta-analyses have reported that combination therapy is more effective in improving cognition than donepezil or memantine monotherapy [58–60]. However, Namzaric may cause adverse reactions such as headaches, diarrhea, anorexia, vomiting, and ecchymosis [57]. In addition, the efficacy and safety of this drug in children is yet to be determined [57, 60].

Overall, despite the positive effects of cholinesterase inhibitors and NMDA antagonists in improving AD symptoms, these effects are only palliative, thereby demanding disease-modifying strategies to eliminate the source of the disease. Furthermore, the degree of efficiency may differ among individuals during drug administration, which contributes to the limited number of trials. The limited assessment of palliative drugs has led to the exploration of other areas of biomedical science that have revolutionized classical pharmacological approaches.

Anti-amyloid therapy

The main purpose of amyloid hypothesis-related treatments is to disrupt the Aβ accumulation in the parenchymal area and lower the levels of amyloid deposits in the brain of patients with AD. The anti-amyloid treatment targets three pathways of amyloid accumulation: Aβ production, aggregation, and clearance [50].

Inhibition of beta-amyloid production *B-secretase inhibitors*. β-secretase enzyme (BACE1, β-site APP cleaving enzyme 1) participates in the APP cleavage producing insoluble plaques [61]. BACE1 inhibitors block the Aβ production pathway, preventing AD progression. Although verubecestat, lanabecestat, atabecestat, umibecestat, and elenbecestat entered phase III clinical trials, these trials were discontinued because the drugs failed to improve cognitive function, and in some cases demonstrated cognitive worsening [62–66]. A possible reason for this is that BACE1's wide range of substrates, besides APP, may have caused side effects regardless of the success in enzyme-specific inhibition [67–71]. Owing to the high substrate compatibility of BACE1, the development of BACE1 inhibitors is considered a challenging task [72].

γ-secretase inhibitors and modulators. The γ-secretase plays a role in final stage of amyloid production, inducing Aβ40 and Aβ42 generation. Two γ-secretase inhibitors, semagacestat and avagacestat, have entered phase III and II, respectively. However, increased occurrence of skin cancer and other adverse effects in the group that received γ-secretase inhibitors led to the discontinuance of the trials [73, 74]. In addition, off-target effects existed in γ-secretase inhibitor trials [75–77]. As alternatives, the γ-secretase modulators were developed to block APP processing while avoiding the secondary effects through minimalized interference with other γ-secretase substrates like Notch [78, 79]. R-flurbiprofen (tarenflurbil) is one of the γ-secretase modulators without inhibitory effects on other substrate such as cyclooxygenase. Despite promising preclinical data, the drug did not achieve significant Aβ42 lowering and improvement on cognition [80, 81]. Therefore, further refinement is required to develop more effective modulators.

Inhibition of beta-amyloid aggregation *Aβ aggregate disruptors*. After Aβ production, peptides aggregate into oligomers or fibrils and deposit into plaques, finally leading to synaptic dysfunction and neuronal loss [82]. Anti-aggregation agents have emerged as potential candidates for disease-modifying therapies. These agents inhibit plaque aggregation by binding to Aβ peptides, thus preventing subsequent neurotoxicity [83]. Unfortunately, scyllo-inositol, an oral-administrating Aβ aggregation inhibitor, failed to improve efficacy and raised concerns in dose-findings in a phase II trial [84–86]. Recently, a study reported an acceptable tolerability and safety profile for the administration of the lowest dose of scyllo-inositol (250 mg). However, it also proposed that additional research is required to demonstrate efficacy [87]. Similarly, another Aβ aggregation inhibitor, tramiprosate, showed no cognitive improvements in a phase III mild to moderate AD trial, leading to suspension. Later, a reanalysis of the trial was conducted, and clinical efficacy was advocated in the subgroup of patients with the homozygous ApoE4 allele [88]. As a confirmatory study, clinical investigations were conducted using ALZ-801, a prodrug of tramiprosate [89].

Promoting beta-amyloid clearance Another potential anti-amyloid treatment is promoting the clearance of existing amyloid plaques. Aβ-directed immunotherapy has currently been regarded as a prominent approach for AD treatment. Active and passive immunization strategies have been widely investigated.

Active immunization (vaccination). The strategy of active immunotherapy is to stimulate the immune system of the patients to produce antibodies through injection of Aβ fragments. In 1999, active immunization using human Aβ42 presented successful clearance of Aβ in preclinical stages [90]. This led to the development of a first-generation anti-Aβ vaccine, AN-1792, consisting of synthetic full-length Aβ42 peptides with adjuvant [91]. Despite high anticipation, a phase II trial of AN-1792 was discontinued as a result of 6% of the patients developing aseptic meningoencephalitis [91, 92]. It was later found that, from post-mortem neuropathological evaluation, a considerable degree of Aβ clearance by AN-1792 was accomplished in the trial [93].

A second-generation vaccine has been developed using short-length Aβ peptides to avoid nonspecific neurological immune responses. Amilomotide (CAD106), a short Aβ fragment (Aβ_{1-6}) vaccine, has entered phase II/III trials [64]. Along with safety approval, it demonstrated adequate Aβ-specific antibody response in treated patients [94, 95]. Vanutide cridificar (ACC-001), an N-terminal Aβ42 fragment (Aβ_{1-7}) vaccine developed by Janssen, has been tested in phase II trials [96, 97]. Despite favorable safety and tolerability findings, further clinical development of this vaccine has been abandoned owing to the lack of benefits [96, 97]. ABvac40, a C-terminal Aβ40 fragment vaccine developed by Araclon, presented safety and tolerability and achieved a favorable antibody response in patients with mild to moderate AD in phase I trials [98]. Therefore, a phase II trial consisting of a blind phase and a crossover study was conducted to test the efficacy and appearance of side effects [98]. Currently, top-line data of phase II studies have been revealed from the presentation at the ADPD 2022 conference [99]. The results showed the safety and tolerability of repeated ABvac40 administration in patients with mild AD and an acceptable immune response was achieved [99]. Other vaccines such as ACI-24, MER5101, UB-311 and AD02, are currently being investigated for preclinical and clinical development [100–103] (Table 2).

Passive immunization. Passive immunotherapy involves the direct injection of exogenous antibodies. In this approach, less variability exists in efficacy among patients, and a lower risk of adverse effects, mostly T-cell-mediated immune responses, is expected compared with active immunization.

Several phase III trials have been conducted using antibodies to prove potential efficacy. However, they failed to show statistically significant improvements in cognitive or functional impairment[107–109]. Bapineuzumab (AAB-001) and solanezumab (LY2062430), drugs that promote Aβ clearance in patients with mild to moderate AD, brought safety concerns. Increased levels of ARIA at high-dose administration and no advancements in disaggregation of Aβ were observed, respectively [108–111]. Crenezumab (RG7412), designed by Roche to target Aβ monomers and oligomers, fibrils, and plaques in patients with mild to moderate AD, failed to demonstrate any benefit [112–114]. Gantenerumab (RO4909832), which binds to Aβ with high affinity inducing microglia-mediated

Table 2 Types of beta-amyloid-related drugs used for the treatment of Alzheimer's disease

Target	Type	Drug	Clinical trial	Concerns	References
Inhibition of Aβ production	β-secretase inhibitors	Verubecestat	Phase III discontinued	Failed to show cognitive improvement	[62, 66, 104]
		Atabecestat			[63, 66]
		Umibecestat			[64]
		Elenbecestat			[66]
		Lanabecestat			[65, 66]
	γ-secretase inhibitors	Avagacestat	Phase II discontinued	Cognition worsened	[73]
		Semagacestat	Phase III discontinued	Cognition worsened	[74, 76]
	γ-secretase modulators	R-flurbiprofen (tarenflurbil)	Phase III discontinued	Insignificant brain penetration	[76, 80, 81]
Inhibition of Aβ aggregation	Aβ aggregate disruptors	Scyllo-inositol	Phase II discontinued	Failed to show efficacy	[84–87]
		Tramiprosate	Phase III suspended	No cognitive improvement, re-analysis proceeded	[83, 88, 89, 105, 106]
Promotion of Aβ clearance	Active immunization	AN-1792	Phase II discontinued	Patients developed aseptic meningoencephalitis	[91–93]
		Amilomotide (CAD106)	Phase II, III entered	Safety approval required, showed adequate Aβ-specific antibody response	[64, 94, 95]
		Vanutide cridificar (ACC-001)	Phase II abandoned	Adequate safety and tolerability, Lack of benefit	[96, 97]
		ABvac40	Phase II entered	Adequate safety and tolerability, Acceptable immune response in patients with mild AD	[98, 99]

phagocytosis in prodromal patients and those with mild AD, showed statistical insignificance [115–117]. Thus, trials for these drugs were terminated.

Despite this, antibodies are still being investigated in ongoing trials that have reported the anticipated results. Aducanumab (BIIB037) that binds Aβ in aggregated forms has been probably the most promising drug in recent years. Along with convincing phase I data of Aβ aggregation decline and extended analysis of phase III trials [118–120], aducanumab met its primary endpoint of clinical scoring and became the first approved drug against AD [121]. Currently, a phase IV confirmatory trial, ENVISION (NCT05310071), has been requested by the Food and Drug Administration to explore its clinical efficacy and safety profile until 2026 [122]. Lecanemab (BAN2401) that selectively binds to soluble aggregated Aβ plaques is another FDA approved antibody. Significant clearance of amyloid plaques was observed in phase I, II, and III trials [123–125]. However, it has also been noted that adverse effects are associated, thereby warranting longer trials to determine its safety [125]. Donanemab (LY3002813) which uniquely binds to deposited amyloid plaques by recognition of the pyroglutamate form of Aβ showed moderate tolerability and safety in a phase I trial [126] and significant aggregated amyloid reduction and neurofibrillary tangles in a phase II trial [127]. Among multiple phase III trials for effectiveness assessment, TRAILBLAZER-ALZ 2 presented the topline results for donanemab with statistically significant clinical benefits [128]. However, continuous observation is required until complete results are obtained (Table 3).

Anti-tau therapy

As therapeutic treatments associated with Aβ have not been as promising as expected, the focus has shifted to tau-targeting trials [131]. Initially, kinase inhibitors, tau aggregation inhibitors, and microtubule stabilizers were investigated as potential anti-tau agents. However, most of these strategies are ineffective because of their toxicity and/or lack of efficacy. Recently, anti-tau clinical research has focused on immunotherapeutic strategies.

Eight active clinical trials (phases I and II) and several preclinical studies on tau immunotherapies are currently underway. A tau aggregation inhibitor (TRx0237) did not show therapeutic effects in phase III studies [132]. Intravenous immunoglobulin, a passive tau immunotherapy, did not meet the primary objectives in patients with mild to severe AD in phase III trials [133]. A tau vaccine, AADvac1, showed moderate immunological response and safety in phase I. Further research is underway to prove its therapeutic efficacy [134, 135].

According to leading experts, investigations on tau-targeted therapeutics are still insufficient. Clinical trials may face challenges like those associated with amyloid-targeted drugs. However, if effective, these trials could lead to the development of alternatives, such as multitarget combination therapies, for the treatment of the early stages of AD.

The blood–brain barrier and brain targeting methods

The BBB is a sophisticated structure composed of multiple cells, including endothelial cells, pericytes, astrocytes, and microglia. It acts as a barricade, restricting and controlling the entry of proteins and ions into the brain while releasing pro-inflammatory and neurotoxic agents into the blood. The tight junctions of endothelial cells form a physical barrier that restricts the paracellular transport of chemicals [136]. Therefore, numerous enzymes and transporters specializing in reducing BBB permeability

Table 3 Types of passive immunization for Alzheimer's disease treatment

Drug	Type	Clinical trial	Concerns	References
Bapineuzumab (AAB-001)	Humanized monoclonal antibody	Phase III discontinued	Insignificant improvement of cognition and functional impairment, safety concerns	[108, 109, 129]
Solanezumab (LY2062430)	Humanized monoclonal antibody	Phase III discontinued	No advancement in disaggregation of Aβ	[110, 111, 129]
Crenezumab (RG7412)	Humanized IgG4 antibody	Phase III discontinued	Failed to show cognitive or functional improvement	[112–114]
Gantenerumab (RO4909832)	Humanized IgG1 antibody	Phase III discontinued	Statistical insignificance	[115–117]
Aducanumab (BIIB037)	Human IgG1 monoclonal antibody	Phase IV entered	FDA approved AD treatment, safety approval required	[118–122]
Lecanemab (BAN2401)	Humanized IgG1 antibody	Phase III entered	FDA approved AD treatment, showed a 27% reduction in cognitive decline	[123–125, 130]
Donanemab (LY3002813)	Humanized IgG1 monoclonal antibody	Phase III entered	Significant aggregated amyloid reduction	[126–128]

are required. Adsorptive-mediated transcytosis (AMT), receptor-mediated transcytosis (RMT), and carrier-mediated transcytosis (CMT) are the major mechanisms involved in transcellular movement.

Adsorptive-mediated transcytosis (AMT)

AMT is a non-specific transcytosis transport mechanism involving electrostatic interactions between positively or amphiphilically charged chemicals and negatively charged membranes of the BBB [137]. When cationic/amphiphilic molecules come in contact with the negatively charged apical membrane, an electrical complex is formed. Subsequently, endosomes are formed and move to the basolateral membrane, where molecules are released into the brain. After crossing the cell membrane, the clathrin-coated pits and molecules are transcytosed as electrical complexes [138]. Although numerous clathrin-coated pits are present in the endothelial layers, they can also be transcytosed by uptake through caveolae. Caveolae transcytosis initially has a different mechanism than that of clathrin, but the internalized complexes converge into endosomes or lysosomes[139]. Although several studies have developed strategies to allow particles to penetrate the BBB using AMT, there have been no significant results, owing to the non-specific targeting of AMT. AMT is simply based on electrostatic interactions, meaning that a positively charged molecule can bind to any type of negatively charged membrane and permeate off-target cells.

Carrier-mediated transcytosis (CMT)

CMT, also known as transporter-mediated transcytosis, allows entry into the brain via approximately 20 transporters expressed in brain endothelial cells [140, 141]. Essential nutrients such as glucose, peptides, and nucleotides are transported via the CMT mechanism. During CMT, the transporter protein first recognizes substrates such as sugars or amino acids. After substrate binding, the transporter-substrate complex changes and is then transported to the lumen according to the difference in substrate concentration [142–144]. Transporter-targeting peptide conjugation to a substrate can be used to achieve more efficient drug delivery. The well-known transporter targets in the BBB are glucose transporter 1 (GLUT1), glutathione transporter (GSH) and amino acid transporters. GLUT1 is a glucose-mediated transporter, while GSH and amino acid transporters are peptide-mediated transporter proteins. Interestingly, a study has reported that an L-type amino acid transporter 1 (LAT1) is overexpressed in the BBB and in brain tumors. This feature allows for the effective targeting of brain tumors while easily penetrating the BBB. Li et al. conjugated glutamate-d-α-tocopherol-polyethylene glycol 1000 succinate to docetaxel-loaded nanoparticles to target LAT1 overexpressed in the BBB and glioma cells. The results showed a higher uptake of docetaxel in glioma cells than in unmodified nanoparticles [145]. This suggests that the transport of molecules across the BBB becomes easier and more efficient, potentially improving drug delivery and disease treatment within the brain.

Receptor-mediated transcytosis (RMT)

RMT is considered the most prominent transcellular movement method and is widely used to achieve the intracerebral delivery of nanoparticles characterized by high specificity, selectivity, and affinity[146]. Most endogenous macromolecules require RMT to enter the brain parenchyma. The RMT is distinguished from the AMT based on its receptor-specific binding. The detailed mechanism of the RMT is as follows: Ligands in the lumen bind to specific receptors expressed on brain endothelial cells and form complexes [144]. After complex formation, the receptor protein is modified [147]. The modified ligand-receptor complex then allows endocytosis in the clathrin-coated pits. During transcellular trafficking, clathrin leaves and fuses with endosomes. At this stage, the receptor is cleaved from its ligands and recycled. Subsequently, the endosome is released from the abluminal side via exocytosis, allowing ligand transport to the target [143]. RMT-based transport is generally energy-dependent and has relatively high efficiency [148]. To leverage this strategy, selective surface modification of the nanoparticles with specific ligands can be performed to facilitate the transport of loaded therapeutics to intracerebral targets. Theoretically, to achieve optimal delivery performance of treatments for brain diseases, target receptors need to be highly expressed in brain endothelial cells, while minimizing the risk of safety due to off-target effects. Recent advances in nanotechnology can provide extended resources for designing enhanced nanoparticle-based RMT.

Lipid-based nanoparticles and their therapeutic applications in Alzheimer's disease treatment

Among the variety of nanoparticles, LBNs that nano delivery systems composed of lipids, it can transport genetic material or medications into the body. LBNs have more advantages of stability, bioavailability, and are pharmacokinetically acceptable. LBNs have also been used in other industries, including agriculture, nutrition, cosmetics, medical imaging, and other cutting-edge fields like nanoreactors [149]. LBNs are nano-delivery systems made of lipids that can carry drugs or genetic material into the body. FDA has authorized LBNs for the delivery of medications and vaccines. LBNs, which are currently in the news as essential parts of the COVID-19 mRNA

vaccines, are crucial for efficiently delivering and preserving mRNA to cells [150]. Nanotechnology is transforming medicine through nanoscale nanoparticles, enhancing drug efficacy while reducing neurodegenerative disease toxicity. These particles safely navigate through biological barriers, improve permeability, and precisely target brain sites, thereby evading phagocytic processes [151]. LBNs, such as exosomes, liposomes, SLNs, and NLCs, have attracted attention in the field of CNS drug delivery. Figure 2 is an illustration of 4 types of LBNs to be introduced in our review paper. Given the enhanced BBB targeting and penetration for AD treatment, LBNs enable precise and sustained drug delivery to the lesion site, along with advantages such as high biocompatibility, ease of synthesis, sustained release of cargo, and enhanced solubility of the hydrophobic drug [152].

Exosomes

Exosomes, also known as small extracellular vesicles, are naturally secreted nanoparticles originating from various cell types within the body that exhibit a size range of 30–150 nm [153, 154]. Different other types of extracellular vesicles, such as microvesicles and apoptotic bodies, exosomes are produced from the inward budding of multivesicles and the formation of internal vesicles within the endosomal system. Exosomes are known to be secreted from every types of cells, being detected from everywhere in our body, including biological fluids, including plasma, serum, urine, saliva, and cerebrospinal fluid [155, 156], serving as a tool for drug delivery system or diagnostic biomarker in medical field [157]. In recent years, exosomes from plants as well as the human body have been utilized to expand the available sources [158]. The structure consists of an outer lipid bilayer membrane with transmembrane proteins, which encapsulates enzymes, growth factors, nucleic acids, lipids, and transcription factors, all inherited from their parent cell [159]. Due to their cell-derived outer membrane, exosomes possess a unique capability to cross barrier tissue via transcytosis, especially the BBB, compared to other biomolecules [160]. Another advantage of exosomal therapy is their capacity to load diverse therapeutic cargos, including small molecules, proteins, and nucleic acids, regardless of their hydrophilicity rendering them as a next-generation vehicles for drug delivery for AD treatment. Nevertheless, productivity and reproducibility have been a critical hurdle for clinical translation of exosomal therapy. Therefore, various exosome isolation methods have attracted increasing attention, including ultracentrifugation, precipitation, immunoaffinity separation and filtration (Fig. 3). Table 4 describes standard exosome isolation methods with their principle and productivity.

Therapeutic applications of exosomes in Alzheimer's disease

Exosomes play a therapeutic role depending on the function of their parent cells. Various cell sources, such as stem cells, immune cells, or glial cells, have been introduced to secrete exosomes that alleviate AD symptoms, by reducing inflammation or Aβ accumulation. In addition, exosomes can be engineered by loading additional therapeutic molecules into the exosome or conjugating brain-targeting molecules onto the membrane to enhance their therapeutic efficacy. Exosomes can be loaded with specific molecules, such as siRNA or enzymes, tailored to target the underlying pathology of AD, such as the accumulation of Aβ plaques. In this section, we introduce

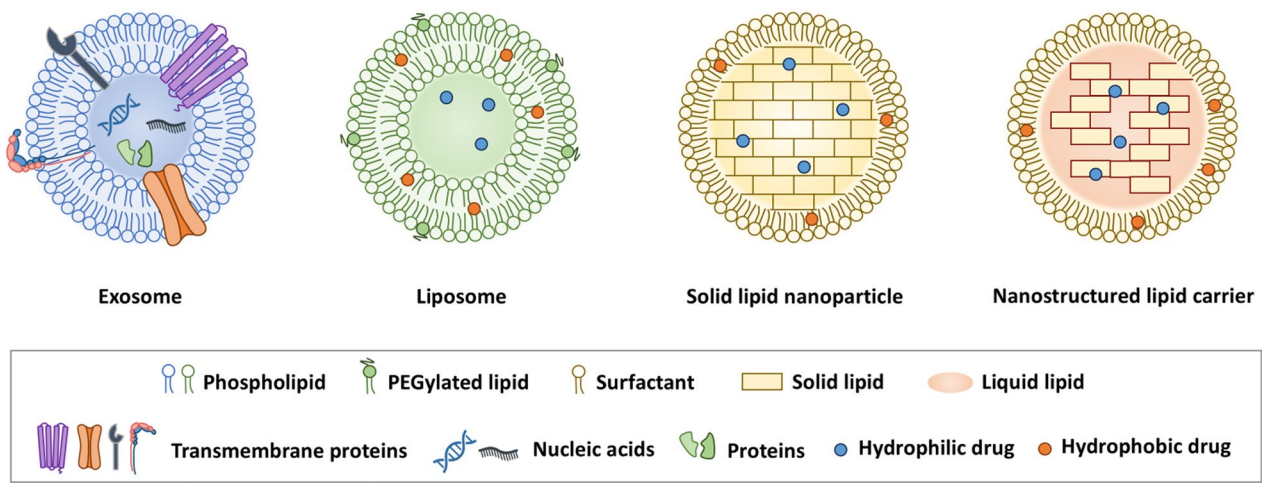


Fig. 2 Illustration of four types of lipid-based nanoparticles; Exosome, liposome, solid lipid nanoparticle, and nanostructured lipid carrier

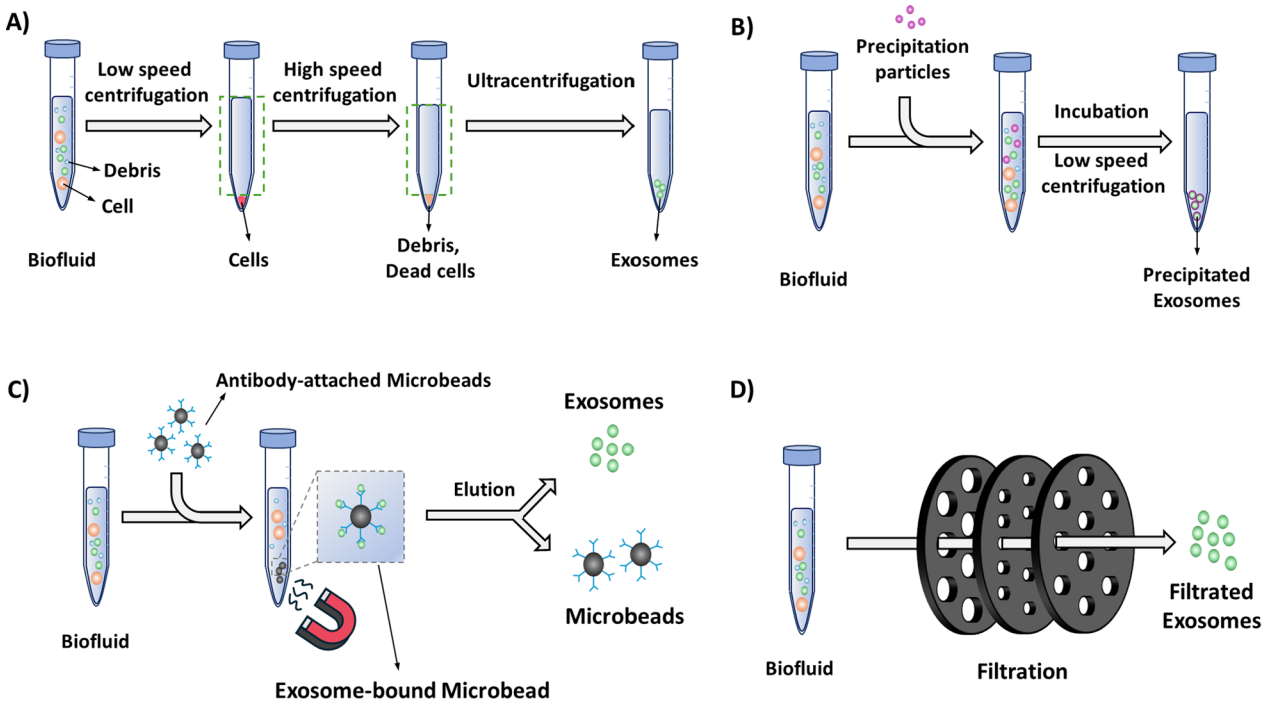


Fig. 3 Illustration showing various methods for exosome isolation. **A** Centrifugation, **B** precipitation, **C** immunoaffinity, and **D** filtration

Table 4 Various isolation methods of exosomes

Method	Principle	Yield/time/purity	Advantage	Disadvantage	References
Ultracentrifugation	Size-based separation	Low/ + /+ +	High purity, handles large volumes and multiple samples, gold standard	Time-consuming, expensive, risk of exosome damage	[161]
Precipitation	The purification of exosomes from biofluids	High/ + /+ +	Convenient, no specialized equipment needed	Non-specific, co-precipitation of contaminants, long run-time, requires pre- and post-cleanups Requires a long run-time and pre- and post-cleanups	[162]
Immunoaffinity	Affinity purification	Low / + +/+ ++	Highly purified, identifies subtypes	Expensive, low capacity, requires specific tags, limited to cell-free samples	[163]
Filtration	Ultrafiltration membranes	Medium/ + ++/+ ++	Concentrates exosomes, separates large particles	Exosome loss due to trapping, potential damage to vesicles	[164]

representative exosome-based AD therapeutics among the numerous articles reported so far (Table 5).

Mesenchymal stem cells (MSCs), one of the most widely studied cells in regenerative medicine, exhibit anti-inflammatory, anti-apoptosis, tissue-protective, and angiogenic effects to treat various diseases. Recent data suggest that MSCs may benefit AD through paracrine effects, but the limitations of cell therapies are repeatedly reported for low its post-transplantation viability and tissue compatibility [165, 166]. Administration of MSC-derived exosomes (MSC-exo) instead of live MSCs have demonstrated therapeutic effect by carrying a variety of regenerative proteins and nucleic acids inherited from MSCs.

To enhance the therapeutic efficacy of MSC-exo, miR-223 was additionally packed into MSC-exo to target the PI3K/Akt signaling pathway, which better reduced apoptosis of AD neurons and promoted neuronal repair in $A\beta_{1-40}$-induced AD model [167]. In another study, rapamycin, which are an autophagy activator, were loaded into MSC-exo and administered to $AlCl_3$-induced AD mice model that progressive memory and learning

Table 5 Alzheimer's disease treatment with various exosomes

Cell source	Engineering strategy of exosomes	Result	Limitation	References
Mesenchymal stem cells	Loading with miR-223 targeting the PI3K/Akt signaling pathway	- Reducing apoptosis - Promoting neuronal recovery	In vivo studies are needed to confirm the protective role of miR-223 in AD models	[167]
	Loading an autophagy activator that rapamycin	- Improved memory - Reduced Aβ and tau pathology - Enhanced neurogenesis - Modulated autophagy - Regulated inflammation in AD rats	Relies on animal models, and further studies are needed to confirm MSC-exosomes safety and efficacy in human patients with AD	[168]
	Conjugated with a brain-targeting rabies viral glycoprotein (RVG) peptide using a DOPE-NHS linker to enhance delivery to the central nervous system	- Improved targeting of the cortex and hippocampus - Reduced plaque deposition, Aβ levels, astrocyte activation, and pro-inflammatory cytokines - Enhancing anti-inflammatory cytokines and cognitive function	Relies on animal models, so further research is necessary to confirm the safety, efficacy, and brain-targeting efficiency of RVG-conjugated MSC-exosomes in human clinical trials	[169]
Dendritic cells	Expressed Lamp2b fused with RVG peptide for neuron-specific targeting and loaded exosomes with siRNA	- Develop a nonimmunogenic - Tissue-specific siRNA delivery	Need for further improvements in exosome production efficiency and development of targeting for other tissues	[171]
Neuronal stem cells (NSCs)	–	- Reduced Aβ and p-tau levels - Suppressed kinase activity - Decreased inflammatory markers - Enhanced SH-SY5Y cell viability	In vivo studies are needed to validate the therapeutic potential of NSC-exosomes for AD	[172]

deficits via intraperitoneal injection significant spatial memory impairment. Due to enhanced neurogenesis, autophagy modulation, inflammatory regulation, it resulted decreased Aβ and tau pathology, leading to improved memory and cognitive function [168] (Fig. 7A).

To enhance delivery to the CNS, MSC-exo was conjugated to a brain-targeting peptide, rabies virus glycoprotein (RVG), via a 1,2-dioleoyl-3-trimethylammonium-propane-N-hydroxysuccinimide linker. When administered intravenously to APP/PS1 mice, a transgenic mouse model with elevated Aβ-amyloid production, the brain-targeting efficiency of RVG-conjugated MSC-exo was greater compared to that of natural MSC-exo with a higher distribution in the cortex and hippocampus. This resulted in the down-regulation of inflammation, Aβ accumulation, and astrocyte activation, while improving cognitive function [169].

Although siRNA delivery to down-regulate the toxic Aβ formation in AD neurons has been identified as a promising strategy for AD therapy, immunogenicity of the siRNA and the delivery vehicle has been frequently reported, particularly when repeatedly injected [170]. To address such limitations, exosomes derived from autologous dendritic cells were employed as a siRNA delivery vehicle to mitigate immunogenicity and treat AD. The exogenous siRNA was electroporated into the exosomes to avoid nonspecific knockdown in the liver and other organs. Moreover, the RVG peptide was fused with the surface Lamp2b protein to improve the protein's capacity to deliver siRNA specifically and safely after systemic administration. Intravenous administration of GAPDH siRNA-loaded RVG-conjugated exosomes specifically targeted neurons, microglia, and oligodendrocytes in the brain, leading to targeted gene knockdown in wild-type mice [171]. Neural stem cell (NSC) is another stem cell source to treat brain disorder, which has a similar therapeutic efficacy with that of MSC but has a potential in differentiating into neuronal or glial cells. A study has demonstrated that NSC-derived exosomes also have a therapeutic potential in neuroprotection, by lowering tau hyperphosphorylation (p-tau) and Aβ level, inhibiting kinase activity, reducing inflammatory markers, and enhancing neuroblast viability from in vitro studies [172].

Limitations of exosome therapy in Alzheimer's disease treatment

Despite the encouraging prospects of exosome therapies in AD treatment, with the potential to alleviate neuroinflammation and reduce Aβ accumulation, successful clinical translation still faces significant limitations. The primary challenge lies in the low productivity of exosomes, as efficient large-scale production methods remain elusive. The yield of exosomes harvested from a million human cells is typically less than 10 μg on average, as quantified by protein analysis, which corresponds to a particle count of between hundred million and one billion, as determined by nanoparticle tracking analysis. The current clinical studies using exosome in other diseases require 100 to 2000 μg per injection, which presents a significant challenge in terms of time and cost-effectiveness. Moreover, the methods used to isolate exosomes and engineer them should be standardized. Recently, the development of advanced exosome isolation platforms using microfluidics, magnetics, electrostatics, as well as the synthesis of exosome-mimetic artificial nanovesicles by fragmentation of living cells using physical methods have emerged as promising alternatives to the conventional methods described in Table 3, with the potential to increase productivity by a factor of ten to a hundred folds.

The second challenge in exosome therapy is heterogeneity, which necessitates precise standardization and quality control for clinical translation. Given that exosomes are released from living cells, their production must be precisely regulated as their characteristics are highly sensitive to the cell culture environment. In addition, the research in exosome therapy as well as the regulatory guidelines are still in its early stages, the methods for quality control should be more precisely established including other things than size measurement, detection of tetraspanin family of proteins, or toxicity.

Finally, the long-term in vivo stability, safety, and efficacy of exosome-based treatments remain uncertain due to the absence of a comprehensive longitudinal study. In the context of AD therapy, further research is imperative to elucidate the pharmacokinetic and pharmacodynamic characteristics of brain-delivered exosomes, to comprehend their therapeutic mechanisms, and to prevent unforeseen adverse effects.

Liposomes

Liposomes are artificially synthesized spherical vesicles consisting of a phospholipid bilayer, with a size ranging from 50 to 100 nm [173]. These versatile lipid-based structures have garnered significant attention as promising drug carriers owing to their capacity to simultaneously encapsulate both hydrophilic and hydrophobic payloads. The distinctive architecture of liposomes allows efficient drug loading, thereby enhancing drug stability and prolonging circulation time, rendering them a viable tool for drug delivery to the brain. Surface functionalization of liposomes with various ligands has emerged as a potent strategy to significantly augment drug solubility within the brain, ultimately elevating drug bioavailability within the cerebral regions. Of the liposome synthesis methods is the favored is the thin film hydration process.

Add lipids to organic solvents, formation of a thin lipid film upon evaporation of organic solvents. Adding an aqueous solution to the film, can multilamellar liposome formation due to agitation and can form unilamellar liposomes [174] (Fig. 4). In this section, we discuss liposomes as efficacious drug carriers for brain-targeted delivery, expound upon strategies for the surface modification of liposomes to optimize drug delivery to the brain and showcase real-world examples of tailored liposomes that enhance therapeutic outcomes in the context of AD.

Therapeutic applications of liposomes in Alzheimer's disease

Several studies indicated the potential benefits of mitigating neuroinflammation in AD using ligands capable of traversing the BBB [175]. Commonly used as a ligand for the drug-targeting BBB, transferrin (Tf) can promote drug accumulation in the brain effectively. Tf enhances drug accumulation in the brain by binding to a particular transferrin receptor (TfR) on the BBB and enabling it to cross the BBB through receptor-mediated intracellular trafficking [176]. Also, delivery systems with lactoferrin (Lf) attached are more effective because diseases like Parkinson's disease and AD cause an increase in lactoferrin receptor (LfR) expression [177]. In this section, based on studies involving diverse drugs and brain-modifying ligands, liposomes have emerged as a promising drug delivery system for AD treatment.

Numerous studies have investigated various liposomal modifications for AD therapy. Among these, the development of transferrin-modified liposomes has several important advantages. Tf-modified liposomes significantly increase brain targeting, facilitating drug delivery across the BBB and allowing higher drug concentrations in the brain. and binding to TfR it can be more bioavailability. Using modifications can target delivery significantly enhances therapeutic efficacy by improving bioavailability [178] and stability [179]. Tf-modified exosome was loaded with Pep63, a small peptide with neuroprotective effects on synaptic plasticity and memory, to reduce Aβ load in the hippocampus and improve cognitive deficits for treat AD [176] (Fig. 7B). In addition, Osthole a coumarin compound, that potentiates hippocampal neurons and neural stem cells against Aβ oligomer-induced neurotoxicity to mice, was studied as a potential drug for the treatment of AD. Treatment of AD with this Tf-liposome increased delivery to brain targets and facilitated drug delivery across the BBB. It also maintained high drug concentrations and improved stability, solubility, and bioavailability. These liposomes utilize transferrin receptors on the BBB for targeted delivery, thereby enhancing drug permeability and efficacy.

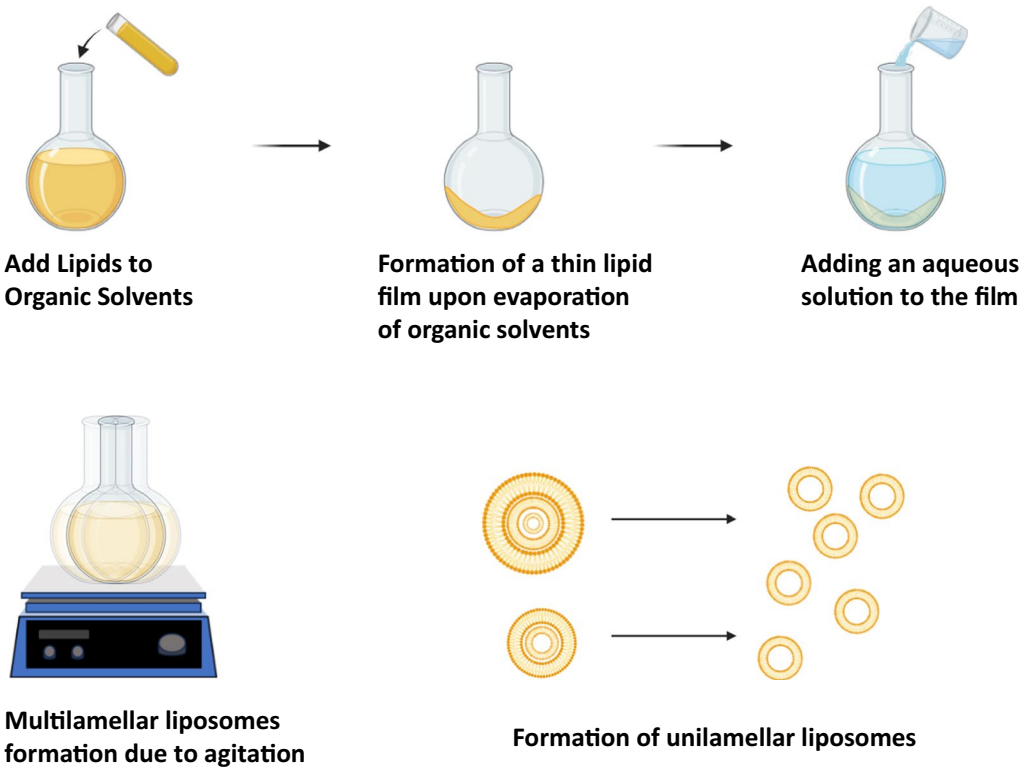


Fig. 4 Illustration of the thin film hydration process for liposomes

Furthermore, the incorporation of hydrophilic components onto liposomes prolongs the circulation time of drugs in the bloodstream, further increasing their therapeutic potential [180].

Lactoferrin (Lf), a positively charged glycoprotein belonging to the transferrin family, exhibits high affinity for brain cells, particularly endothelial cells of the BBB. This property has prompted research into its potential role in brain-targeted drug delivery and AD therapy. Lf-exosomes is the use of nerve growth factor (NGF) as a drug to protect basal forebrain cholinergic neurons in rats from degeneration and improve neuronal survival, in addition to removing Aβ [181]. Primarily, Lf-modified liposomes leverage the natural affinity of Lf for brain endothelial cells to enhance drug delivery across the BBB and ensure higher drug concentrations within the brain [177]. This liposome also holds the potential for treating neurodegenerative disorders such as AD, as indicated by increased Lf receptor expression in pathological conditions, suggesting a targeted therapeutic approach.

In addition to the conventional method for inducing the BBB penetration of liposomes, recent findings that can enhance the BBB penetration compared to previous methods have been reported. In 2024, the Cyclic D, L-α-peptide (CP-2) that selectively targets the Aβ oligomers, has been reported to improve the therapeutic effect against AD and have great permeability towards BBB. CP-2-liposome has been indicated to disrupt Aβ aggregation and also known to mitigate Aβ-mediated toxicity in human neuroblastoma cells. Indeed, the CP-2-liposome has been reported to enhance the behavioral and cognitive abilities in transgenic models of AD in Caenorhabditis elegans [182]. In the other case, co-loading icariin (ICA) and tanshinone IIA (TSIIA) drugs have effects on neuroprotection. Angiopep-2 is a low-density lipoprotein receptor-related protein-1 (LRP1)'s specific ligand that highly binds to LRP1. Since the angiopep-2-ICA/TSIIA liposome targets the AD brain, it can be a new nano drug delivery system that can penetrate the BBB through endocytosis. Angiopep-2-ICA/TSIIA liposomes reduced the apoptosis and regulated the neuroinflammation and oxidative stress in APP/PS1 mice, which ked the enhancement in cognitive function [183]**.** In 2022, chitosan-coated nanoliposomes have been reported to improve stability and bioavailability in drug delivery systems. Chitosan coating polymer modification has been effective in improving the stability of liposomes. Liposomal surfaces are used to resist the oxidation and hydrolysis of lipids so that liposomes can link polymers via electrostatic interactions. For this reason, chitosan coating forms a protective layer to improve liposome stability [178]. Liposome modification therefore has the potential to be extended to the treatment of AD.

Additionally, through sequence-specific targeting of disease-related genes, microRNAs have been reported to regulate the expression of multiple proteins simultaneously. Liposome-released microRNAs-195 has reduced the expression of APP and BACE1, which reduces the production of Aβ and the hyperphosphorylation of tau protein [184]. The other case of gene therapy, brain-derived neurotrophic factor, is an important neurotransmitter that is ubiquitous in the body and helps with synapse formation, neuronal plasticity, memory formation, and learning. Liposomes are delivering the brain-derived neurotrophic factor gene to the APP/PS1 mouse model to promote AD pathology [185] (Table 6). By delivering decreased brain-derived neurotrophic factor, we may be able to improve the treatment of AD.

Limitations of liposome in Alzheimer's disease treatment

However, it is essential to note that while modified liposomes show promise in AD therapy, they are recognized as foreign substances within the body since they are not naturally produced. Additionally, they may exhibit variability, instability, and limited lifespans. Moreover, the production costs associated with liposomes are relatively high, and lipids may occasionally undergo reactions such as oxidation and hydrolysis during drug delivery, indicating the need for further research on this drug delivery system. Liposomes face challenges related to precise target localization, necessitating surface modifications to enhance their stability. Although, formulation and optimization of Tf-modified liposomes and Lf-modified liposomes is a complex and costly process, posing challenges for large-scale production and commercialization. In addition, the potential risk of immunogenic reactions to liposomal formulations and transferrin modifications may limit their clinical application. Furthermore, while preclinical results are promising, large-scale clinical trials are needed to confirm the efficacy and safety of liposomes in humans. Achieving consistent targeted delivery to specific brain regions remains a challenge that could impact overall therapeutic outcomes.

Solid lipid nanoparticles (SLNs)

SLNs are promising drug delivery systems characterized by a hydrophobic lipid core enveloped by phospholipids [186]. Similar to liposomes, SLNs exhibit the ability to encapsulate both hydrophobic and hydrophilic drugs, thus facilitating precise drug release and targeted delivery to specific cells or tissues. SLNs offer numerous advantages, including diminished drug toxicity, sustained drug release kinetics, and prolonged stability. Additionally, precise tissue targeting can be achieved by altering the lipid structure. SLN synthesis methods include high-temperature homogenization, which typically requires

Table 6 Various liposomal modifications in the treatment of Alzheimer's disease

Surface modifications	Drug	Advantage	Disadvantage	References
Transferrin (Tf)- modified liposomes	Osthole	- Increase delivery to brain targets - Facilitate drug delivery across the BBB -Maintain high drug concentrations - Improved stability, solubility, and bioavailability - Prolonged circulation time	- Complex and costly formulation and optimization processes - Difficulty in large-scale production and commercialization - Risk of immune reactions	[180]
	Pep63	- Simultaneous Targeting of Aβ Oligomers and Fibrils - Reduces Aβ load in the hippocampus - Improves cognitive deficits - Induces chemotaxis of microglia - Disrupts Aβ aggregation and degradation - Inhibits binding between EphB2 and Aβ oligomers - Restores NMDA receptor trafficking - No side effects	- Complex and costly formulation and optimization process - Requires large clinical trials - Difficult to consistently target to specific brain regions	[176]
Cyclic D, L-α-peptide	–	- Biocompatible - Effective BBB penetration - Disrupt Aβ aggregation - Improving cognitive and behavioral functions - Reducing toxic Aβ oligomer levels	- Need to do clinical studies before it can be used for actual AD treatment	[182]
Angiopep-2	Icariin and tanshinone IIA	- High binding efficiency - Effective BBB penetration - Inhibiting neuroinflammation - Oxidative stress - Reducing apoptosis - Protecting neurons - Improving cognitive function	- Study of cellular transport processes and human efficacy needed	[183]
Chitosan	Betanin	- Improve stability - Improve bioavailability - Efficient controlled release of betanin	- Need to in vivo trails - Need to process scale-up	[178]
P-aminophenyl-alpha-d-mannopyranoside and cationic cell-penetrating peptide	miR-195	- Higher efficiency of cross the BBB - Minimize toxicity -Increased biodegradability	- Need to do clinical studies	[184]
Glut-1 targeting ligand mannose and cell-penetrating peptide	pApoE2	- Improve transport gene - Increased levels of ApoE - Biocompatible	- Need to therapeutic efficacy of the optimized formulation in in vivo model	[185]

high temperatures that exceed the melting point of the lipids for lipid emulsion formation. There are also low-temperature homogenization methods that allow for a wider range of SLN sizes than high-temperature homogenization [187] (Fig. 5). However, SLNs have certain limitations, such as a notably low collection efficiency during the crystallization process, which restricts the collected material to the solid state. In this section, we describe recent studies that have addressed these limitations and demonstrated the efficacy of surface modifications in potential anti-AD applications.

Therapeutic applications of solid lipid nanoparticles in Alzheimer's disease

Chitosan, recognized for its mucoadhesive properties, biocompatibility, and ability to transiently open tight junctions in nasal epithelial cells, is an ideal polymer for the treatment of AD [188]. Intranasal administration of chitosan-coated SLNs circumvents the BBB, enabling direct drug delivery to the brain via the olfactory and transencephalic routes. This expedites the drug action and augments the efficacy of AD treatment [189]. Previous studies have shown that chitosan-coated SNL not only enhances brain accessibility but also improves oral bioavailability by bypassing the preferential hepatic transit effect and prolonging body residence time. FA has tremendous potential to alleviate various neurodegenerative diseases. In vivo pharmacodynamic behavioral studies in rats using FA-chitosan-SNL showed that cognition was significantly improved when coated optimized SLN and uncoated SLN pure drug were administered [190]. In addition, some drugs cannot cross the BBB, such as dopamine. Dopamine cannot reach the central nervous system through the bloodstream, and less than 100% of

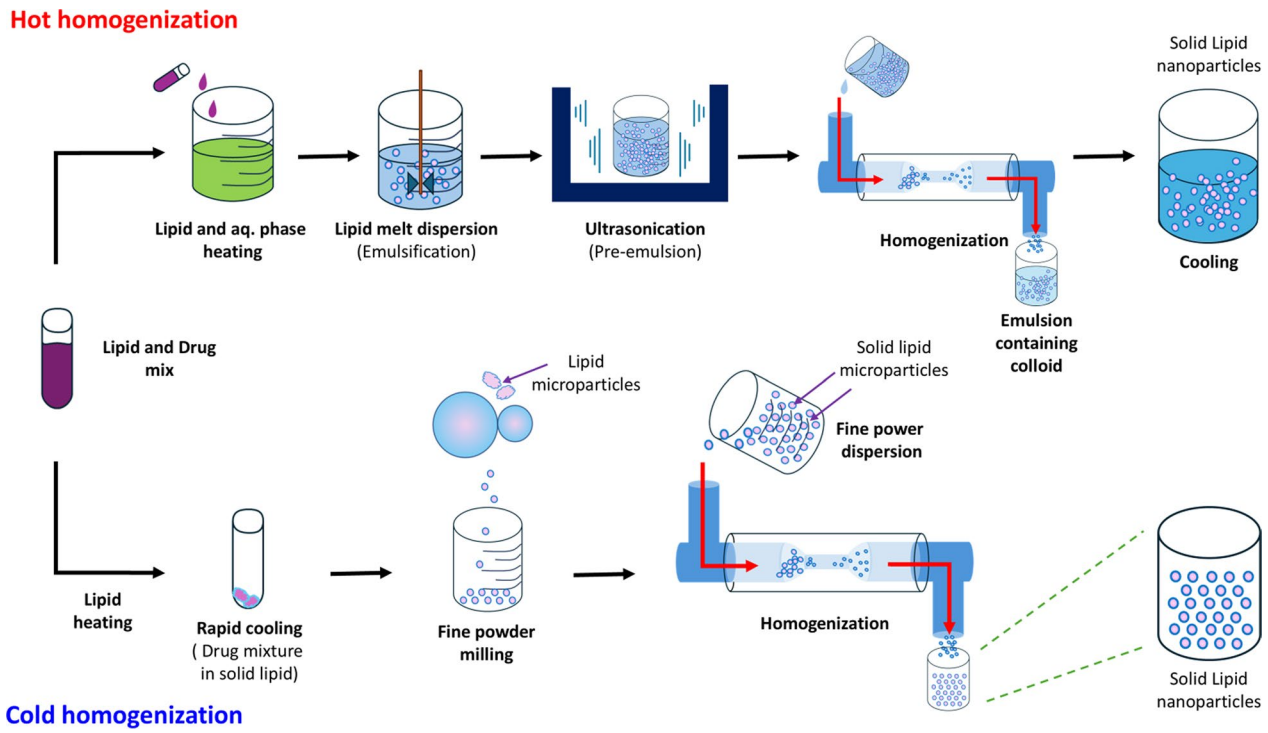


Fig. 5 Solid lipid nanoparticles synthesis procedure using hot homogenization and cold homogenization

the administered dose reaches the central nervous system because only the precursor is metabolized before crossing the BBB. However, using coated chitosan-SNLs can deliver dopamine that cannot penetrate BBB. The release rate and release range were found to be relatively low after chitosan coating, indicating that chitosan-coated SLN has relatively good, sustained release properties. The BBB model showed a significant increase in permeability over time, confirming the absorption study results. This indicates that SNL has good potential for especially penetrating BBB [191]. Hematopoietic factor erythropoietin (EPO) is one of the most promising neuroprotective treatments for neurodegenerative diseases like AD. Using the Morris water maze test in vivo evaluations, it was shown that the rats with cognitive deficits treated with EPO-SLN had a significantly better memory than the rats treated with native drugs. Furthermore, compared to free EPO, EPO-SLN was more effective in reducing Aβ plaque deposition, oxidative stress, and the ADP/ATP ratio in the hippocampal regions [192] (Table 7).

Limitations of solid lipid nanoparticles in Alzheimer's disease treatment

Drug release kinetics from SLNs may be influenced by the amount of drug adsorbed on the nanoparticle surface, potentially affecting therapeutic efficacy. Further research is required to optimize these formulations and address their limitations for effective AD treatment. Also notes a lag time in the drug permeation profiles from chitosan-formulated SLNs, suggesting potential delays in drug release and penetration. Drug release from SLNs is postulated to occur via two potential mechanisms: diffusion through or erosion of the lipid matrix. However, the dominant mechanism or coexistence of both mechanisms remains undetermined, necessitating further investigation. SLNs, while exhibiting anti-AD efficacy, have limitations due to their perfect crystal structure, necessitating a hydrophilic coating to facilitate passage through the BBB, which restricts drug delivery. Addressing these aspects could better transform SLNs into promising tools for the treatment of AD.

Nanostructured lipid carriers (NLCs)

NLCs and SLNs share similar morphological characteristics. However, NLCs have the potential for more robust drug release profiles owing to their high drug encapsulation efficiency and minimal drug leakage during storage. NLCs are recognized as promising drug delivery carriers owing to their biocompatibility and enhanced manufacturing capabilities compared with SLNs [193]. To synthesize NLCs, lipids, and drugs are dissolved in water-immiscible organic solvents and emulsified in an aqueous phase containing a surfactant until the solvent evaporates. The pre-emulsion is sonicated to reduce the

Table 7 Current Alzheimer's disease therapies with solid lipid nanoparticles

Substance or drug	Modification of SLNs	Advantage	Disadvantage	References
FA	Chitosan-coated SLNs	- Direct intranasal drug delivery bypassing the BBB - Improved solubility, permeability, and bioavailability of FAs - Improved cognitive function and prolonged drug release - Improved release control through chitosan coating - Antioxidant and anti-inflammatory properties reduce oxidative stress and inflammation in the brain	- Limitations of FA's low water solubility and fat-soluble barrier permeability - Reduced therapeutic effectiveness due to extensive first-pass metabolism - Formulation and optimization of chitosan-coated SLNs is complex and costly	[190]
Dopamine	Chitosan-coated SLNs	- High encapsulation efficiency and positive surface charge; conducive to effective drug delivery across the BBB - Potential for safe and effective BBB penetration - Suitable for nose-to-brain drug delivery,	- Complex of the formulation process of SLNs - Challenges for large-scale production - Long-term stability of nanoparticles	[191]
Erythropoietin	–	- Improve biocompatibility and organ circulation by enabling sustained drug release - Increase permeability across the BBB - Alleviates Ab-associated mitochondrial oxidative stress	- EPO-SLNs are expensive and time-consuming to commercialize because they involve multiple steps in the processing process - Delivery limits for polymeric drugs	[192]

particle size by precipitating the particles with negative ions. The mixture is then cooled to room temperature to obtain an aqueous NLC mixture [194] (Fig. 6). The distinguishing feature of NLCs is their incorporation of both solid and liquid lipids, offering versatility for material selection while addressing limitations of SLNs, such as drug-loading capacity and long-term stability concerns [195]. In this section, we describe recent studies that various effective nanostructured lipid carriers in the treatment of AD.

Therapeutic applications of nanostructured lipid carriers in Alzheimer's disease

Berberine as an isoquinoline alkaloid has been suggested as a possible AD treatment. NLCs, composed of both solid and liquid lipids, form a unique structure with excellent stability and biocompatibility. Berberine-loaded NLCs offer several therapeutic mechanisms for targeting $AlCl_3$-induced AD rat model, including acetylcholinesterase inhibition, reduction of Aβ levels, antioxidant activity, and cholesterol-lowering effects [196]. Donephezyl (DPL), a specific acetylcholinesterase inhibitor, is used as a first-line treatment to improve cognitive deficits in AD and may have disease-transforming effects. Astaxanthin (AST) is a natural potent antioxidant with neuroprotection, anti-amyloid production, anti-apoptotic, and anti-inflammatory effects. Using NLCs in combination with donepezil and astaxanthin (DPL/AST-NLC), reduced factors associated with AD pathology, increased glutathione and Ach levels in the cerebral cortex and hippocampus, and donepezil measurably improved the cognitive function of AD. It has also been shown to have a neuroprotective effect in neurodegenerative diseases such as AD and shows results of crossing the blood–brain barrier to restore choline neurotransmission and improve cognitive and behavioral defects in $AlCl_3$-induced AD rat model via the intranasal route [193]. Reactive oxygen species (ROS)-induced neuronal mitochondrial dysfunction is a major pathologic factor in sporadic AD. a method that coats the surface of red blood cell (RBC) membranes with NLCs and loads rabies virus glycoprotein (RVG29) and triphenylphosphine cation (TPP) molecules to deliver functional antioxidants to neuronal mitochondria. Sustained drug release made possible by these NLCs enhanced organ circulation and biocompatibility. These NLCs were able to target neurons and localize to mitochondria in addition to crossing the BBB. After encapsulating resveratrol (RSV), a model antioxidant, it could alleviate AD symptoms by alleviating Ab-related mitochondrial oxidative stress in APP/PS mice models via intravenous injection. These NLCs showed potential in the treatment of AD mitochondrial dysfunction brought on by ROS [197] (Table 8) (Fig. 7C).

Limitations of nanostructured lipid carriers in Alzheimer's disease treatment

Nanostructured Lipid Carriers (NLCs) offer potential benefits for the treatment of AD, but they also come with several limitations. As mentioned above Berberine is a promising compound for AD treatment due to its anti-inflammatory and neuroprotective properties. However, it has very low oral bioavailability, making maintaining

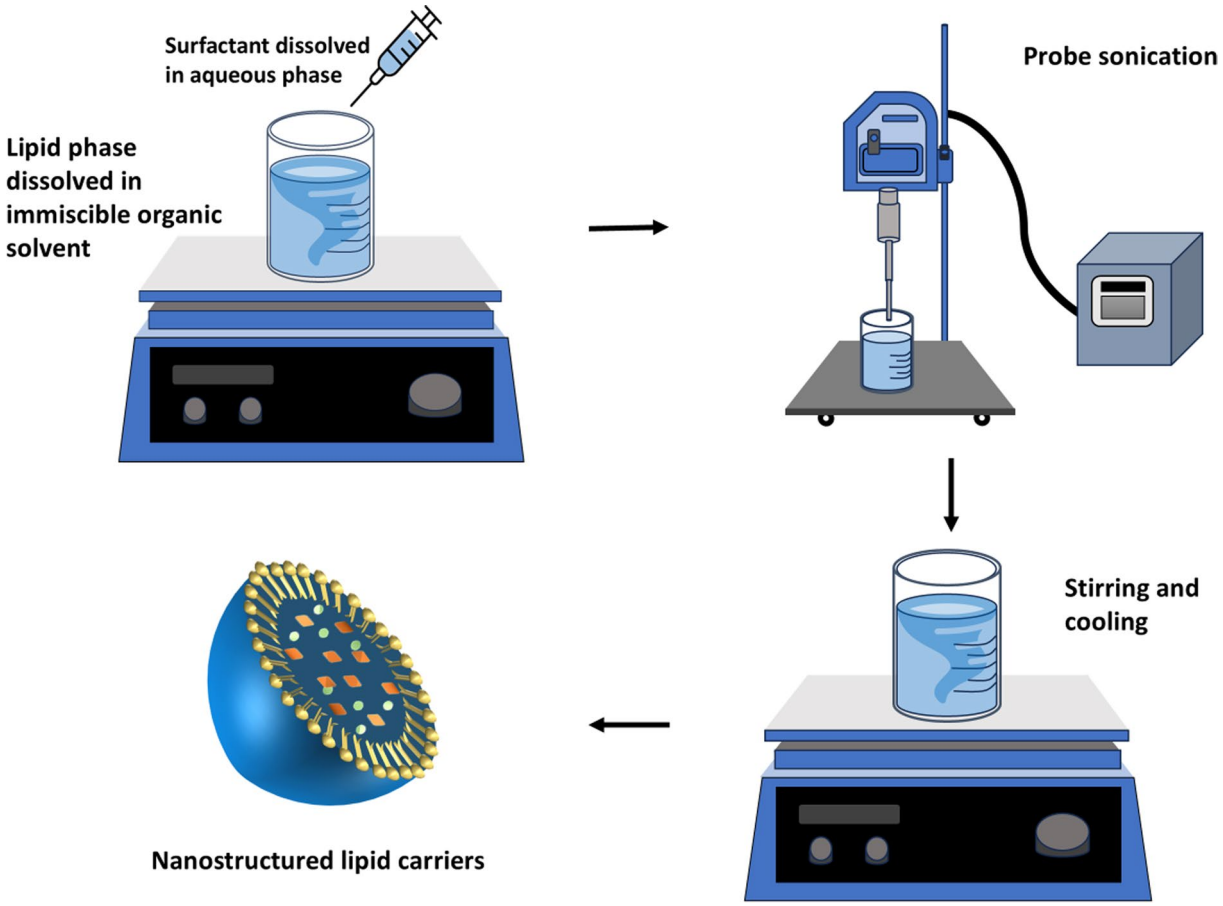


Fig. 6 Illustration of nanostructured lipid carriers manufacturing process using the emulsification-solvent evaporation technique

Table 8 Various nanostructured lipid carriers in the treatment of Alzheimer's disease

Substance	Advantage	Disadvantage	References
Berberine	- Inhibits AChE and monoamine oxidase - Reduces Aβ levels - Antioxidant properties - Cholesterol-lowering effects - Increased brain-targeted effects with NLCs - Improves AD-related deficits	- Limited oral bioavailability of berberine - Formulation and optimization of NLCs is complex and costly - Large clinical trials required	[196]
Donepezil (DPL) and astaxanthin (AST)	- Small particle size and high encapsulation efficiency - Sustained drug release - Reduction of factors associated with AD pathology - Increased glutathione and Ach levels - Improved brain tissue - Multifaceted approach to AD pathology	- Complex and costly formulation and optimization process - Requires large clinical trials - Difficulty in consistent targeted delivery to specific brain regions	[193]
Rabies virus glycoprotein (RVG) and Triphenylphosphine cation (TPP)	- Enhances the targeting of neurons and mitochondria while also crossing the BBB efficiently - Extended circulation time in the bloodstream due to its biocompatibility and the protective outer layer, making it a promising method for delivering treatments for AD	- The complexity of the system may pose challenges in terms of potential immune responses or unexpected interactions in the body - To ensure long-term safety	[197]

therapeutic concentrations in the bloodstream difficult. While NLCs are designed to improve their absorption, achieving sufficient bioavailability remains challenging. The process of developing NLCs is extremely complex and involves optimizing a number of variables, including drug loading efficiency, stabilizers, and lipid selection. This complexity leads to increased production costs and extended development timelines. Also, to ensure the safety and efficacy of NLCs for AD treatment, extensive clinical trials are necessary. Conducting these trials can be expensive and time-consuming, posing significant financial and logistical challenges. Given the novelty of NLC systems, their long-term safety profile remains uncertain. Continuous research and testing are required to evaluate potential side effects and interactions with other therapies, which adds to the overall complexity and cost of developing NLCs for AD treatment.

Conclusions and perspectives

The LBNs which could be classified into two major parts, exosomes and liposomes, share similar characteristics in terms of drug delivery systems. Both exosomes and liposomes have been remarkably investigated as brain therapies due to their advantage of BBB penetration. In consists with the LBNs, among the various lipids, ionizable lipids has been also suggested as a potential candidate for enhancing the BBB penetration and following brain gene/drug delivery. Ionizable LBNs utilize several strategies including prolonged blood circulation time, increased BBB penetration, and promoted interaction and uptake with brain endothelial cells through enhanced cellular uptake [198]. This suggests that LBNs can act as carriers of drugs attenuating specific brain disorders. However, the ways exosomes and liposomes transpassing the BBB and curing specific neurodegenerative diseases are different. Exosomes, derived from various types of cells, preserve most components of their parent cells. Such characteristics allow exosomes to be more biocompatible and less immunogenic. Also, recent investigations of exosome components (e.g. transmembrane proteins, enzymes, and RNAs) have emphasized their roles in contributing AD pathology depending on the type of the parent cell of exosome. For instance, specific transmembrane proteins of the exosomes are known to enhance the brain targeting and BBB transcytosis efficiency towards diseased sites [199, 200]. In addition, several beneficial miRNAs are proven to regulate AD pathological factors [167, 201]. However, the homogeneity of encapsulation of such naturally synthesized biomolecules has been repeatedly reported, which presents a challenge for reproducibility. Furthermore, the lack of productivity and the high cost of production make it an uneconomical choice for clinical translation. In contrast, liposomes and other synthetic LBNs are artificially synthesized from chemically defined molecules, thereby addressing the challenge regarding homogeneity and reproducibility [202]. Furthermore, versatile functionalization techniques of liposomes engineering in accommodating hydrophilic or hydrophobic cargo have enhanced in vivo drug solubility and stability. As ongoing research, refinement and optimization of liposomes by surface modifications involving ligands and polymers have been explored and shown potential for augmenting specific targeting and regulating drug release [202]. However, as a synthetic drug, liposomes exhibit higher immune response than exosomes and shorter circulation time, which requires further chemical consideration such as PEGylation [203, 204].

Recently, hybrid LBNs are recently being developed to address the limitations of the LBNs and combine such advantageous features of exosomes and liposomes [205–208]. For example, fusion of well-defined synthetic liposomes and naturally secreted therapeutic exosomes may offer a synergistic approach to drug delivery systems. Due to the similar structure of those LBNs, the membrane can be integrated by physical or chemical methods, creating a new LBN containing the original cargos. In one example, CD47 expressing exosomes derived from transgenic fibroblasts were hybridized with heat-sensitive liposomes. The hybrid LBNs presented advanced drug delivery to carcinoma, validating potential as therapeutic carriers [205]. In another experiment, milk-derived exosomes and pH-sensitive zwitterionic liposomes were fused to treat Type 2 diabetes mellitus. This hybrid vesicle effectively targeted the jejunum while protecting cargo from gastrointestinal pH levels and mucus adsorption [209]. Thus, the combination of LBNs offers enhanced drug stability and targeted-delivery efficiency. Similarly, we

(See figure on next page.)

Fig. 7 Schematic diagram of lipid-based nanoparticles' mechanism in Alzheimer's disease treatment. **A** Illustration of Alzheimer's disease pathways modulated by MSC-derived exosomes through PI3K/Akt/mTOR axis and autophagy regulation. Reprinted with permission [168]. Copyright 2024 © Elsevier Masson SAS. **B** Schematic diagram of transferrin-Pep63 liposomes improving Aβ clearance, preventing aggregation, and restoring synaptic plasticity for early Alzheimer's disease. Reproduced with permission from [176]. Copyright 2021 Springer Nature. **C** Illustration of neuronal mitochondria-targeted delivery of resveratrol-loaded nanostructured lipid carriers, presenting antioxidant and amyloid. Reproduced with permission from [197]. Copyright 2020 Taylor & Francis

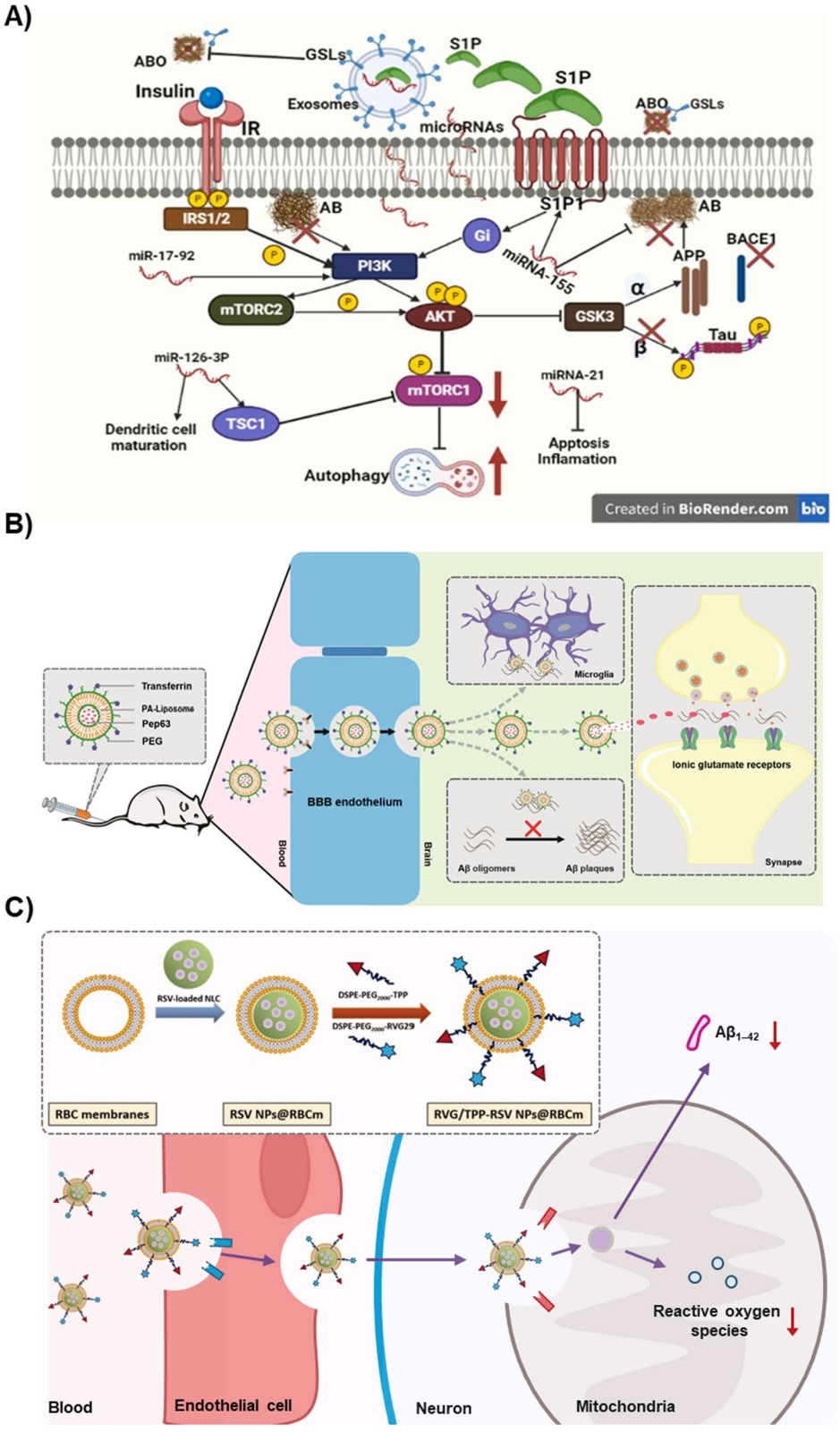


Fig. 7 (See legend on previous page.)

could suggest therapeutic exosomes that lack of brain-targeting efficiency being utilized in AD therapy by fusion with liposomes conjugated with brain-targeting ligand. Or defined cargos within liposomes may supplement therapeutic aspects of natural exosomes. Complementarily, components of exosomes could prolong circulation time of liposomes through enhanced biocompatibility and immunotolerance. Along with proteomic, lipidomic, and genetic investigations, the efficacy of hybrid LBNs could be maximized. Innovative approaches must be devised to unravel the intricate web of pathological complexities that will ultimately lead to enhanced treatment outcomes.

Abbreviations

Ach	Achacetylcholine
AChE	Acetylcholine esterase
ChAT	Acetylcholine transferase
AMT	Adsorptive-mediated transcytosis
AD	Alzheimer's disease
ARIA	Amyloid-related imaging abnormalities
APP	Amyloid precursor protein
AST	Astaxanthin
Aβ	Beta-amyloid
BBB	Blood–brain barrier
CMT	Carrier-mediated transcytosis
CNS	Central nervous system
DPL	Donepezil
FDA	Food and Drug Administration
GSH	Glutathione transporter
Lf	Lactoferrin
LBNs	Lipid-based nanoparticles
MSC-exo	MSC-derived exosomes
NMDA	N-methyl-D-aspartate
NLCs	Nanostructured lipid carriers
NGF	Nerve growth factor
RMT	Receptor-mediated transcytosis
SLNs	Solid lipid nanoparticles
GSLs	Surface glycolipids

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SH Bhang and JK Yoon defined the focus of the review. YJ Jang and SJ Kang summarized these studies. YJ Jang and SJ Kang drafted the manuscript. YJ Jang, SJ Kang, HS Park, and DH Lee contributed to the final version of the manuscript. YJ Jang, SJ Kang, HS Park, DH Lee, JH Kim, and JE Kim revised the manuscript. CH Chung and DI Kim contributed to the editing and revision of the manuscript. All the authors read, reviewed and approved the final version of the manuscript.

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No datasets were generated or analysed during the current study.

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The authors declare no competing interests.

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