J. Phytomol. Pharmacol., 4(1), 84-96, 2025
https://doi.org/10.56717/jpp.2025.v04i01.040
ISSN(Print): 2957-5818, ISSN(Online): 2958-6224

Journal of Phytomolecules & Pharmacology

Review Article

Nanoparticle mediated gene therapy for Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a neurological illness that is gradual and irreversible, characterized by cognitive impairment and memory loss. Although amyloid β plaque deposition has been found to be the most prevalent AD pathology, Alzheimer's dementia is also closely linked to increased acetylcholinesterase activity, reactive oxygen species, and excessive buildup of phosphorylated or total tau proteins. Numerous treatment strategies that aim to address these pathogenic pathways have not succeeded in preclinical or clinical trials, in part because of the existing regimens' low drug half-life, poor cell and blood-brain barrier penetration, and restricted bioavailability. Nanoparticle (NP)-mediated drug delivery methods are superior options because they increase drug solubility and bioavailability. Drug efficacy is also increased by NPs-mediated strategies, which enable targeted drug delivery and multiple drug loadings. However, some NPs have the potential to cause acute toxicity that damages tissue and cellular architecture, hence it is important to choose NP materials carefully. The recent NPs-mediated investigations that detect, classify, and cure afflicted brain diseases in order to take advantage of different pathological mechanisms of AD are compiled in this review. We also discuss about the future elements and drawbacks of specific NP-based deliveries. This study was performed via a systematic literature search in databases such as PubMed, Scopus, and ScienceDirect, utilizing keywords including "Alzheimer's disease," "nanoparticles," "drug delivery," and "gene therapy," concentrating on papers published from 1994 to 2024. We aggregated contemporary NP-based methodologies for the detection, classification, and treatment of AD by utilizing several pathogenic processes. Ultimately, we examined the existing constraints and prospective development of NP-mediated therapeutics.

Article Information
Received: 28 April 2025
Revised: 20 May 2025
Accepted: 21 May 2025
Published: 11 June 2025

Academic Editor
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Keywords
Alzheimer's disease, neurodegenerative disorders, nanoparticles, gene therapy, dementia.

1. Introduction

1.1. Overview of Alzheimer's disease

Between 60 and 80 percent of cases, Alzheimer's disease (AD) cause late-onset dementia globally. Slow cognitive decline and memory impairment are hallmarks of the most prevalent neurodegenerative diseases. The primary indicators of Alzheimer's disease and prerequisites for its diagnosis are the presence of hyperphosphorylated Tau in the brain as extracellular amyloid plaques, intraneuronal neurofibrillary tangles, and amyloid-beta protein (Aβ). Neuroinflammation is another common characteristic. Thus, the persistence and onset of chronic inflammation in AD are mostly attributed to the blood-brain barrier (BBB) [1]. The BBB's defensive role prevents neurotoxic Aβ from being effectively removed from the brain [2]. Tau hyperphosphorylation and other aberrant cascades are triggered by the buildup of Aβ in the brain and dysfunction of the

blood-brain barrier, resulting in loop feedback that eventually leads to cognitive decline and dementia by forming amyloid oligomers and amyloid plaques [3]. As a result, many therapeutic approaches for treating AD concentrate on the distribution, delay or inhibition of Aβ oligomers, plaques and fibrils [4].

1.2. Nanoparticle technology and its potential in gene therapy

According to nanotechnology, a particle is a tiny item that moves and acts as a single unit. Particles are often classified by size: ultrafine particles are described as having dimensions under 100 nm, whilst fine particles vary from 100 nm to 2.5 μm (2500 nm). These discrepancies are crucial in nanomedicine and toxicity, as the particle size affects biological interactions and biodistribution. Nanoparticles have distinct features from their bulk counterparts due to their unique physicochemical qualities, including size-dependent behavior, high surface area-to-volume ratio, and quantum effects. These characteristics have resulted in heightened scientific interest and innovative applications, especially in drug delivery and diagnostics. Although they have distinct states, nanoparticles can only be crystalline or (non-aggregating) amorphous [5]. The methods used to formulate nanoparticles can be divided into two main fabrication techniques: top-down nanofabrication, which breaks down large structures into smaller components, and bottom-up nanofabrication, which builds nanostructures using each atom individually.

According to Tsou *et al*., a novel area of nanoparticle (NP) research has brought about a paradigm shift in medical technology by offering a fresh perspective on the treatment and diagnosis of dangerous chronic human diseases like Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and multiple system atrophy [6]. Nanoparticle-mediated drug delivery methods are emerging as viable instruments for gene therapy owing to their capacity for focused distribution and diminished immunogenicity. Although adeno-associated viruses (AAVs) and lentiviruses are the predominant viral vectors used in clinical applications, nanoparticles especially lipid- and polymer-based varieties, present benefits such as reduced toxicity and capacity to encapsulate diverse therapeutic agents [7]. Their ability to traverse the blood-brain barrier and target specific brain regions renders them a significant possibility for neurodegenerative illnesses like Alzheimer's disease. To overcome the blood-brain barrier and not compromise the biological defenses of the barrier, pharmacogenomics researchers have assisted in the development of functionalized nanocarriers or specific pharmacogenetic nano-markers that are nanoscale and range in diameter from 1 to 150 nm.

Technologies involving drug delivery are being carefully assessed and modified to satisfy the new nanoscaling standards. Drug delivery is intended for certain types of medical nanorobots [8]. These substances pass through veins to deliver medications to a particular region of the body. This feature is applied to antitumor effects of medications. For a variety of malignant tumors and illnesses, researchers are attempting to perform nanoscale wireless intranuclear and intracellular surgeries [9]. Some scientific precautions have been implemented, such as the progress and analysis of mechanical technologies for red blood cells known as respiration rates. In comparison to the normal erythrocytes, nanorobotics can provide more than 200 times more oxygen to bodily tissues. This might help in understanding how nanotechnology can be applied in the future to diagnose, treat, and cure a variety of blood-related conditions [10]. In conclusion, the medical industry has undergone a revolution owing to the use of nanotechnology for drug delivery. This has made it possible for medications to be delivered precisely and efficiently, improve the therapeutic effectiveness of medications and reduce adverse effects. The prospect of drug delivery depends on the further development of nanoparticle-based methods for drug delivery.

1.3. Current treatment methods and their limitations

The current symptomatic pharmacotherapeutic therapies for Alzheimer's disease (AD) mainly aim to maintain intellectual skills and patient's cognitive dysfunctions while reducing the illness's progression, rather than reversing or curing neurodegeneration [11]. Acetylcholine, a neurotransmitter essential for memory and learning that decreases in AD, is increased by cholinesterase inhibitors such as galantamine, rivastigmine, and donepezil. Alhough

https://doi.org/10.56717/jpp.2025.v04i01.040

these medications can reduce symptoms, their effects are limited and they typically wane as the illness worsens. Patients' tolerance may also be impacted by adverse symptoms like gastrointestinal distress and nausea. NMDA receptor antagonists, such as memantine, are another standard therapeutic option. They act by regulating glutamate activity to stop excitotoxicity, which is the process by which excessive glutamate damages the neurons. Memantine basically relieves symptoms; it has no effect on altering the course of the ailment and is most effective in moderate to severe stages of AD. Its usefulness in managing AD is further limited by the frequent adverse symptoms that patients, experience including dizziness and headache.

Amyloid-targeting monoclonal antibodies, like aducanumab, are more recent developments that attempt to lessen the buildup of amyloid-beta plaques, a major pathological feature of AD. Although the effectiveness of these medications is still up for question due to conflicting trial outcomes regarding cognitive enhancement, they do mark a move towards disease-modifying therapy. Because these treatments increase the risk of amyloid-related imaging abnormalities (ARIA), including brain hemorrhage and swelling, safety considerations are also very important. The accessibility of these treatments is further complicated by their high costs and restricted patient eligibility.

Additionally, experimental therapies targeting tau proteins, which cause neurofibrillary tangles in AD are being investigated. The majority of these treatments are undergoing clinical trials and are part of a developing field of study. Given the complexity of AD, it is unclear if focusing solely on tau can appreciably change the course of the illness, and the efficacy and safety profiles of anti-tau therapy remain unknown.

In the management of AD, supportive therapies such as social interaction, physical exercise, and cognitive stimulation are complimentary. The goal of these non-pharmacological treatments is to preserve functional independence and quality of life. They can enhance day-to-day functioning, but do not affect underlying etiology or alter the course of the disease. The advantages of supportive care, however, differ greatly and call for constant work from caregivers and patients.

In summary, existing treatments for AD are limited in their effectiveness and do not address the primary roots of the disease, even though they provide some symptomatic relief. These drawbacks underscore the urgent need for cutting-edge therapeutic strategies with the potential to directly address AD at the cellular and molecular levels, such as sophisticated gene therapies and nanoparticle-mediated delivery systems. Table 1 summarizes the standard drugs used in Alzheimer's disease treatment, including their mechanisms of action, dosage forms, and delivery strategies.

1.4. Objectives of study

The objective of this study is to analyze the literature as follows:

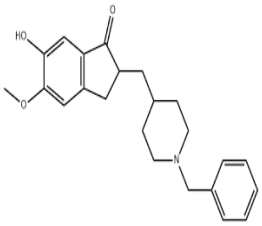
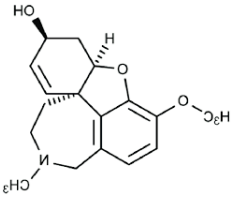
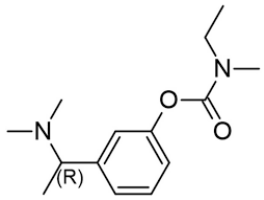
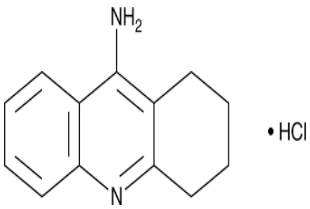
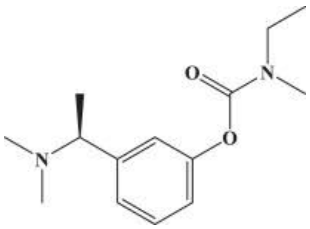
- Provides a comprehensive overview of recent advances in nanoparticle-mediated gene therapy for Alzheimer's disease.
- Examine how nanoparticles can be used to deliver therapeutic genes targeting AD pathology at the molecular level.
- Offer insights to guide the design of future gene-based therapies for AD, with relevance for both preclinical and clinical applications.

1.5. Research questions

1. How do nanoparticles enhance gene therapy for Alzheimer's disease?
2. What are the most promising types of nanoparticles used in Alzheimer's gene therapy?
3. What are the major challenges and limitations of nanoparticle-based gene therapy for Alzheimer's disease?
4. What recent advancements have been made in the application of nanoparticles for targeted gene delivery in neurodegenerative disorders?
5. How do nanoparticles improve the blood-brain barrier (BBB) penetration in gene therapy for Alzheimer's disease?
6. What are the safety and toxicity concerns associated with nanoparticle-mediated gene therapy in Alzheimer's disease models?
7. What are the key preclinical and clinical studies that demonstrate the efficacy of nanoparticle-based gene therapy for Alzheimer's disease?

https://doi.org/10.56717/jpp.2025.v04i01.040

Table 1. Standard drugs administered to target site in AD [15]

Standard drugs	Mechanism of action	Oral dosage form	Side effects	Drug delivery form
Donepezil 	1. Metabolizing enzyme substrate (CYP2D6 substrate, CYP3A substrate 2. Cholinesterase inhibitor 3. Acetylcholinesterase inhi bitor	5 mg per day (p.d.) for adults, 10 mg p.d. in case of severe AD	Insomnia Muscle cramps Fatigue Anorexia Nausea Diarrhea	Intranasal administration of tablets
Galantamine 	1. Reversible inhibitor Acetylcholinesterae 2. Enhance the intrinsic action of acetylcholine on nicotinic receptor	8 mg p.d., increase the dose to 16 mg p.d. after 4 weeks then increase to 24 mg p.d. after another 4 weeks	Blood in the urine Decreased heart rate Depression weight loss	Transbuccal delivery of tablet Capsule Oral solution
Rivastigmine 	1. Cholinesterase inhibitor 2. Acetylcholinesterase inhibitor 3. Butyrylcholinesterase inhibitor	1.5 mg two times p.d., increase the dose to 6 mg two times p.d.	Diarrhea Indigestion loss of appetite Aggression convulsion-ns	Transdermal Delivery of solution capsule
Tacrine 	2. Glycerophospholipid metabolism 3. Reversible inhibitor of acetylcholinesterase 4. Target Cholinergic synapse	10 mg four times p.d., dose increase to 40 mg four times p.d. if all liver reports are normal	Dark Urine Clay-colored stool Loss of appetite convulsion-ns	Intranasal administration of the capsule
Aducanumab 	Neuropsychiatric agents that target amyloid beta protein	First infusion (1 mg/kg), Second infusion (1 mg/kg), Third infusion (3 mg/kg), Fourth infusion (3 mg/kg), Fifth infusion (6 mg/kg), Sixth infusion (6 mg/kg), Seventh infusion onwards (10 mg/kg)	Edema Superficial siderosis Confusion/deli rium/altered mental status/disorien tation Hypersensitivi ty (angioedema, urticaria)	Intravenous (IV) infusion administration of clear to opalescent and colourless to yellow solution currently available in single-dose

1.6. Literature review

1.6.1. Gene therapy approaches for neurodegenerative diseases

In recent decades, there has been noticeable advancement in gene therapy for neurodegenerative illnesses. Numerous technological advancements,

https://doi.org/10.56717/jpp.2025.v04i01.040

such as the discovery of novel treatment targets and vectors, have been made possible by a better understanding of the pathogenic mechanisms underlying these diseases [12]. As our understanding of the underlying roots of neurodegenerative illnesses with both monogenic as well as complicated factors has grown, we have identified significant targets for a variety of genetic therapies. For compartmentalized organs like the eye, central nervous system (CNS), and cochlea, that are challenging to cure because most medications cross physiological barriers like the cerebrospinal fluid barrier (CSFB), red blood cells, blood-brain barrier (BBB), and blood-retinal barrier (BRB), the long-lasting, persistent, medicinal effects of gene therapy are alluring. Furthermore, gene therapy may be used to address some gene targets that do not respond to standard medication. This would enable the treatment of gain-of-function mutations by silencing genes and loss-of-function mutations through gene overexpression.

1.6.2. Application of nanoparticles in medicine

By delivering pharmaceuticals in a focused and efficient means, enhancing therapeutic efficacy and reducing adverse effects, nanotechnology has completely altered the drug delivery industry. Nanoparticles which are used to transport medications and deliver them to the intended site of action are used in the application of nanotechnology in drug delivery [13]. There are various benefits of using nanotechnology for drug delivery. First of all, it makes it possible to deliver medications to particular locations within the body, like inflammatory tissue, infected areas, and tumors, in a targeted and regulated manner [14]. This minimizes adverse effects and lowers the quantity of medications needed. Secondly, by enhancing the solubility and stability of medications, nanoparticles can enhance their efficacy in curing illnesses. Thirdly, nanotechnology can enhance the bioavailability of drugs by increasing their absorption and distribution in the body. This allows for lower doses of drugs to be used, leading to decreased toxicity [9].

1.6.3. Nanoparticle technology and gene therapy

An increasing number of are realizing that nanotechnology is the best way to repair the damage or harm caused by various elements in biological systems, and their understanding of this technology is growing. Gene therapy and gene transfer based on nanotechnology not only form the basis of new treatment methods, but also raise concerns among researchers regarding the cytotoxicity of nanomaterials, adverse effects of gene transfer systems, and dangerous effects of nanoparticle-mediated gene therapy. Release kinetics regulate the leaching rate in aqueous or physiological fluids, where the incorporation of water hydroxides makes these particles extremely vulnerable to nucleophilic attack, affecting the absorption of medications in the system and the eventual fate of these nanoparticles in the matrix.

1.6.4. Types of nanoparticles for gene therapy

Nanoparticles have become essential tools in gene therapy due to their ability to protect genetic material, improve cellular uptake, and enable targeted delivery. These nanoscale carriers overcome key challenges such as enzymatic degradation and immune clearance, making gene therapy more efficient and precise. Various types of nanoparticles, including lipid-based, polymeric, inorganic, and hybrid systems, have been designed to deliver nucleic acids like DNA, RNA, and siRNA. Each type offers unique advantages in terms of biocompatibility, stability, and functionality, providing a versatile platform for addressing genetic disorders, cancers, and other diseases. Fig. 1 illustrates various nanocarrier-mediated drug delivery mechanisms that effectively designed to enhance delivery across the blood-brain barrier, many of which have demonstrated success in preclinical models.

1.6.5. Polymeric nanocarrier

Drugs adsorbed on the surface or entrapped in the polymer core can be loaded into solid polymer nanoparticles with a size range of 1 to 1000 nm and composed of organic colloidal nanoparticles made of natural or synthetic materials [16]. Experiments using glycosylated siRNA-polymer complexes with a phenylalanine-leucine-glycine glycosyl sequence demonstrated the therapeutic efficacy of polymer nanoparticles in AD treatment. Cathepsin B, a cysteine protease found in lysosomes, can cleave these drug transporters [17-18]. Aβ accumulation and other forms of traumatic brain injury may be the result of

https://doi.org/10.56717/jpp.2025.v04i01.040

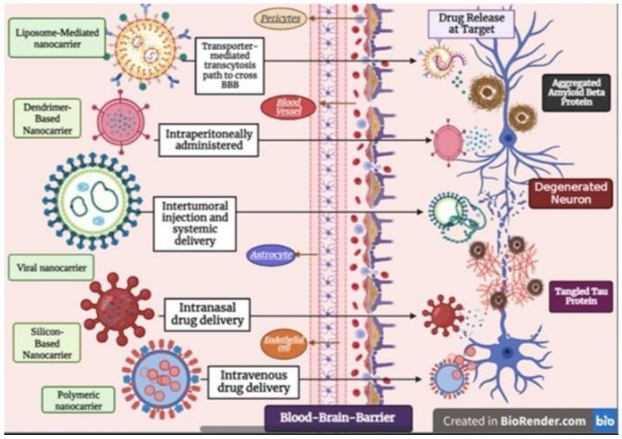


Figure 1. Various nanocarrier-mediated drug delivery mechanisms that surpasses the blood–brain barrier in order to treat the target site in neurodegenerative brain [15].

neurocognitive diseases like Alzheimer's disease, which increase the level of cathepsin B. This protease releases the siRNA-plasmid DNA conveyed by the polymeric NP into the cells at the target site by proteolytic cleavage of the siRNA glycosylated polymer complex [19]. By decreasing Aβ levels, the DNA plasmid, and a messenger RNA-targeting antisense oligonucleotide that improves processing of APP. Its center is hydrophobic, but its shell is hydrophilic, making it stable as a drug carrier and capable to cross the blood-brain barrier. A transgenic AD mouse model was used to study the characteristics of polymeric nanoparticles, and the results indicated that BACE1 was inhibited and Aβ levels were selectively reduced [20].

The core of the nanoparticles contains complicated medications or chemicals that are readily released into the target biological system by taking advantage of the biodegradable qualities and diffusion mechanisms of the polymer nanoshell, even when the nanoshell itself remains stable in the body for a long period. Baysal *et al*., claim that [PLGA bPEG] poly (lactic-co-glycolic acid)-block-poly (ethylene glycol) donepezil-loaded nanoparticles have neuroprotective properties and disrupt fibrillogenesis *in vitro*. In medical research, PLGA is the most studied polymer due to its biocompatibility with cells and tissues, controlled and sustained release, and low side effects. The European Medicines Agency (EMA) as well as the US FDA have authorized the clinical usage of PLGA in tissue engineering, vaccinations, and medication delivery. Zhu et al. recognized and ended the proliferation of tau aggregates in neuronal cells through multivalent binding effects with the aggregated protein on the multipurpose function of polymeric nano-inhibitors was very successful in inhibiting the aggregation of tau protein [21]. Additionally, they included a tau-binding peptide in the polymeric nano-inhibitor, which lessens the cytotoxicity of tau in AD brains by making tau complexes easier to eliminate than mature (hyperphosphorylated) tau aggregates. They concluded that this multipurpose nano-inhibitor would facilitate the development of novel drug delivery methods for the treatment of Alzheimer's disease.

1.6.6. Liposome nanocarrier

Liposomes possess amphiphilic characteristics, indicating the presence of both hydrophilic and hydrophobic domains. This distinctive structure allows the encapsulation of many therapeutic substances, rendering it extremely appropriate for drug delivery applications. Liposomal NPs, which are composed of non-toxic, naturally occurring phospholipids and cholesterol, can now target certain body regions owing to advancements in pharmaceutical formulation and research [22]. To enable liposomes to coalesce with specific cells and function as anti-apoptotic agents for treating diseases that are neurodegenerative, their surface can be modified with specific proteins [23]. According to recent research, the neuronal transport (in the brain) of amyloidtargeting antibodies across the blood-brain barrier is enhanced by glutathione-targeted PEG liposomes. Recent investigations have shown that senile plaques in AD brains can be repaired by liposomes coated with Aβ (monoclonal) antibodies [24]. To lessen the cytotoxicity of cationic nanoparticles, anionic siRNA nanocomplexes were made with cationic targeting peptides and anionic polyethylene glycol (PEG) liposomes. These nanocomplexes may also be used to suppress BACE1 [25]. This study supports the utilization of liposomal amyloid drug delivery systems for future disease diagnosis and therapy by addressing the negative impacts of inflammatory indicators. They are less toxic and have better biodegradability and biocompatibility than other nanomaterials. Their capacity to transport various therapeutic chemicals to

https://doi.org/10.56717/jpp.2025.v04i01.040

brain cells across the blood-brain barrier has led to their recent use in the treatment of AD. Lazar *et al*. conducted research on a polyphenol molecule called curcumin, which is extracted from the spice turmeric. He asserted that because of their antioxidant, anti-amyloid and anti-inflammatory, properties, curcumin- conjugated nano-liposomes are novel possibilities that might be applied to Alzheimer's disease detection and associated targeted delivery of drugs [26]. According to some scientists, liposomes based on phosphatidylserine and loaded with metformin have shown superior effectiveness in enhancing memory and learning and reducing neuroinflammation compared to standard metformin in a rat model of Alzheimer's disease. Amyloid plaques have reduced and other neurodegenerative illnesses in the brain have been cured as a result of the use of numerous other liposome-based nanocarriers in different experimental models.

1.6.7. Silicon-based nanocarrier

Vallet-Regi *et al*. the study of the properties of silicon nanoparticles concerning drug release mechanisms in drug therapy [27]. According to Argyo *et al*., silicon nanoparticles are systematically mesopore-like structures with adjustable sizes between 50 and 200 nm, diameters between 2 and 6 nm, enormous pore volumes between 0.6 and 1 cm3/g, and surface areas between 700 and 1000 m2/g [28]. The most significant and possibly evident benefit of mesoporous silica nanoparticles (MSNs) is the extent to which they interact with biological systems. These MSNs have transformed controlled drug/gene delivery systems intended to treat a variety of diseases in nanotherapy because of their shape robustness, tissue properties, surface modification, small size, functionalization, pore size, and optimal ability to cross the blood-brain barrier [29]. By employing effective ligand-receptor interactions, the architecture of gene-mediated drug delivery nanosystems' makes it simple to differentiate between healthy and disease-specific aggregated cells. The use of gatekeepers to restrict pore opening and create ceramic nanosystems with 0% premature cargo release is one of the the main benefits of employing mesoporous silica nanoparticles (MSNs) as a system for delivery of drug [30]. By using linkers that are capable of cleaving in reaction to specific stimuli to create poreblocking caps, stimuli-responsive activity can be achieved. There are two types of stimuli that can produce premature alterations in nanocarriers: external pathologies, like magnetic fields, ultrasound, and light that can be applied momentarily by clinicians, and internal pathologies such as pH, redox potential and enzymes, that can be addressed. With a binding energy of 452 KJ/mol, the strong chemical bond of siloxane's (-Si-o-) is the primary characteristic that sets MSNs apart from other nanoparticle carriers [31]. Basharzad *et al*. used functionalized polysorbate 80 (PS) and very high biocompatible mesoporous silica nanoparticles (MSNs) to deliver rivastigmine to the AD rat brain across the blood-brain barrier [32]. According to the findings, PS-functionalized MSNs might be a useful medication delivery method for avoiding the blood-brain barrier, which is crucial for the accurate delivery of drugs to the brain.

1.6.8. Dendrimer based nanocarrier

Multivalent molecules with regular branches and distinct three-dimensional shapes are called dendrimers. A functional unit of a dendrimer from which branches grow is called a dendron. Dendrimer-based methods enable the production of dendrimer encapsulated nanoparticles (DENs), which are nanoparticles with a diameter between 1.5 and 10 nm [33]. Using an inventive dual-targeted drug delivery system, Zhang *et al.* conducted experiments in which they coated dendrimer nanoparticles with apolipoprotein A [34]. This allowed them to deliver a modified protein that is expressed at the target site and inhibits BACE1, which causes the body to form Aβ plaques and shrink the brain [35]. In a rat model of AD, Gothwal et al. demonstrated that injecting dendrimers made from lactoferrin and polyamidoamine memantine loaded conjugates enhanced cognition, behavior and memory [36]. Due to their ability to penetrate the blood-brain barrier and reach their target site within the body, dendrimers have shown promise as nanocarriers in preclinical studies, making them appealing candidates for targeted drug delivery in several disease conditions, including cancer and neurological disorders.

1.6.9. Micelles

Micelles are spherical, self-assembling nanodrug delivery systems composed of amphiphilic substances

https://doi.org/10.56717/jpp.2025.v04i01.040

clustered in an inner hydrophobic core and an outer hydrophilic shell. Their particle size ranges from 5 to 50 nm. The type and ratio of the copolymers used can change the size and shape of the micelles. Due to their uniform size distribution and unique core structure, mixed micelles have several advantages, such as improved solubility, stability, sustained release, directional dispersion, and higher efficacy [37]. Mixed micelles are an ideal alternative to drug delivery systems because they can also prevent drugs from losing their activity. Yang *et al.* utilized resveratrol to promote the synthesis of mitochondria-targeted micelles (CT-NM) in the charged neurons of transgenic AD mice. This improved cognitive function and maintained the dynamic balance between fission of the mitochondria and fusion in APP/PS1-deficient mice [38]. In addition, a micellar drug delivery system based on polymer nanoparticles (ABPEG-LysB/CUR) containing the hydrophilic drug curcumin (the active ingredient in turmeric) has been developed, which targets A-β aggregation and ROS reactivity, as well as being able to scavenge ROS [39]. Besides, a new drug delivery method called Soluplus has recently been developed, which is a (poly) vinyl caprolactam, (poly) vinyl acetate and polyethylene glycol graft copolymer. It has excellent solubilization properties for drugs that are poorly soluble in water and can produce micellar structures when they are dissolved. The micelles produced by Soluplus have low critical micelle concentration values and good dilution stabilities.

1.6.10. Gold nanocarrier

At the nanoscale, gold also possesses special optical qualities. If gold is not red at the nano level, it is purple. Because of their exceptional qualities, such as ease of synthesis, size control, distinctive surface plasmon resonance, and superior biocompatibility, gold nanoparticles have demonstrated tremendous promise in the treatment of a wide range of illnesses. The diameter of colloidal gold particles, or AuNPs, ranges from 1 to 100 nm [40]. They are employed in thermal ablation, sensitive diagnostic testing, improved radiotherapy, and drug delivery [41]. Stable AuNPs loaded with L- and D-glutathione were recently produced by Hou *et al*. After being administered intravenously, these AuNPs traversed the blood-brain barrier without harming anything. The AuNPs markedly enhanced spatial relational learning and memory along with improving neuronal survival, as demonstrated by the production of cAMP response element binding protein, stromal interaction molecules such as STIM 1 and STIM 2, and multiple brain-derived neurotrophic factors (BNDF) [4].

1.6.11. Viral nanocarrier

Since viruses are natural carriers that transfer genomes and viral proteins to vulnerable cells, viral vectors were initially used to transfer foreign genes. Lentiviruses, adenoviruses, and adeno-associated viruses are the most widely used viral vectors for gene delivery. Nevertheless, they only carry trace amounts of foreign materials and are intrinsically hazardous [42]. Therefore, virus-based nanocarriers have been designed to replicate the nature of viral vectors. These nanocarriers have superior immunogenicity compared to ordinary soluble protein monomeric antigens and outstanding characteristics to transport biomolecules to target areas in cells. Although VNPs lack the viral genetic components that facilitate replication, they are considered biologically safer, despite sharing many of the same benefits as viral vectors. Cells can absorb VNPs, which are then broken down in the cytoplasm to liberate their contents; they share a nanostructure with the virions [43]. Additionally, VLPs can be designed to deliver certain expressions at specified locations. In a study to identify neuronal protein expression, proliferation, and attenuation in APP/PS1 AD transgenic mice. Arora *et al*. examined the effectiveness of lipid-based viral nanoparticles targeting brain-derived neurotrophic factor (BDNF) [44]. The differentiation and developmental survival of neuronal populations depend on a neurotrophin known as BDNF. BDNF, which regulates both inhibitory and excitatory synaptic transmission as well as activity dependent plasticity, is highly expressed in the adult brain. Tau phosphorylation, neuroinflammation, Aβ buildup, and neuronal cell death are all linked to BDNF deficiency. However, it is unknown, how decreased BDNF signaling affects Alzheimer's disease. Functionalized viral nanoparticles, however, have been shown to enhance BDNF expression while reducing the generation of toxic oligomeric Aβ in AD

https://doi.org/10.56717/jpp.2025.v04i01.040

mouse trials. Another study by Dodart *et al*, investigated the potential of lentiviral nanocarriers based on apolipoprotein E isoforms to minimize the formation of senile plaques in AD brains. The purpose of this study was to modify hippocampal Abeta aggregation and decrease ApoE expression in Alzheimer's disease brains [45].

2. Materials and methods

A systematic search strategy was used to identify the relevant literature. The following electronic databases were searched: Science Direct, PubMed, Google Scholar and Scopus. The search was restricted to peer-reviewed articles published in English language between 1980 and 2024. Keywords and search terms included combinations of "Alzheimer's Disease", "Neurodegenerative Disorders", "Nanoparticles", "Gene Therapy", "Dementia".

To ensure the quality and relevance of the literature, specific inclusion and exclusion criteria were established. The inclusion criteria comprised studies investigating nanoparticle-mediated gene therapy for Alzheimer's disease, including *in vivo*, *in vitro*, and clinical studies, as well as review articles providing a comprehensive overview of the topic. The exclusion criteria encompassed studies unrelated to Alzheimer's disease, articles that did not focus on nanoparticle-mediated gene therapy, and non-peer-reviewed publications, such as conference abstracts and opinion articles.

As this study involved a review of the published literature, no ethical approval was required. However, the review was conducted in adherence to ethical guidelines for ensuring transparency, systematic reviews, accuracy, and integrity in reporting.

3. Results and discussion

The application of nanoparticle-mediated gene therapy in Alzheimer's disease (AD) represents a promising approach to overcome the challenges posed by conventional treatment strategies. Current treatments primarily focus on symptom management rather than addressing the underlying pathology of AD. The integration of nanotechnology into gene therapy offers new ways for targeted drug delivery, increased bioavailability, and the potential to modify disease progression at the molecular level. However, despite significant progress, there are still several challenges and limitations that must be addressed before nanoparticle-based gene therapy can become a viable clinical option.

3.1. Efficacy of nanoparticle-based gene therapy

The primary advantage of nanoparticle-mediated gene therapy is its ability to enhance drug penetration across the blood-brain barrier (BBB), which is a major obstacle in the treatment of neurodegenerative disorders. Different nanoparticle carriers, such as liposomes, polymeric nanoparticles, dendrimers, micelles, and inorganic nanoparticles, have demonstrated varying degrees of success in gene delivery. Liposomal nanoparticles have shown promise in improving the stability and bioavailability of therapeutic agents, while reducing systemic toxicity. Similarly, polymeric nanoparticles, particularly those based on PLGA, have been effective in carrying genetic material with sustained-release properties. Studies have indicated that these nanocarriers can facilitate the targeted inhibition of genes implicated in AD pathology, such as BACE1, which plays a crucial role in amyloid-beta plaque formation.

Additionally, gold nanoparticles and mesoporous silica nanoparticles (MSNs) have emerged as effective platforms for targeted drug delivery due to their unique physicochemical properties. MSNs, provide controlled drug release mechanisms that reduce premature degradation and off-target effects. However, while preclinical models have shown promising results, further studies are needed to validate these findings in clinical settings.

3.2. Challenges and limitations

Despite the advantages of nanoparticle-mediated gene therapy, several challenges remain. One of the major concerns is the potential cytotoxicity and immunogenicity of the nanoparticles. The long-term effects of nanoparticle accumulation in the brain are not yet fully understood, and rigorous safety assessments must be conducted before considering clinical applications. Although, nanoparticles improve drug bioavailability and BBB penetration, their distribution within the brain remains unpredictable. There is a need for more precise targeting mechanisms to ensure that therapeutic

https://doi.org/10.56717/jpp.2025.v04i01.040

agents reach specific brain regions affected by AD pathology without causing unintended side effects in the body.

Another limitation is the reproducibility of the nanoparticle synthesis. The production of nanoparticles with consistent size, surface characteristics, and drug-loading capacity is crucial for clinical translation. Variability in nanoparticle formulations can lead to inconsistent therapeutic outcomes, making standardization a priority for future research. Furthermore, the cost of developing nanoparticle-based therapies remains high, which may impact their accessibility for widespread clinical use.

3.3. Future directions and potential solutions

To overcome these challenges, future research should focus on optimizing nanoparticle formulations to enhance their biocompatibility and minimize toxicity. Functionalization of nanoparticles with targeting ligands, such as peptides and antibodies, can improve their specificity and therapeutic efficacy. Advances in nanotechnology, including the use of biodegradable materials and stimuli-responsive nanoparticles, hold great promise for refining drug delivery systems.

Additionally, integrating nanotechnology with emerging techniques such as CRISPR-based gene editing and RNA interference (RNAi) could enhance the precision of genetic interventions in AD. Nanoparticles carrying gene-editing tools can potentially correct genetic mutations or modulate key pathways involved in AD pathogenesis.

Further preclinical and clinical studies are needed to establish the long-term safety and efficacy of nanoparticle-mediated gene therapy. Collaborative efforts between neuroscientists, nanotechnologists, and pharmaceutical researchers are essential to translate these findings into effective AD treatments. Regulatory considerations and ethical implications must be addressed to ensure the responsible development and implementation of nanoparticle-based therapeutics.

3.4. The role of artificial intelligence in nanoparticle research

Artificial intelligence (AI) is increasingly being used in the development of nanoparticle-based therapies. AI-driven modeling and simulations can help optimize nanoparticle properties, predict their interactions with biological systems, and streamline the drug discovery process. Machine learning algorithms can also assist in identifying potential gene targets, improving delivery mechanisms, and analyzing large datasets from preclinical and clinical trials. The integration of AI in nanoparticle research has the potential to accelerate the development of effective personalized therapies for AD.

3.5. Ethical and regulatory considerations

As with any emerging medical technology, ethical and regulatory considerations must be addressed. The use of nanoparticles in gene therapy raises questions about long-term safety, patient consent, and equitable access to treatment. Additionally, regulatory agencies such as the FDA and EMA must establish clear guidelines for nanoparticle-based gene therapies to ensure their safety and efficacy. Addressing these challenges through transparent and collaborative regulatory frameworks is essential for the successful translation of nanoparticle-mediated gene therapies into clinical practice.

Although, nanoparticle-mediated gene therapy offers a novel and promising approach for AD treatment, significant challenges must be overcome before it can be widely adopted. Future advancements in nanoparticle design, targeted delivery strategies, and gene therapy techniques will be key to unlocking the full potential of this innovative approach. By addressing these limitations through interdisciplinary collaboration and continued research, nanoparticle-based therapies could ultimately provide transformative solutions for AD and other neurodegenerative disorders.

Nanotechnology has the potential to revolutionize medicine, and its application in AD treatment represents a significant step toward developing more effective and targeted therapies. As research advances, a deeper understanding of the mechanisms governing the interactions between nanoparticles and biological systems will be crucial. The synergy between nanomedicine, genetic engineering, and artificial intelligence presents a compelling future in the fight against AD. Ultimately, continued investment in nanotechnology and interdisciplinary collaboration will be essential in bringing

https://doi.org/10.56717/jpp.2025.v04i01.040

nanoparticle-based therapies from bench to bedside, offering renewed hope for millions of patients with AD worldwide.

4. Conclusions

Nanoparticle-mediated drug delivery has the potential to transform Alzheimer's disease treatment. The colloidal size, ability to penetrate the blood-brain barrier, and accurate localization enable nanoparticles to overcome some limitations of previous methods. Advancements in in vitro models and active targeting have enhanced therapeutic efficacy. These findings represent significant prospects for the innovative strategic delivery of brain medications and enhanced Alzheimer's disease therapy.

Notwithstanding this assurance, numerous challenges persist. Nanoparticles require meticulous tuning, rigorous safety testing, and precise targeting to ensure their efficacy. Fundamental scientists and medical experts should interact to connect preclinical and clinical research. By facilitating translational activities, nanoparticle-based therapeutics may transition from laboratory research to clinical use, enhancing outcomes for Alzheimer's disease and other neurodegenerative disorders.

As Alzheimer's disease is the most prevalent neurological ailment and a primary cause of mortality among the elderly, the demand for alternative therapeutic approaches has increased. Despite certain trials demonstrating potential disease-modifying medications, most have not succeeded in converting preclinical success into clinical results. Conventional Alzheimer's disease treatment has focused on pathological symptoms rather than underlying causes. The adjustable platform of nanoparticles for bioengineering therapeutic solutions enables the administration of bioactive pharmaceuticals with exceptional precision. Nanoparticles are multifaceted and promising instruments for combating Alzheimer's disease and other neurodegenerative disorders. These advanced technologies have the potential to revolutionize treatment strategies, enhance patient outcomes and tackle the significant challenges posed by these chronic conditions through ongoing research and development. Regrettably, no Alzheimer's disease treatment genuinely modifies the condition.

Authors' contributions

Conceptualization and edited the manuscript, L.A.H.; Literature reviewed, K.A.N.; Drafted the Manuscript, A.C.O.; Proof read, E.M.H.

Acknowledgements

The authors don't have anything to acknowledge.

Funding

This research received no specific grant from any funding agency (the public, commercial, or not-for-profit sectors).

Availability of data and materials

All data will be made available on request according to the journal policy.

Conflicts of interest

The authors declare no conflict of interest.

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