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Nanotechnology as New Strategy Against Different Dementia Types: Current State of Art

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ABSTRACT

Dementia, mainly Alzheimer's disease (AD), is quite significant worldwide. Several dementia types are expected to affect approximately 140 million people by 2025 due to the global population's aging process. Accordingly, nanotechnology emerges as promising research field. The most important aim of nanotechnology for nanomedicine and Alzheimer's therapy lies in developing an efficient medicine, as safe as possible, based on new assertive research substantiated by subsequent clinical studies. The fast upgrades in nanotechnology and nanomedicine observed in the last few years have opened room for achieving an AD therapy. Nanomaterials have characteristic features, such as physical and chemical stability, high surface area: volume ratios, as well as programmable production. Furthermore, it is possible customizing these nanomaterials to turn them into special candidates to be used as both therapeutic agents and nanomedicine carriers. The present review deals with upgrades and challenges posed on the diversity of AD therapy nanomaterials such as carbon nanoparticles, lipidic nanocarriers, lipid functionalized, polymeric and metallic nanoparticles, biotherapeutics (monoclonal antibodies) and clinical nanomedicine applications. It is possible to avoid, delay or stop AD progression based associated efforts in nanomedicine aimed at raising the expectation of millions of patients worldwide.

Keywords: Dementia, Alzheimer, immunotherapy

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INTRODUCTION

Back in 2023, approximately 60 million people suffered from dementia worldwide and with Alzheimer's disease (AD) accounted for 60%–70% of all these cases. This number is expected to reach 140 million by 2025 due to the world population's aging process, as previously discussed (Sharma et al. 2025; Durán et al., 2025).

It is known that updating efficiency therapies remains a significant confrontation due to intricacies in AD pathological aspects. Furthermore, although AD cure through chemotherapy was not found so far, significant upgrades in this field are clear (Zhang et al., 2024b; Durán et al., 2025; Zhou et al., 2025). The U.S. Food and Drug Administration (FDA) has only approved seven drugs for AD treatment (Figure1), among them, donepezil, rivastigmine, galantamine, memantine, and namzaric, which have been widely used to manage symptoms, since they do not change disease progression (Zhou et al., 2025). Monoclonal antibodies such as donanemab (Mullard, 2024) and lecanemab (van Dyck, et al., 2023) have been proven effective in reducing Aβ plaques and cognitive decay at initial AD stages. Unfortunately, these treatments are not suitable for some individuals due to their secondary effects such as nausea, headache, and other issues, and due to their high prices in the market. Cummings et al. (2024) showed that 127 AD medicines have been subjected to clinical assays. Despite all efforts to go on with these studies, only 25.2% of these medicines have progressed to higher stages (Phase III trials), and this finding underlines the relevant barriers posed on achieving new therapeutic alternatives (Cumming et al., 2024).

Nanotechnology's main aim in both medicine and Alzheimer's therapy lies in developing an efficient medicine, as safe as possible, based on additional investigation and, whenever necessary, on subsequent clinical studies (Mejias et al., 2025). So far, extremely fast upgrades in nanotechnology and nanomedicine (Ikram, 2025; Kurul et al., 2025) have opened an important window of opportunity to the application of AD therapies (Li et al., 2022; Yang et al., 2024). Nanomaterials present unique features including physical and chemical stability, high surface area: volume ratios, and standard production and functioning. These features turn them into ideal applicants to be used as both therapeutic agents and medicine transporters. Artificial intelligence (AI) combination with nanotechnologies notably adds to the progress of several fields including personalized medicine and early diagnosis of diseases like AD (Chakroborty et al., 2025). Metal-functionalized nanoparticles (MNPs) (Liao et al., 2012), carbon-functionalized nanoparticles (CNPs) (Yin et al., 2023, 2024) and quantum dots (QDs) (Ren et al., 2020), for example, can target Aβ or Tau proteins to suppress aggregation or to promote removal. LNPs (Lipid-functionalized nanoparticles, PNPs (polymeric nanoparticles), MSNs (mesoporous silica nanoparticles) and MOFs (metal−organic frame works) showed high selectivity and efficiency in getting associated with biological structures at molecular level (Naqvi et al., 2020). Metallic nanoparticles become important AD nanomaterials through cerium, gold, silver, and selenium (Scarpa et al., 2023; Soghrati et al., 2025).

Nanomaterials' dual role as transporters and active therapeutic agents emerges as favorable and transformative attempts for AD therapy upgrades.

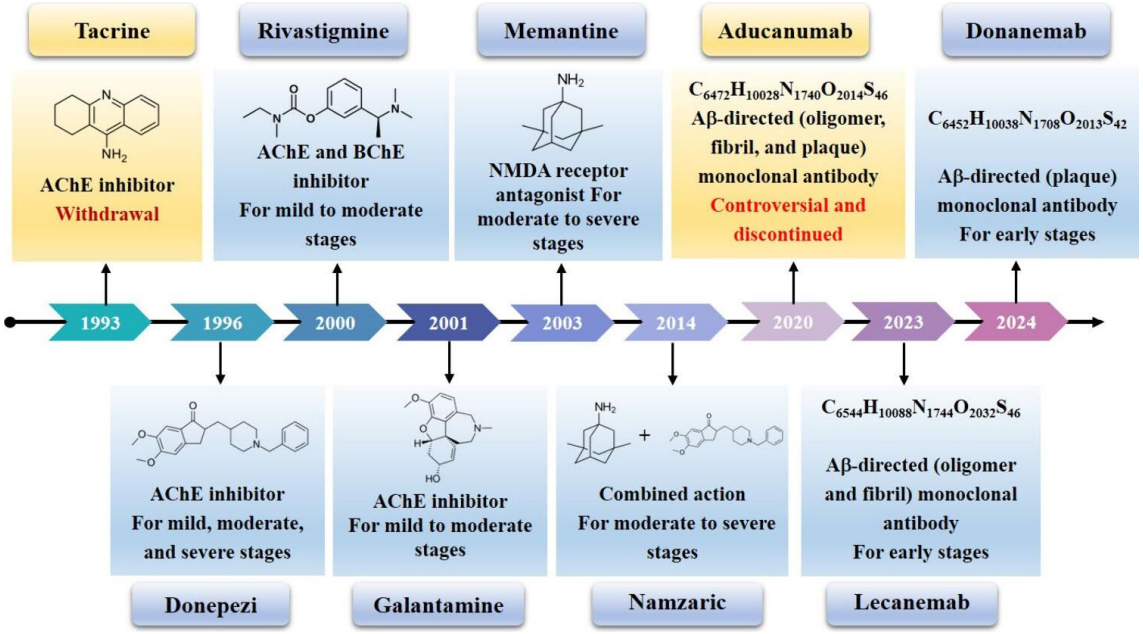

Figure 1. FDA-approved medicines to treat Alzheimer's disease (extracted from Zhou et al., 2025 - licensed under code CC-BY-NC-ND 4.0; open access to American Chemical Society).

The current list of approved medicines to treat AD is all based on oral preparations, except for rivastigmine, which is the only medicine that, besides its oral formulation, can also be delivered through a transdermal patch system (Arya et al., 2019). Most medicines lose their function in both the gastrointestinal tract and the hepatic system; therefore, it is necessary delivering high doses of them to control disease progress or symptoms (Wen et al., 2017; Peeriga and Manubolu, 2024). The medicine must bind to serum albumin in the bloodstream to achieve satisfactory half-life rates before they can finally penetrate the blood-brain-barrier (BBB) (Zhao et al., 2015; Banks et al., 2024). High medicine dosages can lead to secondary effects like nausea and diarrhea - these conditions can likely reduce individuals' empathy.

The current progress in nanotechnology enables NPs (nanoparticles) to cross the barriers. Furthermore, they can reduce secondary effects at lower dosage and fast BBB crossing to release the medicine to a specific field. Nanoparticles must have at least a nano-side to cross the BBB. Formulations must be local-specific, biodegradable, and nontoxic because of this elaborated feature. Thus, nano-systems set for AD procession allow the efficient care and deliver of other neuroprotective molecules and medicines. BBB is ignored and medicines can go straight to the brain in case of intranasal applications. Nanotools can be nasally administered to achieve optimal pharmacotherapy effectivity in AD individuals or i.v. to attain the brain as they cross the BBB to enhance their pharmacodynamic and bio-feasibility features, as well as to reduce unfavorable side effects.

Endocytosis is the usual NP carrying mechanism and it involves receptor-mediated endocytosis, pinocytosis and phagocytosis (Soghrati et al., 2025).

DIVERSITY OF AD THERAPY NANOMATERIALS

Current nanotechnology upgrades lead to a broader use of nanomaterials as main (front-line) element in biomedical fields, which are widely recognized (Chakroborty et al., 2025; Lin et al., 2025). The use of nanomaterials is mainly attractive to treat neurodegenerative diseases due to their sizes (approximately 1-100 nm), since such features allow high BBB infiltration efficiency (Hosny et al., 2025).

CARBON NANOPARTICLES

Carbon nanoparticles (CNPs) such as carbon nanotubes (CNTs), fullerenes and graphene have been broadly assessed for several biomedical uses due to their significant structure and aspects (Zhou et al., 2025). Graphene is known in drug release and biosensing due to its high electrical conductivity and easy surface change (Saharan et al., 2023; Yanikoglu et al., 2024; Cui et al., 2025). CNTs are known for their use in biosensing applications due to their large specific surface area (Schroeder et al., 2019; Tishkevich et al., 2025). It is so, because these materials present nanoscale size, large surface area and BBB penetration ability; these features make them extremely good in remitting AD complex confrontations.

Primary pristine CNPs (i.e., non-transformed C60, graphene, CNTs) were firstly explored for their ability to overcome Aβ agglomerations and to reduce oxidative stress. Graphene and (GO) graphene-oxide nanosheets can break peptide side chains due to their high hydrophobicity; consequently, they produce an extremely ordered hydrophobic core over Aβ aggregation procedures (Jin et al., 2019; Song et al., 2022). Furthermore, they can break into mature Aβ fibrils and extract destroyed peptides. Likewise, CNTs can interact with Aβ through hydrophobic interactions and π-π stacking to show efficient fibrillation (Cai et al., 2025).

Besides the desired effects, pristine structures often face confrontations such as low solubility in general high cytotoxicity and lack of specificity to aim disease-specific proteins or pathways (Guo et al., 2022; Strojny-Cieślak et al., 2025).

Chemical transformation or surface changing through doping is a likely effective minimizer for the previously described issues; in addition, they remarkably expand CNPs potential administrations (Zhou et al., 2025). According to current research, C60 changes like hydroxylation, PEGylation, pentoxifylline association and metal incorporation (e.g., f-Gd@C82) can enhance these structures' solubility in water, which sustains their efficiency in both suppressing Aβ fibrillogenic and trapping free radicals. Interestingly, cellular tests showed that these transformed compounds work as shield for neurons against oxidative injury caused by Aβ and ROS (Yin et al., 2024).

Researchers worked on graphitic carbon nitride (g-C_3N_4-based nanomaterials - i.e. platinum (II)-coordinated g-C_3N_4 nanosheets (g-C_3N_4@Pt) to suppress Aβ aggregation and reduce oxidative stress. It also interacts as nano chelator by breaking Aβ-Cu^{2+} agglomerates and defending cells from Aβ-caused toxicity. Irradiated g-C_3N_4 nanosheets have proven efficient in suppressing Aβ

aggregation and toxicity (Tufail et al., 2024; Zhou et al., 2025). These nanosheets' unique activity can allow BBB penetration, and it overcomes undesirable unstable small chemicals or peptides; consequently, they are actively taken out to the brain. C_3N is another nitrogen-doped CNP, and it has also proven beneficial for AD treatment since it increases aggregation-induced neuron cytotoxicity, avoids neuronal death, and prevents neurite injury *in vitro* (Yin et al., 2023). Yet, they reduce global cerebral Aβ concentration, mainly in fibrillar amyloid plaques, and recover synaptic loss in AD mice. Furthermore, crucial tissue analyses show no obvious pathological injury, and it points out that C_3N nanodots are extremely biologically secure. All these data on super-features associated nanomaterials point towards a new AD therapy approach (Zhou et al., 2025).

Quantum dots (QDs) ranging from 2 nm to10 nm present unique fluorescence abilities. They make photoluminescence size-dependent because of the IR spectrum UV due to the quantum confinement phenomenon. QDs luminescence stability and its ability to join biomolecules turn it into a hopeful platform to either diagnose or/and treat disease such as AD and cancer (Villalva et al., 2021; Pechnikova et al., 2025).

There are two QDs types, namely: inorganic and organic carbon-based semiconductors. Classical inorganic QDs are synthesized from II−VI semiconductor materials (e.g., CdS, CdSe, CdTe, ZnS, ZnSe) that, in their turn, have good optical properties, although they get cytotoxic in case of metallic ions release (e.g., $Cd^{2+)}$, which limits their application as AD therapy. Core−shell modifications and biocompatible surface transformations have been assessed as ways to minimize such a toxicity. These processes increase QD stability and allow their application to feature amyloid and tau proteins, as well as their use for Aβ fibril suppression (Takur et al, 2011; Li et al., 2025a). Chen et al. (2019), for example, synthesized dopamine-transformed CuInS2/ ZnS core−shell QDs presenting relevant luminescence and small toxicity for tau protein identification. Xiao et al. (2010) applied N-acetyl-L-cysteine (NAC) coated QDs (NAC-QDs) to suppress Aβ40 fibrillization through hydrogen bonding interactions for inhibition purpose. Despite all this progress, inorganic QDs have guided investigations aimed at carbon-based QDs (CQDs), which account for higher biocompatibility to biomedical treatments (Zhou et al., 2025).

Chung et al. (2017) passivated CQDs by using bPEI (branched polyethylene imine) and disclosed an easy technique to inhibit Aβ peptide auto assembly and to minimize Aβ-induced neurotoxicity through visible light-active and bio-consistent bPEI@CQDs adopted as β-sheet annihilators (Zhang et al., 2024a). Malishev et al. (2018) prepared enantiomeric CQDs by using chiral lysine, mainly L-lysine and D-lysine, to generate D-Lys CQDs and L-Lys CQDs, respectively. This finding pointed towards L-Lys CQDs efficiency in inhibiting Aβ42 self-aggregation and in minimizing its cytotoxic actions. According to Chung et al. (2017), $-NH_3^+$ (positively charged amino groups) found on L-Lys CQDs surface disrupts the electrostatic associations of Aβ peptides (Yan et al., 2025). Yan et al. (2021) positively prepared EGCG (epigallocatechin gallate) gCQDs (charged glucose-derived CQDs-E) by using glucose as molecule precursor. The gCQDs-E was efficient in minimizing cytotoxicity associated with amyloid agglomeration, which allowed removing Aβ peptide depositions through BBB in the APP/PS1 transgenic AD murine model. This mediation simultaneously enhanced memory deficiency, which suggested its possible

adoption as therapeutic approach for AD; yet polyphenol nanoparticles presented similar actions (Yang et al., 2024b). Lim et al. (2024) effectively synthesized Cur-CQD (curcumin carbon quantum dots) by using curcumin as predecessor. According to cellular tests run *in vitro,* Cur-CQD efficiently minimized Aβ peptides agglomeration and tau proteins hyperphosphorylation. All these outcomes highlighted the possible use of several predecessor molecules, carbon dot structures and morphologies to transmit anti-AD target uses (Zhou et al., 2025).

LIPIDIC NANOCARRIERS: LIPID-BASED NANOPARTICLES

Lipid-based nanoparticles (LNPs) combination to lipid molecules such as oils, fats and similar derivatives has proven to be hopeful nano transports due to their biodegradability, biocompatibility, and ability in nanocapsulating therapeutic agents (Zhou et al., 2025). Several LNP systems like liposomes (Cao and Zhang, 2022; Su et al., 2024; Soghrati et al., 2025), niosomes (Moghassemi and Hadjizadeh, 2014; Bhabad et al., 2024; Pandya and Panchal, 2025), transfersomes (Salem et al., 2024), ethosomes (Gangopadhyay et al., 2023; Kadolkar et al., 2025), SLNs (solid lipid nanoparticles) (Shivananjegowda et al., 2023; Shah et al., 2025) and NLCs (nanostructured lipid carriers) are of easy synthesis; therefore, they have also been broadly assessed as possible AD therapy. These transports improve medicines' stability, avoid their initial degradation, and smooth their targeted release, which turn them into appealing multifunctional bed frame (Chakraborty et al., 2024; Far et al., 2024). Many studies have assessed liposome-loaded medicine transport systems as likely attempt for future AD therapy. It is known that the option for a given medicine, its components and surface changes are important factors at the time to standardize the efficiency of these release systems. Su et al. (2024) created modified MAN (p-aminophenyl-α-D-mannopyranoside) and the TAT (which is a cationic cell-penetrating peptide) nanoliposomes to enhance BBB infiltration. DPMT@PEI/miR-195 liposomes notably reduced Aβ plaques, tau hyper-p-tau and microglial polarization in an AD murine model, and this finding pointed towards the possibility of both primary and acute disease stages. Moreover, niosomes, liposomes and vesicular structures designed through cholesterol combination to alkyl or dialkyl polyglycerol ether-derived nonionic surfactants have also been suggested as liposome options for medicine delivery (Moghassemi and Hadjizadeh, 2014). A new dual drug-loaded niosomes system for nasal rivastigmine and N-acetyl cysteine release has shown great medicine capture ability, stability, retained delivery and direct nose-to-brain release (Kulkarni et al, 2021). Transfersome has four elements, among them, phospholipid, which is an edge inductor (i.e., as sodium cholates) with low ethanol and water concentration (Fernández-García et al., 2020). Phospholipids generate a bilayer and sodium cholate stabilizes this bilayer and changes or deforms the vesicle by forming a high curvature radius (Opatha et al., 2020). Therefore, transfersomes' high elasticity and flexibility make them more beneficial than niosomes and liposomes. Moreover, their excellent features, such as drug-loading ability and extended infiltration turn them into promising medicine carriers in AD treatment (Salem et al., 2024). Nanocarriers known as ethosomes hold phospholipids (ethanol/water) that help their ability to infiltrate the skin. Interestingly, Gangopadhyay et al. (2023) formulated an ethosomal intranasal gel charged with donepezil hydrochloride to improve medicine

carrying through the BBB. This gel reduced plasma levels and oral medicine-related extent actions. Based on the results, the standardized gel formulation attained approximately 100% medicine penetration after 24h, both *in vivo* and *in vitro*. Despite the promising results from preclinical assays, LNPs clinical administration to treat AD persisted at this disease's initial stages. Several crucial items must be followed to achieve their translation into clinical experience. Assessing security aspects, long-term profits and treatment efficiency validation through understandable assessments must be taken into consideration. LNPs' preparation cost, mainly when it comes to those known for aimed release, is high and it places an important barrier to their broad use (Ayub and Wettig, 2022; Song et al., 2024).

Further investigation is needed to improve these NPs' specificity and efficiency to overcome these conflicts, and to develop lipid preparations to enhance medicines' stability, mainly of those susceptible to fast deterioration in biological habitats. Moreover, LNP medicine release systems can be associated with gene treatment or RNA-based therapies, as well as provide nanoscale transport for imaging compounds or for markers' determination or diagnostic (Tenchovn et al., 2021). This process would help with early disease diagnosing and disease-progress monitoring.

POLYMERIC MATERIALS: NANOPARTICLES

Polymeric nanoparticles (PNPS) show solid particles produced by organic colloids with synthetic, natural/hybrid polymeric nanomaterials at the size 10-1,000 nm. They are synthesized from monomers through several polymerization methodologies (Zhang et al., 2021; La Barbera et al., 2022; Austria and Akhavan, 2025). PNPSs are interesting materials due to their invaluable function for brain-aimed therapies, to their biocompatibility, biodegradability, great stability and longer stand life. PLGA is one of the synthetic materials extensibilities assessed among polymers due to its controlled and sustained-release properties, low toxicity and biocompatibility to cells and tissues. Poly lactic-co-glycolic acid (PLGA) has been accepted and approved by both the FDA and EMA for biological use. Saleh et al. (2024) used PLGA to synthesize a brain-targeted formulation (berberine loaded PLGA/Tet-1 peptide NPs (BBR/ PLGA-Tet NPs) and make BBB penetration easy. This preparation decreased neuronal stress in oxidative species on Aβ plaques, NFT agglomeration and improved the hippocampal synaptic role. Chitosan is a biocompatible and biodegradable cationic linear polysaccharide presenting mucoadhesive features that stimulate medicine infiltration into the brain through intranasal administration (Georgieva et al, 2023) and showing an anti-AD treatment *per se* (Wang et al., 2021; Iyer et al., 2024). Nanogels are nano-scale hydrogels generated by polymers' chemical, physical or cross-linking. Nanogels associate the hydration and multiapplication of hydrogels with nanocarriers' advantages for primary AD therapy (Ye et al., 2022; Zhang et al., 2025). Micellar medicine delivery systems are widely known for their small size and other interesting abilities (Katari et al., 2023). An interesting example of this material was reported by Xu et al. (2022), who projected it as ROS-responsive aimed micelle to mainly deliver rapamycin to neural cells in case of AD injuries and to attain efficient delivery in response to high intracellular ROS amounts. This process helps controlling rapamycin entering autophagic flux for AD treatment.

Dendrimers are extremely branched spherical polymers with typical sizes close to 10-100 nm function due to the number of hyper branches. The peripheral groups help BBB infiltration and make dendrimers help the AD treatment (Liu et al., 2021; Mroziak et al., 2024).

Assumingly, PNPs are at the vanguard of medicine release innovation since they propose numerous upgrades that are mainly significant for AD confronting (Cao and Zhang; 2022; Soghrati et al., 2025). Unfortunately, these systems are at the murine testing phase, when the action between polymer and medicine interferes with medicines' metabolism kinetics *in vivo*. Inclusive metabolic stepways of polymeric medicines in the body remain unclear, despite all the observed progress in this field. Moreover, synthetic polymers applications are limited by factors such as cost, purity level and, in some cases, toxicity aspects (Zhou et al., 2025).

METALLIC NANOPARTICLES: CURRENT RESEARCH ON AD TREATMENT

Studies on cerium-loaded nanoparticles in AD treatment have shown that ROS generation and Aβ peptides act in mitochondrial proteins such as ATP (adenosine triphosphate) synthase, alcohol dehydrogenase and cyclophilin D (Balaban et al., 2017; Hub et al., 2023abc). Mitochondrial dysfunction precedes the development of AD plaques in the brain, which is characteristic of this disease (D'Alessandro et al., 2025). Therapeutic factors capable of protecting mitochondria from activated oxygen species and oxidative stress resulting from ROS can efficiently avoid an AD therapy at the first stage. It was recently shown that ceria (CeO_2) NPs can trap ROS by copping catalase and dismutase, given their recycling capacity to reverse oxygen binding and shift between the Ce_4^+ (oxidized form) and Ce_3^+ (reduced form) states on their surface, within a recycling process (Celardo et al., 2011; Li et al., 2025bc). Ceria NPs have been showing positive remedial effects such as neuroprotection therapy (Monroy-Ramirez et al., 2025). Kwon et al. (2016) and Cheng et al., (2024) have shown TPP examples of TPP ceria NPs (triphenylphosphonium-conjugated ceria NPs) generation installed to mitochondria to inhibit neuronal decease in a 5XFAD transgenic AD murine model. TPP can reach mitochondria by exploring its negative membrane potential due to TPP lipophilicity. TPP-ceria NPs mitigated mouse reactive gliosis, which is a reactive change in glial cells in response to CNS damage, and mitochondrial morphological injury. This nanomaterial (TPP-ceria NPs) aims mitochondria for its exceptional colloidal stability, tiny size (approximately 3 nm), hydrophobicity and positive zeta potential (+45 mV) (Kwon et al., 2016).

Gadolinium nanoparticles (AGuIX NPs) are important for AD detection since they efficiently bound to two peptides presenting the KLVFF (Lys-Leu-Val-Phe-Phe) sequence, which relates to Aβ peptide hydrophobic center (or core) and is essential for β-sheets generation (Lowe et al., 2001; Plissonneau et al., 2016). The β-sheets use an unusual anti-parallel β-sheet motif in this process, because their fraction binds to the full-length Aβ peptide (Jokar et al, 2020) that, in its turn, binds the Leu-Pro-Phe-Phe-Asp peptide (LPFFD's hydrophobic region). According to the plasmon resonance spectroscopy assays, both NP modified surfaces reacted with Aβ1–42 fibrils at dissociation constant (Kd) equilibrium level ranging from 350 mgs to 403 mgs - this dose is often adopted for clinical MRI studies (Plissonneau et al., 2016). It was determined that Aβ1–

42 did not interact with V30M-TTR (transthyretin) fibrils. Assumingly, fibrils accounting for producing the amyloid were generated through the transthyretin (TTR) mutant structure combined to FAP (from family amyloid polyneuropathy), which refers to as hereditary TTR amyloidosis. The Aβ peptide difference between amyloid and TTR proteins causes ATTR (amyloidosis TTR), which is a neurodeteriorating disease determinated by fibrillation and wrong protein bending (Gonzalez-Duarte and Ulloa-Aguirre, 2021). A similar experiment was conducted with Pittsburgh compound B (N-methyl-(11c))2-(4'-methylaminophenyl)-6-hydroxybenzothiazole, which is a radiopharmaceutical adopted to detect brain amyloid beta plaques that help differentiating dementia cases. Many published reports describe its interaction with Aβ1–42 and V30M-TTR fibrils. Kd values were close to 6-10 mM, and they pointed out that this compound would be useful for AVD (amyloid vascular dementia) and ATTR detection (Sancey et al., 2015). According to immunohistochemical outcomes, both AGuIX NPs are linked to AD symptoms, just as neuropathologies found in mice's hippocampus. A high positive MRI variation in it was related to NPs, and it improved the MRI response by enhancing image definition. In addition, AGuIX NPs rates did not increase in especial organs as previously observed for iron oxide NPs because their nanotoxicity was narrow (Soghrati et al, 2025).

Gold nanoparticles (AuNPs) are used for AD detection and treatment (Hong et al., 2023; Vijayan et al., 2025) because their application in AD therapy was related to that of metallic NPs applied to mark and kill cancer cells in a provisional methodology (Chiang et al., 2024). AuNPs were associated with Aβ fibrils and subject to monitoring for several propagation days under many exposition hours at weak microwave range to destroy the plaques. Irradiation disperses the fibrils for at least one week (Capocefalo et al., 2021); consequently, these fibrils are disrupted, which reduces the possibility of reorganizing the proteins. According to Liao et al. (2012), uncovered AuNPs suppressed Aβ fibrillation, and it led to the collapse of rounded and fibril oligomers. Thus, uncovered NPs are incorporated to preformed Aβ fibrils. This process generated ragged species and pointed out that AuNPs rather bind within the fibril structure. Carboxylate-coated AuNPs are positively charged AuNPs and their incubation reduced Aβ neuroblastoma-mediated toxicity. According to this research's outcomes, AuNPs presenting negative surface potential can be useful nano-chaperones to suppress and reorient pre-fibrillation; therefore, they can be promising as potential element in AD therapy (Liao et al., 2012; Ray, et al., 2019). Neely et al. (2009) and Tapia-Arellano et al. (2024) assessed two-photon scattering test fundaments on monoclonal anti-tau antibodies-coated AuNPs *in vitro* and observed their commitment to characterize AD tau proteins. AuNPs covered with anti-tau antibody augmented the two-photon Rayleigh scattering power by 16 times after the application of 20 ng/ml tau protein.

Gold nanoparticles show intense optical absorption deriving from the surface plasmon resonance. Accordingly, gold nanorods have been efficiently used as contrast agents in MSOT (multispectral optoacoustic tomography). This same study on cross-linked anti-Aβ antibodies was applied to Au nanorods (Abs-GNR) and showed that the linked ones were specifically connected to Aβ seeds. The resulting seeds-Abs-GNR complexes can be used as optical probes in MSOT imaging to follow Aβ seeds transmission *in vivo* (mice) (Soliman et al., 2022). Gold and silver nanoparticles have shown special physicochemical

features that make them efficiently release any pharmacological therapy in the CN (central nervous) system. Assumingly, this process turns nanoparticles into a new strategy to turn over the current therapeutic attempt, which is based on reducing an irreversible process into an efficient and permanent therapy (Scarpa et al., 2023).

AD studies conducted with silver nanoparticles have assessed their antioxidant action and the anti-Alzheimer effects of curcumin used for the green production of silver nanoparticles (curcumin–Ag NPs). Anti-Alzheimer actions were recorded at 585 µg/ml inhibition of approximately 50% of the acetylcholinesterase activity. It is worth observing that the dual antioxidant and acetylcholinesterase suppressing effects focus curcumin–Ag NPs potential for holding several functions of neurodegenerative disease agents. The current research opens new windows for the green preparation of bioactive NPs and for their potential aspects to AD treatment (Malek and Arasteh, 2025).

Thus, several contending hypotheses such as cholinergic, oxidative stress, amyloid, and metal chelation have been discussed to clear its etiology (Durán et al., 2025). There are two serine hydrolase enzymes in the brain, namely: AChE (acetylcholinesterase) and BChE (butyrylcholinesterase), which can metabolize Ach (acetylcholine) into acetate and choline (Ch) molecules, and it reduces their concentration. This process helps overcome defective learning and mind functions known as crucial AD etiology determining factors. Thus, finding AChE suppressors is one of the logical AD determination attempts. It is known that AgNPs deriving from plants are alternative elements in AD therapy. The inhibitory action of both AChE/BChE extracted from *E. variegata* leaf and Ev-AgNPs were tested in recent studies (Kodiyala et al., 2025). An excellent amyloid production inhibition was observed at 100 µg/mL NPs in other case aimed at characterizing the anti-Alzheimer features of AgNPs prepared with *Pimpinella anisum* seed extract. *Anisum*-AgNPs presenting antioxidant and suppressor features linked to amyloid production can be likely introduced as adequate NP to reduce AD side activities (Ghamarsoorat et al., 2024).

The ability of Ag NPs to enhance imaging methodologies, such as Computed tomography (CT) and SERS (surface-enhanced Raman scattering), also improves tumor diagnosis and allows more accurate targeted therapies by incorporating a photothermal treatment and by providing better medicine release. Their ability in neuro-theranostic therapy to penetrate the BBB is critical to help the imaging and therapy adopted for neurological diseases such as AD. Ag NPs can help managing neurodegenerative diseases like AD and PD (Parkinson's disease) given their anti-inflammatory, antioxidant and neuroprotective features. They enhance the activity of antioxidant enzymes such as superoxide dismutase and catalase; consequently, they reduce oxidative stress, which is a key factor for many of the diseases. Ag NPs internalization mechanism is too active at the IKK/NF-κB signaling stage and it leads to over ROS production (Laib et al., 2025). Biogenic or green AgNPs extracted from *Nepenthes khasiana* leaf in aqueous media could avoid occasional spatial memory and perception deficit in AD mice models due to streptozotocin intracerebroventricular administration (Teixeira et al., 2024).

With respect to selenium nanoparticles (nonmetallic nanoparticles) used in AD treatment, evidence shows that sodium selenite (IV), selenium (II) and sodium selenite (VI) (selenium redox cycles) are efficient in impairing ROS production. Selenite and selenium NPs (SeNPs) can suppress cytotoxicity and reduce

oxidative stress. A current review released a report on Se metabolism, selenium-protein role and on their function in monitoring brain diseases (Li et al., 2025b). The researchers conducted an in-depth study on the SeNPs mechanism to suppress Aβ cluster formation. Sialic acid was applied to change SeNPs and it led to NPs capable of suppressing Aβ cluster formation and of penetrating the BBB (Gupta et al., 2019). EGCG (epigallocatechin-3 gallate) stabilized Aβ cluster formation suppression by SeNPs and disaggregated amyloid fibrils into nontoxic amorphous oligomers *in vitro,* despite SeNPs transformation with sialic acid and higher BBB peptide B6 penetrability (Zhang et al., 2014; Skalny, et al., 2025). Varlamova et al (2021) assessed the action of selenium-having clioquinol in Cu^{2+}-and observed that it caused Aβ oxidation despite the H_2O_2 suppressing action, ROS generation in the intracellular moiety and Aβ association in SH-SY5Y (neuroblastoma) cells (Wang et al., 2014; Varlamova et al., 2021).

BIOTHERAPEUTICS: MONOCLONAL ANTIBODIES AND RNA-CONTENT THERAPIES

Currently, current literature makes it clear that the progress of new dementia therapies focused on CN system diseases is essential, mainly on the neurodegenerative ones like AD, which are worrisome sanity issues of greatest relevance worldwide. RNA-based and mAbs (monoclonal antibodies) treatments, and those linked to the biotherapeutics field, have disclosed the possibility of treating brain diseases; however, their clinical progress is limited by their difficulty in entering their brain targets. The nanotechnique at preclinical level has proven to help these structures overcoming biological obstacles that impair their suitable release in the brain. Crucial nanotechnology-based attempts such as activating the surface with object charging ligands, surface transformation based on using endogenous protein corona and sing ultrasound-mediated microbubble oscillation as therapeutic method were monitored. This report states that chronotherapy, aimed at AD therapy, focuses the concept that nanoparticle-based medicine release oriented by circadian rhythms could enhance therapeutic data. The manuscript provides an analysis on current attempts of achieving CNS medicine release in clinical assays; furthermore, it gives guidelines on this framework, mainly on AD (Pineiro-Alonso et al., 2025).
The therapeutic relevance of mAbs is proven by the large number of published and on-going clinical trials (AS- 2024). Assumingly, CNS diseases like AD are expanding the advantage of mAb-derived treatments, but there is only two mAbs good enough for efficient exploitation given their difficulty in entering the brain tissue to preserve it (Yi et al., 2024). Primary nanomedicine studies have disclosed some positive data linked to ways to overcome these difficulties. Antibodies, such as mAbs, have been accepted as favorite AD therapeutic agents since several clinical assays have highlighted their possibility to inscribe this complex condition. The FDA approved (FDA-2024) three mAbs to treat moderate cognition damage and primary stage AD-associated dementia, namely: Aduhelm® (aducanumab), which was unfortunately discontinued; Leqembi® (lecanemab) and Kisula™ (donanemab). All these mAbs accurately aim Aβ cluster formations, which are AD pathology signals whose goals are to suppress the Aβ plaque charge in the brain and to slow down the cognition decay (Barrera-Ocampo, 2024). However, despite all these improvements in

mAbs release to the brain, barriers are still an issue, mainly when it comes to ensuring appropriate brain feasibility and encapsulated mAbs supported therapeutic efficiency. Confronting scarce mAbs continued investigation filtration is necessary; current evidence points out that nanotechnology combination to ultrasound can be a favorable strategy (Pineiro-Alonso et al., 2025).

On the other hand, RNA-based biotherapeutics show good applicability in AD and CNS disease therapies, as shown by different RNA applications in brain stroke (Gao et al., 2024), cancer (Hologan et al., 2013) and chemotherapy opposition conditions (Hologan et al., 2013). Although many different materials have been assessed in numerous research, the manufacture of a perfect nano-vector for RNA release has not achieved, so far. The discussion comparing LNPs to PNPs (polymeric nanoparticles) remains open, and it suggests that many studies in this field still depend on better established nanomaterials. In addition, one of the highest obstacles to therapy lies in determining the right aims to be held for AD and on finding the most favorable gene-silencing concentration, editing or the protein improvement needed to achieve a therapeutic action (Pineiro-Alonso et al., 2025).

Finally, progress in both biotherapeutics and nanomedicine is changing brain disease therapies. However, an innovative investigation and the progress of new integrated approximation aimed at overcoming current limitations are demanding factors to attain a future disruption.

CLINICAL TRIALS: NANOMEDICINE

There is a large number of patents uses and studies about nanomedicine action in CNS diseases (Table 2 - Cheng et al., 2023) and many on-going research based on clinical trials (Table 3 - Cheng et al., 2023), as well as on the features and use of different nanoparticle types in therapy focused on neurodegenerative diseases (Table 1 - Dhariwal et al., 2025; Table 2, Liu er al., 2025). However, so far, there is no nanomedicine approved to treat CNS diseases. A clinical-stage biopharmaceutical company has developed several nanotechnology-based therapies aimed at CNS diseases and it has also started parallel phase-II clinical trials (NCT03843710, NCT03536559, NCT03815916, NCT04098406, NCT04626921 and NCT05299658) with CNM Au8®, which is an Au nanocrystal suspended in aqueous solution. CNM Au8® has been investigated as disease-modifying therapy focused on individuals with multiple sclerosis, amyotrophic lateral sclerosis, and PD (Parkinson's disease) (Kumar et al., 2022; Vucic et al., 2023). In 2019, Aphios Inc. started a phase-II clinical trial (NCT03806478) to assess the efficiency and security of APH-1105 intranasal nanoparticles in AD therapy (Zagórska et al., 2023). APH-1105 is a nanoparticle that regulates the enzyme α-secretase, which cleaves the amyloid precursor protein into a more soluble product. This enzyme easily removed soluble products from the brain and avoided the formation of insoluble amyloid plaques (Aphios-2021). Their clinical change is the most important feature of individualized AD determination and treatment, no matter if naturally derived exosomes or artificial nanomedicines are used (Jojo et al., 2019).

NanoLithium ($NP0_3$) is a disease-modifying NPs preparation based on lithium citrate in AONYS® inverse microemulsion (Medesispharma-2022)] that has already been tested in preclinical investigations (Wilson et al., 2017,2018. 2020). A phase-II clinical trial (NCT05423522) will provide data on

NanoLithium® $NP0_3$ clinical security and efficiency in individuals with mild to acute AD (Zagórska et al., 2023)

Nevertheless, results from current clinical assays applied to AD nanomedicines did not lead to good outcomes; thus, further investigations are critical to fill gaps observed in the industrial field. However, many nanomedicines were efficiently incorporated into clinical routines (Hu et al., 2023a). Regardless of these interesting findings, several arguments still block the clinical translation of nanocarrier technologies (Wang et al., 2025).

The Aβ, as AD indicator, was initially assumed as key aim in AD therapies, but the inadequacy of clinical assays applied to these therapies rose doubts about the adequacy of such an aim (Karran and De Strooper, 2022). Roche has stopped almost all its Aβ-related clinical assays (NCT05552157). The fast biotechnology development points out that some clinical trials opened room for biological AD theranostic compounds. NCT04040348, for example, is now holding the function of human mesenchymal stem cells (MSCs) in AD therapy and NCT04388982 looks for upgraded MSC-derived exosomes known for their anti-AD efficiency. MSCs-exosomes size ranges from 30 nm to 150 nm (Lotfy et al., 2023). The synthesis of these biological compounds makes this approach more costly than research and updates in green medicines due to the need for strict sterility control, external revitalizers' elimination and limited materials. However, several clinical assays on AD fundamentals under different nanomedicine dosages and based on different aims have been managed in the past 5 years (Table 3 - Cheng et al., 2023), and it suggests that AD treatment is gradually moving to multi-aim and varied strategies (Cheng et al., 2024; Randhawa et al., 2025).

CONCLUSIONS

Currently, nanotechnology and, consequently, nanomedicine emerged as promising AD therapy strategy. Restrictions associated with the release of traditional medicines are among the main challenges in this field. Assumingly, it takes place through controlled and more efficient pharmacokinetics, as well as through the release of nanomedicines to low-toxicity CNS. Another important problem lies in the efficient and effective release of nanomedicines aimed at brain pathology targets to advance over the BBB. Although there are no approved nanomedicines to be used in CNS therapy, many clinical-steps by biopharmaceutical industries have advanced in several nanotechnology-based treatments aimed at CNS diseases. Metallic nanoparticles, nanolipids and exosomes accounting for promising outcomes have emerged among clinical trials and several AD clinical trials related to different medicine dosages and aims have been carried out in the last years. Their outcomes suggest that the AD treatment progressively moves to multi-target or multi-aims strategies.

Nanotechnology emerges as a new age of confidence and possibilities in AD treatments. Financing new research, collaboration from different areas and, most of all, carrying out accurate clinical assessments are essential actions to translate these encouraging upgrades into concrete benefits for AD patients. It is possible to prevent, delay or suspend AD progression through collaborated efforts and to increase the expectations of millions of individuals on the Globo.

Author contributions

ND, WJF, GN: Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - original draft, Data, collection and analyses, Formal analysis, supervision of manuscript. Final editing manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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