



REVIEW ARTICLE

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A Prospective View on Nanotechnology in Alzheimer's Treatment

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ABSTRACT

Alzheimer's disease remains a formidable challenge in today's world of medicine as they are offering only quantized symptomatic relief. A hope for transformative development in exploration of Alzheimer's treatment could be achieved by the involvement of nanotechnology, as it is contributing unique advantages for the diagnosis and treatment of many other indications. This review provides an insight about challenges, promises and scope in providing effective treatment for Alzheimer's by incorporating novel technologies. In this article, we reviewed nanoscale diagnostic methods, tools, therapies targeting indications from cancer therapy to autoimmune disorders. As nanotechnology provides immense possibilities for personalized medicine, improved drug delivery systems and enhanced diagnosis, it could become a good tool in the quest to combat Alzheimer's treatment along with other medicinal challenges.

Key words: Alzheimer's disease, nanotechnology, autoimmune disorders, acetylcholine.

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INTRODUCTION

In the monarchy of modern medicine, the bonding of effective treatments for Alzheimer's disease stands as one of the intimidating challenges of our time. Alzheimer's disease affects millions of individuals globally, causing amnesia, debilitation, extreme disfigurement of day-to-day functioning. Regardless of extensive research, there is still no cure for this ruinous condition, and the available treatments offer only finite easing of symptoms. Regardless of the perception of biomedical revolution, a ray of hope emerges through the merging of nanotechnology into Alzheimer's disease research and therapy.[1]

Nanotechnology, an innovative field that deals with matter and gadgets at the nanofabrication level, holds the budding to transform the way we proceed towards the diagnosis and treatment of Alzheimer's disease. By rendering the unique properties and ability of nanoparticles, researchers are exploring novel avenues to combat this complex and enigmatic disease. In this review, we go on board on an elucidate journey through an enchanting intersection of nanotechnology and Alzheimer's treatment. Our goal is to provide an overview of the present state of nanotechnology-based approaches, focusing their promise, challenges, and potential impact on the existence of Alzheimer's patients and their families.[2]

This review will hunt through the essential concepts of nanotechnology and its application. We will explore the various strategies employed to develop the latest nanoscale diagnostic tools, preventive methods and research capable of curing peptides and neurofibrillary tangles composed of hyperphosphorylated tau proteins. As we journey through the landscape of nanotechnology propelled Alzheimer's research, its remarkable potential raises questions about its long-term effects on human health and the environment, necessitating a balanced examination of its benefits and risks.[1]

In closing, this review article focuses to provide a panoramic and perceptive overview of the rapidly growing field of nanotechnology in Alzheimer's treatment. By shedding light on the cutting-edge developments, challenges, and ethical deliberation, we hope to devote ourselves to a deeper understanding of the potential that nanotechnology holds in the search to reduce the burden of Alzheimer's disease. Ultimately, our survey seeks to inspire researchers, clinicians, and associates to collaborate in the pursuit of innovative solutions that may one day change the course of Alzheimer's disease supervision.[3]

Importance

Nanotechnology holds significance and an eminent role as a promise in the field of Alzheimer's disease research and treatment. In the area of drug delivery nanotechnology is directed to carry through drugs across the blood brain barrier, a major hurdle in the treatment of Alzheimer's, furthermore it can also be

used to target a peculiar area of the brain. Hence reducing the side effects and providing enhanced treatment.[4] A nanoparticle can be used as a contrast agent in imaging techniques like a PET (Positron Emission Tomography) or MRI (Magnetic Resonance Imaging) scan. As a result, initial intervention and personal treatment plans can help conjure up and supervise the progression of Alzheimer's disease. AD is characterized by beta-amyloid plaques, which can be targeted with nanoparticles. It is feasible for them to bind to these toxic proteins, thereby expediting their removal from the brain.[5]

Also, Alzheimer's disease can be treated with gene therapy based on nanotechnology. Treatments can now be tailored to a patient's unique genetic and molecular profile thanks to nanotechnology. For those suffering from Alzheimer's, this individualized approach to treatment may produce better results. This is possible by delivering therapeutic genes directly to brain cells, it can likely prevent or reverse the progression.[6]

Nanoparticles have the ability to enter cells and strike intracellular targets. This is crucial for therapies that delve to vary Alzheimer's-related fundamentals, such as tau protein modulation. Nanoscale sensors can steadily audit biological processes and chemical levels in the brain. This real-time data can provide important observations on the course of the disease and its response to treatment.[7] Nanotechnology allows for the rework of treatments based on an individual's specific genetic and molecular structure. This tailoring of therapies can lead to more effective outcomes for Alzheimer's patients. Nanotechnology may lessen the negative effects connected with conventional Alzheimer's treatments by accurately focusing on the afflicted areas and eliminating off-target effects.[2]

Researchers have access to effective tools thanks to nanotechnology to investigate the fundamental causes of Alzheimer's disease at the nanoscale. Improved treatments may be created as a result of this improved understanding.[4] It is important to note that although nanotechnology has great potential, many of these applications are still in the empirical or initial stages. As of the last knowledge refurbished in the previous years, current research continues to explore the full potential of nanotechnology in Alzheimer's disease.[1]

Role of nanotechnology in several diseases

Many academics feel that nanotechnology applications in medicine can be essential in achieving early and efficient treatment of various ailments that the human race suffers from. These applications include all-inclusive surveillance control, creation, repair, and defense of all biological human systems, employing designed nanodevices functions from a molecular level.[8] There is currently research ongoing in nephrology, cardiovascular disease therapy, gene therapy and cancer therapy. A significant improvement in the area of traditional treatment has been made, as well as advancements in the quality of nanoparticles and nanotechnology.[9] As a sub specification of medicine, nanomedicine uses nanotech to treat, prevent and diagnose deadly diseases, like that of cancer and other complicated ones like heart diseases. There are now a number of nanomedicine products under clinical trials that target cardiovascular, neurological, musculoskeletal and inflammatory ailments.[10]

There is a need for sincere advancements in healthcare and nanomedicine is an essential for personalized, targeted and regenerative approaches. This enables doctors and patients to access the next level of innovative medications, therapies and implausibility. It contributes essential modern tools for acclimating the major problem being faced by aging people and is seen as an instrument in advanced and economic health care as it is critical to make medications and treatments accessible to one and all.[11]

In the battle against cancer nanotechnology has shown promising results in the area of drug delivery. Nanoparticles, usually that are not manufactured by the pharmaceutical industry, are foreseen to deliver conventional cancer therapy showing fewer side effects on tumors and initiate the targeted demolition of cancer cells in novel therapies. A large number of cytotoxic medications can be given at the intended site thanks to nanoparticles.[12]

Nanomaterials also offer opportunities to resolve or overcome the down graders in autoimmune disease diagnosis and treatment due to their unique features.[13] To this date, inorganic nanomaterials as in gold, silver, and iron oxide or organic nanomaterials such as polymers, dendrimers and liposomes have abetted to construct latest diagnostic and therapeutic techniques. These nanoparticles have many favorable characteristics which include built in physicochemical properties like proper solubility, high surface area to volume ratio, malleable size, exceptional optical and electrical properties. They also possess passive targeting capabilities as well as active targeting after surface modifications.[14] Immunoadjuvant effects with low or no immunogenicity have good biodegradability of nanomaterials, contributing towards the refinement of approaches to treat autoimmune disorders. The above characteristics of nanotechnology have been explored for its influence in the diagnosis and treatment of autoimmune diseases.[15]

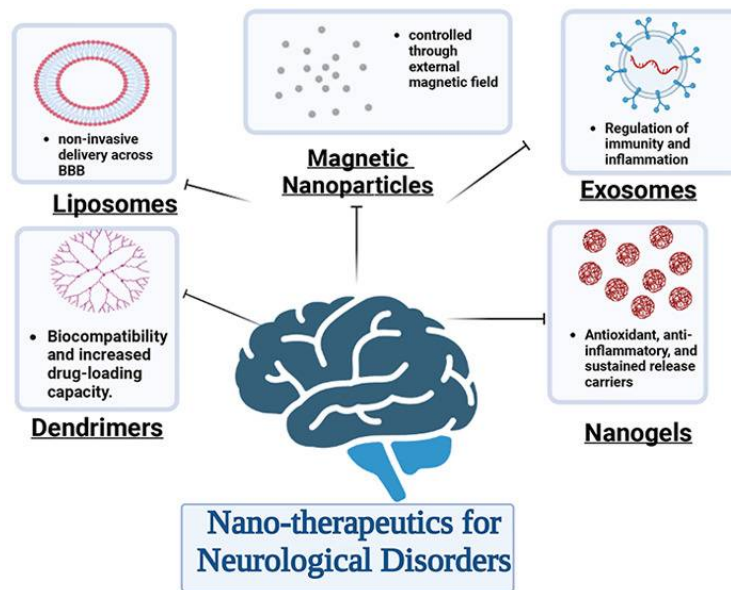


Figure 1: Nanotherapeutics for neurological disorders

As viral particles and nanodevices operate in similar dimensions, upcoming vaccines and also operating immune engineering depends massively on this strategy. Nano pharmaceuticals can be the optimal counterfeit for cutting-edge vaccine development technologies since nanoparticles are tools that may imitate the functional and structural aspects of viral infectious components. In COVID-19 directorate, the nanotechnology-based path has a huge range of implications and can act at various phases. For instance, a unique nanoparticle-based vaccine metastatic platform, helps nanomedicines for treating SARS-CoV-2 infections, and a nano-based formulation for SARS-CoV-2 therapies are all being composed.[16]

Magnetic nanoparticles are under investigation as probable therapeutics for a variety of neurological disorders, in addition to Alzheimer's disease, epilepsy, Parkinson's disease, muscular dystrophy, brain tumours and NeuroAIDS. Magnetic particles with sizes of less than 5 nm were synthesised and covalently conjugated with oligosaccharides, and the ability to pass through the BBB was ascertained in the orthotopic mouse model. Another example, Poly (lactic-co-glycolic acid) functionalized magnetic iron oxide nanoparticles (Fe_3O_4) were modified along with carnosine and dexamethasone for targeted treatment for ischemic stroke. The magnetic particles can also be coated with ligands such as lactoferrin, curcumin, transferrin, and BBB penetrating peptides, complaint to BBB penetration.[17]

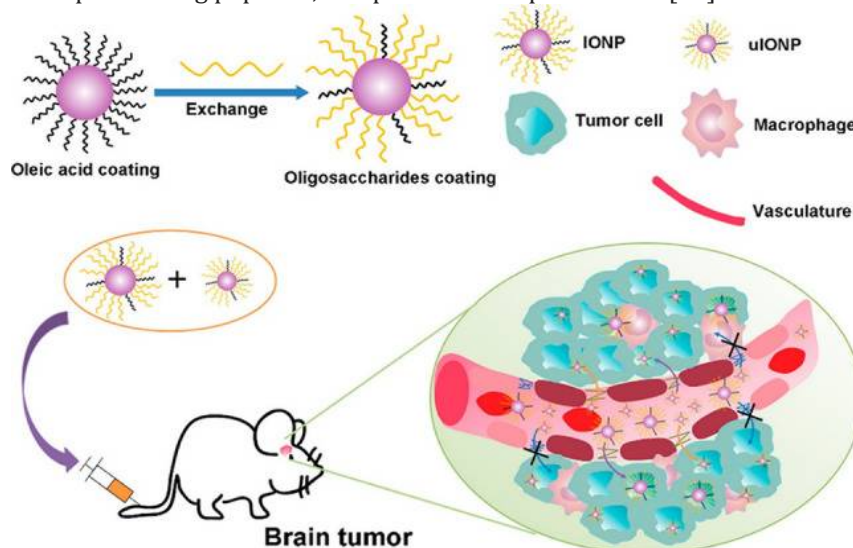


Figure 2: Schematic representation of immobilizing oligosaccharides onto magnetic particles and targeted therapeutic applications

Future aspects of nanotechnology

Nanotechnology speeds up the process using a compact portable device that takes small samples and enables almost instantaneous processing and analysis. The in vitro diagnostic testing will continue to

increase the size of samples and biosensors. The formulations of nanoparticles, when used for iron oxides and specialty polymers, will increase their imaging capacity by using lower and more effective doses of the diagnostic compounds, thus allowing early detection of genetic abnormalities, tumours, and the entire variety of disease states. Nanomedicine, like biotechnology, has been of concern in certain areas, particularly regarding safety and privacy. Immunoassays are appropriate applications because of the robust connectivity between antibodies and antigens, leading to excellent sensitivities. Regenerative immune sensors are an interesting new challenge that allows repetitiveness for statistical rigidity and semi-continuous monitoring. Nanomedicine is a very immature subject in cancer, so the clinic needs to determine the possible influence.[9]

Present scenario of Alzheimer's

A detailed clinical estimation is frequently the initial decision in making an Alzheimer's diagnosis. A thorough medical history and reasonable testing, and conversations with patients and their families about their symptoms and how they are evolving are all part of this process. These estimations of diverse cognitive processes, such as memory, inquiring, and language abilities, are used to diagnose Alzheimer's disease and distinguish it from other types of dementia.

PET and MRI scans can produce comprehensive pictures of the brain that can be used to spot structural abnormalities and changes in the brain that are related to Alzheimer's. Specific brain areas may exhibit atrophy (shrinking) as a result of these examinations. Beta-amyloid and tau proteins are two examples of biomarkers that might indicate the presence of Alzheimer's disease in blood tests or cerebrospinal fluid (CSF). These biomarkers might help with aid in the early detection and tracking of illness development.[18]

Treatment

Cholinesterase inhibitors and memantine are two medication groups that have been authorized for the treatment of Alzheimer's. Acetylcholine, a neurotransmitter involved in memory and learning, is made more abundant in the brain as a result of cholinesterase inhibitors (such as donepezil and rivastigmine). Another neurotransmitter, glutamate, is controlled by memantine. Drugs and treatments are used to treat particular symptoms of Alzheimer's disease, such as agitation, sadness, insomnia, and anxiety.[19,20]

Non-pharmacological interventions can improve general health and cognitive performance. Examples include, fitness programs, lifestyle changes, and cognitive stimulation programs. Current studies are looking at brand-new treatments, such as immunotherapies, anti-amyloid medications, and other strategies focusing on the disease's fundamental causes. Clinical studies are essential for assessing the effectiveness and safety of these potential procedures.[21]

Present difficulties

As of the most recent update, Alzheimer's illness is incurable. Treatment options offer symptomatic alleviation and, in certain situations, may halt development. Making an early diagnosis is difficult, and many instances are not discovered until the illness has advanced noticeably. Personalized treatment plans based on unique genetic and molecular profiles are a current topic of research, although they are not yet extensively used. It's vital to remember that research on Alzheimer's is ongoing, and that after September 2021, advancements could have occurred. For the most recent information, always turn to reliable, current sources or healthcare specialists.[22]

Nanotechnology based drugs for Alzheimer's

Currently, no drugs on the market can stop or reverse AD (Alzheimer's disease) progression. The acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine, huperzine A, and the N-methyl-D-aspartate receptor antagonist memantine hydrochloride, which are the current clinical drugs for AD that can only temporarily relieve the cognitive symptoms of patients. Several new AD drugs have been terminated in clinical trials, including sodium oligomannate (launched in November 2019 and terminated in an international phase III clinical trial in 2022), anti-amyloid antibody aducanumab (launched in June 2021 and terminated in Europe in 2022), and gantenerumab (produced negative phase III clinical data at the end of 2022). Fortunately, the monoclonal antibody (mAb), known as lecanemab, which binds to a β -soluble protofibrils, achieved promising outcomes in its global phase III clinical trial in September 2022. The U.S. Food and Drug Administration (FDA) approved this mAb in January 2023, through the accelerated approval pathway for treating AD. However, because the exact cause of AD has not yet been identified, the disease is still incurable, and most of the above therapeutic drugs can only delay its progression.[23]

Studies found that AD drug development fails up to 99.6% between 2002 and 2012. The blood-brain barrier (BBB) is a physical barrier that regulates how drugs enter and exits the central nervous system (CNS). BBB is one of the most crucial defense mechanisms of the CNS, and it is another significant factor hindering the development of AD drugs. Traditionally, the BBB has been difficult for almost all macromolecular drugs, including peptides, mAb, polyclonal antibodies, recombinant proteins, RNA drugs and gene drugs, and >98% of small-molecular drugs cannot do so. Therefore, a critical issue in AD drug development is to find the effective drug delivery strategies. Novel strategies are urgently required to overcome BBB issues,

thereby increasing the possibility of success in drug development programs, considering AD drug development's extremely high failure rate.[24]

As nanotechnology advances quickly, several nanomaterials can assist macromolecular drugs and small-molecular drugs in penetrating through the BBB and successfully delivering them to brain, which is important for developing new drugs and treating CNS diseases. More than 80 nanomedicine drugs have received worldwide regulatory approval, mainly antitumor drugs, including doxorubicin liposomes, paclitaxel albumin nanoparticles, paclitaxel polymer micelles, etc. Nanomedicines can be loaded with macromolecular drugs and small-molecular drugs to successfully cross the BBB through masking, encapsulating, and embedding. Additionally, nanomedicine can be modified and grafted onto macromolecular drugs and small-molecular drugs to ensure safe targeting and controlled release. It has the benefits of a long half-life, strong targeting, a high drug loading rate, good biocompatibility, high bioavailability, and low systemic toxicity.[24]

Developing anti-AD drugs is challenging due to the complex etiology and unclear pathogenesis, and getting adequate drug delivery across the BBB is another major challenge. However, nanomedicine-based drug delivery strategies provide complementary opportunities for AD. Increasing efforts have been made in recent years to deliver drugs to the brain, some of which have entered clinical trials. Nanomedicine is one of the effective methods for delivering drugs to cross the BBB. Additionally, nanomedicines can improve the biodistribution and pharmacokinetics of drugs through oral, intravenous, and intranasal delivery. Therefore, nanomedicines have been thoroughly researched for the treatment of AD. However, inorganic materials are difficult to break down, which may result in toxicity and restrict clinical applications, including metal nanoparticles (NPs) and carbon nanotubes (CNTs). In contrast, liposomal and polymeric NPs are widely used in approved nanomedicines due to their high drug loading, good biocompatibility, and nontoxicity. The ideal AD nanomedicine typically possesses the following characteristics: particle size 10-100nm, BBB penetration, high drug loading, long action time, good drug stability, non-toxicity, biodegradability, simple fabrication process, non-invasive administration, low cost, and stable storage.[24] In 1971, Gregoriadis discovered that, using liposomes as drug carriers could reduce the toxic effects of drugs and increase their ability to work as intended. Liposomal amphotericin B, the first nanomedicine, was introduced in the Irish market in 1990. After more than 50 years of rapid development, nanomedicine is currently a topic of interest in treating AD. Liposome drugs were listed earlier and made up most of the currently commercialized nanocarrier drugs, such as amphotericin B liposomes, daunorubicin liposomes, doxorubicin liposomes, paclitaxel liposomes, etc. Followed by microspheres, common ones include octreotide, risperidone, leuprolide, etc. Many nanoparticles for AD have been studied and developed with the continuous innovation of drug delivery systems. The reported nanomedicines of AD mainly include liposomes, solid lipids NPs, polymer NPs, dendritic NPs, albumin NPs, metal NPs, non-metal, inorganic NPs, etc. [25,26] (shown in below Figure 3).

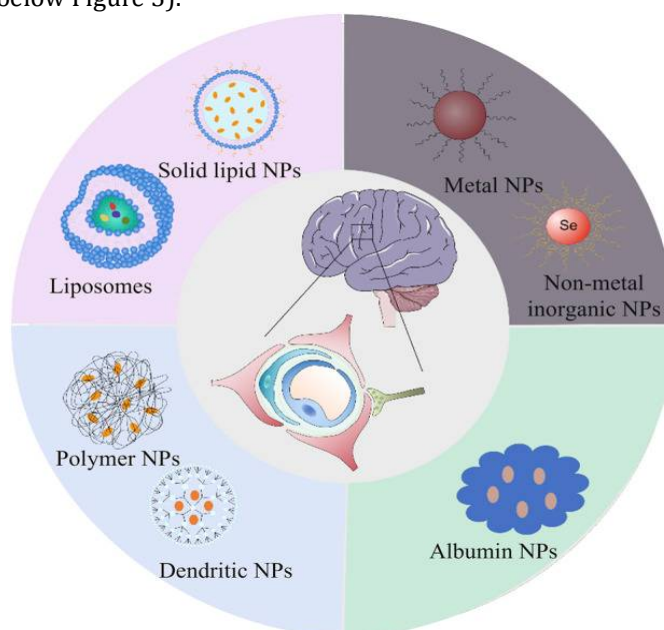


Figure 3: Schematic representation of the structures of the most commonly used nanomedicine types for Alzheimer's disease: lipid (liposomes and solid lipid), organic (dendritic and polymer), inorganic (metal and non-metal inorganic) and biomimetic (albumin)

Impact of nanotechnology in Alzheimer's

This number is expected to almost double in the next 20 years, from 78 to 139 million from 2030 to 2050, respectively. It is anticipated that by the middle of the twenty-first century, 13.8 million Americans aged 65 and older will have Alzheimer's disease symptoms. AD is the sixth largest cause of death in the United States, where the death rate grew to 146.2% in 2018 and 122,019 individuals died. Memory loss, illusions, confusion, and a lack of self-sufficiency are common symptoms of Alzheimer's disease. Various markers, such as α , β -plaques, NFTs, α , β -dimers, APP (Amyloid beta-precursor protein) imbalance, gene mutations, and synaptic degradation of AD conditions, such as cardiovascular problems, infections, limited oxygen supply to the brain, nutrition, vitamin B₁₂ deficiency, malignancies, and other variables, may contribute to the progression of AD. Notably, not only environmental and lifestyle factors but also AD commencement, age of onset, and disease advancement impact disease progression. These components may have an impact on cell differentiation, gene expression, and the pathophysiology of AD.[27]

The major obstacle in AD management is the BBB. Owing to the unavailability of effective medications for AD, only supportive treatment is prescribed. However, recent advances in nanotechnology have shown promising potential for overcoming this limitation. Nanotechnology is a technique for designing drugs or phytoconstituents in the nanoscale range. Nanomaterials (NMs) have a large surface area with an elevated surface/volume ratio and are preferred because of their unique benefits. They are shorter, stronger, faster, lighter, and more durable, rendering them potential drug delivery materials, especially for the treatment of AD and cancer. The mechanism of NPs along with current polymeric nanoparticles (PNPs), lipid nanoparticles (LNPs), and magnetic nanoparticles (MNPs) has also been discussed. Recent developments and the advantages of nanomedicines for the treatment of AD have been discussed. Research advancement in this area may be promoted by promising clinical accessibility of NM for AD and other CNS illness diagnoses and monitoring therapeutic actions.[4]

CONCLUSION

As this review briefly summarizes the various aspects involved with Alzheimer's treatment aided by nanotechnology, we may come to a conclusion that the present research work has shown positive outcomes, is promising and relevant. As time progresses these findings will help both pharma and medical industries to establish a wider base for the effective diagnosis, prevention and cure of the disease. Nanotechnology has also shown promising results in a variety of other fields and has been reliable for the treatment/therapy of a number of ailments. Nanotechnology will find its legitimacy in different fields and prove to be highly resourceful in the pharma and medical sector.

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