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# Nanomedicine and Neurodegeneration: Targeting Alzheimer's Disease Pathology and Drug Delivery Challenges

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**Abstract: Alzheimer's disease (AD) is a progressive neurological disorder and the leading cause of dementia in older adults, characterized by memory loss, cognitive dysfunction, and behavioural disturbances. The disease is associated with the abnormal buildup of beta-amyloid plaques and hyperphosphorylated tau tangles, along with oxidative stress, mitochondrial impairment, neurotransmitter imbalances, and neuroinflammation. Genetic factors, particularly the presence of the APOE-ε4 allele, further increase disease susceptibility. Despite the availability of FDA-approved drugs targeting cholinergic and glutamatergic systems, current treatments provide only symptomatic relief and do not halt disease progression. One of the major challenges in AD therapy is the limited ability of drugs to cross the blood-brain barrier (BBB). Nanotechnology presents a promising alternative by enabling the targeted delivery of therapeutic agents across the BBB with improved bioavailability and minimal systemic side effects. This review discusses the underlying mechanisms of AD and recent advancements in Nano formulations such as liposomes, polymeric nanoparticles, dendrimers, and lipid-based carriers for delivering anti-amyloid, anti-tau, and antioxidant therapies. These innovative approaches may offer new hope in managing and potentially modifying the course of Alzheimer's disease.**

***Keywords:*** *Alzheimer's, Liposomes, Nanosomes, Nanomedicine.*

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## I. INTRODUCTION

Among dementias, Alzheimer's is common among neurodegenerative illnesses, is defined by behavioural problems in the elderly population together with a loss of thinking, memory, and reasoning. The World Health Organization (WHO) projects that by 2050[1], there will be over 131 million dementia sufferers worldwide, having doubled over the previous several decades.

It is frequently identified by the buildup of extracellular β-amyloid (Aβ) plaques and intracellular tangles of neurons [2], which are composed of clusters of increased phosphorylation of Tau protein. Although neural Fiber tangles (NFTs) made of increased phosphorylation of tau protein and Aβ peptide-based plaques are pathologically linked to AD, mounting evidence suggests that these abnormal protein deposits are unlikely to be the cause of AD because neither the NFT volume nor the Aβ plaque are highly correlated with the severity of memory impairment [3].

Alzheimer's illness is classified as a Multi neurotransmitter deficient condition. Corticotropin-releasing factor, somatostatin, noradrenaline, and serotonin are all inadequate[4]. One of the brain's main neurotransmission systems, the cholinergic system is necessary for psychological and retention of information. As a result, a major pathophysiological component of AD is cholinergic activity reduction[5]. Acetylcholinesterase (AchE), a metabolic enzyme that breaks down acetylcholine (Ach) into choline and acetate, has been observed to be more prevalent in AD patients. AchE accelerates the β-amyloid peptides that form insoluble plaques in Alzheimer's patients' brain [6].

AD was previously divided into two categories: sporadic and inherited. Numerous genes, especially α-secretase and apolipoprotein E (APOE), have been connected with the hereditary component [7]. Furthermore, the sporadic form has a later onset age and a stronger correlation with variables such neural inflammation, vascular dysfunction, and free radical harm than the hereditary variety, which usually manifests earlier in life. Whatever their origin, we now understand that these elements generate aberrant Aβ peptide accumulation, which in turn causes neuronal deregulation [8].

oxidative stress: Aβ induces mitochondrial malfunction, initiates lipid peroxidation, encourages the production of free radicals and reactive oxygen, and damages the equilibrium

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state of ions, all of which lead to the burning loss of ATP energy [9].

Nanotechnology is the design and manufacturing of systems, gadgets, and structures by modifying their size and shape at the nanoscale [10]. Carrier-based drug delivery is a promising method for delivering medication to the brain. This chapter covers a number of carrier-based drug delivery techniques, such as liposomes, nanocrystals, nano emulsions, dendrimers, polymer-protein/drug conjugates, nanoparticles, antibody-conjugated medications, nanotubes, nanogels, and micelles for Alzheimer's disease treatment [11].

➢ *The Pathophysiology of Alzheimer's Disease*

Because the nano formulation has valuable properties like low toxicity, a large surface-to-volume ratio, a modifiable degradation rate, and the capacity to load a variety of drugs and biomolecules, they enhance therapeutic outcomes by acting as drug carriers for drug delivery across biological barriers [12].

Disease-modifying treatments, such as the administration of cholinesterase inhibitors, anti-amyloid, anti-tau, antioxidants, and hormone medications, are made easier by nanomedicine. Instead of only treating symptoms, these therapies seek to alter the trajectory of the disease [13].

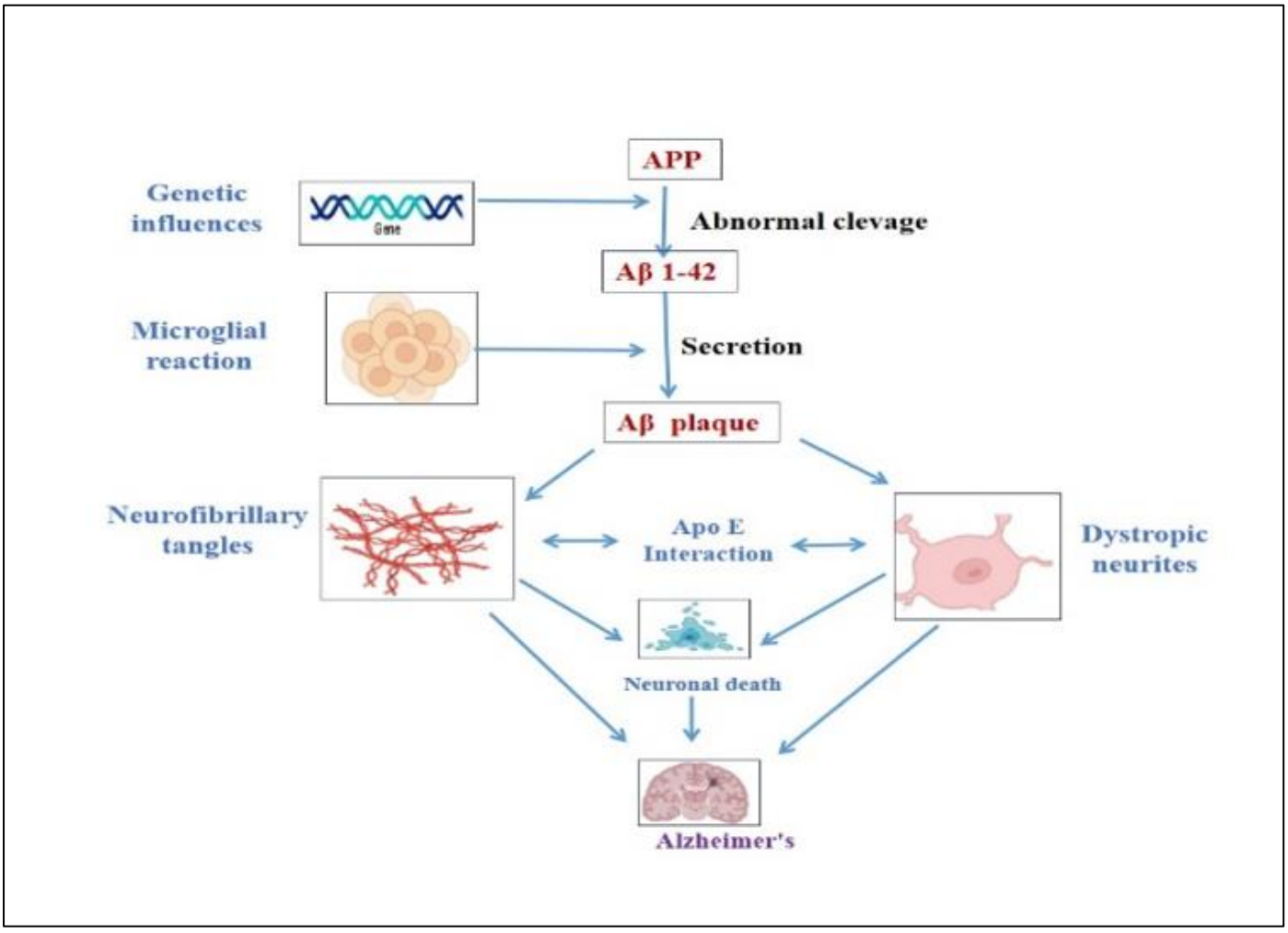


Fig 1 Pathophysiology of Alzheimer's Disease

➢ *Beta-Amyloid Protein Hypothesis:*

The development of β-amyloid protein plaques (Aβ plaques) in the brain and the ensuing death of neurons serve as the foundation for this notion. The cleavage of the amyloid precursor protein (APP) by a series of secretase enzymes explains this mechanism. The enzymes β secretase and γ-secretase split APP into distinct subunits (such as Aβ40 and Aβ42) and traverse cell membranes, meaning that parts of it are found both attaches to cell surfaces; as a result, additional proteins clump together or entangle with Aβ 42 to form Aβ plaques, which destroy neurons and cause AD [14].

➢ *The Tau Protein Hypothesis:*

The key notion of this theory is that tau proteins form neural fibre tangles (NFTs), which are functionally linked to the microtubules that promote axonal transport resulting in the development of paired helical fragments that hinder axonal transit and cause neuronal death [15]. Nonetheless, the most widely recognized explanation for the pathophysiology of AD is complex and includes a number of elements, including lipid distribution, inflammation, and protein buildup [16].

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➢ *AChE Hypothesis:*

An additional mechanism happening here is the breakdown of acetylcholine into choline and acetate by the central nervous system through enzymes AChE. For the rest of the message, choline will subsequently be recycled into a new neurotransmitter. This enzyme has been found to be overexpressed in AD patients, and as a result, a deficiency of Ach leads to decreased neuronal cell communication. Apart from its catalytic function, AChE also causes aberrant β-amyloid (Aβ) peptides to aggregate and amyloid fibrils to deposit[17].Approaches that inhibit AChE activity may slow the progression of AD because AChE interacts with a pool of amino acids close to its peripheral anionic site (PAS) to promote the formation of amyloid fibrils, which build up in the brain and cause plaques, inflammation, oxidative stress, and disruption of synaptic function[18] presently, the best way to treat AD is to use AChE inhibitors to decrease Ach hydrolysis and increase cholinergic neurotransmission. These inhibitors improve cholinergic signalling and neurotransmission by raising Ach levels at synapses [19].

➢ *Mitochondrial Cascade Hypothesis:*

Inadequate ATP synthesis is the outcome of mitochondrial dysfunction, which is caused by protease dysfunction or oxidative stress caused by accumulating somatic mutations that occur during the replication of mitochondrialDNA[20].

As a result, AD patients experience aberrant synapses and neuronal damage. Furthermore, mitochondrial dysfunction also affects NFT and β-amyloid plaque in AD brains. Mitochondrial damage, which worsens with age and affects the survival and wellbeing of neurons, is one of the primary objectives for treating AD[21].

## II. A SOLID GENETIC RISK FACTOR FOR ALZHEIMER'S PATHOGENESIS: APOE4

The most common inherited genetic risk factor is believed to be the APOE4 ε4 allele [22]. Between 40 and 80 percent of AD patients carry at least one APOE allele4[23]. APOE encodes three different proteins, apoE2, apoE3, and apoE4, which are isoforms of a secreted 299 amino acid protein that differ in amino acid sequence at positions 112 and 158[24]. By increasing amyloid deposition and medial temporal lobe dysfunction, the APOE-ε4 allele not only increases disease risk but also exacerbates AD-related brain alterations. Increased brain amyloid is linked to the APOE-ε4 genotype in moderate cognitive impairment in early stages [25] and as determined by post-mortem APOE-ε4 AD brains, and late stages of AD[26].

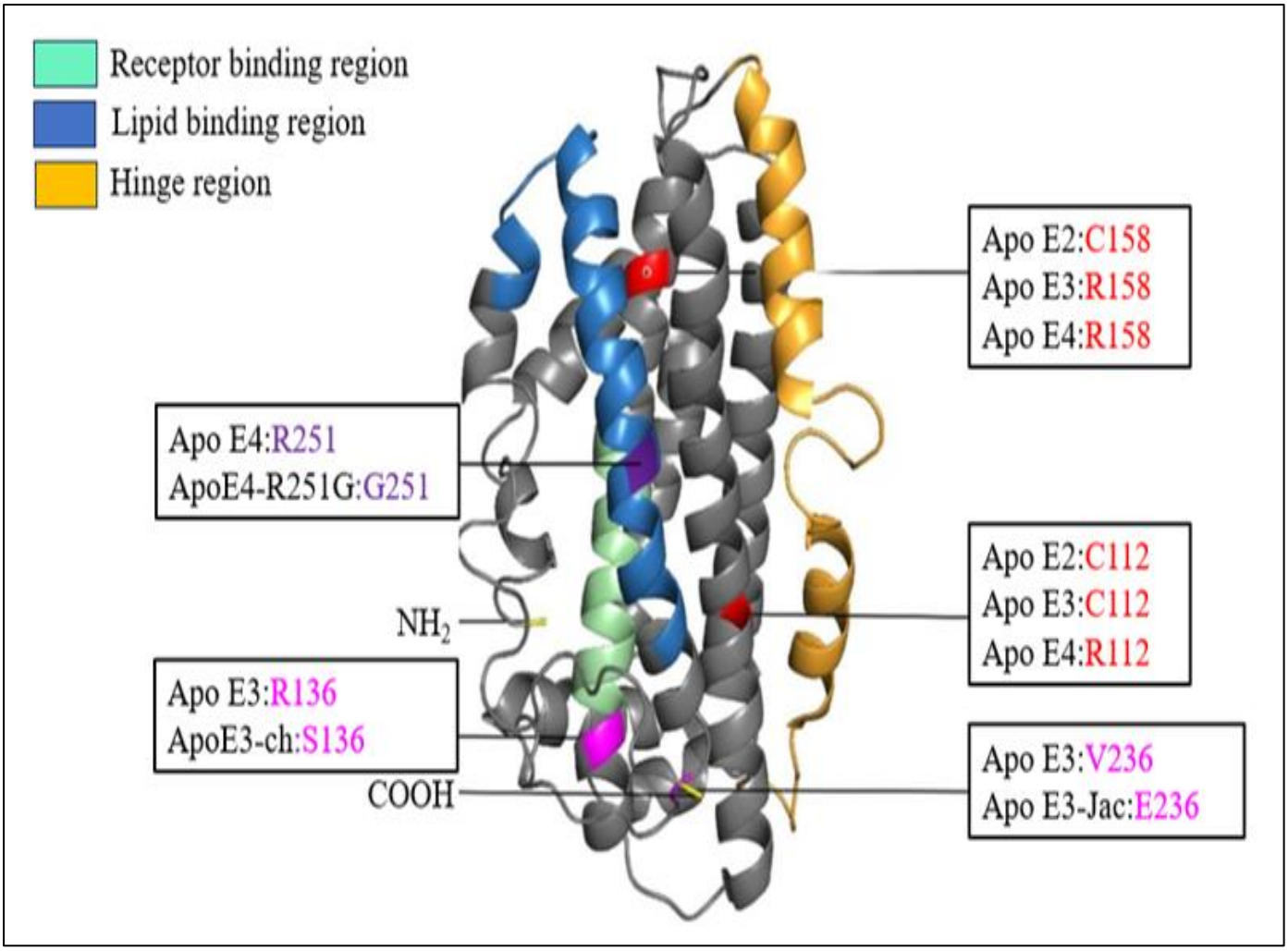


Fig 2 Structure Model of Apo E Highlighting AD-Related Amino Acid Variation

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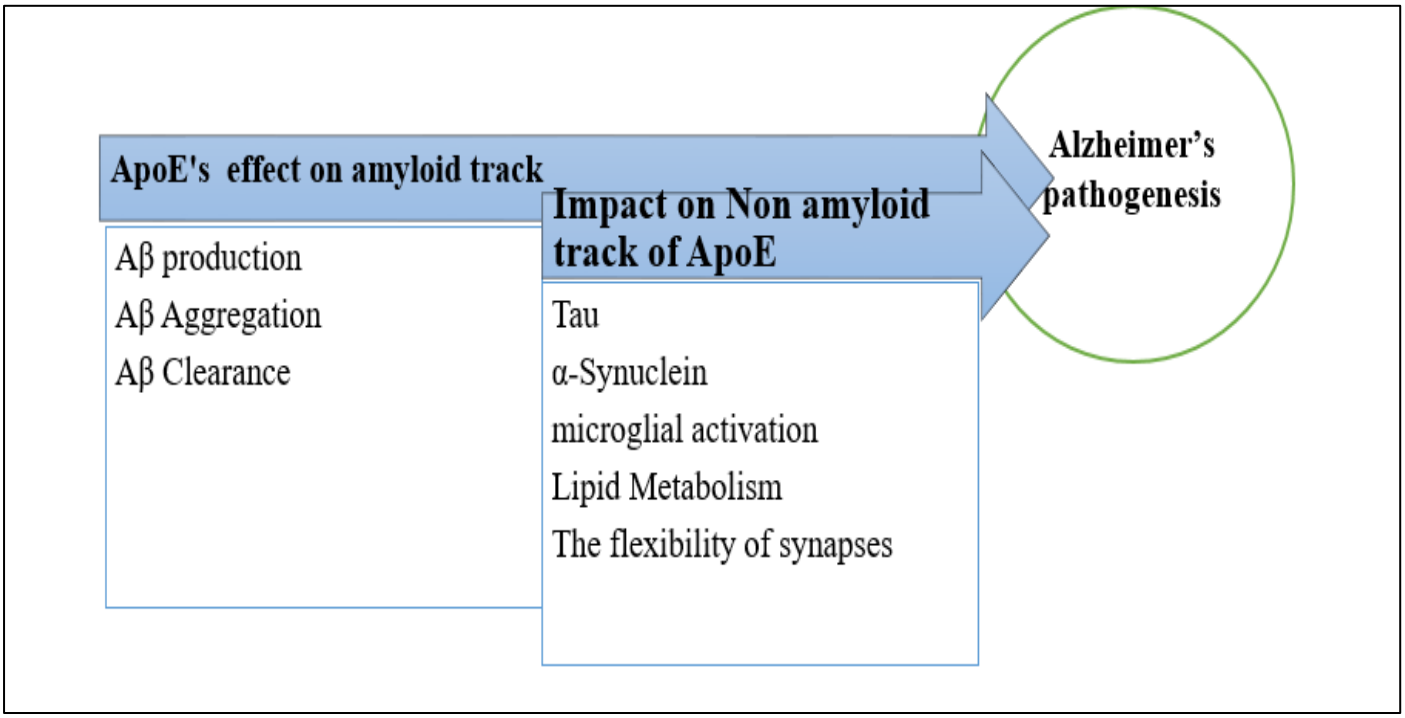


Fig 3 The Pathogenic Effect of Apo E in Alzheimer's Diseases

➢ *Risk Factors Associated with Ad [27-31]*

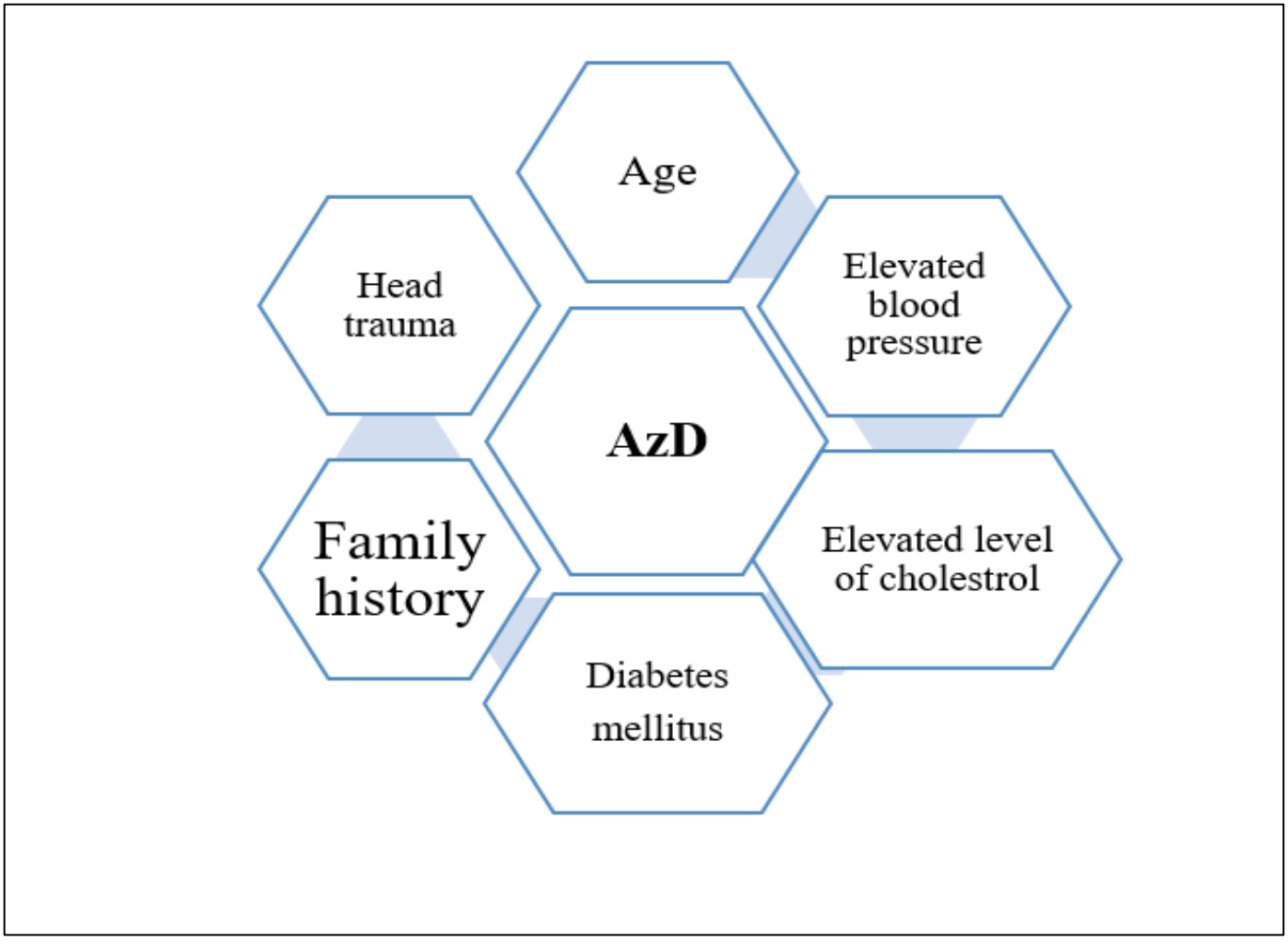


Fig 4 Risk Factors Associated with AD

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➢ *Fda-Approved Medications to Address Alzhemiers' Diseases [32,33]*

Table 1 FDA-Approved Medications to Address Alzheimer's' Diseases

| S.NO | DRUG NAME | | PRINCIPALLY TARGETED | USED IN STAGES OF ALZHEIM-ER |
|---|---|---|---|---|
| | GENERIC NAME | BRAND NAME | | |
| 1 | Memantine | Namenda | NMDA receptor antagonist | Moderate to severe |
| 2 | Donepezil | Aricept | Selective AchE inhibitor | All stages |
| 3 | Galantamine | Razadyne | AchE and BchE inhibitor | Mild to moderate |
| 4 | Rivastigmine | Exelon | AchE inhibitor | Mild to moderate |
| 5 | Memantine+ donepezil | Namzaric | Mixed action | Moderate to severe |

➢ *Blood Brain Barrier*

A membrane called the blood-brain barrier protects the brain, the most sensitive and complex organ in the body. For protecting brain neurons from the potentially dangerous chemicals present in blood, this barrier is perfect. Diffusion of drugs to brain tissue is also affected.The brain is separated from the bloodstream by the blood-brain barrier (BBB). About 100 billion neurons make up the human brain. Only 7–10 µm could be the diameter of the capillaries in the brain. The brain-brain barrier (BBB) has no valvar or intracellular gaps, and the brain has extremely few external entry points[35,36].

Drug Distribution to The Central Nervous System and Strategies for Utilizing Nanotechnology to Break Through the Blood-Brain Barrier

Technologies and materials that are functionally organized in at least one nanoscale dimension, spanning from a few to around 100nanometers, are referred to as nanotechnologies. The fundamental design of nanoengineered materials and technologies for biologic applications, medicine in general, and neurology in particular involves molecular-level interaction and contact with cells and their tissues.

A multitude of factors must come together in order for medications or other compounds (such oligonucleotides, genes, or contrast agents) capable of crossing the blood-brain barrier (BBB) and may target a particular cell type. Ideally, a nano delivery-drug complex should be administered systemically (e.g., intravenously) but manage to reach the central nervous system (CNS) with minimal systemic effects, be able to penetrate the blood-brain barrier and precisely target cells in the CNS, and then carry out its primary active function, such as releasing a drug[37]. It is well established that a drug's physio-chemical properties, including its molecular mass, net-charge, polarity, the solubility, and affinity towards hydrophilic and lipophilic nature have a significant impact on its therapeutic failure. Nanotechnology dramatically changes these properties of the drug candidates and improves the therapeutic potential through a range of functional carrier systems [38,39].

Systems for nano-delivery can be broadly categorized as either inorganic (silica, carbon, and gold) or organic (liposomes, polymers, emulsions, solid-lipid NPs, and dendrimers) depending on the kind of carrier material [40].

## III. A POSSIBLE ALZHEIMER'S TREATMENT USING NANOTECHNOLOGY

These days, increasing research is looking at the potential of employing nanoparticles (NPs), which are extraordinarily tiny structures that can be coated with drugs to provide targeted therapies for a range of diseases without having adverse reactions. Novel techniques to drug development are as desperately needed to get past the barrier that prevents CNS medications from passing through the blood-brain barrier. Polymers, solid lipid carriers, lipo-carriers, lipoprotein-based nanoparticles, curcumin-loaded nanoparticles, metal-based carriers, nanoparticle conjugates, cubosomes, intranasal delivery of nanoparticles, and inorganic nanoparticles are a few examples of nanotechnology-based strategies[41].

➢ *Amyloid-Targeting Therapies for Alzheimer's*

The amyloid cascade theory states that the neurodegeneration seen in AD is caused by an abnormal accumulation of Aβ plaques in several different parts of the brain. According to the theory, Aβ plaques are a pathogenic initiator of a cascade that results in cell death, tau protein-mediated neurofibrillary tangle development, and neuritic damage. Aβ is produced by the amyloidogenic pathway through the action of β-secretase and γ-secretase[42]. More therapies that target Aβ directly or indirectly are urgently needed because of the crucial role that Aβ plays in the development of AD. For widely developed applications for diagnostic and therapeutic, Aβ-binding compounds have been coupled to NPs. PEG-PLA NPs with liposomes may be the most widely used NPs among others because of their complete biodegradability, low immunogenicity, and reported absence of toxicity[43].

In vitro, liposomes coupled with derivatives of curcumin demonstrated a strong affinity(1–5 nm) for Amyloid fibrils[44].The production of Tet-1 peptide-conjugated curcumin nanoparticles coated with water-soluble polylactic-co-glycolic acid (PLGA).The elements used in this work made it extremely significant[45]. One of the most widely used natural compounds is curcumin due to its diverse range of bioactivity, which includes anti-AD activity. The water-soluble PLGA Tet-1 peptide, which has been demonstrated to have neuronal affinity and retrograde transport characteristics, is used to encapsulate curcumin. It was discovered that PLGA nanoparticles Captured in curcumin had antioxidative properties and eliminated Aβ aggregates without showing any signs of cytotoxicity[46,47].

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➢ *Therapies that Target Tau in Alzheimer's*

AD pathogenesis is influenced by tau phosphorylation and neurofibrillary tangle development. Numerous studies have been conducted to find treatments for tauopathy for AD therapy after some amyloid-targeted medications failed. These treatments include methylene blue, curcumin derivatives, N744, rhodamines, and aminothienopyridazines (ATPZs), which aim to prevent tau aggregation and improve tau degradation. Numerous investigations have demonstrated that methylene blue can be used to stop or dissolve tau aggregation in tauopathies in AD. Curcumin, a naturally occurring polyphenol made by Curcuma longa plants, has been shown to have certain potentially neuroprotective qualities. Curcumin derivatives have been created and tested as dual inhibitors of tau protein aggregation and Aβ[48,49].

To transport drugs for the treatment of AD, several tau-targeted nanomaterials have been created, such as Gold-Fe3O4 core-shell NPs (AuFeNPs) and generated folic acid-functionalized gold nanoparticles (FA-AuNPs). These nanomaterials showed a strong affinity for both tau and tubulin, indicating that tau aggregation in AD could be inhibited by protein-capped metal nanoparticles[50,51].

Table 2 Aβ, Tau Protein, and Mitochondrial Treatment are Targeted Using Nanocarrier-Based Systems in Alzheimer's Disease [52-56].

| Nano-formations | polymers | Possible drug | Model of investigation | AD's target |
|---|---|---|---|---|
| Liposomal | Sphingomyelin and cholesterol can be functionalized with PA alone or biofunctionalized with dimyristoylphosphatidic acid (PA) and modified Apolipoprotein E-derived peptide. | Curcumin derivatives | sanguine fluid and CSF | Cholinergic dysfunction and Aβ |
| Gold Nps | PEG-coated 5 nm gold nanoparticles | Anthocyanin | Mouse brain endothelial cells/ Aβ1–42 Mouse Model | Amyloid cascades and tau hyperphosphorylation |
| Carbon dots | Carbon nanotube | Tunable zero-dimension | Implicit/explicit lipid models and coarse-grained nanoparticle models | Cascades of amyloid - The enzyme acetyl cholinesterase |
| Dendrimers | Dendrimers of hydrophobic pyridyl phenylene | o-phenylene diamine | The inclusion bodies of the ovine prion protein are indicative of clumps of amyloid proteins. | Cascades of amyloid |
| Metallic Nps | PEG-functionalized iron crystal structure | Iron oxide | In vitro amyloid fibrillation experiments | Cascades of amyloid |

## IV. POSSIBLE TREATMENT FOR ALZHEIMER'S DISEASE USING NANOTECHNOLOGY

➢ *Polymer-Based NPS*

The most desirable NPs are polymeric NPs because to their extended shelf life, stability in storage, biodegradability, and biocompatibility. These characteristics might ensure a controlled and extended load release[57]. The polysaccharide most commonly used as a form of NPs in medical applications is lactic-co-glycolic acid (PLGA). Synthetic polymers include poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and poly (D, L-Lactic-co-Glycolic acid) (PLGA). Additionally, PLGA-b-PEG-TPP NPs, which target inflammation in the treatment of AD, are created by combining PLGA-block-PEG with triphenyl phosphonium (TPP). Specifically, in an AD animal model, coenzyme Q10 (CoQ10)-loaded PLGA NPs have been demonstrated to stop the cytotoxicity of Aβ and restore memory, and biodegradable PLGA NPs have been linked to neuroprotective properties intended to cure AD. Depending on the preparation technique, the polymer NPs could take the form of nanospheres or nano capsules. Furthermore, some ligands and antibodies have been coupled into solid lipid nanoparticles and shown in both in vitro and in vivo experiments to decrease Aβ aggregation[58,59].

➢ *Inorganic Nanoparticles*

It has also been studied if inorganic substances, such SiO2, can cross the blood-brain barrier. Silicon quantum dots are also being investigated for usage in therapeutic and diagnostic contexts because silicon is believed to be very biocompatible[60]. Graphene oxide sheets, carbon-based NPs, gold carriers, a magnetic core, monomers, and other inorganic nanoparticles have all been proposed as ways to stop Aβ fibrillation and stop Aβ aggregation. While nano-metallo-supramolecular complexes could prevent Aβ-induced heme synthesis and iron uptake by PC12 cells, graphene oxide (GO)/Au-NPs were the majority of NPs that could efficiently suppress Aβ aggregation and have minimal cytotoxicity in vitro[61].

➢ *Liposomes*

Because of its special properties which include flexibility, biocompatibility, low toxicity, biodegradability, and non-immunogenicity liposomes have gained importance

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since their discovery in the 1960s. Multifunctional liposomes that function as a BBB transport mediator include an anti-transferrin antibody (TrF) and a derivative of curcumin. In post-mortem brain samples from AD patients, liposomes containing the curcumin derivative or the curcumin derivative + anti-TrF showed a high affinity for amyloid plaques. Furthermore, the scientists observed that neither Ab aggregation nor Ab deposit staining were inhibited by liposomes containing curcumin derivatives. However, the inclusion of a curcumin–PEG–lipid combination had no effect on the brain-targeting ability, suggesting that these multifunctional NLs could be useful in the treatment of AD[62].

- *Lipid -Based NPS*

Lipoprotein-based NPs are used therapeutically and help break down Aβ due to their high affinity for it. In order to prevent Aβ aggregation, the ApoE3–reconstituted high-density lipoprotein (ApoE3–rHDL) NP system was developed and obtained, suggesting that ApoE3–rHDL could be employed therapeutically to treat AD. Tarenflurbil (TFB) was delivered to the brain intranasally (i.n.) using TFB-loaded poly(lactide-co-glycolide) NPs (TFB-NPs) or solid lipid NPs (TFB-SLNs). This decreased Aβ by modifying the enzyme γ-sec retainase, which cleaves APP[63].

- *Nano Dispersions – Dual Drug Delivery Systems*

Water and oil combine to form a kind of binary nano colloidal systems known as nano emulsions. Usually, a stabilizing agent is given to the system to make it more stable. This stabilizing component is a surfactant, which makes the solution isotropic and metastable. It is composed of emulsified oil and amphiphilic water molecules. Therefore, oil, surfactants, cosurfactants, and an aqueous phase combine to form thermodynamically stable colloidal dispersions known as nano emulsions. The sizes of their particles range from 20 to 500 nm. Water, oil, and a surfactant combine to create the resulting clear or translucent dispersions. The surfactant acts as an emulsifying and stabilizing agent by forming molecular films at the water/oil interface[64].

Curcumin-loaded nano emulsion stabilized by a mixture of surfactants and cosurfactants. It was shown that the formulation significantly increased the water solubility of curcumin.

Ferreira et al. evaluated a pullulan-stabilized ketoprofen nano emulsion. Brain penetration was enhanced via in vitro release studies that showed a rapid release pattern (less than five hours) and significantly higher bioavailability.
In the SH SY5Y cell line, Shadab et al. found that a naringenin nano emulsion reduced the neurotoxic effects of tau phosphorylation and b-amyloid plaque, suggesting that it might be employed as an AD therapy[65].

## V. FUTURE PERSPECTIVES

Traditional methods of treating Alzheimer's disease (AD) fail because of the complicated physiological aspects and multifaceted nature of the disease. Despite substantial research efforts, AD treatment outcomes remain disappointing, highlighting the gap between promising research findings and their successful clinical implementation. Nanotechnology offers an innovative approach by specifically modulating targeted biological pathways, with mitochondrial dysfunction representing a key target for potential AD treatment. While the mechanisms behind AD's pathophysiology are still not fully understood, nanotechnology provides a promising avenue for managing the disease, perhaps slowing down development and enhancing cognitive function.

The toxicity concerns are a major challenge in nanomedicine, but these can likely be addressed through the development of more biocompatible nanoparticles. Despite the promise of this technology, it has yet to be fully developed for clinical application, with much research still limited to preclinical studies. Magnetic nanoparticles, dendrimers, and nano emulsions are promising drug delivery systems for the central nervous system (CNS) that warrant further investigation. For nanotechnology-based AD therapies to succeed, improvements in pharmacokinetics and toxicity profiles must be made to ensure successful clinical trials.

## VI. CONCLUSION

Alzheimer’s disease remains one of the most complex and challenging neurodegenerative disorders, with a multifactorial pathogenesis involving amyloid and tau pathologies, neurotransmitter imbalances, oxidative damage, and genetic predispositions. Despite the availability of several approved drugs, current treatments largely focus on symptomatic relief and fail to address the underlying causes or halt disease progression. The blood-brain barrier continues to pose a major obstacle in delivering effective therapeutics to the brain. In this context, nanotechnology offers a promising strategy by enabling targeted, sustained, and efficient delivery of therapeutic agents directly to affected brain regions. Nano formulations such as liposomes, dendrimers, metallic nanoparticles, and lipid-based carriers have demonstrated potential in preclinical studies to overcome pharmacological limitations and enhance treatment outcomes. While these advancements are encouraging, further research is needed to improve safety profiles, optimize delivery systems, and validate these approaches in clinical settings. With continued innovation and refinement, nanomedicine may pave the way for more effective, disease-modifying therapies for Alzheimer’s disease in the near future.

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