NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | MINI-REVIEW ISSN: 2576-828X

Role of nanotechnology in therapeutics and diagnosis of Alzheimer's disease

Dhivya P Sundaram [1]*, Swathy Govindaswamy [2], Sobiya Mathiazhagan [3] and Jayalakshmi Venugopal [2]

[1] Department of Biomedical Sciences, Bharathidasan University, Tiruchirappalli, Tamil Nadu 620024, India
[2] KMCH College of Pharmacy, Department of Pharmacy Practice, Coimbatore, Tamil Nadu 641048, India
[3] Department of Pharmaceutical Technology & Centre for Excellence in Nanobio Translational Research, Anna University, Bharathidasan Institute of Technology Campus, Tiruchirappalli, Tamil Nadu 620024, India
* Correspondence: dhivyapsundaram@gmail.com; Tel.: +919994539553

Received: 9 January 2023; **Accepted:** 3 October 2023; **Published:** 31 January 2024
Edited by: King Hwa Ling (Universiti Putra Malaysia, Malaysia)
Reviewed by: Lilach Soreq (University College London, United Kingdom);
Muhammad Danial Che Ramli (Management and Science University, Malaysia)
https://doi.org/10.31117/neuroscirn.v7i1.225

ABSTRACT: Alzheimer's disease refers to a pathological topography accompanied by the loss of neurons in the brain regions including entorhinal cortex and hippocampus, resulting in memory impairment, cognitive dysfunction, behavioural problems, and difficulties in activities of daily living that ultimately lead to mortality. This disease typically affects the elderly population. Even if the underlying pathophysiological mechanisms are unclear, Alzheimer's disease is unquestionably associated with dysfunction in the cholinergic system, resulting in a decreased level of acetylcholine in specific brain regions, including the entorhinal cortex and hippocampus. Although significant progress has been made in understanding the molecular and cellular causes of Alzheimer's disease, there is presently no medication available to reduce or stop the loss of brain cells. As the number of individuals with Alzheimer's disease continues to rise, there is a pressing need to develop ways for early diagnosis and offer viable treatments to avert a public health crisis. In recent years, nanoparticles have been seriously studied as a diagnostic and therapeutic tool for Alzheimer's disease. Here, we discuss the recent growth in nanoparticles for Alzheimer's disease diagnosis and treatment.

Keywords: Alzheimer's disease, Nanomedicine, Nanotechnology, Diagnostics, Nanoparticles

1.0 INTRODUCTION

Alzheimer's Disease (AD), a persistent neurodegenerative condition characterised by progressive deterioration in cognitive function, including memory loss and abnormalities in function and behaviour, is the most prevalent form of dementia among the elderly (Aisen & Davis, 1997; Masters et al., 2006). AD was first described by the Bavarian neuropsychiatrist Alois Alzheimer in 1906 (Hostettmann et al., 2006). The global impact of AD affecting nearly 50 million people worldwide, are projected to reach 150 million by 2050. AD poses significant clinical, social, and economic challenges (Dumurgier et al, 2020; Feigin et al., 2019). Although there are only four FDA-approved treatments for AD, their limitations contribute to therapy failure, stressing the need for alternative

therapeutic interventions and the importance of finding new biomarkers in order to better understand the pathophysiological mechanisms to develop effective treatment strategies (Cao et al., 2022).

Current drug therapies for AD consist primarily of FDA-approved cholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine, and Huperzine A), an N-methyl-D-aspartate receptor antagonist (Memantine), and some neuroprotective agents. Although these medications relieved several psychological and behavioural symptoms of AD patients, effective pharmacological approaches for the prevention and treatment of AD, i.e., disease-modifying therapies, are missing (Hong-Qi et al., 2012).

The pathology of AD is progressive. Presently, there is no single diagnostic method for precision screening or early and reliable identification of AD, and clinical criteria (including laboratory tests, neuroimaging, and neuropsychological testing) can only provide a likely diagnosis with an average confidence level of 80% (Fradinger & Bitan, 2005). In addition, the widely given drugs are symptomatic and do not halt the progression of the disease's pathology. Even the most advanced treatments currently on the market or under study can only delay or stop the advancement of the disease's pathophysiology; they cannot restore lost brain function. Therefore, AD is incurable (Masters et al., 2006; Mattson, 2004).

In addition, the limited potential for repair and regeneration of brain tissue renders this progression nearly irreversible (Masters et al., 2006). This necessitates an early detection and prevention of the condition. The sooner we stop the pathogenetic process, the less symptomatic the patient will be. Therefore, the current treatment approach is to conduct particular diagnostic techniques to screen the group at high risk for AD (Mortimer et al., 2005).

The complex structure and functional features of the central nervous system (CNS) are primarily responsible for the prominence of nanotechnology's medical applications in CNS-related illnesses (Silva, 2005). Nanotechnology is revolutionizing neurology, offering various therapeutic options for neurological disorders like Alzheimer's and Parkinson's diseases. Stem cell research uses nanoparticles to stimulate regeneration without immune response. Nanomedicine, specifically theranostics, integrates diagnostic and therapeutic nanotechnology for neurodegenerative disorder treatments. Advancements include drug targeting, magnetism, and nanoformulated particles. Nanoprotection against nerve injury is being addressed using antioxidants like fullerene. Nano-level neuroprotection involves carbon nanotube electrode arrays for neurorepair through nanoscaffolds, enabling surgeries at micro- or nanolevels for axon renovation and monitoring neural activity (Badry and Mattar, 2017; Milane et al., 2021).

2.0 NANOPARTICLES IN TREATMENT OF AD

2.1 Nanoemulsion

Twenty years ago, nanoemulsions with 20–200 nm discrete droplet sizes were produced (Anton et al., 2008; Gutierrez et al., 2008; Mason et al., 2006; Solans et al., 2005) In fields such as pharmaceutics, cosmetic science, food technology, etc., they can be used as innovative formulations (Acosta, 2009; Sonneville-Auburt et al., 2004; Sosnik et al., 2010). Because they are non-toxic and non-irritant, they are great therapeutic agents because they do not harm human or animal cells. Their physical durability provides an extra edge (Aboofazeli, 2010).

The intranasal administration of an acetylcholinesterase inhibitor in conjunction with a neuroprotective and anti-amyloid medication is a potential method for the treatment of AD. Sood et al. (2013) effectively created donepezil-loaded mucoadhesive nanoemulsions for intranasal delivery to direct brain distribution. These nanoemulsions can be utilised to deliver donepezil for treating AD. The nanoemulsion of curcumin and donepezil for intranasal delivery to the brain has been produced. The combination therapy was built on the cholinergic replacement idea in conjunction with the anti-amyloid and anti-inflammatory approach for improved AD management via intranasal administration for improved brain targeting (Sood et al., 2013).

2.2 Nanosuspensions

The nanosuspensions are defined as drug carriers by particle size range between 10 and 1000 nm (Muller et al., 1999). Nanosuspensions diminish drug administration doses, adverse effects, and therapeutic costs (Zhang et al., 2007). The formulation of a nanosuspension containing donepezil via ionic cross-linking demonstrated a greater drug concentration in the brain, with no mortality, haematological changes, body weight fluctuations, or histological alterations in mice. The formulation was provided in varied doses compared to normal saline administered intranasally, and it was determined that donepezil-loaded nanosuspension could provide direct nose-to-brain

delivery, hence increasing drug concentration in the brain (Bhavna et al., 2013).

2.3 Biodegradable polymeric nanoparticles

The biodegradable polymeric nanoparticles are matrix-type, solid colloidal particles in which pharmaceuticals are dissolved, entrapped, encapsulated, or chemically bonded to the polymer matrix (Allen & Cullis, 2004; Huwyler et al., 1996; Kwon, 1998). Compared to other colloidal carriers, polymeric nanoparticles are more stable in biological fluids and resistant to enzymatic degradation (Lockman et al., 2003). It has been explored that biodegradable polymeric nanoparticles can transport medications through the blood-brain barrier for the treatment and diagnostics of neurological illnesses such as Alzheimer's disease (Roney et al., 2005). Using the single emulsion-solvent evaporation approach, it has been reported that nanoparticles containing Rivastigmine tartrate were successfully created. As an alternative to enhancing the drug's stability, this formulation strategy may improve absorption, bioavailability, and therapeutic effectiveness (Pagar & Vavia, 2013).

To target the brain with rivastigmine-loaded poly (ethylene glycol)–poly (lactic-co-glycolic acid) (PEG–PLGA) nanoparticles, a novel formulation was developed. Therefore, the proposed formulation was designed to be a capable carrier, especially for the blood-brain barrier, which is a challenging factor for brain drug delivery, and the delayed drug release of rivastigmine may be advantageous for treating AD. The developed formulation decreased the total dose of the medicine required for therapy to a minimum level (Prakash et al., 2014).

Chitosan is a biocompatible, bioactive, and biodegradable polymer commonly employed in preparing micro- and nanoparticles. Chitosan has been used as a delivery system for genes, proteins (including antibodies), and medicines due to its cationic charges, biocompatibility, and low toxicity (Singh & Lillard, 2009; Wilson et al., 2010). Ionic gelation was used to create chitosan nanoparticles that were loaded with rivastigmine and successfully treated streptozotocin-induced dementia in mice (Bajaj & Chopra, 2013).

2.4 Dendrimers' effect on the amyloid-beta (Aβ)-peptide

Dendrimers are nanomaterials with spherical macromolecular structures and a densely packed surface (Klajnert et al., 2006). Their architecture has afforded them numerous biomedical opportunities (Mansoori et al., 2007; Nikakhtar & Nasehzadeh, 2005). Preventing Aβ's cytotoxic effects is another nanotechnology possibility for the anti-amyloid strategy. Recent recommendations for this strategy involve modified dendrimers (Nazem & Mansoori, 2008). Patel et al. (2006) revealed that dendrimers can shield the cell membrane against membrane-mediated neurotoxicity resulting from electrostatic contact with the cell membrane. In addition, dendrimers are capable of sequestering poisonous A species, thereby preventing their detrimental effects on the cell membrane. Due to the possible toxicity of dendrimers on cells, further research is required before this approach may be used *in vivo* (Patel et al., 2006).

Patel et al. (2007) demonstrated that attachment of sialic acid to dendrimer termini via the anomeric hydroxyl group, as opposed to the carboxylic acid group, slightly improves their ability to ameliorate A-induced neurotoxicity. These results contribute to our understanding of the A/sialic acid interaction and support further research into developing sialic acid-modified materials to prevent A toxicity (Patel et al., 2007).

2.5 Anti-Aβ-fibrillation magnetic nanoparticles

Magnetic nanoparticles (MNPs) are candidates for various biomedical applications. They have a magnetic core, such as maghemite, and a biocompatible coating, such as polyethylene glycol (PEG). Functionalising MNPs, i.e. combining them with biological vectors, luminous labels, antibodies, medicines, etc., makes them more appealing and valuable (Cai & Chen, 2007). Ideal MNPs are non-toxic to cells and tissues and have a lengthy shelf life (Amiri et al., 2013). According to the amyloid cascade hypothesis, research on the use of MNPs in AD has concentrated on suppressing A-peptide aggregation and amyloid-beta-derived diffusible ligand (ADDL) production or on finding sensitive ways to assess biomarkers (Busquets et al., 2014). The physicochemical impacts of superparamagnetic iron oxide nanoparticles (SPIONs) on the Aβ fibrillation process were explored by Mahmoudi et al. (2013). They discovered that SPION size significantly affects the Aβ fibrillation process's inhibition (Mahmoudi et al., 2013).

2.6 Lipoprotein-based nanoparticles to accelerate amyloid beta clearance

Lipoproteins, natural nanoparticles with a well-established biological function, are ideally suited as a nanoplatform for medical diagnostics and therapies. Due to its ultra-small size and constructive surface features, high-density lipoprotein (HDL), the smallest

lipoprotein, is very interesting. Viola and colleagues (2015) designed an amyloid-targeted lipid compound and put it into stealth liposomal nanoparticles that target amyloid plaque deposits in a preclinical model of AD. Their chemical traverses the blood-brain barrier and binds to Aβ plaque deposits by labelling parenchymal amyloid deposits and vascular amyloid characteristics of cerebral amyloid angiopathy (Viola et al., 2015).

ApoE3 is an anti-atherogenic protein that plays a significant role in plasma cholesterol homeostasis. HDL, an endogenous nanoparticle serving as a "good" lipid transporter and a natural vehicle with accurate navigation for biomolecule delivery *in vivo* (*e.g.*, proteins, micro-RNAs, vitamins, and hormones), plays a crucial part in lipid metabolism and cell-to-cell communication. According to Song et al. (2014), lipoprotein-based nanoparticles (ApoE3 rHDL) enhanced amyloid clearance in AD mice. The findings were direct evidence of a bio-mimetic nanostructure crossing the blood-brain barrier, capturing amyloid, and facilitating its degradation by glial cells, indicating that ApoE3 rHDL may provide a new nanomedicine for disease modification in AD by accelerating amyloid clearance, which also supported the notion that nanostructures with amyloid-binding affinity may offer a novel nanoplatform for AD therapy (Song et al., 2014).

Curcumin is a recognised amyloid ligand that inhibits the development of A142 oligomers and binds to plaques *in vivo.* Diverse types of curcumin-phospholipid conjugates have been designed for liposomal and solid-lipid nanoparticle incorporation. It is anticipated that peripheral treatment with these multivalent nanoparticles will reduce the level of amyloid in the brain by altering amyloid equilibrium, thereby reducing brain amyloidosis (Moghimi, 2011).

3.0 NANOPARTICLES IN ALZHEIMER'S DISEASE DIAGNOSIS

It is crucial to diagnose AD early to prevent permanent neuronal damage and dementia. As studying a real human brain is difficult and time-consuming, developing methods for detecting AD in its early phases is vital.

3.1 Magnetic nanoparticles as contrast agents for MRI (Magnetic Resonance Imaging)

Since it is widely accepted in the scientific community that the formation of senile plaques leads to neurofibrillary degeneration, the majority of efforts are focused on the detection and identification of amyloid plaques by magnetic resonance imaging (MRI) with nanoparticles doped with contrast agents (Brambilla et al., 2012).

Co-deposition and surface modification techniques were used to develop a contrast agent with magnetic nanoparticles and Aβ peptide. To explore *in vivo* imaging, the brains of AD transgenic mice were imaged using an MRI apparatus. The results demonstrated that the contrast agent is approximately 5 nm in size and has excellent MRI enhancement of senile plaque (Sillerud et al., 2013).

A sensitive contrast probe for molecular MRI has been reported to be unique to amyloid oligomers (AOs). Antibodies specific for AOs bound to magnetic nanostructures demonstrated the complex's stability; they bind to AOs on cells and brain tissues to produce an MRI signal. When delivered intranasally to an AD mouse model, the probe rapidly reached hippocampus AOs. In isolated human brain tissue samples, an MRI signal distinguishing AD from controls was detected. Such nanostructures that target neurotoxic AOs may be beneficial for evaluating the efficacy of novel medicines and, eventually, for diagnosing and treating AD in its earliest stages (Viola et al., 2015). Moreover, it has been reported that the creation of monocrystalline iron oxide nanoparticles (MIONs) covalently bonds to the N-terminus of the A1-40 peptide via amide coupling and that their progress has been made for the coupled targeting and imaging of senile plaques (Wadghiri et al., 2003).

3.2 Nanogels

Nanogels, an effective pharmaceutical delivery system that offers enhanced cellular absorption, reduced toxicity, higher drug loading, and controlled release at the target site, have been applied in drug delivery systems for AD. A recent study demonstrated the efficacy of chitosan and tripolyphosphate nanogels for the delivery of deferoxamine in AD treatment. Modified pullulan backbones with cholesterol moieties serve as artificial chaperones that mitigate AD pathology by preventing Aβ amyloid development. In preclinical mouse experiments, nanogels enhanced the delivery of insulin to the brain, a potential AD drug, especially when combined with polysaccharides, showcasing non-toxic, stable, hydrophilic, and biodegradable properties (Ashrafi et al., 2020; Kamei et al., 2018).

Researchers are exploring nanomaterials for precision medicine to address the limitations of current AD treatments that cannot cross the blood-brain barrier. They highlight various nanocarrier categories, including

metallic/non-metallic nanoparticles, organic nanoparticles, lipid vesicular, and emulsion-based carriers. Metallic nanoparticles, such as gold, silver, selenium, iron, and cerium, show therapeutic potential for AD through targeted drug delivery. Other nanocarriers, such as nanostructured lipid carriers and polymeric nanoparticles, also show potential in developing effective treatment strategies (Ayaz et al., 2020; Liu et al., 2020; Mir Najib Ullah et al., 2023).

4.0 ADVANTAGES AND DISADVANTAGES OF NANOTECHNOLOGY IN ALZHEIMER'S DISEASE

The diagnostic and treatment-related advantages and disadvantages of AD are listed in **Table 1.**

Table 1: Advantages and Disadvantages of Nanotechnology in Treatment and Diagnostic of Alzheimer's Disease

ADVANTAGES	DISADVANTAGES
Capable of overcoming the constraints inherent to blood-brain barrier transit (Silva, 2010; Kreuter, 2001).	Possibility to produce nanoparticle-mediated toxicity and adverse responses (Moghimi et al., 2005; Dobrovolskaia et al., 2007).
Atomic force microscopy with sub-nanometer resolution makes it easier to discriminate between amyloid beta protofibrils and fibrils in terms of height variation than electron microscopy studies (Mansoori, 2005; Harper et al., 1999).	Imaging with nanoparticles of iron oxide as an MRI contrast agent may not be useful for diagnosing Alzheimer's disease in its earliest stages. Because the production of amyloid plaques occurs in the later, more advanced stages of the illness (Nazem & Mansoori, 2011).
Fluorescence resonance energy transfer microscopy is a nanoscale method that applies to both *in vitro* and *in vivo* research on AD (Selvin, 2000).	Several components of polymeric nanoparticles and nanoconstructs may block the operation of P-glycoprotein efflux pumps on the luminal side of brain capillary endothelial cells and generate cytotoxicity (Batrakova et al., 2003; Hunter & Moghimi, 2003).
NanoSIMS (Nano Secondary Ion Mass Spectroscopy) microscopy demonstrated advantages for portraying chemical and morphological changes in diseased brain regions (Quintana et al., 2007).	Nanoparticles may alter or inhibit the transit of hemostatic mediators in the CNS (King et al., 2001).
NanoSIMS depicts senile plaques with higher resolution than optical imaging (Quintana et al., 2007).	Polymeric nanoparticles can alter gene expression, which could pose significant challenges to the transport of nucleic acid to the capillary endothelial cells of the brain (Akhtar & Benter, 2007; Kabanov et al., 2003).
Gold nanoparticles based Bio-barcode assay a viable method for diagnosing Alzheimer's disease and other forms of dementia (Keating, 2005).	
Magnetic nanoparticles exhibit a high degree of similarity to circulating amyloid beta forms, resulting in a "sink effect" and, ideally, a revolution in AD treatment (Brambilla et al., 2012).	
Nanodrop can be used to determine RNA concentration in AD brains (Gok et al., 2022).	

5.0 CONCLUSIONS

Nanotechnology presents promising prospects for the future of medical treatment and diagnosis. Researchers can conduct experiment with novel concepts to advance the treatment and diagnostics of Alzheimer's disease and dementia due to the unique capabilities of

nanotechnology. However, numerous unanswered problems remain regarding the biocompatibility of nanoparticles and nanodevices, particularly in complicated biological environments such as the brain's high cell density. The visualised nano-neurosurgical techniques for healing CNS illnesses appear to have a long and complex road ahead before becoming a practical technology and, eventually, a standard clinical practice.

Author contributions: D.P.S., S.G. and S.M. prepared, reviewed, edited and drafted the paper. J.V. reviewed and approved the paper.

Conflicts of interest: The authors declare no conflict of interest.

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