A Comprehensive Review on The Use of Nanoparticles in Alzheimer's Disease: A Promising Therapeutic Approach

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Declaration

It is hereby declared that

1. The thesis submitted is my own work while pursuing a degree at Brac University.
2. The thesis does not contain any formerly published or written materials by a third party, exception of where this is properly cited with complete and accurate references.
3. The thesis does not contain materials that has been approved or submitted, for any other degree or certificate at a university or other institution.
4. All sources of help have been acknowledged.

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Approval

The thesis titled "A Comprehensive Review on The Use of Nanoparticles in Alzheimer's Disease: A Promising Therapeutic Approach" submitted by Sadia Jahan (20146074) has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trials.

Abstract

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. Currently, there is no definitive cure for this condition. Traditional treatment approaches face challenges, such as limited drug bioavailability and the difficulty of drugs crossing the blood-brain barrier (BBB). However, nanoparticles (NPs) have emerged as a promising solution, offering a targeted and efficient drug delivery system. These nanoscale carriers can enhance the bioavailability of therapeutic agents and enable controlled release of active substances while bypassing the BBB. This paper reviews the therapeutic applications of nanoparticles in AD, emphasizing their potential to deliver anti-inflammatory, antioxidant, and amyloid-targeting drugs directly to affected brain regions. It discusses various types of nanoparticle-based formulations, including liposomes, polymeric NPs, and metallic NPs, highlighting their multifunctional roles in diagnostic imaging and the early detection of AD biomarkers. Furthermore, the paper addresses concerns regarding potential cytotoxicity, long-term biocompatibility, and regulatory challenges. This comprehensive review underscores the transformative potential of nanoparticles in managing AD, paving the way for innovative and personalized medical interventions.

Keywords: Alzheimer's Disease, blood-brain barrier, nanoparticles, anti-inflammatory, antioxidant, and amyloid-beta, bioavailability, biocompatibility

Dedication

Dedicated to my parents who encouraged me to choose this path.

Acknowledgment

I want to begin by thanking Allah for all his blessings and my parents and loved ones for their constant support and faith in me throughout the whole university journey.

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List of Acronyms

AD	Alzheimer's Disease
Aβ	Amyloid-Beta
NFTs	Neurofibrillary Tangles
MCI	Mild Cognitive Impairment
APP	Amyloid Precursor protein
BACE1	Beta-Secretase
ROS	Reactive Oxygen Species
IL-1β	Interleukin-1β
TNF-α	Tumor Necrosis Factor-alpha
PSEN1	Presenilin 1
PSEN2	Presenilin 2
CSF	Cerebrospinal Fluid
PET	Positron Emission Tomography
MRI	Magnetic Resonance Imaging
PEG	Polyethene Glycol
BBB	Blood Brain Barrier
PLGA	Poly (lactic-co-glycolic acid)
SLNs	Solid Lipid Nanoparticles
AuNPs	Gold Nanoparticles
AgNPs	Silver Nanoparticles
CNTs	Carbon Nanotubes
GO	Graphene Oxide
PAMAM	Polyamidoamine
QDs	Quantum dots

PAI	Photoacoustic Imaging
SeCQDs	Selenium-doped Carbon Quantum Dots
CeO2 NPs	Cerium oxide Nanoparticles
RMT	Receptor-mediated Transcytosis

Chapter 01

1.1 Background of Alzheimer’s Disease

Alzheimer's disease (AD) is a progressive and irreversible neurological condition that stands as the leading cause of dementia globally, affecting millions of people and their families (Alzheimer's Association, 2024). (Alzheimer's Association, 2024). It is distinguished by a progressive deterioration in cognitive abilities, which slowly causes major difficulties in day-to-day living and, eventually, the loss of independence. According to the World Health Organization (2022), AD is responsible for 60% to 80% of the dementia cases that affect over 50 million individuals worldwide. Currently, 10% of people over 65 and 30% to 50% of those over 85 have AD, a prevalence that is rising exponentially with age (Brookmeyer et al., 2018).

Despite extensive research, the exact cause of Alzheimer's remains unclear, and current treatments only provide symptomatic relief without halting or reversing the disease's progression (Brookmeyer et al., 2018). In recent years, nanoparticles have emerged as a promising avenue for addressing the challenges associated with Alzheimer's disease. Their unique physicochemical properties such as high surface area, customizable surface functionalization, and ability to cross biological barriers make them an ideal candidate for the treatment of AD (Brookmeyer et al., 2018).

1.2 Disease Progression

AD primarily targets the brain's cortex and hippocampus, which are crucial areas for memory and cognitive processes (Deture & Dickson, 2019). It involves the accumulation of amyloid-beta (Aβ) peptides, which aggregates to form extracellular plaques and hyperphosphorylation of tau protein that leads to the formation of intracellular neurofibrillary tangles (NFTs) (Deture & Dickson, 2019). These

degenerative alterations impair neuronal function and synaptic connectivity, leading in widespread neurodegeneration and brain shrinkage.

Alzheimer's disease develops in phases, each with its own set of signs and symptoms.

Preclinical Stage: In the preclinical stage, pathological alterations in the brain take place years before symptoms really manifest.

These changes are only detectable through biomarker tests and advanced imaging processes (Jack et al., 2018).

- **Signs:** The presence of amyloid plaques and tau tangles in the brain.
- **Symptoms:** No noticeable symptoms.

Mild Cognitive Impairment (MCI): Mild cognitive impairment (MCI) is seen when individuals start to experience noticeable memory issues but can do daily life activities independently (Petersen et al., 2014). But these noticeable memory issues can often progress to AD with the passing time.

- **Signs:** Minor changes in thinking and reasoning abilities.
- **Symptoms:** Mild memory problems, such as forgetting recent events, misplacing items, etc.

Mild Stage: Cognitive decline becomes more apparent in the mild stage, affecting daily life activities and social interactions (Alzheimer's Association, 2024).

- **Signs:** Mood changes, anxiety, poor judgment of happenings around, etc.
- **Symptoms:** Increasing memory loss, confusion, difficulty in organizing tasks, etc.

Moderate Stage: In the moderate stage, individuals require assistance with the daily activities of their lives and symptoms start to get worse with time (Alzheimer's Association, 2024).

- **Signs:** Behavioral changes such as aggression, agitation, wandering, etc.
- **Symptoms:** Significant memory loss, confusion about time and place, difficulty in recognizing people, etc.

Severe Stage: In the severe or last stage, individuals lose the ability to respond to happenings around them and are unable to control movements. Severe complications are also seen in the brain, which often leads to death (Alzheimer's Association, 2024).

- **Signs:** Complete dependence on caregivers for daily living.
- **Symptoms:** Severe memory loss, loss of awareness of surroundings, difficulty in swallowing, loss of bowel and bladder control.

Figure 01: Progression of AD (Compton, 2023)

1.3 Pathogenesis of AD

The pathogenesis of AD involves complex molecular and cellular processes that lead to several complexities in the brain.

Amyloid-Beta (Aβ) Pathology

One important aspect of AD pathogenesis is the buildup of amyloid beta (Aβ) peptides (Hardy & Selkoe, 2002). Aβ peptides are derived from the cleavage of amyloid precursor protein (APP) by beta-secretase (BACE1) and gamma-secretase. In the brain's extracellular spaces, insoluble Aβ plaques develop as a result of an imbalance between the synthesis and removal of Aβ peptides. Neurotoxicity and disruption of neuronal transmission result from this aggregation (Hardy & Selkoe,2002). These plaques mostly form in the brain's neocortex and hippocampal regions, which are essential for memory and learning.

Tau Protein Dysfunction

Tau is a microtubule-associated protein that stabilizes axonal microtubules under normal conditions. In AD, hyperphosphorylated tau splits from these microtubules and results in the development of neurofibrillary tangles (NFTs) inside the neurons. These tangles interfere with intracellular transport, which leads to neuronal death and dysfunction (Goedert & Spillantini, 2006).

Oxidative Stress

Oxidative stress results from the imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses in the brain (Butterfield & Halliwell, 2019). Mitochondrial dysfunction, combined with oxidative damage caused by Aβ plaques, increases ROS production, leading to protein oxidation, lipid peroxidation, and DNA damage in neurons (Butterfield & Halliwell, 2019).

Neuroinflammation

Activated microglia and astrocytes surrounding Aβ plaques cause inflammation in the brain by releasing pro-inflammatory cytokines, like interleukin-1β (IL-1β) and

tumor necrosis factor-alpha (TNF-α) (Heneka et al., 2015). When inflammation becomes chronic, it causes neuronal injury and perpetuates a cycle of toxicity, amplifying both Aβ deposition and tau pathology (Heneka et al., 2015).

Synaptic and Neuronal Loss

The combined effect of Aβ plaques, NFTs, oxidative stress, and neuroinflammation causes synaptic dysfunction and neuronal death, leading to cognitive and functional deficits (Serrano-Pozo et al., 2011).

Genetic and Environmental Factors

Mutations in the APP, PSEN1, and PSEN2 genes are linked to an early onset of Alzheimer's disease, resulting in increased development of Aβ plaques (Karch & Goate, 2015). The APOE ε4 allele is a genetic risk factor for late-onset Alzheimer's disease, affecting Aβ peptide deposition and clearance in the brain (Karch & Goate, 2015).

Environmental and lifestyle factors, such as hypertension, diabetes, obesity, smoking, and physical inactivity, all contribute to the likelihood and progression of Alzheimer's disease by contributing to vascular dysfunction and metabolic abnormalities (Livingston et al., 2020).

1.4 Aim of the research

The main goal of this study is to explore the therapeutic potential of nanoparticles by assessing the efficacy various nanoparticle-based formulations, which can help to reduce Aβ plaque accumulation and tau hyperphosphorylation and provide enhanced neuroprotection in Alzheimer's disease models more successfully than outcomes of existing conventional treatments. This research provides a comprehensive understanding of various nanoparticles that are currently under

investigation which can offer a novel treatment strategy, leading to improved patient outcomes and quality of life.

1.5 Objective of the Research:

- To conduct a thorough review of the current literature on the use of nanoparticles in the treatment and diagnosis of Alzheimer's disease.
- To highlight the potential benefits and therapeutic advantages of nanoparticle-based approaches in Alzheimer's disease management.
- To evaluate the effectiveness and safety of nanoparticle-based therapies in both preclinical and clinical settings.
- To identify the challenges and limitations associated with the use of nanoparticles in Alzheimer's disease treatment.
- To propose potential solutions and future research directions for enhancing the application of nanoparticles in Alzheimer's disease.

Chapter 02

Methodology

For this review paper, a comprehensive collection of research articles related to the topic was collected from Google Scholar, PubMed, and Frontiers. The writing of this paper is based on cross-citations, with a focus on highly cited journal articles and leading papers in the field of Alzheimer's disease and nanoparticles. This approach allowed for a more detailed gathering of information, which was cited through the American Psychological Association (APA) 7th edition style.

Chapter 03

3.1 Conventional treatment strategies for Alzheimer's Disease

The treatment of AD primarily relies on clinical evaluation. Such as-

Cerebrospinal Fluid (CSF) Biomarkers: Cerebrospinal Fluid (CSF) biomarkers are some of the most well-known and often utilized biomarkers. They are used to measure amyloid-beta (Aβ), total tau (t-tau), and phosphorylated tau (p-tau) levels for diagnosing AD (Dubois et al., 2023).

Blood-Based Biomarkers: Recent breakthroughs have resulted in the creation of blood-based biomarkers as a less intrusive alternative to CSF sample (Dubois et al., 2023). Blood tests can measure the levels of Aβ peptides, tau proteins, and other molecules associated with AD pathogenesis.

Imaging Biomarkers: Imaging techniques, like positron emission tomography (PET) and magnetic resonance imaging (MRI), help in assessing AD pathology (Dubois et al., 2023). PET scans can visualize amyloid plaques and tau tangles, providing a direct assessment of AD-related changes in the brain. Meanwhile, MRI can detect structural alterations and brain atrophy-related pictures (Dubois et al., 2023).

Genetic Biomarkers: Genetic biomarkers can help identify people who are predisposed to Alzheimer's disease. They can assist in stratifying patients for clinical trials and develop personalized treatment approaches (Dubois et al., 2023).

In addition, several drugs are commercially available to manage AD, each targeting different aspects of the condition. Such as-

Cholinesterase Inhibitors (ChEIs)

Drugs: Donepezil, Rivastigmine, Galantamine

Mechanism of Action: ChEIs inhibit acetylcholinesterase, which breaks down acetylcholine in the synaptic cleft. This increases acetylcholine levels, enhancing cholinergic neurotransmission, which is crucial for memory and cognition (Buccellato et al., 2023).

NMDA Receptor Antagonists

Drug: Memantine

Mechanism of Action: Memantine modulates the activity of N-methyl-D-aspartate (NMDA) receptors by blocking excessive glutamate activity. This prevents excitotoxicity, a process where overactivation of NMDA receptors damages neurons. It helps to maintain synaptic plasticity and cognitive functions, especially in moderate to severe stages of AD (Buccellato et al., 2023).

Combination Therapy

Some treatments combine AChEIs and NMDA antagonists to provide a more comprehensive therapeutic approach. This combination targets multiple pathways involved in the disease process, potentially offering enhanced benefits by addressing different aspects of neuronal dysfunction simultaneously (Buccellato et al., 2023).

Amyloid-Beta Targeting Therapies

Drug: Aducanumab (FDA-approved in select cases)

Mechanism of Action: Aducanumab is a monoclonal antibody designed to reduce amyloid-beta plaques in the brain by clearing amyloid deposits, targeting the potential root cause of AD (Cummings, 2021).

Symptomatic Treatments

Drugs: Antidepressants (e.g., SSRIs), Antipsychotics, Anxiolytics

Mechanism of Action: These drugs address behavioral and psychological symptoms such as depression, agitation, and anxiety. The applications of these treatments improve quality of life but do not directly modify the disease (Cummings, 2021).

Non-Pharmacological Interventions

Examples: Cognitive therapy, exercise programs, social activities, and Mediterranean diet

Mechanism of Action: Includes cognitive therapies, physical activity, social engagement, and dietary modifications. These interventions help to maintain mental function and improve patients' overall quality of life (Cummings, 2021).

While these drugs aid to treat Alzheimer's symptoms, they do not give a definitive cure. Despite years of research, there is no cure for this disorder, emphasizing the need of continued research into the underlying disease mechanisms and the development of effective treatment techniques. Exploring novel techniques, such as nanoparticle-based medicines, offers great prospects to improve treatment results. As our understanding of Alzheimer's disease advances, early detection and thorough care techniques are critical for improving the quality of life for those affected by the illness.

Chapter 04

4.1 Introduction to Nanoparticles

Nanoparticles (NPs) are tiny materials with at least one dimension ranging from one to a hundred nanometers. These tiny particles have unique properties like enhanced reactivity and modified surface chemistry which significantly differ from those of bulk counterparts due to high surface area-to-volume ratio and quantum effects (Patra et al., 2018). They have a small size and large surface area that provides numerous advantages in drug delivery mechanisms, enhancing their interaction with biological systems at the molecular and cellular level (Patra et al., 2018).

One of the significant benefits of using nanoparticles for drug delivery is their ability to enhance the bioavailability of poorly water-soluble drugs and protect them from degradation before reaching the target site (Yusuf et al., 2023). Moreover, nanoparticles can be engineered to carry a variety of therapeutic agents, including drugs, genes, and proteins, directly to targeted cells or tissues in the brain (Patra et al., 2018). This targeted delivery makes them highly effective for drug delivery and therapeutic applications, reducing side effects associated with traditional drug delivery methods.

Different types of nanoparticles possessing unique properties have been studied over the years for Alzheimer’s disease therapy to encapsulate or bind drugs to the affected areas of the brain in order to enhance the ability of the particles to penetrate the blood-brain barrier (BBB) and regulate drug release (Brookmeyer et al., 2018). With their potential for both diagnosis and treatment, nanoparticles are paving the way for more effective and precise management of Alzheimer's, marking a significant advancement in neurodegenerative disease research (Brookmeyer et al., 2018).

4.2 Properties and Characteristics

Size and Surface Area

Nanoparticles are smaller in size, allowing them to interact with biological systems at the molecular and cellular levels, which is critical for targeted medication delivery and intracellular settings (Afzal et al., 2022). Furthermore, the high surface area-to-volume ratio enables a greater amount of drug to be loaded onto or into the particles, increasing drug capacity (Afzal et al., 2022).

Shape and Morphology

Nanoparticles' shape has a significant impact on their cellular absorption and dispersion inside the body (Chithrani et al. 2006). Spherical nanoparticles are easier for cells to ingest than rod-shaped or irregularly shaped nanoparticles. Rod-shaped nanoparticles, on the other hand, can resist phagocytosis more successfully than spherical particles, allowing them to circulate in the bloodstream for longer periods of time.

Surface Modification

Surface modification is the process of modifying the surface properties of nanoparticles utilizing different techniques such as polymer coating, functional group attachment, and conjugation with targeted ligands to obtain desired functionalities (Afzal et al., 2022). PEGylation is a typical sort of surface modification that includes coating nanoparticles with polyethene glycol (PEG) to increase their circulation duration in the bloodstream (Afzal et al., 2022).

Surface Charge

The surface charge of nanoparticles influences their behavior and efficacy in drug administration and therapeutic applications (Afzal et al., 2022). Nanoparticles

having a high surface charge, whether positive or negative, are often more stable in suspension due to electrostatic repulsion, which helps to avoid aggregation and is critical for maintaining constant drug administration (Afzal et al., 2022). Positively charged nanoparticles have more cellular absorption than negatively charged ones. Negatively charged nanoparticles, on the other hand, may benefit from longer circulation periods because they interact less with plasma proteins and phagocytic cells (Patra et al., 2018).

Functionalization

Functionalization is the process of attaching particular molecules or ligands to the surface of nanoparticles, allowing for targeted medication administration via covalent or non-covalent interactions (Yusuf et al., 2023). Covalent bonding provides long-term stability by creating strong chemical interactions between the nanoparticle surface and functional molecules like antibodies or peptides. These compounds can be covalently linked to nanoparticles to target specific cell receptors, increasing the specificity of medication delivery. Non-covalent functionalization approaches, such as electrostatic interactions or hydrogen bonding, offer greater flexibility but may be less stable than covalent connections (Yusuf et al., 2023).

Ability to cross the Blood-Brain Barrier (BBB)

Nanoparticles have demonstrated great potential in medication delivery due to their capacity to pass the blood-brain barrier (BBB), a highly selective barrier that protects the brain from toxins and infections while limiting drug delivery to the central nervous system (Zhao et al., 2020). Nanoparticles can use a variety of ways to efficiently cross this barrier, including receptor-mediated transcytosis, in which nanoparticles are modified with ligands that bind to particular receptors on the BBB, allowing them to penetrate (Saraiva et al., 2016). Furthermore, nanoparticles may be

made to imitate natural transport pathways such as transferrin or insulin receptors, which aid in their entrance into the brain (Gabathuler, 2010).

Biocompatibility

Biocompatibility refers to nanoparticles' capacity to perform their intended tasks without harming the host. Nanoparticles used in medication delivery must be nontoxic, nonimmunogenic, and patient safe. Surface changes, such as coating nanoparticles with biocompatible polymers like PEG, can improve their biocompatibility, guaranteeing that they do not cause adverse immune responses or toxicity when delivered (Patra et al., 2018).

Biodegradability

Biodegradability refers to nanoparticles' ability to break down into harmless metabolites that can be readily removed from the body. Biodegradable nanoparticles are useful because they limit the possibility of long-term buildup and toxicity (Yusuf et al., 2023). Poly (lactic-co-glycolic acid) (PLGA) is a common material used in biodegradable nanoparticles because it degrades into lactic acid and glycolic acid, which the body naturally metabolizes (Yusuf et al., 2023).

4.3 Nanoparticles for Alzheimer’s disease therapy

Polymeric Nanoparticles

Polymeric nanoparticles are submicron-sized particles made from biodegradable and biocompatible polymers that can be functionalized with ligands to target receptors, specifically on the BBB (Mathew et al., 2012). Through direct targeting, these particles can reduce systemic exposure and minimize adverse effects. Polymeric nanoparticles can also enable controlled and sustained release of therapeutic agents, maintaining optimal drug concentrations over time (Mathew et al., 2012).

Curcumin (a natural compound with anti-inflammatory and antioxidant properties that has been shown to reduce Aβ aggregation) loaded PLGA nanoparticles have been extensively studied for the treatment of AD (Mathew et al., 2012). The encapsulation of curcumin in PLGA nanoparticles enhances the stability and bioavailability of the drug, allowing for effective targeting and prolonged release in the brain (Mathew et al., 2012).

Lipid-Based Nanoparticles

Lipid-based nanoparticles are a promising new class of drug delivery systems that offer several advantages for AD therapy, such as improved solubility, enhanced stability, and targeted delivery of the drug to the brain (Liu et al., 2023). These nanoparticles can also increase the shelf life and effectiveness of the drug by protecting it from degradation (Liu et al., 2023). For example- Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles (SLNs) are solid particles made from lipids that can encapsulate drugs, providing controlled release and better stability. Donepezil (an acetylcholinesterase inhibitor that helps to improve cognitive function in AD patients)-loaded SLNs have been developed for the treatment of AD (Tsakiri et al., 2022). They can enhance the bioavailability and targeting of the drug to the affected areas of the brain, leading to better therapeutic outcomes (Tsakiri et al., 2022).

Metallic Nanoparticles

Metallic nanoparticles can be functionalized with targeting ligands to enhance their delivery to specific regions of the brain. These nanoparticles act as antioxidants that help to reduce oxidative stress and can also alleviate neuroinflammation, which is a significant contributor to AD progression (Senthilkumar & Rajeshkumar, 2019). Gold Nanoparticles (AuNPs) have been studied for their ability to disrupt Aβ fibrils,

which can be achieved by applying a near-infrared femtosecond (fs) laser in combination with AuNPs (Senthilkumar & Rajeshkumar, 2019). This offers a potential therapeutic approach for treating AD.

Carbon-Based Nanoparticles

Carbon-based nanoparticles have shown significant potential in the treatment of AD due to their unique physicochemical properties (Bai et al., 2024). They function as antioxidants, which help to reduce oxidative stress and provide neuroprotective effects by shielding neurons from oxidative damage and inflammation (Bai et al., 2024). For example- Carbon Nanotubes (CNTs).

Carbon Nanotubes (CNTs) are cylindrical nanostructures known for their exceptional electrical conductivity, mechanical strength, and high surface area. CNTs loaded with therapeutic agents have been studied for their ability to target Aβ plaques and reduction of oxidative stress in AD models (Bai et al., 2024). The high surface area of CNTs allows for efficient drug loading and targeted delivery to the brain, which enhances the efficacy of the encapsulated drugs (Bai et al., 2024).

Dendrimers

Dendrimers are highly branched, tree-like macromolecules with well-defined three-dimensional structures. They have shown significant potential in the treatment of AD due to their unique properties, such as multivalency, controlled size, and ability to carry multiple therapeutic agents, which enables combination therapy that can target different aspects of AD (Moreira et al., 2023).

Polyamidoamine (PAMAM) dendrimers have been studied for their ability to inhibit the aggregation of Aβ peptides (Mroziak et al., 2024). They can bind to Aβ peptides and prevent their aggregation into toxic fibrils. Additionally, these dendrimers can

be functionalized with targeting ligands to enhance their delivery to specific regions in the brain (Mroziak et al., 2024).

Nanoemulsions

Nanoemulsions are colloidal dispersions consisting of two immiscible liquids stabilized by a film of surfactant molecules at their interface. They can improve the solubility and bioavailability of drugs, facilitating their delivery to the brain (Kaur et al., 2020). They can also protect drugs from degradation, thereby increasing their shelf life and effectiveness. For example- Donepezil-loaded nanoemulsion.

Donepezil-loaded nanoemulsion formulation has been developed to enhance its delivery to the brain (Kaur et al., 2020). This formulation uses an oil-in-water (o/w) phase that can be administered intranasally, providing a direct nose-to-brain delivery route that bypasses the BBB (Kaur et al., 2020).

4.4 Nanoparticle-based Imaging agents for Alzheimer's Disease

Quantum Dots (QDs)

Quantum dots (QDs) are semiconductor nanoparticles with unique optical characteristics. They feature size-tunable fluorescence and good photostability, making them attractive candidates for imaging applications in Alzheimer's disease detection and therapy (Ghosh et al., 2022). The fluorescence wavelength of QDs may be accurately changed by altering their size, allowing for multiplexed imaging of different targets. They can identify low levels of Alzheimer's disease biomarkers, allowing for an earlier diagnosis. These nanoparticles preferentially target AD-related proteins, increasing imaging accuracy (Ghosh et al., 2022). These QD-based imaging approaches are non-invasive, which reduces danger for patients. Recent advances have demonstrated increased biocompatibility of QDs, making them safer for in vivo applications (Ghosh et al., 2022).

Selenium-doped carbon quantum dots (SeCQDs) have been created for multi-target treatment in Alzheimer's disease due to their antioxidant capabilities that prevent Aβ aggregation, decrease oxidative stress, and reduce neuroinflammation in the brain (Zhou et al., 2021). SeCQDs have been shown to increase memory and reduce Aβ buildup in rat models (Zhou et al., 2021).

Photoacoustic Imagining (PAI) Nanoparticles

Photoacoustic imaging (PAI) is a hybrid imaging technology that combines optical imaging's high contrast capabilities and ultrasonic imaging's high spatial resolution. This approach is particularly useful for deep-tissue imaging and has showed promise in the diagnosis and treatment of Alzheimer's disease (Liu et al., 2024). Furthermore, it is a non-invasive procedure that does not employ ionizing radiation, making it safer for patients. PAI can penetrate deeper into tissues than typical optical imaging. Gold nanocages (AuNCs) are a developing class of optically adjustable nanoparticles that are being actively studied for use as contrast agents in PAI (Suffredini et al., 2013). They contain extremely porous, hollow, cube-like shapes that display maximum optical absorption in the NIR region, also known as the optical window of living tissues due to low light attenuation by soft tissues and blood (Suffredini et al., 2013). These properties make AuNCs an excellent choice for PAI, delivering improved contrast and deeper tissue penetration methods, allowing for clearer visibility of brain regions (Liu et al., 2024).

Fluorescent Nanoparticles

Fluorescent nanoparticles have emerged as a significant tool for the diagnosis and treatment of Alzheimer's disease due to their high sensitivity, specificity, and capacity to give real-time imaging of pathological changes in the brain. These nanoparticles enable continuous monitoring of disease development in the brain and

may detect low quantities of AD biomarkers such as QDs, allowing for early detection (Zhou et al., 2024). They can also be functionalized with targeted ligands that precisely bind to amyloid-beta and tau proteins. Notably, near-infrared (NIR) fluorescent probes have gained popularity due to their capacity to penetrate deeper into tissues and produce high-resolution pictures. These probes can increase the accuracy of AD diagnosis by increasing imaging depth and lowering background fluorescence (Zhou et al., 2024).

Magnetic resonance imaging (MRI) Contrast Nanoparticles

Magnetic resonance imaging (MRI) is a sophisticated diagnostic technology that uses magnetic fields and radio waves to create detailed pictures of the body's interior components. MRI contrast chemicals can improve the visibility of certain tissues, making it simpler to detect abnormalities or pathological changes in the brain (Agraharam et al.,2022). Recent research on Alzheimer's disease has demonstrated that MRI contrast nanoparticles offer tremendous promise for both diagnosis and therapy. Nanoparticles can be functionalized with targeted ligands to bind to Aβ plaques and tau tangles (Agraharam et al., 2022).

Superparamagnetic iron oxide nanoparticles (SPIONs) are commonly utilized as MRI contrast agents due to their high magnetic characteristics. SPIONs can be customized with targeted ligands to selectively attach to Aβ plaques in the brain (Agraharam et al., 2022). This focused method improves MRI picture contrast, making it easier to diagnose and track the course of Alzheimer's disease.

Chapter 05

5.1 Mechanism of Action of the Nanoparticles

Nanoparticle-based therapies for AD employ various mechanisms to effectively address the underlying pathology of the disease compared to traditional treatments. Such as-

Inhibition of Amyloid-Beta Aggregation

One key strategy for addressing amyloid beta (Aβ) peptide aggregation involves the functionalizing of nanoparticles with specific ligands that bind to these peptides and prevent their aggregation into toxic plaques. Gold nanoparticles (AuNPs) have shown effective response in the inhibition of Aβ aggregation by binding to the peptides and disrupting their assembly into fibrils, offering a dual therapeutic effect (Huang et al., 2021). Research has shown that nanoparticles can also stabilize Aβ peptides in a non-toxic conformation, such as the α-helical structure, which is less prone to aggregation than the β-sheet structure. This stabilization helps to prevent the formation of amyloid plaques contributing to neuronal cell death (Jha et al., 2019).

Clearance of Tau Protein Aggregates

The clearance of tau protein aggregates is primarily achieved by promoting autophagy, which is a cellular process responsible for degrading and recycling damaged proteins and organelles (Harrison et al., 2020). Nanoparticles can be engineered to deliver autophagy-inducing agents directly to neurons which can help to enhance the clearance of tau proteins. For example, polymeric nanoparticles have been shown to facilitate the delivery of autophagy-related genes or small molecules

that activate autophagy pathways and lead to the degradation of tau protein aggregates (Harrison et al., 2020).

Another mechanism for the clearance of tau proteins involves modulating the glymphatic system, which is a brain-wide clearance pathway that facilitates the removal of waste products, including tau proteins. This can be achieved by increasing the exchange of cerebrospinal fluid (CSF) with interstitial fluid (ISF), thereby enhancing the clearance of tau proteins from the brain (Harrison et al., 2020). Nanoparticles that target aquaporin-4 (AQP4), a key protein involved in glymphatic clearance, can improve the efficiency of tau protein removal. This approach not only helps to reduce the accumulation of tau aggregates but also supports overall brain health by maintaining proper fluid balance and waste removal (Harrison et al., 2020).

Reduction of Oxidative Stress

The reduction of oxidative stress involves the use of antioxidant nanoparticles like selenium-doped carbon quantum dots (SeCQDs) and cerium oxide nanoparticles (CeO2 NPs), which can effectively scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the brain (Jiang et al., 2022). By neutralizing these harmful species, nanoparticles help to alleviate oxidative stress, which is a significant factor contributing to neuronal damage in AD.

Anti-Inflammatory Effects

Studies have shown that gold nanoparticles (AuNPs) can reduce neuroinflammation by promoting the polarization of macrophages toward the M2 phenotype (Aili et al., 2023). This process decreases the brain's inflammatory response by lowering the expression of pro-inflammatory cytokines. In addition, AuNPs can also inhibit leukocyte adhesion, which prevents the infiltration of inflammatory cells into brain

tissues (Aili et al., 2023). This dual action of AuNPs helps to alleviate neuroinflammation and protects neuronal cells from damage.

Targeted Drug Delivery Across the Blood-Brain Barrier (BBB)

One effective approach for the targeted delivery of the drug is the surface modification of nanoparticles with specific ligands that can bind to receptors on the endothelial cells of the brain, facilitating receptor-mediated transcytosis (RMT) (Kaya et al., 2023). For example, poly (lactic-co-glycolic acid) (PLGA) nanoparticles can be conjugated with ligands such as the DAS peptide, which shows an affinity for alpha-7 nicotinic acetylcholine receptors found on brain endothelial cells (Kaya et al., 2023). This technique enhances the transport of nanoparticles across the BBB, ensuring therapeutic agents reach the central nervous system (CNS) more effectively.

Another strategy involves the use of shuttle systems that exploit the natural transport mechanisms of the BBB (Pornnoppadol et al., 2023). For this, nanoparticles can be designed to bind to the heavy chain of the large neutral amino acid transporter 1 (LAT1), which is highly expressed in the endothelial cells of the brain. By targeting LAT1, nanoparticles can be efficiently transported across the BBB, delivering therapeutic antibodies or drugs to specific CNS cell subtypes (Pornnoppadol et al., 2023). This method not only enhances drug delivery to the brain but also ensures prolonged and targeted release of the drug, thereby improving the overall efficacy of the treatment.

Gene Delivery Mechanism

Nanoparticles can encapsulate genetic materials, such as DNA, RNA, or CRISPR-Cas9 components, and deliver them directly to brain cells. This method protects genetic material from being degraded by enzymes in the bloodstream. Once these

nanoparticles successfully cross the blood-brain barrier (BBB), they can release their genetic payload into the target cells. This process can be utilized to silence harmful genes, correct mutations, or introduce new genes that encode beneficial proteins (Ansari et al., 2023).

One of the emerging gene delivery mechanisms is the CRISPR-Cas9 gene editing process (Lu et al., 2021). Researchers are utilizing nanoparticles to transport CRISPR-Cas9 components directly to specific target cells in the brain. This innovative technology enables precise editing of genes associated with AD, particularly those involved in the processing of amyloid precursor protein (APP) or the aggregation of tau proteins. By using nanoparticles, scientists can specifically target genes in neurons and glial cells and potentially correct genetic mutations or silence genes that contribute to the progression of disease (Lu et al., 2021).

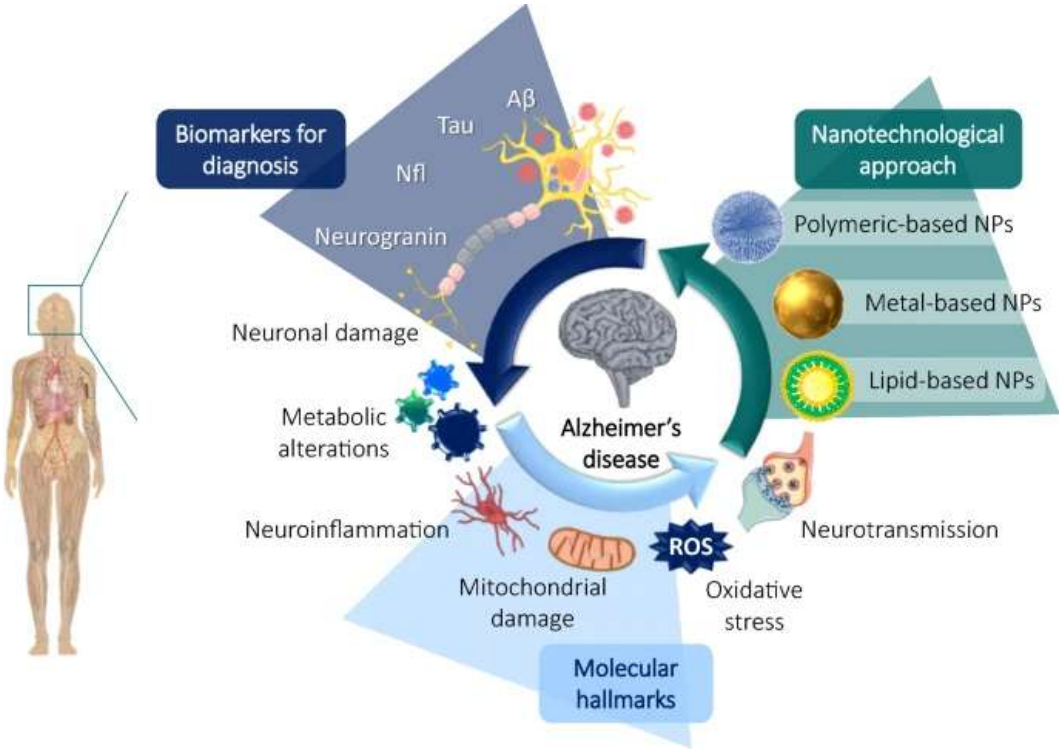

Fig: Mechanism of actions of various nanoparticles in the treatment of AD (Cano et al., 2021).

5.2 In-Vivo & In-Vitro Studies

Nanoparticles have been extensively studied over the years for their potential to treat AD. These studies demonstrate the effectiveness of nanoparticles in targeting key pathological markers of AD in in-vitro (test tube or culture studies) and in-vivo (animal model) research. Additionally, nanoparticles have also shown the ability to deliver therapeutic agents across the BBB that help to improve cognitive function.

Below is a detailed discussion of the key findings from the in-vitro and in-vivo studies.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
Liposome							
Metformin	Phosphatidyl serine	-	145	−41	Intraperitoneal, 50 mg/kg	Adult male Wistar rats	*in vivo*: Decreased neuroinflammation. Enhanced cognition restoration.
-	Chitosan	pApoE2	167.8 ± 2.47	19.8 ± 3.6	Intravenous, 1 mg/kg	bEnd.3 cells C57BL/6 mice	*in vitro*: Decreased cell viability in all cell lines. Increased concentration of phospholipid. *in vivo*: Approximately 2 times higher ApoE protein expression than endogenous ApoE levels.
Osthole	-	Transferrin	104.28 ± 3.76	−6.95 ± 0.56	Tail vein intravenous, 10 mg/kg	hCMEC/D3 cells and APP-SH-SY5Y cells APP/PS-transgenic mice	*in vitro*/*in vivo*: pH-controlled release up to 72 h. Enhanced penetration and drug accumulation.
	GSH-PEG	VHH-pa2H Glutathione (GSH)	108		IV bolus injection, 5 mg/kg	APP_{swe}/PS1dE9 transgenic mice	*in vivo*: Increased standard uptake values (SUV) of VHH-pa2H in the blood.
Galantamine HBr	Soya Phosphatidylcholine	-	112 ± 8	−49.2 ± 0.7	Oral and intranasal, 3 mg/kg	PC-12 cell, male SD rats	*in vitro*: Reduced cytotoxicity Enhanced BBB penetration. *in vivo*: More bioavailability in brain. Enhanced efficacy.

Figure 03: Nanoparticle-based drug delivery systems (Poudel & Park, 2022).

Figure 03: Cont.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
Donepezil	1,2-distearyl-sn-glycero-3-phospholine (DSPC)	-	102 ± 3.3	−28.31 ± 0.85	Oral and intranasal, 1 mg/kg	Male Wistar rats	*in vitro*: 75.5% drug release in 8 h. *in vivo*: Enhanced penetration. Enhanced bioavailability.
Rivastigmine	EPC, Cholesterol, DSPE-PEG-CPP	CPP	178.9	−8.6 ± 2.4	Intranasal and intravenous, 1 mg/kg	Endothelial cells, male SD rats	*in vitro* High encapsulation efficiency. Sustained-release behavior. *in vivo* IN route shows more activity
Micelles							
Resveratrol	PEG-PLA	C3 peptide	43.85 ± 0.94	12.9 ± 0.17	Intravenous, 10 mg/kg	HT22 cells, APP/PS1 transgenic mice	*in vitro*: Improvement on brain accumulation and increased targeting. *in vivo*: Enhance cognitive performance. Inhibited Aβ aggregation. Enhanced activity.
Curcumin	PEG	Aβ peptide	65		Intravenous	SH-SY5Y, APP_{swe}/PS1dE9 transgenic mice	*in vitro/in vivo*: Increased efficacy. Inhibited Aβ aggregation. Improved memory behavior.
-	Linoleic acid	Lactoferrin	120 ± 12.4	−32.8 ± 3.66	Oral, 4 gm/mL	Adult male Wistar rats	*in vitro/in vivo* Enhanced cognition Reduced oxidative stress. Reduced Aβ aggregation.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
	PMO-b-PBM, POEG-b-PBM and PF	-	70		-	PC-12 cells	*in vitro*: Reduced Aβ aggregation. Reduced Aβ fibrillation-induced cytotoxicity.
Solid–lipid NPs							
galantamine HBr	Glyceryl behnate, pluronic F-127, tween 80	-	88 ± 1.89	−18.75 ± 1.7	Oral route, 2.5 mg/kg	Adult Wistar rats	*in vitro*: Maximum drug entrapment. Drug release >90% for a period of 24 h. *in vivo*: Enhanced bioavailability 2-fold Memory restoration.
Rivastigmine	Campritol 888 ATO	-	82.5 ± 4.07	3.20 ± 1.44	-	Franz diffusion cell, goat nasal mucosa	*in vitro*: Higher diffusion with SLN. Ex-vivo: Maximum diffusion was seen with up to 8 h.
Donepezil	Stearic acid, oleic acid, lecithin, sodium taurodeoxytauro-cholate	-	177.05 ± 2.12	−55.35	Transdermal	-	*in vitro*: Increased drug skin permeation. Enhanced drug delivery.
Rivastigmine	GMS, castor oil	-	134.5 ± 15.1	−11.8 ± 2.24	Transdermal	Albino Wistar rats	*in vitro*/*in vivo*: Non-irritant. Enhanced bioavailability.

Figure 03: Cont.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
Lipid NPs							
Quercetin	-	Transferrin	219 ± 13	−28 ± 2	-	hCMEC/D3 cells	*in vitro*: 80–90% of entrapment efficiency Minimum cytotoxicity at BBB cell line.
Curcumin	PC, cholesterol oleate, glycerol trioleate	Lactoferrin	103.8 ± 0.6	−5.80 ± 0.73	Intravenous, 10 mg/kg	BCECs, SD rats	*in vitro*/*in vivo*: Effective BBB penetration. Long-term leads to enhanced activity.
Polymeric-NPs							
Galantamine	PLA-PLGA	-	198.00 ± 0.02	−27.42 ± 0.03	Intranasal, 3 mg/kg	Wistar rats	*in vitro*/*in vivo*: Good stability between NP and drug. More bioavailability in the brain.
Donepezil	PEG-PLGA	-	174 ± 12	−20.45	-	HBMEC and HA cell	*in vitro*: High destabilizing effect on fibril formation. Decreased neuroinflammation.
Rivastigmine	L-Lactide-depsipeptide	-	142.2 ± 21.3		-	-	*in vitro*: Entrapment efficiency of 60.72 ± 3.72% was obtained. Showed sustained release with 90% of drug for up to 72 h.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
-	PEG-PLA	B6 peptide	118.3 ± 7.8	−22.65 ± 0.85	Intravenous, 1 mg/kg	bEnd.3 cells, male ICR mice	*in vitro*: Enhanced brain penetration. *in vivo*: Enhanced cognition.
Galantamine	Thiolated-chitosan NPs	-	149.3	27.2	Intranasal 4 mg/kg	Swiss albino mice	*in vivo*: Effective acetylcholinesterase activity.
Memantine	PAMAM (dendrimer)	Lactoferrin	131.72 ± 4.73	20.13 ± 0.94	Intraperitoneally, 2 mg/kg	Swiss albino mice	*in vitro*: PAMAM-MEM maximum release concentration was 77.14 ± 6.0% after 6 h. *in vivo*: Improvement in behavioral responses. Enhanced acetylcholinesterase (AChE) activity.
Nanoemulsions							
Memantine	-	-	~11	−19.6	Intranasal, 5 mg/kg	Neuro 2a, Sprague-Dawley rats	*in vitro*/*in vivo*: 98% cell viability and sustained its antioxidative potential. Increased bioavailability.
Donepezil	Labrasol (10%) as oil, CPC (1%) as surfactant in water (80%), glycerol (10%) as co-surfactant		65.36	−10.7	Intranasal, 0.45 mg/kg	Neuro 2a, Sprague-Dawley rats	*in vitro*/*in vivo*: Maximum drug release of 99.22% in 4 h in PBS. Non-toxic Effective drug delivery.

Figure 03: Cont.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
Huperazine A	Capryol 90 (oil phase), cremophor EL & labrasol (surfactant & co-surfactant) & lactoferrin (targeting ligand)	Lactoferrin	16.75 ± 0.4	5.67 ± 0.39	Intranasal	hCMEC/D3 cells, adult Wistar rats	*in vitro/in vivo*: No nasal mucosal toxicity. Effective BBB penetration. Enhanced activity.
Quantum Dots							
-	Graphene QDs	-	10 ± 1.3	−40 ± 0.4	-	Adult male Wistar rats	*in vitro/in vivo*: Enhanced penetration across BBB. Improved learning and memory. Reduced level of lipid peroxide and nitric oxide.
-	Black phosphorous QDs	-	~3		-	PC12 cells	*in vitro*: Low cell toxicity. Inhibited insulin and Aβ aggregation.
-	Selenium-doped carbon QD	-	~25		Intravenous	PC12 cells, adult male Wistar rats	*in vitro/in vivo*: High cell viability. Inhibited Aβ aggregation. Improved memory and cognitive function of an AD rat model.
Curcumin	Graphene QD & indium-tin-oxide Electrode	-	~8		-	-	*in vitro*: High sensitivity on detection of ApoE4 DNA. Enhanced efficacy.

Drug	Carrier Material	Ligand	Particle Size (nm)	Zeta Potential (mV)	Route of Administration, Dose	*In Vitro*/*In Vivo* Model	Outcome
Gold nanoparticles							
-	-	L and D glutathione	4		Intravenous, 25 mg/kg	SH-SY5Y cells, C57BL/6 mice	*in vitro/in vivo*: Effective BBB penetration. Improved behavioral performance.
AuNP	-	-	20		Intraperitoneal, 2.5 mg/kg	Male Wistar rats	*in vivo*: Normalize Tau phosphorylation. Prevented oxidative stress and neuroinflammation.
AuNP	-	Bucladesine	5	−47.7 ± 10.9	Intrahippocampal, intraperitoneal	Male Wistar rats	*in vivo*: Better acquisition and retention of spatial learning and memory. Improved neuron survival.
-	3D-Au-PAMAM, electro grafted PABA	CAb-GA conjugate			-	-	Detection: Effective detection of tau protein. LOD value of 1.7 pg/mL.
Magnetic Nanoparticles							
Quercetin	SPIONs	-	50		Oral, 50 and 100 mg/kg	Male Wistar rats	*in vivo*: Increased penetration. Enhanced Bioavailability.
-	Sialic acid (SA)-modified selenium (Se) NPs	B6 peptide	95	−14.4	-	PC12 cells and bEnd.3 cells	*in vitro*: Effective in crossing BBB. Inhibitory effects on Aβ peptide.

5.3 A comparison between nanoparticle based approach and traditional treatment method for treating AD.

Aspects	Nanoparticle-Based Approach	Traditional Treatments
Mechanism of Action	Nanoparticles can be engineered to potentially inhibit Aβ plaques, clear tau protein aggregates, reduce oxidative stress, enhance anti-inflammatory effects, and deliver genetic components in the brain (La Barbera et al., 2022).	Traditional treatments primarily include-cholinesterase inhibitors (e.g., donepezil) and NMDA receptor antagonists (e.g., memantine) that provides symptomatic relief without addressing the underlying pathology (La Barbera et al., 2022)
Blood-Brain Barrier (BBB) Permeability	Nanoparticles can be engineered to cross the BBB more effectively, reducing the need for higher doses and potentially minimizing systemic side effects (La Barbera et al., 2022).	Drugs such as memantine have limited permeability across the BBB, which restricts its effectiveness in reaching target areas of the brain and often require higher doses (La Barbera et al., 2022).
Bioavailability	Nanoparticles have enhanced bioavailability that protects the encapsulated drugs from degradation, allowing for more consistent therapeutic	They have low bioavailability which often results in inconsistent therapeutic effects (La Barbera et al., 2022).

	effects (La Barbera et al., 2022).	
Side Effects	Nanoparticles are being designed for targeted delivery of the drugs which leads to lower side effects (Martínez et al., 2023).	Common side effects are nausea, vomiting, dizziness, fatigue, insomnia, constipation etc. due to off-target activity (Martínez et al., 2023).
Duration of Effect	Nanoparticles can be designed for prolonged circulation, which helps to maintain stable drug concentration over an extended period (Martínez et al., 2023).	Available treatment primarily provides symptomatic relief which often require multiple doses to maintain consistent therapeutic levels (Martínez et al., 2023).
Impact on Disease Progression	Emerging research suggests that nanoparticles may deliver drugs targeting the underlying pathologies of AD, offering a potential approach for disease modification (Martínez et al., 2023).	Available treatments have limited effects on halting or reversing the disease progression (Martínez et al., 2023).
Administration Methods	Nanoparticles enable alternative routes, including intranasal delivery, for direct brain targeting, potentially	Oral, transdermal, or intravenous (Tapia-Arellano et al., 2024).

	increasing patient compliance (Tapia-Arellano et al., 2024).	
Combination Options	Nanoparticles can be combined with other drugs for synergistic effects (Tapia-Arellano et al., 2024).	Available treatments have limited combination options (Tapia-Arellano et al., 2024).
Current Status	Currently, nanoparticle-based therapies are still in experimental stages yet not available for clinical use (Tapia-Arellano et al., 2024).	Several FDA-approved drugs, such as, donepezil, rivastigmine, memantine etc. (Tapia-Arellano et al., 2024).

Chapter 06

6.1 Challenges and Limitations

The application of nanoparticles has shown significant potential for the treatment of Alzheimer's disease (AD). However, there are several considerable challenges and limitations that must be addressed before moving the approach from research into clinical practice.

One of the primary challenges in developing nanoparticle-based therapies for AD is ensuring effective delivery of the particles across the blood-brain barrier (BBB) (Cao & Zhang, 2022). Although they can be engineered to cross the BBB through surface modification strategies or mechanisms like receptor-mediated transcytosis, achieving consistent and efficient penetration remains a significant challenge (Cao & Zhang, 2022). Incomplete or inconsistent BBB penetration can lead to suboptimal drug concentrations, which may limit the effectiveness of treatment.

Another crucial challenge is the precise targeting of nanoparticles to specific cells or regions within the brain (Pornnoppadol et al., 2023). Nanoparticles must selectively bind to pathological targets like Aβ plaques or tau protein aggregates without affecting healthy brain tissues. Functionalization strategies, such as attaching ligands or antibodies to nanoparticles, can enhance targeting specificity. However, off-target effects and non-specific binding remain a concern, as they can reduce the effectiveness of the therapy, leading to an increased risk of side effects (Pornnoppadol et al., 2023).

The possibility that nanoparticles may trigger immune responses is another major concern in AD therapy (Motireddy et al., 2024). Nanoparticles can be recognized as a foreign substance in the body by the immune system which could lead to the activation of inflammatory cytokines. This activation may result in either acute or

chronic inflammation, leading to further neural damage. To address these immune responses, strategies such as modifying the surface with biocompatible materials or coating them with substances that can help to avoid immune detection have been proposed (Motireddy et al., 2024).

Ensuring the biocompatibility and toxicity level of the nanoparticle is very important for their safe use in AD therapy (Kumar et al., 2017). Nanoparticles can interact with biological systems in unpredictable ways, leading to potential cytotoxicity, oxidative stress, and inflammation. Different factors, such as the size, shape, surface charge, and composition of the particles, can significantly influence their toxicity. Though these particles can be effectively used in inhibiting Aβ aggregation, they can also show toxicity at higher concentrations (Kumar et al., 2017). So, it is very important to thoroughly evaluate the biocompatibility of different nanoparticles to minimize adverse effects.

The stability and biodegradation of nanoparticles are another critical factor that affects their therapeutic potential (Ansari et al., 2023). Nanoparticles must maintain their structure and functionality during storage, transport, and administration. Simultaneously, they need to be biodegradable to prevent long-term accumulation in the body, which could lead to chronic toxicity (Ansari et al., 2023). The rate of biodegradation varies depending on the material and design of the particles. Therefore, it is important to maintain a careful balance between stability and degradation rate to ensure sustained release and therapeutic effectiveness.

6.2 Regulatory and Ethical Considerations

The development and clinical use of nanoparticle-based therapies are subjected to regulatory and ethical considerations. The regulatory framework for the use of nanomedicine is still evolving, and significant gaps exist in the legislation pertaining

specifically to nanomaterials (Devasahayam, 2019). Regulatory agencies must establish clear guidelines for assessing and maintaining the safety and efficacy of nanoparticles, including standardized testing protocols for toxicity, biodistribution, and long-term effects on the body.

Ethical considerations like informed consent, data privacy, equitable access to treatment, and environmental impact must be of great concern. Patients must be fully informed about the experimental nature of nanoparticle-based therapies and any risks associated with the process to ensure ethical clinical practice.

6.3 Future Directions and Prospects

Given the multifaceted nature of AD, future therapies are likely to focus on multi-target approaches (Ansari et al., 2023). Nanoparticles can be designed to carry multiple therapeutic agents, addressing various aspects of the disease pathology. By targeting multiple pathways, these therapies can offer a more comprehensive treatment strategy that can slow down the disease progression more effectively than traditional single-target approaches (Ansari et al., 2023).

The application of nanoparticles in gene therapy represents a promising future direction for the treatment of AD (Tsakiri et al., 2022). Nanoparticles can deliver genetic materials, such as small interfering RNA (siRNA) and CRISPR-Cas9 components, to modulate gene expression and correct genetic defects associated with AD (Tsakiri et al., 2022). Advancements in nanoparticle technology are expected to enhance the stability, specificity, and efficiency of these genetic therapies, offering new avenues for personalized medicine.

Another promising avenue is nanoparticle-based immunotherapies, which can deliver immunomodulatory agents that target Aβ plaques and tau proteins (Ansari et al., 2023). Nanoparticle-based immunotherapies can promote the clearance of toxic

proteins and reduce neuroinflammation by enhancing the immune response of the body to the pathological features of the disease.

Chapter 07

Conclusion

Nanoparticles hold substantial promise for advancing the treatment of Alzheimer's disease, offering significant potential to overcome the limitations of traditional therapies. The unique physicochemical properties of these particles have shown the ability to penetrate the blood-brain barrier through targeted delivery of therapeutic agents directly to the brain. By serving as carriers for drugs, genes, or bioactive molecules, they can effectively respond to the key pathological hallmarks of AD. Their adaptability allows for the attachment of specific ligands, enhancing precision in targeted interventions at the molecular level. Recent breakthroughs in biodegradable and biocompatible nanomaterials like liposomes, polymeric nanoparticles, dendrimers, and metal-based nanostructures have yielded promising outcomes in preclinical models, demonstrating increased drug efficacy and improved neuroprotection.

Furthermore, nanoparticles facilitate groundbreaking diagnostic applications that can both detect and treat AD. However, the challenges and limitations in the application of nanoparticles must be addressed carefully to understand their full therapeutic potential. Regulatory and ethical landscapes also needed to be thoughtfully addressed in the development of safe and effective nanoparticle-based therapies. Continued research and innovation in nanotechnology, combined with collaborative efforts among scientists, clinicians, and regulatory bodies, is essential for translating the promise of nanoparticles into clinical reality, enhancing the quality of life for millions of people impacted by this devastating neurodegenerative disorder.

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