İstanbul Journal of Pharmacy

İstanbul Journal of Pharmacy,
IJP 2025, 55 (1): 222–230

https://doi.org/10.26650/IstanbulJPharm.2025.1592251
Submitted: 27.10.2024
Revision Requested: 18.01.2025
Last Revision Received: 23.02.2025
Accepted: 27.02.2025

Review Article

Open Access

Theranostic nanoparticles and their applications in Alzheimer's disease

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Abstract

Nanotechnology is the field of science that investigates materials at the atomic scale and designs materials with unique qualities via changes in their molecular features. Nanomaterials, which can participate actively in several industrial sectors, provide numerous advantages across every field. Nanomedicine is a medical application of nanotechnology to improve health. It aims to provide an early diagnosis and targeted treatment of diseases with high efficacy. Theranostic nanoparticles are established by combining diagnostic and therapeutic agents within the same nanoparticle. The imaging agent (diagnostic) offers insights into the location and severity of the pathological cells, while the therapeutic agent (therapy) administers lethal medication dosages to the same affected cells. Theranostic nanoparticles, which can be prepared in many types (iron oxide nanoparticles, polymeric nanoparticles, quantum dots, carbon nanotubes, etc.), can be used in compatibility with imaging devices (Positron Emission Tomography (PET), magnetic resonance imaging (MRI) etc.). These nanoparticles constitute an important target for the treatment of many diseases, such as neurodegenerative disorders, where organ pathology is out of reach without invasive methods. Therefore, this innovative technology, which is capable of diagnosing and predicting illnesses at the molecular level, facilitates early diagnosis and treatment, prevents patients from undergoing unneeded interventions, and diminishes superfluous pharmaceutical expenditures within the healthcare system, thus yielding more effective clinical outcomes. The design of theranostic nanoparticles according to the context-dependent necessities is crucial and valuable for the effectiveness of targeted and personalised medicine. In this review, we discuss the types and properties of theranostic nanoparticles, imaging technologies, and their applications in Alzheimer's Disease treatment.

Keywords Alzheimer's disease · Nanomedicine · Neurodegeneration · Theranostic nanoparticle

Citation: Akyüz Şengün, D. & Ersoy Tunalı, N. (2025). Theranostic nanoparticles and their applications in Alzheimer's disease . *İstanbul Journal of Pharmacy*, *55*(1), 222-230. https://doi.org/10.26650/IstanbulJPharm.2025.1592251

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INTRODUCTION

Nanotechnology is an interdisciplinary field of science, where new structures are established by changing the atomic and molecular properties of the materials. Nanotechnological applications in the field of medicine have quickly introduced the term "nanomedicine" into the literature. The primary goals of nanomedicine are to detect pathological processes at the early stages, provide more efficient treatment responses, boost the efficacy of targeted medicines, and decrease adverse effects. For this purpose, organic or inorganic nanoscale materials have proved to be very effective (Vural & Özer, 2015). Their surface effects confer specific physicochemical properties, and they have the advantage of having large specific surface areas for loading huge amounts of drugs while preventing enzymatic decomposition (Xu et al., 2021). They provide high intracellular targeting owing to their small size and mobility (Ramanathan et al., 2018). Drug-loaded nanoparticles can be designed to accumulate in pathologically damaged cells and tissues upon modification of the surface molecules. In this way, target specificity can be enhanced while decreasing off-target uptake and side effects (Saenz del Burgo et al., 2014).

The term "theranostic" was defined as "therapy" and "diagnostics" by Funkhouser in 2002 (Funkhouser, 2002). Theranostic drugs detect both the location of damaged cells and the severity of the disease load with diagnostic/imaging capabilities (Duan et al., 2022). The main concept behind theranostic drugs is that the application of the correct molecular probe, which includes the diagnostic and therapeutic agents, reduces toxicity and improves treatment efficacy in the patients. In this way, unnecessary trial-and-error type of treatments might be avoided. In addition, disease-specific molecular biomarkers can be identified, the biodistribution of the molecule can be observed, and the response to therapy can be monitored (Xie et al., 2010a).

Theranostic nanoparticles are defined as multifunctional nanosystems designed at the nanoscale for unique and individualised medical therapies. Theranostic nanoparticles combine diagnostic and therapeutic approaches with biocompatible and biodegradable features in the same particle. In broader terms, theranostic nanoparticles easily pass biological barriers and provide convenience in the diagnosis, treatment, and treatment response. Any nanoparticle consists of the carrier part and the loaded drug, which can be further tailored for specific medical purposes. Theranostic probes provide early disease detection, imaging throughout the body, and customised targeted therapy. In terms of diagnosis, changes at the molecular level can be recognised long before they are reflected in the phenotype, without detectable anatomical alterations. One of the most significant benefits is that it enables early evaluation of the therapy response and detection of recurrence (Duan et al., 2022; Jokerst & Gambhir 2011). In this article, the types of theranostic nanoparticles, imaging methods (Figure 1), and their use for treating neurodegenerative diseases are discussed.

Types of Theranostic Nanoparticles

Theranostic nanoparticles can be designed in many different forms (Figure 1) like quantum dots, iron oxide nanoparticles, carbon nanotubes, polymeric nanoparticles, lipid

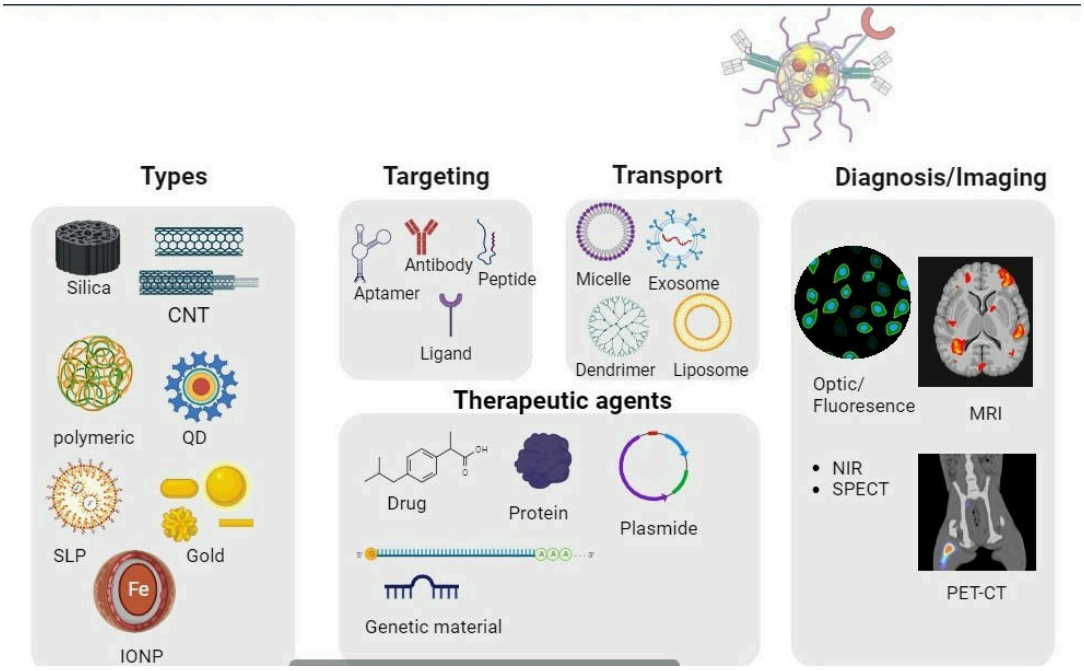


Figure 1. Types, targeting, diagnosis, and transport systems of nanoparticles

nanoparticles, cerium nanoparticles, silica nanoparticles, and gold nanoparticles (Xie et al., 2010a).

Iron Oxide Nanoparticles

Iron oxide nanoparticles (IONP) are nanocrystals created from magnetite or haematite. Unlike bulk materials, IONPs smaller than 20 nm are defined as superparamagnetic (SPION). For example, they show zero magnetism if there is no magnetic field in the environment except for the particles, but they can be magnetised when even one magnetic field is present. IONPs are preferred like contrast probes in magnetic resonance imaging because they have superior magnetic properties and can generate a significant amount of heat in an alternating magnetic field. In addition, changes in the signal can be used to indicate aberrant biological activities when they are designed with targeting specificity (Xie et al., 2010a). Using proper coatings, drug molecules can be coupled with IONPs. *In vitro* studies showed that theranostic nanoparticles produced by encapsulating therapeutic molecules and loading them onto IONPs performed better than predicted (Xie et al., 2010b).

Quantum Dots

Quantum dots (QD) are fluorescent semiconducting inorganic nanocrystals with a metallic core and a semiconducting shell (Landrigan et al., 2020). They have unique optical properties such as stability, high quantum yield, narrow photoluminescence spectrum, increased brightness, high signal-to-noise ratio, long fluorescence lifetimes, and broad absorption spectrum, and optical imaging is mostly preferred (Shen et al., 2017). Indium arsenide (InAs), cadmium telluride (CdTe), and cadmium selenide (CdSe) are frequently utilised in semiconducting QDs. QDs have large stokes shifts, small energy loss, and higher fluorescence efficiency than organic dyes and fluorescent proteins. They have a fixed excitation wavelength and a relatively narrow emission spectrum, allowing the simultaneous excitation of multiple QDs with a single light source (Pelley et al., 2009). However, they need to be conjugated to a peptide to facilitate their entry into the cell (Landrigan et al., 2020). On the other hand, QDs should be handled with caution since they may have cytotoxic effects in in vitro and in vivo studies (Pelley et al., 2009).

Gold Nanoparticles

Gold nanoparticles (AuNPs/GNPs) are the most commonly used nanoparticles in imaging, diagnostic, and targeted treatment approaches. They have special physical and chemical features, including intense light absorption and scattering, biocompatibility, low toxicity, significant photothermal conversion rate, stability, biosafety, and surface modification with various molecules. They can be synthesised easily and formed in different shapes such as prisms, spheres, cubes, lattices and wires (Carvalho et al., 2018).

AuNPs have a unique optical performance, called localised surface plasmon resonance (LSPR), which is defined as the collective oscillation of conduction band electrons upon excitation with a specific wavelength of light (Wilson et al., 2020). The LSPR-induced light extinction includes both absorption and scattering mechanisms, and the rate of light extinction depends on the AuNP size. Due to their increased light absorption and scattering, they are advantageous in computed tomography scanning and photothermal treatment and are resistant to photobleaching. Also, the LSPR of AuNPs can be adapted easily and precisely to be visible to the near-infrared (NIR) regions via a variety of modifications like changes in shape, reduction of the shell thickness, etc. (Vinhas et al., 2015). However, the major drawback is their high production cost (Xie et al., 2010a).

Silica Nanoparticles

Silica nanoparticles (SNPs) are widely preferred due to their ability to control their morphologies at desired sizes, presence of a large surface for conjugation, biocompatibility, stability, and modifiable porosity (Jana et al., 2007). SNPs are good candidates for theranostic applications, as they have a perfect platform that lets a wide range of imaging and therapeutic functions be easily loaded (Xie et al., 2010a).

Carbon Nanotubes

Carbon nanotubes (CNTs) are carbon cylinders composed of either single-walled (SWNT) or multi-walled (MWNT) benzene rings. While the SWNT consists of a single layer of graphene ranging from 0.4 to 2 nm in diameter, the MWNT has several concentric graphite layers ranging from 1.4 to 100 nm in diameter. Although CNTs are virtually insoluble in most solvents, current chemical functionalization and modification technologies have enabled the modulation of their solubility. CNTs can be used for photoacoustic and fluorescence imaging purposes, as well as for NIR radiation-based localised heating (Carvalho et al., 2018).

CNTs are an ideal platform for cellular penetration and surface adsorption. Owing to their distinct physical and surface features, they play a crucial role in the field of nanomedicine. Other nanoparticles, such as IONP or AuNP, can readily be added to the carbon nanotubes for additional enrichment of the nanoplatforms (Xie et al., 2010a). The most significant problem appears to be the difficulty in their biodegradation. It is currently controversial whether CNTs may cause chronic and long-term harm to the host, and the source of toxicity is

not entirely known. The physicochemical properties (diameter, length, type, etc.), aggregation behaviour, and covalent/non-covalent modifications of CNTs may have important effects on the biological reactions. Therefore, CNTs may cause membrane disruption, induce oxidative stress and genotoxicity through induced membrane damage, and ultimately lead to cellular apoptosis (Emerce et al., 2019). Further studies are necessary for a better understanding of the signaling pathways and molecular mechanisms involved in CNT toxicity and to reduce the associated hazards.

Cerium Oxide Nanoparticles

Cerium (Ce) is a non-toxic semiconductor, abundant, and inexpensive. Cerium's two redox states of cerium, Ce^{2+} and Ce^{4+}, as well as the increased oxygen vacancies, make it an excellent antioxidant (Ranjbar et al., 2018). Although cerium oxide nanoparticles (CeO_2NP-Nanoseria) have poor solubility in biological applications, their antioxidant properties can increase their stability, biocompatibility, and solubility via polymer coating. Polymer-coated nanoceria demonstrated enhanced stability and water solubility, as well as antioxidant properties against hydrogen peroxide (H_2O_2) in mouse embryonic fibroblast cells (Kim & Chung, 2016). Nanoserias were shown to enhance thiol content and initiate caspase-3 activity in mouse brain tissue, which increased antioxidant activity and acted as a neuroprotective agent (Ranjbar et al., 2018).

Polymeric Nanoparticles

Polymeric nanoparticles can be manufactured from natural and synthetic polymers. Alginate, fibrin, chitosan, gelatine, collagen, albumin, and silk are examples of natural polymers. Poly-glycolic acid (PGA), poly (ε-caprolactone) (PCL), and poly(amino acids), poly-lactic acid (PLA), poly-D, L-Lactic-co-Glycolic acid (PLGA), and dendrimer are examples of synthetic polymers (Gupta et al., 2019). They are of great interest in theranostic studies because of their biosafety, biodegradability, and flexibility offered by macromolecular synthesis methods, diversifiable (co)polymer compositions, and the possibility of functionalising them for imaging and/or targeting purposes. They are also considered controlled drug delivery systems that can improve the pharmacodynamic and pharmacokinetic features of encapsulated drugs by extending drug release and particle retention (Nicolas et al., 2013).

PLGA is a block copolymer made of PLA and PGA, which is authorised by the European Medical Agency (EMA) and the Food and Drug Administration (FDA) for human use. PLGA, which has great biocompatibility, is hydrolysed to the natural metabolites lactic and glycolic acids when exposed to the human physiological environment. Polyethylene glycol (PEG) is an inert and hydrophilic polymer that acts as a steric barrier on the nanoparticle surface, reducing opsonisation. The PEGylation technique improves a compound's water solubility and stability, decreases intermolecular aggregation, reduces immunogenicity, and prolongs its systemic circulation duration. The incorporation of PEG into the structure of nanoparticles increases their circulation lifetime while at the same time decreasing early drug release and enabling controlled release (Cai et al., 2016). Because of these properties, PEGylated PLGA nanoparticles are widely preferred among drug delivery systems.

Dendrimers are extremely branched polymeric macromolecules composed of radially branching polymer repeating units. They are comparable in size and can be under 20 nm due to their well-known chemical structure. The numerous binding sites on the terminal branches facilitate drug delivery (Zhu et al., 2019).

Chitosan is another type of polymer with biocompatibility and various characteristics including antibacterial, anticancer, anti-inflammatory, and immune-boosting activities. Use of chitosan bioglass scaffolds may also help in the management of allergic reactions and pathogen transmission due to collagen use in tissue engineering applications (Vukajlovic et al., 2019).

Polymeric micelles, being either spherical or layered, have an average size of 10 nm. They are designed using amphiphilic polymers, which self-assemble into a sphere with a hydrophilic shell and hydrophobic core and are especially useful for the encapsulation of hydrophobic drugs (Elezaby et al., 2017).

Lipid Nanoparticles

Lipid-based nanoparticles, which have been developed and used for years as a drug delivery system, mimic the human cell membrane due to their lipid bilayers. They have many advantages such as production in desired sizes, low toxicity, biocompatibility, biodegradability, both hydrophilic and hydrophobic drug encapsulation, and targeted and controlled drug release (Viegas et al., 2022).

Liposomes are double-layered, aqueous, nucleated, non-toxic, and inert structures. In the cell membranes, by lowering fluidity and permeability, cholesterol inhibits the outflow of molecules in the bilayer structure (Vural & Özer, 2015). In that case, PEG can be added to limit the clearance (Carvalho et al., 2018), and being in circulation for a long period increases the chance of reaching the target cell, thereby serving as a diagnostic, therapeutic, or imaging material (Vural & Özer, 2015). Liposomes have been used in the clinic for many years. Liposomal amphotericin prevents drug interaction with

renal distal tubules, prolongs the drug's half-life, and reduces nephrotoxicity (Stone et al., 2016). Liposomal doxorubicin decreases cardiotoxicity, nausea, and vomiting while enhancing the doxorubicin's pharmacokinetic effects. This is due to the liposome's distribution in regions with capillaries, such as tumour growth or inflammation, and away from places with tight capillary connections, such as the gastrointestinal and heart tract (Rafiyath et al., 2012).

Lipid micelles do not have a bilayer structure like liposomes. Because they carry both hydrophilic and hydrophobic groups, they can easily solubilise active substances such as enzymes and vitamins. In addition, they are preferred because they are easily available and they can be labelled radioactively (Vural & Özer, 2015).

Solid lipid nanoparticles (SLNs) are lipid-based biocompatible nanocarrier systems that can be formed in the range of 10-1000 nm in size. They include a solid hydrophobic lipid core capable of dispersing both hydrophilic and lipophilic drugs. Because they can easily cross the reticuloendothelial system of the blood-brain barrier, they are good alternatives to liposomes and polymeric nanoparticles in combatting the biochemical degradation of the active drug. By arranging the specific ratios of solid lipids, drugs, and additives, drug-loaded SLNs can be prepared to exhibit prolonged diffusion and sustained release. They have low production costs and excellent physicochemical stabilities. SLNs can be used as perfect drug delivery systems with high drug bioavailability, controlled release kinetics, and specific tissue targeting. Owing to their sufficient drug-loading capacities, they can deliver conventional pharmaceutical formulations and biomolecules with a minimal immune response throughout the body via various routes like transdermal, parenteral, oral, and pulmonary routes (Carvalho et al., 2018; Satapathy et al., 2021).

Imaging Via Theranostic Nanoparticles

Methods used for imaging theranostic particles (Figure 1) include Positron Emission Tomography (PET), magnetic resonance imaging (MRI), single-photon positron emission computed tomography (SPECT), optical and NIR imaging, and computed tomography (CT) (Thangam et al., 2021). Although the term theranostic entered the medical literature in the 2000s, the first clinically accepted example of a theranostic study, iodine-131 treatment and scintigraphy, was performed in 1941 for the diagnosis and treatment of thyroid cancer. For treatment purposes, the biodistribution of iodine-131 was monitored by scintigraphy, and imaging was performed by PET or SPECT. The radioisotopes to be administered to the body are placed in the nanoparticle, enabling it to easily find the diseased tissue by targeting and treating it (Durak, 2015). Low-penetration radiation emitted from the theranostic nanoparticle is used to accumulate large amounts of energy in the nuclei of targeted cells. This leads to deoxyribonucleic acid (DNA) chain breaks and programmed cell death is activated. For diagnostics at the molecular level, SPECT/CT, PET/CT, or PET/MRI can be used. The radiopharmaceutical of choice is a positron emitter for PET and a gamma-emitter for SPECT. Positron- and gamma-emitting radiopharmaceuticals exhibit low energy transfer, high tissue absorption, and an extended radiation range, which result in low-level radiation exposure for the patients, providing optimum imaging. Molecular imaging characterises the pathological state of the cells and aids in describing the biological processes in tissues. It also assesses whether the molecular target is expressed sufficiently based on the diseased cell uptake compared to the background uptake and normal tissue, and whether the patients can benefit from the targeted therapy (Duan et al., 2022). The suitability of magnetic IONPs as therapeutic agents has been demonstrated through evaluation with MRI applications. Drugs can be conjugated with surface modifications, targeting agents (antibodies, peptides, small molecules, etc.), fluorescent dyes, and other substances to improve imaging (Yu et al., 2012).

Optical imaging uses photons emitted by bioluminescent or fluorescent probes. The major advantages are that it is cheaper than other methods and the body is not exposed to ionising radiation. Features such as a wide imaging scale and high spatial resolution are also among their advantages. However, it has the major disadvantage of inability to reach deep tissues (Xia et al., 2003). During fluorescence imaging, the presence of noise caused by scattering photons in the tissue can be overcome using a slightly higher beam rate. Therefore, photon scattering can be prevented, allowing easy access to deep tissues (Debbage & Jaschke, 2008).

Fluorescence imaging offers great sensitivity, quick data capture, and high resolution, making it useful for early disease detection. NIR-emitting dyes provide various benefits over other fluorophores, including excellent tissue permeability and strong photo-stability. NIR imaging is a helpful method especially to assess the efficacy of drug therapy under *in vivo* conditions (Wang et al., 2021).

Management of Neurodegenerative Diseases

Neurodegeneration, the Blood-Brain Barrier, and the Need for Nanomedicine

Neurodegenerative diseases are characterised by the gradual loss of cognition, memory, and skilled movements. Most of the time, the major pathology involves the central nervous system (CNS); therefore, sophisticated methods are required for the efficient transfer of the drugs through the blood-

brain barrier (BBB) (Ramanathan et al., 2018). The BBB tightly controls the flow of ions, molecules, and cells between the CNS and the blood. This extremely restrictive barrier capacity enables the endothelial cells that make up the BBB firmly to control CNS homeostasis, which is necessary for optimal neuronal function while protecting the CNS from toxins, damage, inflammation, and infection. The restrictive nature of the BBB is the biggest barrier to drugs being effective in the CNS. The BBB is controlled by astrocytes, microglia, pericytes, and neurons. Brain endothelial cells are connected with tight junctions and they close the paracellular diffusion pathway to prevent intercellular passage. It constitutes the first barrier between the blood vessels and the brain parenchyma. Pericytes are arranged in rows along the cerebral capillaries. They are surrounded by the basal lamina, which is adjacent to the plasma membranes of astrocyte endfeet and endothelial cells. Astrocyte endfeet is important in maintaining barrier properties and providing cellular connectivity to neuronal cells. Neurons contain vasoactive neurotransmitters (which affect the diameter of blood vessels and blood pressure) and peptides, which control local cerebral blood flow. The release of vasoactive peptides from cells that are in connection with endothelial cells maintains BBB permeability. Microglia are responsible for immunity by sensing and managing the neuronal damage to BBB (Abbott et al., 2010; Zenaro et al., 2017).

Molecules can be transported through the BBB via five major pathways, which are paracellular and transcellular pathways, and carrier-, receptor-, and adsorption-mediated transcytosis (Dereli et al., 2016; McCarthy et al., 2015). In the paracellular pathway, water-soluble molecules diffuse freely from the tight junctions. This is because disruption of the BBB as a result of local inflammation and inflammation-induced circulatory factors causes weakening of the tight junctions between endothelial cells, which allow polar solvents to enter brain extracellular fluids from blood vessels. The transcellular pathway is a passive transport system that is not dependent on energy. Structural and physicochemical features such as lipophilicity, molecular weight, charge, and hydrogen-binding capacity of substances or carrier systems that cross the BBB affect passive transport. Some small lipophilic and low molecular weight compounds (<500 Da) can passively diffuse into the BBB. In carrier-mediated transcytosis, transport can be bidirectional between the blood and the brain. In this way, specific transport proteins carrying hydrophilic small molecules (ions, nucleosides, glucose, and amino acids) are carried from the blood vessels to the extracellular site of the brain via the endothelial cells. In receptor-mediated transcytosis, transport is mediated by insulin, low-density lipoprotein, transferrin, and leptin receptors on the luminal surface of the capillary endothelium, resulting in the endocytosis of the receptor-bound ligand. It is considered a promising approach for the treatment of neurodegenerative diseases as it enables targeting of the brain via transporter systems and protects the active substance against multiple drug efflux pumps. Adsorption-mediated transcytosis is another transport system that involves electrostatic interactions between positively charged macromolecules and negatively charged brain endothelium surfaces. The cell surface interacts with the binding sites of the molecules, and endocytosis and subsequent transcytosis occur.

Nanomaterials can be used as carriers to deliver drugs efficiently to the brain because of their small size and high penetrability. This is very valuable since an effective treatment for neurodegeneration requires efficient transfer of the drug molecules to the brain tissue. Moreover, conventional therapies have limitations such as non-specific distribution, reduced drug response, and development of drug resistance (Xu et al., 2021). As a result, there is a great need to develop various targeting and treatment strategies.

Nanomedicine in Alzheimer's Disease

Alzheimer's Disease (AD), the most prevalent dementia in the World, is characterised by neuronal degeneration in the brain and cognitive disabilities. The pathology of AD involves the accumulation of different forms of amyloid-β (Aβ) peptides and neurofibrillary tangles (NFTs) (Wang et al., 2021).

The Aβ hypothesis is a widely well-known mechanism in the pathogenesis of AD. The non-amyloidogenic cleavage of amyloid precursor protein (APP) by α- and γ-secretases is the predominant pathway and results in the formation of various fragments that do not accumulate. On the other hand, due to genetic mutations and/or interacting environmental factors, APP is cleaved in the amyloidogenic pathway by γ-secretases and β-amyloid precursor protein-cutting enzyme1 (BACE1/β-secretase), leading to the formation of Aβ fragments of different lengths (25-42 amino acids), Aβ42 being the most toxic species (Ricciarelli & Fedele, 2017). The Tau protein also plays an important role in the function of microtubules in the brain, ensuring healthy axonal transport. In AD, Tau is largely hyperphosphorylated (pTau) and aggregates in helical filaments (Spillantini & Goedert, 2013). Increased Aβ and pTau accumulation leads to oxidative stress, cellular inflammation, neurotoxicity, synaptic impairment, and neural cell death over time (Breijyeh & Karaman, 2020). Because these molecular pathologies develop slowly over a very long period of time, early diagnosis and treatment with targeted theranostic agents would be extremely helpful in the management of AD.

The application of molecular theranostic agents has become a promising therapeutic approach to monitor treatment response and increase therapeutic effectiveness. The development of sensitive, specific, and preferably non-invasive biomarker-specific imaging probes will be useful for monitoring disease progression, understanding the complicated disease mechanism, and evaluating the potential of new drugs for AD (Chen et al., 2017).

Using PET to show the Tau protein and Aβ42 fragments is critical for the early-stage AD diagnosis. Because most contrast agents in imaging are non-specific, they are rapidly cleared from the brain tissue. To overcome this problem, fluorescent, quantum, or multimodal-based nanoparticles can be utilised to identify early pathological indicators of AD, such as imaging probes that specifically bind to Aβ or Tau (Pansieri et al., 2017).

DNA-nanoparticle complexes can detect protein biomarkers even at very low molar concentrations. This detection technique, also known as bio-barcoding, uses AuNPs labelled with antibodies targeted to the specific protein. The method has revealed satisfactory results for detecting Aβ-derived diffusible ligands in the cerebrospinal fluid for the in vitro diagnosis of AD (Georganopoulou et al., 2005).

In an *in vivo* study, antibody-SPION nanoparticles were synthesised to target MRI of Aβ plaques in AD mice. SPIONs were shown to perfectly enhance the MRI contrast in Aβ plaques. SPIONs coupled with antibodies demonstrated two-fold greater detectability compared to the untreated group (Sillerud et al., 2013). In another study, with metal nanorods, nanoplasmonic fibre-tipped probes (nFTP) were displayed to bind to Aβ42 and Tau in an *in vitro* culture medium using inverted light microscopy and spectrometry (Liang et al., 2016).

Another study reported that NIAD-4, a fluorescent dye in the NIR region, can quickly cross the BBB due to its low molecular weight and excellent structure. The chemical structure of the NIAD-4 core is similar to that of thioflavin T (ThT), the best known detection marker for Aβ fibrils. This makes NIAD-4 a highly specific binding agent for Aβ structures (Nesterov et al., 2005). In another study, gelsolin, horseradish peroxidase (HRP), and AuNP were combined in the form of HRP-Au-gelsolin. This electrochemical nanoprobe provided sensitive results for assessing Aβ levels in AD mice brains (Yu et al., 2015).

In another study, dibutyl-2-naphthylamine-based cyanines, which are DBAN-SLM, DBAN-SLOH, and DBAN-OSLM, were synthesised like NIR fluorescent probes for real-time Aβ imaging. These cyanines have a stronger affinity for monomers and oligomers than for fibrils, resulting in stronger fluorescence enhancement. DBAN-SLM showed the highest binding activity with Aβ species. There was an efficient reduction of Aβ aggregation and a strong neuroprotective impact against Aβ-induced toxicities. Aβ-induced ROS production was also suppressed. DBAN-SLM was shown to be a viable theranostic molecule for the NIR imaging of Aβ oligomers in AD therapy due to its high BBB penetration. Further studies are needed to investigate the pharmacodynamic and pharmacokinetic features of the probe for clinical applications and to determine its age- and dose-dependent imaging capacity (Wang et al., 2021).

In another study, Congo red/Rutin/MNPs (iron oxide nanoparticles) that can specifically detect Aβ plaques (with Congo red) in MRI were prepared. In this way, the targeted delivery of a therapeutic agent with antioxidant properties, Rutin, was achieved, providing controlled drug release in an H_2O_2-induced environment and preventing oxidative stress. In this study, nanoparticles inhibited Aβ-induced cytotoxicity and ROS production in vitro, and both memory and neurological deficits were improved in the mouse model (Hu et al., 2015).

CONCLUSION

Nanoparticles are materials in the range of 1 to 100 nm in all three dimensions. Their mechanical, chemical, optical, electrical, and magnetic properties vary with size, making them unique and preferable. Due to their small size, distinctive features, and ability to adapt to specific requirements, they attract great interest in many areas such as chemistry, biology, physics, engineering, agriculture, electronics, food technology, defence industry, bioengineering, and medicine. Applications in medicine, defined as nanomedicine, aim to diagnose and treat diseases in the early stages before the symptoms are apparent in the clinic; to enable the treatment processes to be more efficient and effective; and to reduce or eliminate the side effects of drugs. Most of the time, treatments based solely on imaging or nanotechnology may be insufficient to meet current needs. Theranostic nanoparticles can fulfil this need by providing diagnosis and treatment simultaneously.

Theranostic nanoparticles can be prepared in different shapes, structures, or sizes and can be coated with materials that can circulate without side effects on the immune system. Thus, theranostic nanoparticles can support effective disease management by enabling the diagnosis of early biomarkers and treatment of the disease before it progresses. Unlike traditional analyses, which take a long time, they can enable the rapid acquisition of similar information with imaging techniques, simultaneous drug delivery, visualisation of the biological effect as well as the accumulation of an active

substance in the specific target. However, there is insufficient scientific evidence to comprehend both the interaction of all nanoplatforms within the body and the potential adverse effects, as well as how the body will react to nanoplatforms. Therefore, detailed *in vivo* studies are needed to characterise the chemical, physical, and metabolic features of nanoparticles to prevent the toxicity of inorganic materials used in imaging studies before nanotechnology is applied in routine clinical applications.

Applications of theranostic nanoparticles in the management of neurodegenerative processes, especially in the diagnosis and treatment of AD, are of high importance. Theranostic approach will be able to provide early detection of the disease pathology and early feedback about the therapeutic efficacy. The most important problems with current medications for neurodegeneration are that they have only symptomatic effects and have limited ability to penetrate the BBB. Nanoplatforms hold out hope for the treatment of these diseases by allowing the drugs to pass through the BBB and treat the tissue pathology. It is promising that the elevated/reduced levels of antioxidant and anti-inflammatory molecules due to the AD pathology can be improved through nanoplatforms. Together with recent technical improvements and promising studies in the literature, some of the problems must be overcome, including the selection of the most effective nanoplatform, higher reproducibility, improvement of ligand conjugation efficiency, and lower cost for clinical trials. When these gaps are filled, future customised nanotreatment strategies for AD will be established to actively target molecular pathology at several levels with higher efficacy and lower side effects.

Peer Review: Externally peer-reviewed.
Author Contributions: Conception/Design of Study: D.A.Ş., N.E.T.; Data Acquisition: D.A.Ş.; Data Analysis/Interpretation: D.A.Ş., N.E.T.; Drafting Manuscript: D.A.Ş.; Critical Revision of Manuscript: N.E.T.; Final Approval and Accountability: D.A.Ş., N.E.T.
Conflict of Interest: The authors have no conflict of interest to declare.
Financial Disclosure: The authors declared no financial support.
Acknowledgement: The authors would like to thank İMÜ-BİLTAM for providing the infrastructure for this work.

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