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A REVIEW ON: NANOSCALE INNOVATIONS IN ALZHEIMER'S TREATMENT AND MANAGEMENT

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ABSTRACT

Alzheimer's disease (AD) is still one of the most difficult neurodegenerative diseases to treat, consisting of amyloid-beta-based plaques, lowering tau proteins, oxidative stress and neuroinflammation. Traditional ways to treat AD have several drawbacks such as poor drug bioavailability, low blood-brain barrier (BBB) permeability and systemic side effects. Nanoscale particles including liposomes, dendrimers, polymeric nanoparticles, have become a viable tool in recent years for improving drug delivery, increasing the accuracy of diagnostics and possibly altering the effect of the disease. These exhibit valuable properties like high surface to volume ratio, variable sizes and adaptability that allows controlled release of drugs, target sites and promote the early identification of Alzheimer's Disease biomarkers. Their ability to reduce drug toxicity, improve the emptying rate of amyloid-beta molecules and regulate neuroinflammatory pathways providing protection are examined in this review. We go over their benefits over traditional treatment, possible issues with clearance and biocompatibility and potential future prospects for clinical research. Multifunctional platforms merged with therapeutics, personalized medicines according to genetics and various nanocarriers showing enhanced biocompatibility are just a small part of the vast world of nanotechnology. Although, some demerits include drug toxicity, large-scale manufacturing and its cost, along with the regulatory issues that need to be checked on before the execution. Thus, the nanoscale approach towards Alzheimer paves a novel treatment and management perspective

for patients.

KEYWORDS: Alzheimer's, nanomaterials, blood-brain barrier, neurodegenerative disease, drug toxicity, poor dug permeability.

INTRODUCTION

1. Pathophysiology of Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative condition causing irreversible dementia syndrome, affecting 32.6 million people worldwide. It is more common in older people and is expected to double every 20 years without new treatments. Alzheimer's disease is caused by the extracellular aggregation of amyloid beta plaques and the accumulation of intraneuronal neurofibrillary tangles of tau protein.[1] It is the major cause of disability among older adults and affects their daily lives in various ways. Researchers are developing effective AD therapies to prolong lives and improve life quality. The US Food and Drug Administration has approved seven drugs so far, but advancements in nanotechnology can deliver targeted therapies by selectively delivering therapeutic nanoparticles to the lesion site.[2] Alzheimer's Disease treatment primarily targets cholinergic or glutamatergic neurotransmission in the central nervous system, providing symptomatic relief rather than a cure. The underlying cause is unknown, but it is characterized by the accumulation of Aβ plaques and neurofibrillary tangles due to tau protein hyperphosphorylation.[3][4]

Early Alzheimer's Disease is related with higher Aß deposition in some neocortical areas, including the prefrontal, bilateral superior medial frontal, and lateral temporal cortex. It is worth noting that Aß deposition begins prior to the appearance of any obvious clinical signs.[5] Treatment strategies focus on suppressing, deferral, or dispersion of Aβ oligomers, fibrils, and plaques, with nanotechnology-based gene therapy approaches being reviewed for potential targets.[6]

Autophagy is a biological mechanism that destroys macromolecules within the cells. It is an important pathway for eliminating defective proteins or organelles, especially in animals' neurological systems. This process involves the sequestration of proteins and damaged organelles into lysosomes, which is largely dependent on lysosome activity. Lysosomes are important intracellular organelles that contain over 60 proteolytic enzymes that break down proteins, nucleic acids, and a variety of endogenous and foreign biomolecules. They are responsible for maintaining intracellular protein homeostasis and stability, as well as serving

as the principal digesting compartments. Growing evidence suggests that lysosomal dysfunction plays an important role in the genesis and progression of Alzheimer's disease. Lysosomes play a central role in neurodegenerative disorders like Alzheimer's Disease and Parkinson's disease.[7][8]

Autophagy function declines in individuals with Alzheimer's Disease, leading to neuronal death and neurofibrillary tangles. Furthermore, the elevation in amyloid plaque frequently leads to other neuropathologic (elevated accumulation and generation of NFTs) and morphologic (decreased total brain and hippocampus volumes) changes. The APP gene encodes for amyloid precursor protein.[9][10][11]

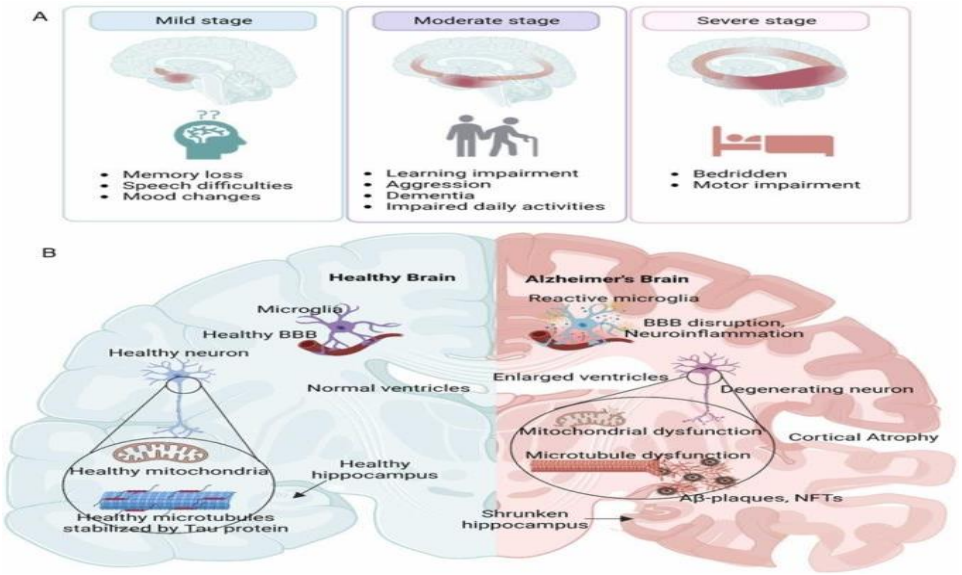

Fig. 1: A. Different stages and symptoms of Alzheimer's. B. Comparison between a healthy human brain and an Alzheimer affected brain.

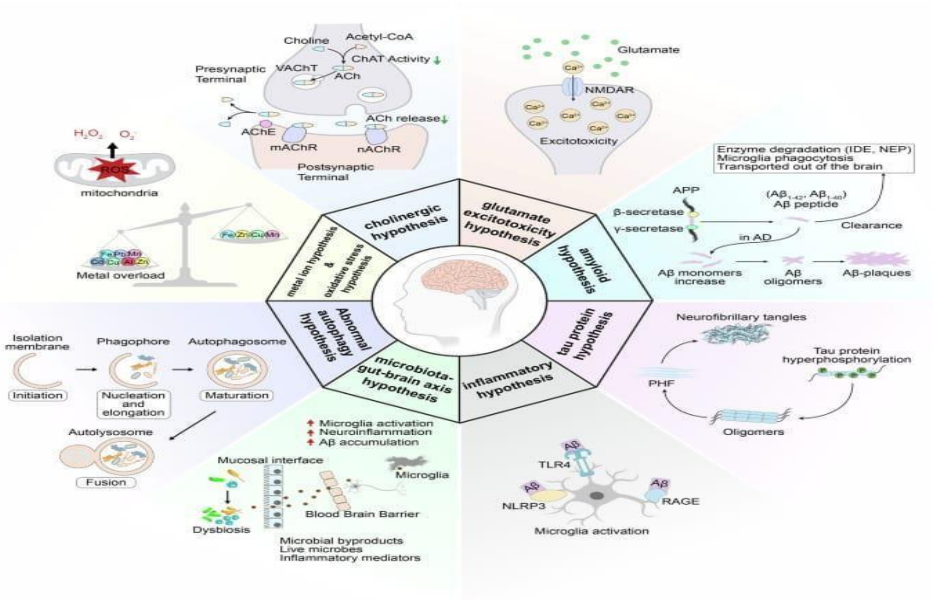

Fig. 2: Diagram for the pathogenesis of AD, including the cholinergic hypothesis, glutamatergic hypothesis, amyloid hypothesis, tau protein hypothesis, inflammatory hypothesis, microbiota-gut-brain axis hypothesis, oxidative stress hypothesis, metal ion hypothesis and abnormal autophagy hypothesis.

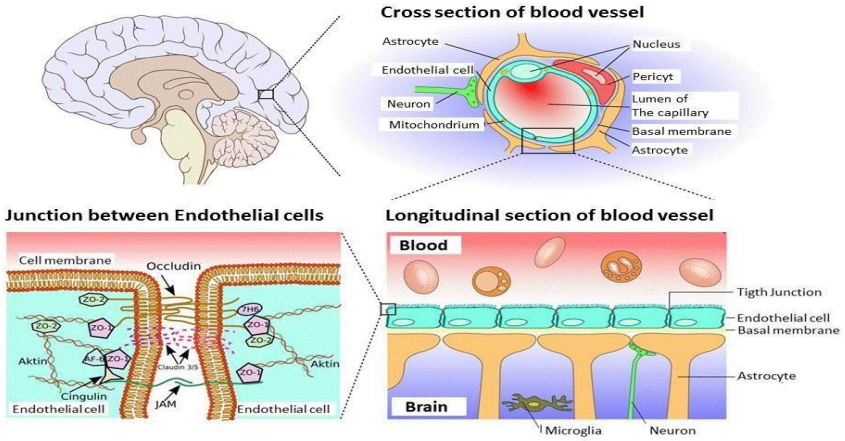

Fig. 3: Blood Brain Barrier.

Physiology of BBB

The target site for the treatment of Alzheimer's disease should primarily affect the brain. Yet, the BBB is the major obstacle facing medicine delivery into the brain since it is a sophisticated interface in intimate relationship with the rest of the CNS and modulated by the peripheral tissues. The main role of the BBB is to shield the brain from possibly dangerous chemicals in the blood; however, this characteristic also blocks most drugs from entering the brain. It bars large molecules and nearly 98% of small molecules from entering the brain. The surface area is approximately 20 m², whereas the total length of human brain capillaries is

about 400 miles. The endothelial cell (EC) layer contains brush-like extensions composed of glycoproteins (glycocalyx) and is held tightly together by junction proteins. A continuous basement membrane envelops the endothelium, supplemented by pericytes and feet of astrocytes surrounding the ECs. Since neural cells are located no more than 25 µm away from a capillary, utilizing the blood-brain barrier (BBB) for drug delivery offers a more favorable alternative than other, more time-consuming options. This need propels researchers to find effective methods to alter BBB permeability to facilitate targeted drug delivery systems.[12,13]

2. Nanomaterials for Neurodegenerative Disease (NDD) Targeted Therapy

The living conditions of the elderly, particularly those over fifty, are adversely affected by NDDs. The creation of novel treatments is necessary to meet the pressing medical need to address NDDs. These diseases share cellular characteristics and disease-progression signaling pathways, despite their different histopathological features. Multiple pathogenic proteins can collect, even though each neurodegenerative disease has its own unique protein aggregation.[14]

Although the precise mechanism by which protein aggregation and misfolding lead to neurodegeneration is unknown. In an effort to create strong medications for neurodegenerative diseases, scientists are currently exploring a number of strategies to prevent and possibly even repair protein misfolding and aggregation. Researchers have demonstrated that the majority of these aggregates are composed of denatured pathogenic proteins. By delaying the onset and progression of illness, developments in nanomedicine have made it easier to eradicate these dangerous proteins. Reducing the quantity of harmful Aβ aggregates is a popular method for treating AD.

For example, liposomes functioned as nano-capsules to aid in drug dispersion and improve tolerance. These nanomedicines were often straightforward carriers. Furthermore, the main medications that nanomedicines provided were anticancer agents and antibiotics.[15]

Additionally, during the past 10 years, drug delivery nanoparticles have seen significant advancements, leading to the development of several clever and well-designed drug delivery systems that can help treat difficult-to-treat illnesses. These nanoparticles are unique, have complex compositions, and serve a variety of purposes. When used as delivery vehicles for these particular medicinal compounds, nanoparticles have the potential to address a number of unforeseen issues, including toxicity, immunogenicity, and instability. According to related

research, oral administration is a recently established method of delivering nanoparticles that has demonstrated increased compliance and less toxicity.[16]

Since nanotechnology increases drug concentration at the desired site of action, decreases the negative side effects associated with non-specific drug distribution, and thereby improves therapeutic effectiveness, it is a crucial tool in the development of new systems for the efficient delivery of potential therapeutic and diagnostic compounds to specific areas of the brain. As a result, nanoparticles (NPs), which are thought to be a viable tool for medication development, have drawn more interest in the medical area.[17]

Properties like nanometric size, surface charge, morphology, and—most importantly—the molecular recognition and interaction between a particular ligand conjugated on the surface of the nanoparticle and the molecule overexpressed on the brain target location (active targeting) determine whether nano-delivery systems are suitable for brain delivery. The size, zeta potential, and encapsulation efficiency (EE) of nanoparticles (NPs) are among their intrinsic characterization criteria that are crucial to their biological effects and, ultimately, to their efficacy and safety. The order of magnitude makes it possible to interact with cells, which results in a cell response, which makes the nanoscale crucial. Therefore, it is possible to manipulate and modify the size and content of nano-systems to produce particles that can cross the blood-brain barrier.[18]

THE BENEFITS OF NANOTECHNOLOGY FOR ALZHEIMER'S

The therapeutic advantages of nanotechnology-derived drug delivery are becoming apparent and will soon be associated with every route of drug administration. The advantages over current treatment modalities include lower drug toxicities, improved bioavailability, reduced economic costs of treatment, and increased patient adherence to treatment. Due to the drug's inability to cross the blood-brain barrier, the current treatment for Alzheimer's disease focuses mostly on reducing symptoms. Because nanotechnology-based therapy offers so many benefits, it may be able to overcome this restriction.

1. **Nanotech Immunotherapy:** Immunotherapy is a new and promising cancer treatment option. Since immunotherapy starts with the extraction of cancer patients' T cells for in vitro rebuilding, which enables them to be targeted to certain cancer receptors, its concepts and design are simple. The patient is subsequently given these altered T cells again, which causes tumor cells to undergo apoptosis in the bloodstream without producing any negative side effects. Immunotherapy's primary disadvantage, however, is

that it may hinder the immune system's ability to eradicate tumors because of the development of tumor malignancy and subsequent patient immune suppression. In addition, the recreated and altered T cells might not be entirely safe for usage by humans. By making immunotherapy safe and efficient, nanotechnology or nanoparticles is a proposed substitute that can get over these restrictions and increase its success rate.[19]

2. **Safe Sterilization**- In the medical industry, silver nanoparticles have found widespread application in medicine formulations and medical equipment. Direct sterilization using γ-radiation and autoclaving is possible for citrate-stabilized silver nanoparticles, which have a size range of 20 to 80 nm. Replication of the sterilization-based size and morphological alterations that suggested a free radical mechanism of action was made possible by the introduction of silver nanoparticles to a chemical that produces hydroxy radicals. Furthermore, it was noted that, in contrast to the unsterilized silver NPs employed as controls, the sterilized silver NPs had a higher potential to induce platelet accumulation, an in vitro indicator of thrombogenicity.[20]

3. **Methods for Diagnosing Disease Early**- The application of nanotechnology in medical imaging for disease detection as well as treatment has drawn a lot of attention. The contrast in spectroscopic imaging can be improved by superparamagnetic iron oxide nanoparticles. In addition, certain biomarkers can be attached to NPs, allowing for the assessment of the biomarkers and the ultrasound detection of particular tumor morphologies. In addition to its use in advanced medical imaging-based detection, nanotechnology is recognized for its stability and dependability in performance features and is used as a high- sensitivity disease detector for early diagnostics purposes.[21]

4. **Sustainability**: Nanotechnology is often regarded as one of the facilitators for sustainable development because of its many potential advantages, such as improving the efficiency of numerous manufacturing systems. Nanotechnology is still not being applied widely since there are still unanswered questions and unintended consequences that need to be thoroughly investigated. The initial buzz was followed by a decline in interest, despite extensive research and development efforts that resulted in new and interesting outcomes and products every year. With an exponential rise in patents and a number of intriguing commercial uses, engineered nanomaterials are a novel class of materials with exceptional qualities.[22] There are also numerous more applications under development. Cell sorting, DNA diagnostics, kidney dialysis, tips for scanning probe microscopes,

targeted drug delivery devices, pharmaceutical purification, lab-on-a-chip, proteomics, single-cell analysis, BioMEMS, Cyto- sensing, enzymes, identification of toxic compounds, cancer treatment, and biophotonics are just a few examples of the breadth and potential applications of nontechnology in various scientific fields, particularly in medicine, pharmaceuticals, and biology.[23]

5. **Biosensors**- A biosensor is a device that combines a physical transducer, enzyme antibodies, and sensitive biological recognition—such as nucleic acids—to detect analytes. Following that, both qualitative and quantitative conclusions are drawn from the results. Due to the need for high sensitivity and selectivity, quick detection, and low cost, nanomaterials like graphene, carbon nanotubes, gold nanoparticles, and photonic crystals are being widely employed in biosensors. In addition, the incorporation of nanotechnology into biosensors has resulted in numerous breakthroughs in signal transmission. Biosensors that interact with tiny molecules and need to be assessed have grown as a result of the development of tools and processes to measure and image objects at the nanoscale.[24]

NANOTECHNOLOGY-BASED RECENT DEVELOPMENTS IN NEUROLOGY

1. Stem Cell Regeneration using Nanoparticles[25,26]

Table 1: Stem cell Regeneration.

Components	Details
Nanoparticles (NPs)	- Interact effectively with the biological systems at the nanoscale.
Functions of NPs in stem cell research	- Stem cell collection and separation (magnetic NPs) - Stem cell tracing & imaging (Quantum Dots) -Influence stem cell differentiation & proliferation
Tissue Engineering	- Use of natural scaffolds (decellularized ECM) - Recellularization with iPSCs to restore organ function
Benefits	- Promote tissue regeneration - No immune response - Infection prevention - Enhances microenvironment management for transplant cell

2. Nanomedicine[27]

Table 2: Nanomedicines.

Components	Details
Theranostics	- Combination of therapy and diagnosis using nanomedicine
Drug Targeting	- Carmustine loaded NPs guided magnetically to reduce brain tumors

	- Ligand targeted nano-formulations for dose reduction
Antiretroviral Applications	- Coupling theranostic NPs with antiretroviral drugs for targeted delivery
Liposome-Encapsulated Hemoglobin	- Targets ischemic areas during halted blood flow - Tracks insufficient circulation in stroke models

3. Neuroprotection[28]

Table 3: Neuroprotection.

Components	Details
Significance	- Key approach in treating neurodegenerative diseases
Causes of Cell Damage	- Necrosis & apoptosis due to interrupted blood supply - Oxidative stress, inflammation, and structural damage
Targets	- Oxidative stress Excitotoxicity
Damage mechanisms	- Lipid peroxidation - Mitochondrial dysfunction - Deactivation of transporter proteins
Neuroprotective NPs	- Fullerene and its derivatives neutralize harmful free radicals

TYPES OF NANOMATERIALS

Smart nanomaterial types used in Neuro-drug delivery can be categorized according to how they interact with their surroundings. Nanoparticles in the first class are environment-responsive, meaning they can detect and respond to changes in their surroundings. Biochemical features like pH, redox potential, homeostatic pathways and enzymatic activity are known to change as a result of a number of disorders. Nanoparticles can be engineered to precisely target and immobilize pre-existing disease problems by taking advantage of these modifications.[29] Environment-primed nanoparticles, work by modifying the host environment. The injection of many stimuli, including heat, medications, radiation (like infrared or X-rays) and extra nanoparticles can accomplish this. It is possible to facilitate and regulate interactions between nanoparticles and the host by using these strategies.[30]

1. **Metallic nanostructures-** MNPs have special qualities such as high surface area-to-volume ratio, adjustable surface chemistry, and remarkable optical, electrical, and catalytic properties; which makes them extremely useful in a variety of sectors, including environmental remediation, industrial chemistry, engineering, and pharmacy. MNPs such as copper, gold, and silver are essential in engineering for photonics, energy storage, and sophisticated sensors. Nanoparticles of gold and silver have revolutionary uses in pharmaceuticals for both medication delivery and diagnostics. Because of their biocompatibility, drugs can be delivered precisely, minimizing negative effects and

increasing therapeutic effectiveness.[31] Gold nanoparticles (AuNPs) have the potential to treat neurological illnesses such as AD or Parkinson's disease due to their biocompatibility, surface plasmon resonance, and ability to transport therapeutic chemicals. They may be tailored to target specific brain regions and cell types, and their unique optical features allow them to function as imaging agents. AuNPs have been shown in studies to have neuroprotective effects against inflammation and neuroinflammation, reducing symptoms in Alzheimer's animals and enhancing motor coordination.[32][33]

2. **Polymeric nanostructures**- In preclinical research, polymer-based nanoparticles have shown promise in the transport of medications for gene therapy, pain relief, and neuroprotection.[34] Researchers used RIN administration in research on brain-targeting treatment for Alzheimer's disease. They created methoxy poly (ethylene glycol) NPs coated with Tween 80 to improve RIN's targeting and activity. During in vitro and in vivo, the nanoparticles demonstrated their promise for neurodegenerative disease therapy by exhibiting safety, enhanced penetration, and increased transport across the blood–brain barrier. Additionally, their biocompatibility has driven their adoption in medical devices, drug delivery systems, and tissue engineering, offering tailored functionalities and a lower risk of rejection.[35]

3. **Magnetic nanostructures:** Iron oxide nanoparticles and other magnetic nanoparticles have garnered interest due to their dual use in neuro-drug delivery. These nanoparticles may be steered and targeted using external magnetic fields, enabling precise localization within the brain. They can also be used as imaging contrast agents, which makes it easier to track drug administration in real time. Applications in neuro-oncology, neurodegeneration, and neuroimaging have investigated the use of magnetic nanoparticles for targeted drug delivery.[36] Different coatings have been employed to generate iron nanoparticles (IONPs) as contrast agents for magnetic resonance imaging. When administered intravenously, these IONPs were seen to enter the brain by passing through the choroid plexus, as demonstrated in mouse models with induced neuroinflammation.[37]

4. **Lipid nanostructures:** Lipid-based nanoparticles, like liposomes and solid lipid nanoparticles (SLNs), have drawn a lot of interest for neuro-drug delivery.[38] These have the ability to be biocompatible and biodegradable, which allows for the efficient encapsulation and protection of neuroactive drugs. Additionally, their surface can be

modified to improve BBB penetration, extend circulation time, and target particular cell types or brain regions; these offer controlled release and have proven effective delivery of therapeutics to treat neurodegenerative diseases and brain tumours.[39] For example, Ye et al.'s study used mannosylated-DSPE-PEG liposomes to encapsulate chlorogenic acid (CHA) for targeted delivery to Tamoxifen (TAM). The authors showed that the nanostructures they created acted as an antitumor immunomodulator, encouraging the polarisation of TAMs from the M2 to the M1 phenotype. Additionally, they showed that the targeted delivery of CHA activated STAT1 and inhibited STAT6 proteins, which in turn inhibited the growth of Glioblastoma (GBM).[40]

5. **Carbon nanotubes-** Carbon-based nanomaterials, including carbon nanotubes (CNTs) and graphene, offer unique properties for neuro-drug delivery. CNTs possess exceptional mechanical strength, high aspect ratios, and unique electrical conductivity, making them suitable for both drug delivery and neural tissue engineering. Functionalized CNTs can carry drugs and enhance their transport across the BBB. Graphene-based nanomaterials possess high drug-loading capacity, stability, and excellent biocompatibility, making them promising candidates for targeted neuro-drug delivery.[41]

6. **Micelles-** A type of co-polyphosphate, which is amphiphilic (having both hydrophilic and hydrophobic parts), has been used to create tiny micellar structures for delivering drugs. These micelles have the unique property of being responsive to changes in the redox environment. They are also biocompatible and biodegradable and the micelles have many functional groups on their surface that can attach to drug molecules and targeting agents. They respond to environmental cues and can release drugs, especially anticancer drugs, inside the nuclei of tumor cells, inhibiting the growth of cancer cells. By taking advantage of the sensitivity to redox conditions, these drug delivery systems can be designed effectively for the treatment of diseases.[42] In cellular and tissue environments, the decrease in pH has been utilized in different nanoparticle systems to induce various effects. These effects include altering the shape or solubility of nanoparticles, modifying the binding strength between receptor and ligand pairs, or initiating the breakdown of acid-sensitive bonds. In the field of pharmaceuticals, delivering antimicrobial peptides (AMPs) that have poor water solubility is a significant challenge; pH-sensitive nanomaterials can undergo changes in shape or solubility in response to acidic conditions, thereby facilitating the improved delivery of AMPs and enhancing their effectiveness in treating

infections.[43]

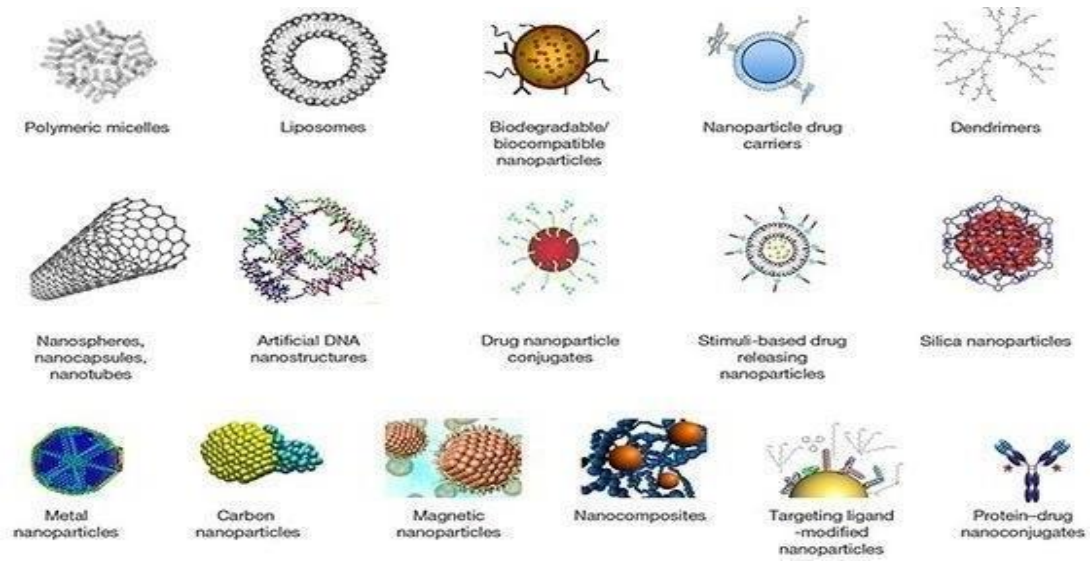

Fig. 4: Various types of nanoparticles.

DIFFICULTIES IN DRUG DEVELOPMENT FOR THE TREATMENT OF AD

The brain is thought to be the body's best-protected organ. The brain is surrounded by a number of protective layers, including the BBB, meninges, cerebrospinal fluid, and skull. These components aid in maintaining the brain's health and defending it against both internal and external threats. However, these protective barriers make it more difficult for therapeutic medications to access the brain in a diseased state. The main barriers are briefly covered, including the blood–cerebrospinal fluid barrier (BCFB), the blood–brain barrier (BBB), and multidrug resistance proteins (MDRPs).[44]

1. Blood-brain barrier-The BBB is the main obstacle that keeps nanomedicines from getting into the brain, which restricts their capacity to diagnose and treat AD. Thus, it is important to construct nanomedicines wisely to enhance their ability to accumulate in the brain.[45] Treating neurological disorders is hampered by the BBB, which keeps many drugs from reaching the brain in sufficient amounts. Pericytes, astrocytes, basal membranes, and endothelial cells make up the blood-brain barrier. The BBB has special qualities because of tight connections. As a result, the BBB blocks the admission of drugs that are useful in the treatment of numerous neurological conditions. Intercellular interstitial gaps seem to be virtually absent in brain capillaries. As a result, lipid-soluble substances can readily cross the BBB and flow freely through all endothelial membranes.[46] Recent research has highlighted a number of various approaches, such as direct injection, the nose-to-brain route, breaking the

blood-brain barrier, blocking efflux transporters, and using nanocarriers.[47] Engineered nanoparticles (NPs) smaller than 100 nm have a variety of uses in addressing these biological and pharmacological issues due to their unique physicochemical characteristics and ability to cross the blood-brain barrier. Early detection and effective treatment of neurological disorders are more likely when NP can pass the blood-brain barrier.[48]

2. The Cerebrospinal Fluid Barrier -The Barrier between Cerebrospinal Fluid and Blood. The BCFB, which is made up of choroid plexus epithelial cells and methodically handles drug molecules, is the next barrier to be broken after the BBB. The secretory systems that underpin the choroid plexus epithelium (CPE), one of the most efficient tissue types, balance cellular transport pathways. The way the blood and CSF are separated by this epithelial barrier is comparable to how the BBB works. The surrounding CPE was tightly retained in cells close to the CSF-facing surface. The multi-specific efflux transport proteins and detoxifying enzymes that make up the CPE cooperate to prevent potentially lethal chemicals from entering the central nervous system. A number of drug delivery methods have been developed, the majority of which target the microvascular endothelium and are appropriate for the blood-brain barrier.[49][50] Targeting not just the BBB but also the BCFB, which is shaped by the choroid epithelium, is essential for the treatment of CNS diseases.[51] Accordingly, the use of precise and dependable in vitro models of the BCFB can save the time and effort spent on redundant or unnecessary research. Three major categories of potential transporters that could be targeted to help deliver drugs to the central nervous system are protein receptors, solute carriers, and amino acid transporters.[52]

3. Proteins with Multidrug Resistance: The cerebral endothelial cells that make up the blood-brain barrier (BBB) are asymmetrically arranged and function as a barrier. These cells also contain a variety of metabolic enzymes, such as cytochrome P450 enzymes, alkaline phosphatases, and glutathione transferases, as well as energy-dependent efflux transport proteins, such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP; ABCG2), and MDRPs.[53] MDR transporters, P-gp and BCRP, are members of the ATP-binding cassette (ABC) superfamily and limit the brain's exposure to a wide variety of molecules, which hinders the precise therapeutic effects of some medications and decreases drug accumulation in the brain.[54] Among these transporters, MDRP is a main barrier for drug distribution to the brain due to its concentrative efflux activity. Nanotechnology can, however, get around these restrictions by creating new carrier-based platforms that

concentrate on the selective release of pharmaceutical payloads with on-demand and controlled release kinetics and enhanced reach by modifying or avoiding the blood-brain barrier. Anti-AD medication delivery using nanomaterials has been investigated in AD experimental models.[55]

4. Low Drug Permeability

Low drug permeability refers to the poor ability of drug molecule to pass through biological membranes which can lead to reduced absorption limited bioavailability and decreased therapeutic effectiveness.[56-58] Low drug permeability means the drug does not easily cross cell membranes (e.g. intestinal epithelium, blood brain barriers) which is crucial for reaching systemic circulation or its site of action.[59][60]

Factors affecting Permeability

- Physiochemical properties
- High polarity or hydrophilicity- can't pass through lipid bilayers easily.
- Large molecules weight- bigger molecules cross membranes slower.[61][62]
- Low lipophilicity- less partitioning into the lipid membranes.
- Ionization at physiological pH- charged molecules are less permeable.[63]

5. Toxicity

The term toxicity described how much a chemical can damage or poison an organism. Both acute (short-term) and chronic (long-term) forms are possible.

I. Toxicological factors include:

- Carcinogenicity: The capacity to induce cancer.
- Mutagenicity: The capacity to induced genetic alterations. The capacity to result in birth abnormalities is known as teratogenicity.

II. Variables affecting toxicity:

- Dose: The quantity of substance exposed.
- Duration: Exposure time

III. Route of exposure:

- Way of drug entering the body (skin contact, ingestion, or inhalation).
- Individual vulnerability factors include age, health and genetics.
- Air quality, humidity, and temperature are examples of environmental factors.

IV. Toxic substances

- Heavy metals: lead, mercury, and arsenic.
- Insecticides: pesticides, herbicides, fungicides.
- Industrial chemicals: solvents.
- Air pollutants: nitrogen dioxide, carbon monoxide, ozone, sulphur dioxide.
- Biological toxins: microbes.

Management of Toxicity

1. Toxicological study: Laboratory test to evaluate toxicity.
2. Risk assessment: Determining potential hazards to humans and environment.
3. Regulatory guidelines: Establishment of safe exposure limits.
4. Personal protection: Using head gears, gown, gloves and glasses to minimize exposure.
5. Proper handling and disposal: Safe storage, use and disposal of substances. Below are

some significant restrictions or difficulties:

1. The biodegradable nature of the nanocarrier.
2. Various functional group types.
3. Various research studies with varying protocols and biodistributions of nanomedicine at different times.
4. The ability of nanomedicine to regulate its morphological and chemical properties in the bloodstream/blood stability.
5. Non-toxic, target-specific, pharmacodynamic, and pharmacokinetic nanomaterials that do not aggregate.
6. Should be in In vivo state.
7. Reproducibility, predictability, cost-effectiveness, and accessibility.
8. Needs to pass through the blood-brain barrier and another CNS barrier.[64]

NANOPARTICLE - CHEMICAL AND BIOPHYSICAL CHARACTERISTICS

Drug delivery nanoparticles come in a range of sizes, shapes, and materials, and each one has a unique drug loading capacity, release, cell targeting, and stability.[65] The targeted drug delivery through nanoparticles can be greatly impacted by their biophysical and chemical characteristics, including size, geometry/shape, surface charge, surface chemistry, hydrophobicity, roughness, hardness, and degree of combinability.[66]

1. Size of particles- The distribution of the particle size affects how the drug loads and unloads. Compared to micron-sized particles, nanoparticles can penetrate cells more deeply; nanoparticles can serve a variety of biological functions because of their small size and

mobility. Particle size can regulate the adsorption of nanoparticles, according to studies conducted in a lab setting.[67] Most medications that adhere to the outside portion of nanoparticles are released more quickly because smaller nanoparticles have a larger specific surface area. The active ingredient is situated close to the outer part due to the wide surface area, which speeds up the release of the non-solvent alternative.[68]

2. Charge on the surface -According to recent research, one of the key elements influencing a nanoparticle's capacity to enter cells is its surface charge. Additionally, studies reveal that spherical nanoparticles are more readily and quickly able to penetrate the cell structure than their spherical counterparts, which are receptors with two different configurations.[69] In 2011, Demimonde and associates synthesized nanoparticles in different shapes and discovered that rod-shaped nanoparticles penetrate cells more quickly than cylindrical ones. Furthermore, one of the key elements influencing the biological dispersion and internal circulation of nanoparticles is their form.[70]

Load on the surface- The particles effective entry into the endosomes by the surface charge is another crucial characteristic which may influence them into the drug delivery systems. Gold particles enter the endometrium and are surface loaded with cytosol and polyethylene glycol. According to Aronov et. al., the nanoparticles leave the endometrium and enter the cytoplasm.[71] This phenomenon shifts the nanoparticles to surface charge, from negative to positive. When medication enters the brain, the electrostatic blood-brain barrier serves as a barrier. Researchers have discovered that the permeability of the blood- brain barrier can be changed by the surface charge of nanoparticles.[72]

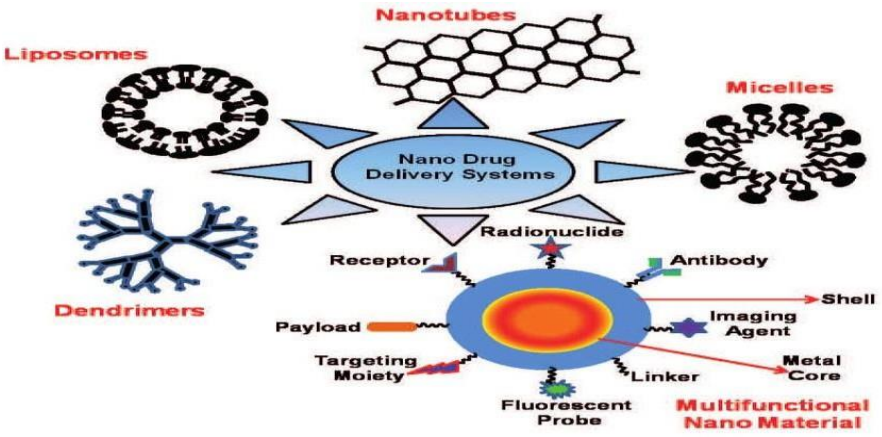

Fig. 5: Nanodrug delivery system.

MECHANISM OF NANOMATERIALS

Biomaterials used in the creation of various nano drug delivery systems, such as polymeric nanoparticles, lipid-based nanocarriers, inorganic nanoparticles, hydrogels, biodegradable scaffolds, and carbon nanotubes, among others.[73] There are various types of nanomaterials used in the treatment of AD like metallic nanoparticles (gold, selenium, iron, cerium) silica nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers (NLC'S) polymeric nanoparticles (PNP'S). In all these gold and selenium are to be known for good anti-AD properties.[74]

- **Gold nanoparticles**

AUNP'S mainly shows neuroprotective, anti- inflammatory properties.

Gold nanoparticles, known as AuNPs, might naturally help protect brain cells through their antioxidant effects. These nanoparticles clean up harmful molecules called reactive oxygen species (ROS), which can cause oxidative stress. This stress isa major contributor to brain diseases. Additionally, AuNPs prevent proteins from sticking together, maintaining the health and function of neurons.

It's important to understand that how AuNPs work depends on their size, shape, and any changes made to their surface, as well as the specific brain disorder being studied. Animal research on brain disorders shows that AuNPs may offer strong protection for neurons.[75] The delivery of brain tissues to the targeted areas can be achieved by these positively charged nanoparticles, which can also contain bioactive chemicals. Au-NPs have better BBB permeability and neuroprotection. Glutathione-conjugated Au-NPs have been found to possess an anti-Alzheimer's activity due to their ability to prevent Aβ aggregation.

Anthocyanin-conjugated Au has anti-inflammatory and anti-Aβ aggregatory activities. Along with lowering the level of AchE, oral administration of Au-NPs provides anti-inflammatory and anti-Alzheimer's benefits.[74]

- **Selenium nanoparticles**

Since they promote bioenergetics and antioxidant defensive measures and reduce oxidative stress, selenium nanoparticles possess efficient antioxidant properties. Selenium nanoparticles exert an important role in regulating the redox system. Low levels of selenium have been associated with rapid deterioration of cognitive functions.[76] A key process of avoiding ROS production is executed by selenium nanoparticles. Through regulating the oxidative defence

system, inflammatory responses, cellular metabolic state, and functional features of hippocampus neurons, selenium nanoparticles promote the extension of neuron lifespan.[77] Also, selenium nanoparticles have been found to show less cytotoxicity and higher biological activity and bioavailability. Moreover, it was found that selenium nanoparticles can significantly suppress tau hyperphosphorylation, mitigate neuroinflammation, and degrade Aβ fibrils into nontoxic fibrils, all of which downregulate the progression of AD.[78]

MANUFACTURING OF NANOMATERIALS:

I. Gold nanoparticles

Physical, chemical, and biological processes produce AuNPs. The two fundamental types of these physical, chemical, and biological approaches are "top down" and "bottom up." In bottom-up methods, nanoparticles are formed by the aggregation of atoms or molecules such as sol-gel, colloidal synthesis, chemical vapor deposition, and microemulsion synthesis. The "top- down approach" for AuNPs production involves the downsizing of bulk materials with the help of physical and chemical means such as laser ablation and mechanical milling.[79]

Table 4: Manufacturing methods of gold nanoparticles

Sr. No.	Biological methods	Physical methods	Chemical methods
1	High productivity	Less productivity	High productivity
2	No use of toxic chemicals	Use of toxic chemicals	No use of toxic chemicals
3	Large scale production	Small scale production	Small scale production
4	Definite size and shape	Difficult to control size and shape	Controlled size and shape
5	Low stability	Low stability	High stability
6	Effective cost	High cost	Low cost

I. Selenium nanoparticles

Physical processes include PLA, physical evaporation, hydrothermal treatments and sonochemical processes with microwave irradiation.[80][81] For example, PLA in liquid is a widely utilized physical technique for synthesizing SeNPs ranging from 5 to 120 nm in size. The process involved transforming Se pellets into colloidal solutions, employing liquid phased PLA in deionized water. The electrical charge at the surface of the pellets acts to prevent the SeNPs from agglomerating.[82] PLA obviates the need for the chemical reagents and potential polluting byproducts, therefore endowing it with a low-cost, environmentally safe process. We find that these SeNPs become much more stable in the colloidal solution enabling their easy collection. The method using PLA also preserves the stoichiometry of the material and the dimensions of the resulting SeNPs are adjustable by the parameters of the laser used (fluence, wavelength, pulse duration) and gas phase conditions (flow and

pressure).[83]

II. Carbon nanotubes

These processes rely on forming one or more carbon atoms that can combine to create carbon nanotubes. At each step of carbon nanotube production, carbon and energy are necessary.[84] Carbon sources include gases or carbon electrodes, while energy can come from arc discharge, heat, or laser beams. What's more, experts suggest that the size of the metal catalyst particle has an impact on the CNT diameter.[85]

Three methods are frequently utilized to create carbon nanotubes:

1. Arc Discharge method
2. Chemical Vapor Deposition (CVD) method
3. Laser Ablation method.[86]

Table 5: Manufacturing methods of carbon nanotubes.

Sr. No.	Arc Discharge method	nical Vapor Deposition (CVD) method	Laser Ablation method
1	Electric discharge generates energy.	Higher temperature generates energy around 900 degree celsius.	MWCNTs consist of pure carbon electrodes.
2	Carbon electrodes supply the carbon source.	The carbon source is supplied by gases such as methane, carbon monoxide or acetylene.	Carbon electrodes supply the carbon source.
3	MWCNTs consist of pure carbon electrodes.	CNTs are created using a metal catalyst to break down the carbon source on a solid support.	SWCNTs consist of metal-doped electrodes.
4	SWCNTs consist of metal-doped electrodes.	With a hydrogen-methane mixture over metal catalyst such as nickel or cobalt and magnesium oxide as a base, high yields of the SWCANTs	MWCNTs consist of pure carbon electrodes.
5	A disadvantage is a high degree of contaminants.	Precursor may be toxic.	Owing to the expensive nature of the laser system, it possesses huge investment costs.

COST FOR MANUFACTURING NANOMATERIALS

Costs of using nanoparticles for Alzheimer's disease treatment could vary significantly, based on several factors such as the stage of the development (i.e., preclinical, clinical trials, or commercial availability), the specific type of nanoparticles to be used, and the method of delivery or treatment.[87]

1. Research and Development Costs

The development of nanoparticle-based therapies for Alzheimer's disease is still mostly at the

experimental stage and is actively being studied. The cost of developing nanoparticles, including preclinical research, safety testing, and early clinical trials, can be from several to tens of millions of dollars.[88] These costs are mainly due to:

- Synthesis of nanoparticles.
- Optimization of drug delivery systems and their formulation.
- Preclinical studies and safety assessments.[89]

2. Clinical Trial Costs

Clinical trials are expensive. This, in particular, applies to Alzheimer's disease treatment. Its trials for safety and effectiveness need to be large. As for the nanoparticles, they are not an exception. The Alzheimer's treatment for Phase 1-3 clinical trial can cost between $10-100m. The cost depends on the trial's size and complexity.[90]

3. Commercial Production Costs

After the nanoparticle-based treatment is shown to be safe and effective, it still needs funding for commercial scaling. The manufacturing process for nanoparticles, especially for complex or personalized nanoparticles (for example, those that need to get past the blood-brain barrier), can be very expensive.[91] Nanoparticle costs can be anywhere from $10,000 to $100,000 per dose to make, depending on the complexity of the formulation.

On top of that, one should keep in mind other costs of the readymade nanoparticle therapies like regulatory approval, marketing, distribution, and post-market surveillance.[92][93]

4. Treatment Costs

Nanoparticle treatments for Alzheimer's will alter the current cost structure based on whether such a treatment is a one-time cost or requires ongoing administration. For example, a typical Alzheimer's drug today will cost anywhere from $5,000 to $50,000 per year. It is to be seen whether the cost of nanoparticle-based treatments will be in the same range or even pricier due to the additional complexity of the production and delivery systems involved.[94]

5. Insurance and Accessibility

Nanoparticle treatments' cost to patients will depend on insurance coverage government subsidies, and healthcare system infrastructure if these treatments become FDA-approved or are approved by any other regulatory bodies.[95] It may also be that healthcare providers will cut down the cost, but it is only possible due to specific healthcare policies and insurance plan

of a specific country. The cost of Alzheimer's disease treatment using nanoparticles may significantly vary. It depends on several factors including the type of nanoparticles used, delivery method, and stage of the treatment's development (preclinical, clinical trials, commercial availability).[96]

FUTURE SCOPE FOR NANOMATERIALS

It is the first time that the highlights of nanomaterials for the diagnosis and therapy of Alzheimer's disease (AD) have been very much potential in diagnosis and therapy. Alzheimer's is a neurodegenerative condition marked by a buildup of amyloid- beta plaques and tangles of tau protein in the brain, resulting in cognitive impairment. Nanotechnology is the use of materials and devices at the nanoscale (1-100 nm) which allows for the development of systematic strategies for diagnosis, treatment, and prevention of AD.[97]

1. Targeted Drug Delivery

- **Nanoparticles for targeted delivery**: Nanoparticles can be created to get into the particular areas of the brain where amyloid plaques or tau tangles gather. With the help of nanoparticles that can break through the blood-brain barrier (BBB), the drugs can go straight to the damaged brain sections, thereby making the treatments more effective and side effects less.
- **Surface Functionalization**: Gold nanoparticles may be coated with specific molecules (such as peptides, antibodies, or small molecules) that allow them to direct an attack towards amyloid-beta plaques or tau tangles in the brain. This one-on-one drug delivery system could be more effective in therapy and, at the same time, it could enable less systemic side effects.[98]
- **Controlled Release:** Nanomaterials can be designed to release drugs in a manner that is controlled, and thereby be able to maintain a stable therapeutic effect over time. This would more easily prevent AD from worsening and it would also give long-term relief of the symptoms.[99]

2. Early Diagnosis

- **Biosensors**: Nanomaterials, with gold nanoparticles and quantum dots as the typical bodies, are playing a significant role in the modern, cutting-edge diagnostic methods such as biosensors. These materials can be purposefully equipped to attach to certain Alzheimer's disease-related biomarkers, such as amyloid-beta or tau proteins. They can be

further designed to release signals to help in early disease detection, even before cognitive decline is observable.

- **Imaging**: Nanoparticles can also be used to enhance imaging technology, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), for the detection and monitoring of amyloid plaques and other disease markers. With better imaging, clinicians can keep track of how the disease progresses and can also monitor the effectiveness of the medication.[100]

3. **Amyloid Beta Plaque Clearance**

- **Nanoparticles for Plaque Removal**: Functionalized carbon nanotubes or dendrimers amongst other nanomaterials can be the ideal choice to give plaque-free brain. These particles attach to amyloid plaques and help in their removal by natural cell processes, thus resulting in the stop or decrease in the advance of the disease.

- **Nanozymes:** Nanoparticles known as nanozymes, capable of imitating the functionality of real enzymes, are likely to be the solution to the problem of amyloid-beta plaques and/ or tau tangles in the brain. The efficiency and specificity of these nanozymes could match the similarity of natural enzymes, if not be higher.

4. **Neuroprotection**

- **Antioxidant Nanomaterials**: In Alzheimer's disease, oxidative stress is known to accelerate the disease progression. Nanomaterials having these nanoparticles as antioxidants, for example cerium oxide nanoparticles or other metal-based.
- nanoparticles, would have the potential to alleviate oxidative damage in the neurons and subsequently decrease the disease progression.
- **Neurotrophic Factor Delivery**: The preparation of nanoparticles could be intended so as to be able to contain and hence deliver to the brain neurotrophic growth factors for instance brain-derived neurotrophic factor (BDNF) that can assist in the functions of neuron growth, maintenance and repair. Such factors could possibly be harnessed to renew cells that have been idled or brought the rate of the decline low.[101]

5. **Gene Therapy**

- **Nanoparticles for Gene Delivery**: An incredibly interesting field in nanotechnology lies in the delivery of genetic material using nanomaterials, e.g. small interfering RNA

(siRNA) or CRISPR/Cas9 systems to the brain. It is possible that these systems might select genes that are responsible for Alzheimer's (e.g., those dealing with APP protein production or tau phosphorylation) and may silence or change them in a way that the disease does not spread.

- **Targeted RNA Interference**: The purpose of nanoparticles is to dispatch a special sort of interference RNA directly to the neurons in the brain, therefore, the process is called RNA interference, which in turn will help to hinder the genes that are potentially responsible for the disease and support the restoration of normal brain function.[102]

6. Improved Blood-Brain Barrier (BBB) Crossing

- The major issue in the case of Alzheimer's treatment has always been that drugs cannot be transported to the brain owing to the BBB. Moreover, lipid-based nanopartigos such as nanomaterials are superior in this function to drugs and they can be engineered to pass the BBB easily, thus bringing more therapeutic agents into the brain. Not only did the research show that the treated disease disappeared, but also indicated the therapeutic approach was reused.[101][103]

7. Inflammation Modulation

- **Anti-inflammatory Nanomaterials:** The chronicity of brain inflammation is one of the major signs of an active form of Alzheimer's disease. Since it is known that these nanomaterials have the ability to affect the inflamed brain cells (microglia, which are a type of immune cells in the brain), the inflammation that causes neuro-injury is lessened.
- **Nanoparticles for Immune System Regulation**: The attack by nanomaterials on the immune system in the brain is seen to be possibly of help in fighting off diseases like Alzheimer's through the reduction of the rate at which inflammation is propagated.[104]

8. Nanomaterial Therapeutics for Tau Aggregation

- **The application of therapeutics at the nano level to modulate Tau**: Besides the amyloid plaques, the Tau tangles are likewise an important feature of Alzheimer's. The spherical materials can be designed to interact with the tau protein directly and thus, the formation of the toxic tangles may be restricted. Such therapeutic options would not only slow down but might also stop the degeneration of the nervous system in AD.[105]

9. Clinical Trials and Personalized Medicine

- Upon the accomplishments of the research, nanomaterials could be incorporated into

personalized treatment plans especially for people with Alzheimer's disease. After examining personal disease characteristics (biomarkers, genetics, etc.) of a person, such a person, for example, could receive a treatment that is nano-induced and is tailored to his or her needs. Thus, this is likely to lead to a more effective and safer therapy.

10. Antioxidant and Neuroprotective Effects

- **Selenium Nanoparticles as Antioxidants**: In the periodic table, selenium is an element with strong antioxidant features, and nanoparticles made from selenium can mop up free radicals and hence, reduce stress in the brain. Oxidative stress is the leading cause of the breakdown of neurons that initiates Alzheimer's, and, as a result, selenium nanoparticles shall play the role of preventing the oxidative stress. Thus, they could work as a protective shield for neurons and decelerate the cognitive decline process.
- **Seleno proteins and the Protection of Neurons**: Seleno proteins are proteins whose role in protecting the neural cells is due to the fact of selenium being their essential component. By using nanoparticles to deliver selenium to the brain, we can cause the seleno proteins level to rise. Hence, the results could be further neuronal protection and the reduced possibility of the development of AD.

11. Anti-inflammatory Properties

- **Neuroinflammation Regulated by Selenium**: The brain's chronic inflammatory state is also a characteristic of Alzheimer's disease in addition to the amyloid deposits. It is assumed that selenium nanoparticles can change the behaviour of microglia and astrocytes leading to the reduction in the number of cases of neuroinflammation. In this way, the progress of the Alzheimer's disease can be considerably slower and the inflammatory response damages can be lessened.
- **Tau Pathology as a Target**: The fact that selenium possess an ability to have an effect on tau protein aggregation has been proved. The use of selenium nanoparticles may, thus, assist in pinning down the phosphorylation and aggregation of tau, leading to the attenuation of tau-related neuronal degeneration in Alzheimer's patients.[106]

CONCLUSION

Smart nanomaterials are promising for drug delivery and managing neurological diseases due to their responsiveness to external stimuli. They enable precise and controlled release of therapeutic agents, enhancing efficacy while minimizing side effects. However, translating

smart nanomaterials into clinical applications faces challenges such as safety, biocompatibility, toxicity, long-term effects, and potential immunological reactions. Future research should focus on understanding nanomaterials' toxicity, biodistribution, clearance mechanisms, and potential accumulation within the body. Ethical considerations should also be prioritized in developing nanomaterial-based therapies. Collaboration between material scientists, engineers, and industry leaders is urgently needed to unlock the full potential of nanomaterials. 2D nanomaterials are intriguing contenders for emerging biomedical applications, but challenges include optimizing delivery efficacy, improving biocompatibility, and enhancing nanoelectrode stability and efficiency.

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