

Systematic Review Alzheimer's Disease; Mechanism, Mutations, and Applications of Nano-Medicine

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Abstract

Background: In the past 10 years, significant progress has been made in understanding the pathogenic chain of events that causes Alzheimer's disease (AD). According to the most widely accepted concept, the production and aggregation of β -amyloid (A β) peptides play a critical role in AD. As a result, therapeutic intervention with these processes is the focus of intense research. The A β peptide is cleaved by the α -secretase, β -secretase, and γ -secretase enzymes in a region near the pathogenic amyloid precursor protein (APP) and mutations occurring site. **Methods**: In the current review, a complete picture of the risk factors behind AD has been investigated. Mutations involved in AD progression have also been screened in various studies. **Results**: Most of the mutations in the amyloid precursor protein (APP) can lead to the accumulation of APP oligomers in the brain, leading to AD. Several point mutations in APP can cause familial AD (FAD), including the Swedish mutation (K>M670/671N>L) and the A673>V mutation. The pathogenic A673>V mutation and Swedish mutation (M670>K/N671>L) are present in the same region of amyloid precursor protein (*APP*). However, the A673>T mutation has been shown to confer protection against AD. **Conclusion**: More investigations are needed from geographically distinct regions on mutations associated with AD development and applications of nanomedicines for better management of the disease burden in the future. Nanotechnology-produced metal nanoparticles (NPs) have gotten much attention because of their wide range of uses in the medicinal and agricultural industries. Nanomedicine containing potential phytochemicals, including GX-50 and curcumin conjugated with NPs, maybe a potential candidate for treating AD.

Keywords: Alzheimer's disease; mutations; APP; tau; nanoparticles

1. Introduction

In older people, Alzheimer's disease (AD) is a progressive, slow brain disease characterized by plaque formation in the hippocampus [1]. Researchers have found that plaque formation starts about 20 years before clinical symptoms begin, so it is difficult to determine the exact trajectory of AD pathologies [2]. The incidence of AD is rising worldwide. The number of people affected by AD in 2019 exceeded 50 million; as a result, the world economy and the human workforce could be negatively affected by its increasing burden. The prevalence of AD symptoms in Americans 65 and older is estimated to reach 13.8 million by the middle of the twenty-first century. AD is the sixth leading cause of death in the United States; according to the Centers for Disease Control and Prevention, 146.2% of Americans died from AD in 2018 [1].

According to the current research on AD neuropathology, the primary histopathologic lesions of AD are the extracellular amyloid plaques and the intracellular tubulin associated unit (tau) neurofibrillary tangles [3]. The main component of the amyloid or senile plaques (SPs) is a very insoluble and proteolysis-resistant peptide fibril created by the cleavage of β -amyloid (A β). Following the subsequent breakdown of the amyloid precursor protein (APP) by the two enzymes β -secretase (BACE1) and γ -secretase, A β peptides are generated, with A β -38, A β -40, and A β -42 being the most prevalent types. However, A β is not produced if APP is initially acted upon and cleaved by the enzyme α secretase [4]. The "amyloid hypothesis" postulates that the creation of A β in the brain starts a series of events that eventually result in the clinical syndrome of AD. The amyloid cascade is initiated, and neurotoxicity is mainly attributable to the formation of amyloid oligomers [5].

Local inflammation, oxidation, excitotoxicity (excess glutamate), and tau hyperphosphorylation are some of the components of the cascade. A microtubule-associated protein called tau binds to microtubules inside cells to help the neuronal transport mechanism. Additionally, developing axons need to be stabilized by microtubules for neu-



Fig. 1. Formation of β -amyloid (A β) peptides. (1) β -amyloid peptides are made when the APP within the neuron membrane is cleaved. (2) Amyloid forms oligomers in the space between neurons, which are considered to disrupt synaptic function and act on receptors within the neuron plasma membrane. (3) Amyloid-oligomer fibrils are incorporated into plaques, interfering with the activity of neurons. (4) Hyperphosphorylation of tau in neurons creates neurofibrillary tangles, which displace intracellular organelles and impede vesicular transport [16].

rons to function and development. Intraneuronic tangles are formed by abnormally hyperphosphorylated tau, generating insoluble fibrils. As a result, it separates from microtubules, prevents transport, and causes microtubule breakdown. It was initially believed that tau hyperphosphorylation happened after amyloid was deposited. Still, it's as likely that tau and amyloid work parallel to cause AD and amplify each other's adverse effects. The deficiency of some neurotransmitters (like acetylcholine, dopamine, and serotonin) and an imbalance among these neurotransmitters are the root causes of the cognitive impairments linked to Alzheimer's disease (AD) [3].

AD is the most prevalent cause of memory loss in older people [6]. Cognitive abnormalities, memory loss, and behavioral changes are all indicators of AD [7–9]. Dementia in AD is linked to neurodegeneration, which begins with synaptic damage and progresses to neuronal death [10,11]. Recent research has indicated that some other components of the neurodegenerative process in AD may interfere with the adult neurogenesis process in the hippocampus [12,13]. Loss of synapses in the limbic and neocor-

tical systems is connected with cognitive impairment in Alzheimer's patients [14,15]. Several lines of evidence point to AD's pathophysiology linked to the rising levels of A β deposition produced by the APP's proteolysis (Figs. 1,2) [16,17].

Abnormal A β accumulation results from uneven dispersion between the A β production, aggregation, and clearance rates [18]. Proteolytic enzymes like neprilysin, chaperone molecules like APOE, lysosomal processes like autophagy, and non-lysosomal processes like the proteasome cleared A β . However, familial forms of AD are caused by mutations that increase A β production or aggregation, whereas failure of clearance mechanisms may be a major factor in AD (Fig. 2) [19].

However, loss of synapses and axonal damage are probably crucial neuropathological elements that cause dementia [20]. Alterations in neurogenesis have recently been related to the neurodegenerative process in AD, along with impairments in neuronal integrity and synaptic plasticity in mature neuronal circuitries [21]. This shows that the double attack on the brain causes AD, the degradation of ma-



Fig. 2. Different phases of the pathophysiology of AD. AD, Alzheimer's disease.

ture neurons, and the alteration of neurogenic regions in the adult brain [22] as the A β peptide influences AD advances, neuronal and synaptic impairment, the main component of senile plaques. Numerous data suggest that A β oligomers are neurotoxic instead of A β fibrils, although A β monomers are generally recognized as non-toxic in healthy proportions [23]. On the pathophysiology of AD, A β -42 is likely to have a considerable effect and plaque development [24]. Moreover, the A β -38 and A β -42 ratio ranges within the cerebral spinal fluid (CSF) were validated to be beneficial in distinguishing AD from other dementias [25,26].

Patients with advanced AD experience significant memory loss, hallucinations, confusion, and a lack of independence, finally dying from a respiratory syndrome, infection, or starvation [27,28]. A β plaques, neurofibrillary tangles (NFTs), neuronal losses, and gliosis are the characteristics of AD, which are also marked by cerebrovascular amyloidosis, infection, and significant synaptic alterations [29,30].

Nanotechnology is a comprehensive science that involves manipulating atoms, electrons, protons, and neutrons in various ways to provide new insights into how materials might be developed to tackle numerous problems in

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numerous fields [31]. It has been suggested that NPs are exciting tools that may address the unmet need to improve drug transport from the blood to the brain, particularly by functionalizing their outer layer with blood-brain barrier (BBB)-targeting agents. Because they share characteristics like biocompatibility, stability, biodegradability, nontoxicity, limited antigenicity, and suitability for surface functionalization, Gold nanoparticles (GNPs), liposomes, solid lipid NPs (SLN), and polymeric NPs are the most studied NPs for brain drug delivery. They may also contain drugs that are both hydrophobic and hydrophilic, and controlled drug release is an option. Liposomes are spherical vesicles ranging from 20 nm to 500 nm. They contain an aqueous interior and a membrane bilayer typically composed of naturally occurring phospholipids and cholesterol [32]. Pharmaceutical interests were already shifting due to the potential usage of multiple biological sources for nanoparticle manufacturing and application. Silver is the most preferred metal for producing NPs because it has specific antibacterial, antifungal, anti-inflammatory, anti-angiogenic, and anti-permeability properties, among others [33].

Vegetables, nuts, whole grains, fruits, and other foods contain phytochemicals. Combined or used alone, these

phytochemicals have tremendous therapeutic potential for treating various diseases [34]. Since ancient times, phytochemicals have been employed to cure various human diseases. Carotenoids, catechin, curcumin, diosgenin, quercetin, GX-50, sulforaphane, polyphenols, flavonoids, and other chemical elements originating from different parts of plants, such as fruits, leaves, and bark possess potential therapeutic properties. Phytochemicals and their analogs are now widely employed as antioxidants, inhibitors, substrates, modulators, enzymatic cofactors, and potential molecules in drug discovery in the medical and pharmaceutical industries. Curcumin can potentially prevent AD because it contains anti-amyloidogenic, antioxidative, and anti-inflammatory effects [35]. In vitro tests have demonstrated the anti-amyloidogenic properties of curcumin and its analog, rosmarinic acid, which inhibit in a dose-dependent manner the elongation of neurotoxic A β fibrils from fresh A β and destabilize preformed A β fibrils to regenerate A β monomers [36]. Inhibiting A β fibril formation is an exciting therapeutic approach for treating AD; curcumin is a prospective drug for curing and preventing AD due to its direct action on $A\beta$ fibrilization. They are plant-based bioactive components with disease-preventive qualities but are non-nutritive. They are non-essential nutrients that plants make [37]. This new drug candidate was suggested as a potential AD treatment based on numerous biomedical studies. In vivo, research indicated that GX-50 might cross the BBB, minimize the accumulation of A β -oligomers in the cerebral cortex, and improve cognitive function. In vitro research demonstrated that GX-50 could disassemble A β -oligomers, inhibit A β -induced neuronal apoptosis and apoptotic gene expression, and reduce neuronal calcium toxicity [38].

2. Methodology

A literature review was conducted utilizing various search engines, including PubMed, Science Direct, Scopus, and Google Scholar. The search was limited to papers published between 2000 and 2022, and specific search terms were employed, such as Alzheimer's disease, neurological disorders, amyloid, nanoparticles, tau pathology, dendrimers, nanotechnology, phytochemicals, and liposomes. Only papers that appeared in the relevant search engine results were included in the review.

3. Review

One to six percent of all instances of AD are earlyonset (onset before the age of 60 or 65), and sixty percent of these cases are familial. Thirteen percent of these cases appear to be inherited through an autosomal-dominant mechanism [39,40]. The distinction between early-onset family AD (EOAD), which starts before 60 or 65 years, and lateonset familial AD (LOAD), which starts after that age, is arbitrary. Early-onset cases may show up in families where the disease has a history of progressively developing [41].

3.1 How AD is Diagnosed?

AD is a chronic, irreversible brain disorder that progressively impairs memory, thought, reasoning, and other cognitive abilities. Additionally, it leads to behavioral problems that may interfere with a person's regular activities and daily life. A patient suspected of having AD should undergo several tests, including medical and family history, neurological examination, Magnetic resonance imaging (MRI) for the neurons, and vitamin B12 lab tests [42].

For a very long time, vitamin B12 insufficiency has been linked to neurologic issues, and some studies have found that it raises the chance of AD. Elevated homocysteine levels are a specific indicator of vitamin B12 deficiency and are toxic to the brain because they increase oxidative stress, calcium influx, and apoptosis. The diagnosis of vitamin B12 deficiency may be made using measurements of serum levels of vitamin B12, complete blood counts, and serum homocysteine levels [43,44]. The pathophysiologic process of AD starts years or even decades before clinical dementia and apparent cognitive abnormalities. As a result, the phrases "AD dementia" and "AD pathophysiologic process" are distinct.

3.2 Three Distinct Clinical Phases

There have been no clinical indications in preclinical AD. Measurable alterations in molecular and imaging biomarkers are being studied for pre-symptomatic evaluation.

With proper assessment, mild cognitive impairment AD can show moderate periodic changes in cognitive state and memory that do not interfere with everyday activities. It is essential to rule out any other dementia-causing factors. Genetic testing is an option in cases with early-onset familial AD to look for specific mutations.

The hallmark of Alzheimer's dementia is a growing cognitive impairment that makes day-to-day tasks challenging. It may be possible to confirm the diagnosis using abnormal biomarkers such as elevated levels of tau protein in the CSF, low levels of $A\beta$ on positron emission tomography (PET) imaging, and temporal lobe atrophy on MRI [45].

A complex neurological ailment called AD causes memory loss and progressive cognitive deterioration. For early identification, diagnosis, and the creation of efficient treatments, it is essential to comprehend the clinical stages, genetic components, and biomarkers related to AD. Here is a more thorough examination of the current state of knowledge, including any gaps and disagreements that may exist.

3.3 Biomarkers

Diagnosing AD, tracking the course of the condition, and determining the effectiveness of treatment depends heavily on biomarkers. Three biomarkers can be distinguished: neurodegenerative markers, tau biomarkers, and $A\beta$ biomarkers. $A\beta$ biomarkers include indicators of $A\beta$ buildup in the brain, such as amyloid PET imaging and $A\beta$ -

Table 1.	. Molecular	genetics o	of EOFAD	[53].
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Locus name	Percentage	Gene symbol	Chromosomal locus	Protein name	Test availability
AD-3	20-70%	PSEN1	14q24.3	Presenilin 1	clinical
AD-1	10-15%	APP	21q21	Amyloid β A-4 protein	clinical
AD-4	rare	PSEN2	1q31- q42	Presenilin2	clinical

EOFAD, Early-onset familial AD.

42 levels in CSF. Tau protein levels in CSF or by tau PET imaging are measured as tau biomarkers. Neurodegeneration markers, such as measurements of CSF tau, CSF neurofilament light (NfL), and structural and functional imaging, evaluate neuronal damage or neurodegeneration. Although these biomarkers have potential, their applicability and standardization in various clinical contexts and patient populations still need to be improved [46].

3.3.1 Gaps and Controversies

The current understanding of AD has several gaps and difficulties despite significant progress. Among the crucial areas are:

3.3.1.1 Early Diagnosis. Research is still being done on developing reliable biomarkers and clinical standards for the early and precise diagnosis of AD. The timely application of disease-modifying therapies depends on early identification [47].

3.3.1.2 Biomarker Validation. To define standardized and verified biomarker cutoff values and criteria for clinical application, discussion and research are underway. This is necessary for reliable and consistent interpretation of biomarker results in various labs and clinical contexts [48].

3.3.1.3 Genetic Factors. While the APOE4 allele is a recognized genetic risk factor, other genetic variants that increase the risk of AD also need to be identified and understood. To find new risk genes, genome-wide association studies (GWAS) and other genetic research projects are ongoing [49].

3.3.1.4 Treatment Efficacy. The designing of efficient AD disease-modifying medicines is still a difficult task. There is a need for additional studies to determine the best therapy options and potential combination therapies because the results of several clinical trials targeting tau and A have been inconsistent [50].

4. Early-Onset Familial AD

Early-onset familial AD (EOFAD) is the term used to describe multiple AD occurrences in families. While some investigation has utilized ages 60 or 70, the average beginning age is frequently younger than 65. The average beginning age is between the 40s and early 50s, but instances of beginning in the 30s and early 60s have also been reported.



Previous research shows that 41.2 out of every 100,000 atrisk individuals have EOAD in the population (between the ages of 40 and 59) [51].

Thirteen percent of patients with EOAD satisfied rigorous criteria for an autosomal-dominant inheritance, 61% had an excellent familial background EOFAD, and nonfamilial AD cannot be clinically distinguished, except for the age of initiation and family history. The phenotype of dementia might have a prolonged prodrome and is analogous to late-onset AD [52].

Molecular genetics: Based on the gene that causes EOFAD, at least three subtypes (AD-1, AD-3, and AD-4) (Table 1, Ref. [53]). Provides an overview of the causal genes and the proportional frequency of each subtype. The A β peptide comprises most of the extracellular amyloid plaque generated in AD. It is created when the α breaks the APP- β and γ -secretases (Fig. 1) [54,55].

Finding more genes linked to the disease may be made possible by new technologies that significantly use genomewide association studies, genetic markers, cutting-edge statistical techniques, and collaborative efforts to expand the number of study-able cases. In addition, many tools have been developed for identifying genes linked to AD.

Researchers are given access to clinical information and biological samples for their genetic analysis. The National Institute on Aging (NIA) has set up numerous systems to preserve genetic data produced by National Institute of Health (NIH) funded investigations. These data can be re-examined and used in conjunction with different datasets. Another useful tool is the AlzGene database, which has organized and examined over 900 AD association research and about 400 genes. NIA has set up numerous systems to preserve genetic data that gather current data on genetic association research carried out on AD and AD traits. In hundreds of AD-associated studies with potential AD susceptibility genes, the AlzGene database arranges and classifies these results [56].

4.1 APP and AD

Even though amyloid precursor protein (APP) and its derivatives have been discussed and extensively studied over the previous 20 years, it is still unclear how their normal physiological functions and metabolites work. There is proof that APP is associated with gene regulation, cell-cell, and cell-substrate interaction, brain development, and synaptogenesis. It is found in many tissues and as a membrane protein in the brain [57,58].



Fig. 3. Processing of a precursor protein for $A\beta$. The non-amyloidogenic route, two pathways (left, Blue), and the amyloidogenic pathway can both be used to degrade the β -amyloid ($A\beta$) precursor protein (APP) (right, light green). To make a complex of secreted APP (sAPP) and membrane-bound C83, α -secretase cleaves typically the vast majority of APP in the β -amyloid domain. The intracellular carboxy-terminal fragment (CTF) and extracellular fragment (p3) of C83 can be produced by subsequent cleavage of C83 by γ -secretase as part of the amyloidogenic pathway. β -secretase initially breaks down APP to create sAPP and membrane-bound C99. C99 is broken down by γ -secretase to produce $A\beta$ and intracellular CTF. Secretase breaks down APP at several locations adjacent to the inner membrane leaflet, resulting in varying lengths of $A\beta$ peptide. The main hazardous $A\beta$ in AD is thought to be the 42 amino acid peptide A42 (after the γ -cleavage shown in the Fig. 3). The clinical characteristic of AD, neuritic plaques, are formed in the brain by depositing and accumulating insoluble $A\beta$ carboxy-terminal fragment.

APP was the first gene susceptible to AD located on chromosome 21 and encoded for a single 770 amino acid transmembrane-spanning polypeptide [59,60].

The *APP* gene is duplicated due to the triplication of chromosome 21, which may improve *APP* expression and $A\beta$ buildup. Patients with Down syndrome reportedly had earlier AD pathology (the development of neurofibrillary tangles and senile plaques) than people without the condition [61]. These results imply that AD pathogenesis may be connected to *APP* overexpression. The APP gene has 18 exons used to make the APP protein. Exons 16 and 17 code for the $A\beta$ peptide. At least five isoforms of the APP protein contain the $A\beta$ peptide sequence after transcription and alternative splicing [62].

However, 21 and 3 mutations at Exons 17 and 16 suggest that APP is a very uncommon risk factor for AD since most pathogenic APP mutations were found close to the regions where the α -secretase family of secretory

and transmembrane proteins, which have an average length of 750 amino acids, are widely expressed and have roles in the proteolytic processing of the ectodomains of various cell-surface receptors and signaling molecules, and cell adhesion. In the non-amyloidogenic route, a disintegrin and metalloprotease10 (ADAM10) is the primary α secretase that breaks down APP, preventing the creation of A β , whose buildup and aggregation causes neuronal degeneration in AD. In addition to APP, the membrane-anchored metalloprotease ADAM10 also sheds the ectodomains of numerous other cell-surface proteins, such as cytokines, adhesion molecules, and notch. sAPP, an APP-derived fragment produced due to ADAM10 cleavage, is neuroprotective [63],

 β , and γ -secretase enzymes cleave the A β peptide; these mutations contributed to the development of AD [64,65]. The endosomal/lysosomal and β -secretase cleavages of A β are susceptible to N-terminal alterations in the A β sequence. β -secretase, contain 501 amino acids with a signal peptide of 21 amino acids at the amino terminus and an amino acid range from 22 to 45 in the proprotein domain. Beta site cleaving enzyme 1 (BACE1) shares less than 30% amino acid sequence with members of the human pepsin family. The BACE1 gene is found on chromosome 11q23.3 and is unrelated to AD [66].

A transmembrane domain with 17 residues and a 24amino-acid-long cytoplasmic tail of 24 amino acids follow the mature protein's lumenal domain, which runs from 46 to 460. The lumenal domain of BACE1 has two active site motifs, each containing the remarkably preserved hallmark aspartic protease sequence. These are located at amino acids 93 to 96 and 289 to 292. BACE1 is anticipated to function as a type I transmembrane protein, with the location of its active site positioned on the lumenal side of the membrane. -secretase enzyme cleaves APP at the amino terminus of $A\beta$ in this location, resulting in membranebound C99 and the secretion of a modified form of APP known as sAPP. The BACE1-specific amino acid sequence is believed to determine this protein's transmembrane orientation [67].

The complex of γ -secretase, which consists of a membrane-embedded protease known as presenilin 1 (PSEN1), presenilin enhance 2 (Pen-2), Aph-1, and Nicastrin, goes on to cleave C99, which is then involved in many essential cellular processes. Amyloid peptide aggregates due to abnormal amyloid precursor protein cleavage, which leads to AD building up in the brain. The transmembrane domain of γ -secretase is structured like a horseshoe and has 19 transmembrane segments (T.M.s). Nicastrin's (NCT) large extracellular domain (ECD) just over the depression is situated space created by the T.M. horseshoe. Interesting similarities exist between Nicastrin ECD and an extensive family of peptidases, including the Prostate-specific membrane antigen (PSMA) or glutamate carboxypeptidase. Understanding the γ -secretase complex's functioning processes is greatly aided by its structure to produce the intracellular carboxy-terminal fragment (CTF) and the amino acid [68].

To cleave C89 and shortened amyloid species, β -Secretase may cleave APP in the A β region; nevertheless, most APP proceeds via a non-amyloidogenic cleavage mechanism. The A β domain of APP is cut by α -secretase, producing membrane-bound C83 and the secreted form of APP (sAPP). By cleaving C83, γ -secretase creates the intracellular CTF and extracellular fragment p3 (Fig. 3). Presenilin (P.S.), NCT, Pen-2, and anterior pharynx defective 1 make up the γ -secretase complex. Although other proteases may be involved, numerous members of the ADAM (a disintegrin and metalloproteinase) family, including ADAM-9, ADAM-10, and tumor necrosis factor- α -convertase (also known as ADAM-17), are linked to the activity of α secretase. In the *APP* gene, there have been discovered to be about 63 coding mutations associated with AD [69]. Most of them are risk factors for AD, including the A673V and the Swedish mutation (KM670/671NL). They may either encourage A β accumulation or increase the creation of the A β -42/A β -40 ratio [70,71]. Following the identification of this protective mutation in 2012, the Icelandic mutation A673T has drawn the interest of an increasing number of researchers [72].

Recent research has identified an uncommon new mutation, APP S198P, found in the ectodomain of the APP, acting as a helix-breaker rather than inside or next to the A β domain. Experiments demonstrating increased A β buildup in the APP S198P transgenic mouse brain provided evidence of pathogenicity. Accelerated endoplasmic reticulum (E.R) folding and quick transport to endosomal-lysosomal compartments caused by APP S198P in cultured cells increased A β aggregate.

What mechanisms does the APP S198P mutation use to affect APP metabolism? In the APP 695 ectodomain, involving two unique structural domains of about 160 amino acids and about 190 amino acids, referred to as the E1 and E2, respectively, serine 198 is found. This amino acid is part of a versatile and prolonged acidic-rich domain (Ala 191-Val 290) [73]. In contrast to the creation and aggregation of the wild-type serine at position 198 of full-length APPS we, from which these metabolites were generated. Researchers discovered that soluble, extracellular APPs and cellular APP C-terminal fragments (CTF) originating from full-length APP S198P precursors comprising the Swedish mutation (APPSwe-S198P) at earlier points and accumulated to elevated amounts.

Furthermore, researchers present immunoprecipitation results implying transitory folding intermediates are generated more quickly in APPSwe-S198P-expressing cells than in APPSwe-expressing cells. This significant discovery may prove that the S198P variation encounters faster folding. The N-terminal E1 domain of APP has a structural epitope that is sulfhydryl-dependent, and pulse-chase tests using the P2-1 antibody have demonstrated that this domain does fold more quickly in cells showing the APPSwe-S198P variation than in cells expressing APPSwe. This discovery confirms the dependence of this structural epitope on sulfhydryl. According to the researchers, the proline at position 198 accelerates the folding process. It makes it easier for newly created synthetic APPSwe-S198P to migrate from the endoplasmic reticulum to the Golgi complex late compartments, where the enzymes BACE1 and γ -secretase are active to cleave APP at the β -site and γ -site respectively.

Compared to APPSwe, how can the folding pace of the APPSwe-S198P version be sped up? Proline, an amino acid that either bends or breaks a helix as it lacks amide hydrogen, is the deciding factor because of how much conformational space it takes up due to its bulky pyrrolidine



Fig. 4. This figure displays the molecular features of the *APP* gene and protein region where α - β and γ -secretases cleave App, the A β peptide is formed (top right), and the areas where many disease-causing mutations are found (bottom line).[50]

ring. Interestingly, a study of the Protein Data Bank was used to determine the local conformations of each proline residue, indicating that the residue before the proline is crucial for defining the protein's conformation. There is a high chance that the proline will adopt the conformation when it follows an aspartate residue (α : β = 9:1). Aspartate is included in the APP residue that comes right before residue 198.

The formation of a local helix is facilitated by an Asp-Pro pair, which in turn accelerates the folding of the neighboring E1 and E2 domains and the adjacent adaptable domain. Pulse-chase experiments were carried out to support this assertion, utilizing the sulfhydryl-dependent, structural-epitope-specific antibody mAbP2-1. These investigations revealed that APPSwe-S198P binds preferentially over APPSwe [74].

The processing of APP may change as a result of mutations (Table 2, Ref. [74–123]) around the cleavage site of α -secretase (Glu693Lys, Glu693Gly, Glu693del, and Asp694Asn), which may increase the A β peptide's proteolytic resistance [124,125]. Previously researchers studied the APP mutations near the cleavage of γ -secretase (Fig. 4). In the APP, 13 missense mutations at codons 714–715 lowered A β -40 secretions, while mutations at codons 716–717 enhanced A β -42 secretions. According to this study, the ratio of A β -42 to A β -40 may rise due to γ -secretase cleavage [126,127].

4.2 Tau and AD

Frontotemporal dementia, with or without supranuclear palsy, corticobasal syndrome, or parkinsonism, is associated with 40 mutations in the microtubule-associated tau (MAPT) gene, as reported by AlZFORUM [128]. The site of a mutation in a gene determines how it affects tau mRNA and protein as well as the disease that results. Exons 9 to 12 and exon 13 are where most coding mutations are found; however, Exon 1 mutations and intronic mutations in the intron after exon 10 that influence exon 10 splicing have also been described [129,130].

Only two sequence changes in exon 7 of *MAPT* have been identified: Pro176 (silent point mutation) and Ala178Thr, although neither is harmful [131,132]. Several types of tauopathies without mutations in the *MAPT* gene fall into one of several categories, such as Argyrophilic grain disease (AGD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and neurofibrillary tangle dementia, Pick's disease, and AD. There are also other so-called unclassifiable tauopathies. These categories are based on tau immunoreactive structures' cellular and anatomical distribution [133,134].

While certain *MAPT* gene mutations display characteristics of sporadic tauopathies, others have notable variances, such as a broader anatomical distribution and an elevated load of tau immunoreactivity. This study describes a patient with a progressive neuropsychiatric condition and a neuropathological tauopathy phenotype incompatible with sporadic disease entities. In addition, we report on the discovery of a *MAPT* gene variant in exon 7 [135]. Exons 2, 3, and 10 of the human genome are used for alternative splicing; this might generate up to six distinct tau isoform variations [136,137].

S. No	Mutation	Clinical	Pathogenicity	Biological effect	Genomic region	References
1.	IVS>17	AD, None	AD Benign	Unsure; deletion seems unaffected by APP splicing	Non-Cod	[75]
2.	H733>P	None	AD Not Classified	Considerably increased A β -42 without significantly affecting the cells' A β -42/A β -40 ratio	Cod Ex 17	[76]
3.	K724>N (Belgian)	AD	AD Not Classified	↑ A β -42/A β -40 ratio; Higher A β -42; \downarrow A β -40	Cod Ex 17	[77]
4.	L723>P (Australian)	AD	AD Pathogenic	Rise of A β -42 in CHO cells	Cod Ex 17	[78]
5.	M722>K	AD, None	AD Pathogenic	$\uparrow A\beta$ -42/A β -40 ratio, \uparrow phosphorylated tau	Cod Ex 17	[79]
6.	T719>N	AD	AD Pathogenic	The T719N mutation resulted in $\uparrow A\beta$ -42 and an $\uparrow A\beta$ -42:A β -40 ratio	Cod Ex 17	[80]
7.	T719>P	AD	AD Not Classified	Total A β in CSF was \downarrow particularly A β 1-40 and A β 1-42, with a relative \uparrow A β 1-38	Cod Ex 17	[81]
8.	V717>G	AD	AD Pathogenic	A ratio of A β -42/A β -40 that is \uparrow , an \uparrow A β -42; a lower A β -40	Cod Ex 17	[82]
9.	V717>I (London)	AD	AD Pathogenic	Increased A β -42/A β -40 ratio; \uparrow A β -42; little effect on A β -40	Cod Ex 17	[83]
10.	V717>L	AD	AD Pathogenic	Increased A β -42/A β -40 ratio; \uparrow A β -42; \downarrow A β -40	Cod Ex 17	[84]
11.	V717>F (Indiana)	AD	AD Pathogenic	\downarrow A β -42/A β -40 ratio	Cod Ex 17	[85]
12.	I716>M	AD	AD Not Classified	Unidentified; in silico projected to be harmful (PHRED-scaled CADD score >20)	Cod	[86]
13.	I716>T	AD	AD Not Classified	Unidentified, although in silico studies (PHRED-scaled CADD score >20) suggested a negative impact	Cod Ex 17	[87]
14.	I716>V (Florida)	AD	AD Not Classified	$\uparrow A\beta$ -42	Cod Ex 17	[88]
15.	I716>F	AD	AD Pathogenic	Increased APP C-terminal fragments; reduced synthesis of APP intracellular domain; $\uparrow A\beta$ -42/A β -40 ratio: $\uparrow A\beta$ -42; $\downarrow A\beta$ -40	Cod Ex 17	[76]
16.	V715>A (German)	AD	AD Pathogenic	$\uparrow A\beta - 42/A\beta - 40$ ratio	Cod Ex 17	[89]
17.	V715>M (French)	AD	AD Pathogenic	Total A β dropped, A β -42 remained constant, while A β -40 drastically declined	Cod Ex 17	[90]
18.	T714>I (Austrian)	AD	AD Pathogenic	\uparrow A β -42/A β -40 ratio (about 11-fold)	Cod Ex 17	[91]
19.	T714>A (Iranian)	AD	AD Pathogenic	Unknown, although in silico techniques suggested it would be harmful (PHRED-scaled CADD score >20)	Cod Ex 17	[92]
20.	A713>V	None	AD Benign	Cellular A β -42 and A β -40 secretion are reduced; the A β -42/A β -40 ratio is unaffected	Cod Ex 17	[93]
21.	A713>T	AD, None	AD Uncertain Significance	\uparrow A β -42/A β -40 ratio due to \downarrow A β -40 secretion in cells	Cod Ex 17	[94,95]
22.	G708>G	None	AD Benign	\uparrow production of A β -42 without noticeably changing the cells' A β -42/A β -40 ratio	Cod Ex 17	[96]
23.	F690_V695>del	AD	AD Pathogenic	produces quickly aggregating A β peptides missing amino acids 19–24 and appears to largely abolish non-	Cod Ex 17	[97]
				the amyloidogenic processing of APP		
24.	V695>M	AD	AD Not Classified	Unknown. Mixed findings were obtained using in silico techniques, but the integrative PHRED-scaled	Cod Ex 17	[98]
				CADD score was more than 20, indicating a negative impact		
25.	E693>del (Osaka)	AD	AD Pathogenic	Unchanged A β -42/A β -40 ratio; lower levels of A β -42 and A β -40; mutant A β more sensitive to neprilysin	Cod Ex 17	[99]
				and insulin-degrading enzyme degradation		
26.	E693>G (Arctic)	AD	AD Pathogenic	Protofibrils formation by Arctic A β -40 is enhanced and more rapid; Neprilysin inhibits the proteolytic breakdown of A β	Cod Ex 17	[75,100]
27.	A692>G (Flemish)	AD	AD Pathogenic	\uparrow levels of A β -42 and A β -40 secreted in CHO, HEK-293, and H4 cells; Modified APP processing	Cod Ex 17	[101]

Table 2. App mutations, pathogenicity, clinical and biological effects.

S. No	Mutation	Clinical	Pathogenicity	Biological effect	Genomic region	References
28.	K687>N	AD	AD Not Classified	reduces cleavage of the APP by α -secretase \downarrow production of sAPP overall and sAPP α in particular. A β -40 and A β -42 have increased	Cod Ex 16	[102]
29.	K687>Q	AD	AD Likely Pathogenic	Unknown; however, PolyPhen-2 and SIFT suggested it would likely be harmful	Cod Ex 16	[103,104]
30.	E682>K	AD	AD Not Classified	\uparrow total A β levels and A β -42/A β -40 ratios noticeably; shift BACE1 cleavage to the β -site	Cod Ex 16	[105]
31.	D678>N (Tottori)	AD	AD Pathogenic	higher cytotoxicity and accelerated oligomerization kinetics compared to wild-type A β	Cod Ex 16	[106]
32.	D678>H (Taiwanese)	AD	AD Pathogenic	\uparrow A β -42/A β -40 ratio in a conditioned medium; elevated levels of A β -42 and A β -40 in secretions. \uparrow <i>In vitro</i> toxicity as compared to A β -42 wild-type	Cod	[107]
33.	H677>R (English)	AD	AD Not Classified	\uparrow cytotoxicity and accelerated oligomerization kinetics compared to wild-type A β	Cod Ex 16	[108]
34.	A673>V	AD	AD Not Classified	Incubation of mutant and wild-type $A\beta$ reduces amyloidogenesis and toxicity but results in more significant cytotoxicity and faster oligomerization kinetics	Cod Ex 16	[109]
35.	A673>T (Icelandic)	None	AD Protective	reduced amyloidogenic A β peptide synthesis by roughly 40%. The resulting A β is less likely to aggregate	Cod Ex 16	[110,111]
36.	KM670>671NL	AD	AD Pathogenic	↑ total Aβ; unchanged Aβ-42/Aβ-40 ratio; ↑ production and secretion of Aβ-42 and Aβ-40	Cod Ex 16	[112]
37.	V669>L (Seoul)	AD	AD Not Classified	Unknown. Despite conflicting results, a comprehensive in silico prediction technique foresaw nega- tive consequences (PHRED-scaled CADD score >20)	Cod Ex 16	[113]
38.	E665>D	None	AD Benign	A β -42, A β -40, and the A β -42/A β -40 ratio did not differ substantially from cells expressing wild-type APP	Cod Ex 16	[114]
39.	P620>L	AD	AD Uncertain Significance	\uparrow A β -40/A β -42 secretion in cells without significantly changing the A β -42/A β -40 ratio in cells	Cod Ex 14	[115]
40.	P620>A	AD	AD Not Classified	\uparrow A β -42 and the A β -42/A β -40 ratio in cells	Cod Ex 14	[116]
41.	S614>G	AD	AD Uncertain Significance	$\uparrow A\beta$ -42/A β -40 ratio, with an \downarrow in A β -40 and an \uparrow in A β -42 secretion in a cellular assay	Cod Ex 14	[117]
42.	V604>M	AD,	AD Uncertain Significance	Unknown. Estimated to have a negative effect in silico (PHRED-scaled CADD score >20)	Cod Ex 14	[118]
43.	T600>M	None	AD Benign	A β -42 secretion and the A β -42/A β -40 ratio were not significantly changed in cells, although A β -40 secretion was reduced	Cod Ex 14	[119]
44.	E599>K	AD, PD	AD Benign, P.D.: Not Classified	In cells, A β -40 secretion did not significantly alter A β -42 secretion nor the A β -42/A β -40 ratio	Cod Ex 14	[120]
45.	V>562I	None	AD Not Classified	A β -40 secretion was modestly reduced in cells; however, A β -42 secretion remained unaltered	Cod Ex 13	[120]
46.	Y538>H	AD	AD Benign	\downarrow A β -42 and A β -40 in cells, without changing A β -42/A β -40 ratio	Cod Ex 13	[120]
47.	A500>T	None	AD Not Classified	In cells, A β -40 and A β -42 Productivity resembled that of wild-type APP	Cod Ex 12	[119]
48.	K496>Q	AD	AD Not Classified	In cells, slight \uparrow in A β -40, but A β -42/A β -40 ratio did not differ substantially from controls	Cod Ex 12	[115]
49.	R486>W	AD	AD Not Classified	Unknown, however, in silico techniques estimate it will likely be harmful (PHRED-scaled CADD score >20)	Cod Ex 11	[121]
50.	A479>S	None	AD Benign	No discernible impact on the synthesis of A β -40 or A β -42 in cells	Cod Ex 11	[122]
51.	R468>H	None	AD Benign	Neither the synthesis of A β -40 nor A β -42 in cells was greatly impacted	Cod Ex 11	[119]

Table 2. Continued.

S. No	Mutation	Clinical	Pathogenicity	Biological effect	Genomic region	References
52.	E380>K	AD	AD Uncertain Significance	Unknown, but estimated by PolyPhen-2 to likely be harmful, harmful by SIFT, and neutral by PROVEAN.	Cod Ex 9	[123]
				CADD score >20 on the PHRED scale		
53.	V340>M	AD	AD Uncertain Significance	Unknown, although its CADD score when scaled by PHRED was >20, indicating a negative impact	Cod Ex 7	[117]
54.	D332>G	AD	AD Not Classified	Unknown; however, PolyPhen-2 and SIFT suggest they will be harmful and tolerable	Cod Ex 7	[116]
55.	P299>L	AD	AD Not Classified	Unknown, however, in silico, it is considered harmful (PHRED-scaled CADD score >20)	Cod Ex 7	[116]
56.	T297>M	AD	AD Uncertain Significance	Unknown but expected to be unfavorable by SIFT and PolyPhen-2 (PHRED-scaled CADD score >20)	Cod Ex 7	[103]
57.	E296>K	AD	AD Not Classified	Unknown, although a PHRED-CADD score of >20 in silico suggests a negative impact	Cod Ex 7	[116]
58.	E246>K	AD	AD Likely Benign	No considerable impact in cells on A β -40 or A β -42 production	Cod Ex 6	[122]
59.	D244>G	AD	AD Not Classified	Unknown, although PolyPhen-2 and SIFT suggested that it would likely be harmful. CADD score as	Cod Ex 6	[103]
				measured by PHRED >20		
60.	D243>N	AD	AD Benign	No effect on A β -42 or A β -40 production in cells	Cod Ex 6	[116]
61.	A235>V	AD	AD Benign	\downarrow A β -40 and A β -42 without changing A β -42/A β -40 ratio in cells	Cod Ex 6	[116]
62.	A201>V	None, PD	AD Benign, PDD: Not Classified	In cells, no effect on A β -42, A β -40, and A β -42/A β -40	Cod Ex 5	[120]
63.	S198>P	AD	AD Benign	In transgenic mice as an amyloidosis model and cultured cells, the S198P mutation boosted ${\rm A}\beta$ production	Cod Ex 5	[74]

AD, Alzheimer's Disease; P.D, Parkinson's Disease; Cod, Coding; Ex, Exon; BACE, β -secretase; \uparrow , Increase; \downarrow , Decrease.

The domain that binds to microtubules of tau interacts with microtubules through C terminal repeats, which explains why 4R tau isoforms are more likely than 3R tau isoforms to stimulate microtubule assembly [138]. In the mammalian brain, tau is a crucial regulator of axonal transport that is highly expressed in neurons and normally localizes largely to axons [139].

However, tau gene deletion had little effect on axonal transport, suggesting that Microtubule-associated proteins 1 (MAP1) and Microtubule-associated proteins 2 (MAP2) may make up for tau in other proteins involved in micro-tubule regulation or binding [140].

Although tau is involved in oligodendrocyte process outgrowth and myelination, it is still uncertain if tau regulates the physiological functions of astrocytes. Tau also plays two other physiological roles, regulating insulin signaling and iron export [141].

4.3 Presenilins

PSENs were discovered for the first time in 1995 while searching for the genes causing beginning, autosomal dominant variants of familial AD (FAD) [142,143]. A few years after their identification, it was determined that PSENs encode proteins that sustain the cleavage of APP by γ -secretase to create A β peptides [144,145]. *PSEN* genes have exhibited significant levels of evolutionary conservation, with homologs present in taxa as numerous as lower chordates, Drosophila melanogaster, and Caenorhabditis elegans [146].

In several tissues from mice and humans, including parts of the brain, PSEN1 and PSEN2 mRNA are conveyed equally and widely [147], with the cerebellum and hippocampus expressing at the highest levels. They can be seen in glial cells but are primarily expressed in neurons [148,149]. *PSEN-1* on chromosome-14 (14q24.3) and *PSEN-2* on chromosome 1 (1q42.2). The membranes of the plasma membrane, the Golgi apparatus, the E.R, and the endosomes where PSEN-1 and PSEN-2 are 50-kDa polytopic transmembrane (PTM) proteins interacting with around 65 percent of their amino acid sequences [150].

PSENs have lately been concentrated at membranes connected to mitochondria (MAM) [151–153]. The placenta and skeletal muscle have PSEN-2, while the brain, heart, liver, pancreas, kidney, and placenta all include PSEN-2 isoform-2. Isoform 2 lacks amino acids 263–296 [148]. The hydrophilic, flexible N-terminus of PSENS is organized in the cytoplasm, but the C-terminus of PSENS protrudes into the extracellular space's lumen. On PSENS, there are nine helical T.M. domains. PSENs make up the catalytic core of the γ -secretase [154].

Nicastrin, anterior pharynx deficient 1, P.S., and the heterotetrameric compound with a high molecular weight (PSEN-1 or PSEN-2) make up this enzyme (PEN-2) [155]. Voltage-dependent Na+channel subunit 2, APP, Notch, Delta1, E- and N-cadherins, CD44, Nectina-1, and ErbB4, are also included [156]. The NTF and CTF, formed by the endoproteolytic cleavage of the N- and C-terminal regions of the PSEN-1 or PSEN-2 subunit, respectively, remain connected to one another in a stable manner throughout γ -secretase assembly and development [154,157].

The immature holoprotein 7th hydrophobic domain undergoes an autocatalytic cleavage when P.S. is integrated into the enzyme complex, yielding about 20 kDa for the CTF and 30 kDa for the NTF (which is part of a long cytosolic loop). P.S. cleavage is autocatalytic; however, P.S. maturation is a saturable process and calls for additional molecular partners. Full length (F.L.), an excessive amount of which is an immature form of PSENS results in its proteasomal breakdown. Because of this deterioration, FL-PS has a much lower half-life than the mature form, 24 hours instead of 1.5 hours. FAD is caused by about 150 autosomal dominant mutations in PSEN-1 and 14 in PSEN-2 [158].

According to recent research, FAD-linked PSEN mutants are more active and produce more $A\beta$ peptides in various cell types and transgenic mice with FAD-PSEN mutations. This aligns with the discovery that the catalytic center of the γ -secretase comprises PSENs [159]. Other investigations have cast doubt on this initial hypothesis, revealing decreased total enzymatic activity in FAD-PS expressing mice with just an elevation in the ratio of $A\beta$ -42/A β -40, primarily due to a decrease in $A\beta$ -40 production [160].

Consequently, although this topic is still intensely debated, the initial gain-of-function theory of loss of function has resulted from FAD-PSEN mutation. The total amount of A β generated reduces due to the less precise cleavage of APP brought on by FAD-PSENs. As a result, there is an increase in the synthesis of A β -42 and a decrease in the creation of A β -40, changing the physiological homeostasis of the process. Another approach has recently been proposed, according to which PSEN1 mutations reduce γ secretase's ability to trim proteins by limiting its ability to operate as a carboxypeptidase favoring the production of A β -42 [159,161].

PSENs are well-known for their pleiotropic γ secretase-independent functions in addition to their welldescribed catalytic activity within the γ -secretase complex, particularly in maintaining Ca²⁺ homeostasis but also in protein trafficking, cell adhesion, and autophagy.

5. Late-Onset Familial AD (LOAD)

Many families have more than one individual suffering from dementia, the majority of whom develop the disease around the age of 60 to 65. The disease lasts an average of 8–10 years; however, it can last for a long time, from 2 to 25 years. The APOE epsilon-4 (e4) allele is linked to LO-FAD (Table 3, Ref. [53]). The age of onset appears to be pushed toward an earlier age by the APOE e4 allele through unknown mechanisms [162,163].

The major lipid transporter APOE, a protein with 299 amino acids, is a prominent component of the brain. The

Table 3. Molecular genetics of Late-onset familial AD (LOFAD) [53].

Locus-name	Gene-symbol	Chromosomal-locus	Protein-name	Test-availability
AD-2	APOE	19q13.2	APOE	Clinical

astrocytes in the BBB are primarily responsible for its synthesis [164]. APOE2, APOE3, and APOE4 are humans' three main APOE polymorphic alleles. Only two amino acids, cysteine/arginine polymorphisms at locations 112 or 158, differentiate these proteins' N-terminal domains from one another. Furthermore, only 1% of instances of AD are EOFAD, the primary cause of early-onset Alzheimer's disease, which typically appears before the age of 65, is an excess amount of A β that results from mutations in the APP gene, presenilin 1 (PSEN1), or presenilin 2 (PSEN2) genes. These three genes are the essential elements of the γ secretase complexes that cleave and release A β [165,166].

The most prevalent type of AD is LOAD, which often develops in adults over 65. The primary risk factor for the pathophysiology of LOAD, which is frequently present in 15% of people, is APOE4 [167]. This study likewise found a small correlation between APOE4 and AD among Hispanics and African Americans but a larger correlation in Japanese individuals. The researchers found evidence of the APOE4 influence between the ages of 40 and 90. Still, it diminished after age 70, and the possibility of AD associated with a particular genotype varies according to gender [168]. Although APOE4 is not the primary cause of AD, only a small percentage of patients have at least one copy of the allele. In reality, only one-third of people living with AD have APOE4. It's interesting to note that some homozygotes of APOE4 even never get AD. However, the chance of developing AD in individuals with two copies of APOE4 can be as high as 20 times. On the other hand, there is evidence that APOE2 plays a protective role in AD patients [169].

The likelihood of developing Alzheimer's disease is greatly increased by having the APOE4 allele. However, individuals with APOE2/APOE2 and APOE2/APOE3, despite having a reduced odds ratio, are still less likely to develop AD compared to those with APOE2/APOE4, APOE3/APOE4, and APOE4/APOE4 [170]. A study, however, discovered that a variety of particular risk factors, such as high blood total cholesterol, any combination of the APOE alleles, and midlife hypertension, may collectively double the chance of developing AD in the future [171].

5.1 APOE's Role in AD

 β -Amyloid (A β) synthesis, oligomerization, and deposition are all known to be crucial factors in AD. The hypothesis that excessive A β production contributes to the onset of AD has been underlined by mutations in the APP and presenilin genes, which enhance the synthesis of A β (1-42). Evidence shows that the apolipoprotein E (APOE)

protein's isoform APOE4 may interact with the A β cascade and cause AD pathogenesis.

First, APOE is present in neuritic plaques, and AD patients with APOE4 have higher amounts of $A\beta$ in their brains. Similar results have been seen in transgenic mice expressing human APOE isoforms [172].

Second, research has indicated that APOE3 and APOE4 attach to $A\beta$ differently. However, it is unknown whether APOE4 actively promotes $A\beta$ aggregation and deposition or if APOE3 and E2 play a protective function by preventing $A\beta$ aggregation or encouraging $A\beta$ clearance. Compared to APOE3, APOE4 has a higher affinity for $A\beta$ in a lipid-free state. However, it has also been shown that APOE3 and E2 bind to $A\beta$ faster when bound to lipoproteins [173]. It has been discovered that APOE dose significantly impacts plaque deposition in mice models, indicating that APOE is actively involved in plaque formation. However, research has revealed that whereas APOE4 promotes greater $A\beta$ deposition, APOE3 improves $A\beta$ clearance [174].

Thirdly, APP processing, $A\beta$ clearance, and $A\beta$ production may all include neuronal APOE receptors in one way or another. APOE4 has been reported to improve the synthesis of $A\beta$ by encouraging the endocytic recycling of APP. Last but not least, *in vitro* research has shown that APOE amplifies the neurotoxicity of $A\beta$, with APOE4 having more neurotoxic effects than APOE3. Furthermore, the buildup of intraneuronal $A\beta$ has been linked to the defects in neuroplasticity brought on by APOE4 in a transgenic mouse model. These results indicate a synergistic pathogenic interaction between APOE4 and $A\beta$ [175].

5.1.1 APOE and β -Amyloid Hypothesis

A β is more easily broken down by the enzyme APOE. Direct interactions between the proteins APOE2, APOE3, and APOE4 and A β can result in APOE/A β complexes that impact A β clearance, aggregation, and plaque production [176]. Despite reports of varying A β affinities that vary by isoform, they are generally contradictory [177,178].

Recent studies show that increasing astrocytic APOE4 expression during the amyloid seeding stage increases amyloid deposition [179]. A β clearance may also be impacted by APOE/A β complex formation and APOE4 competing for the same clearance pathway in the brain. When both proteins use the same A β clearing pathway, the total rate of A β clearance is slowed [180]. For the cellular absorption mechanism dependent on the Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1), APOE4 and A β compete in astrocytes [179,181]. Competitively, APOE4 decreases LRP1/A β binding, increasing the total burden of A β (Fig. 5, Ref. [182]). The question of whether APOE also affects A β synthesis arises since APOE influences lipid metabolism. Poor lipid management has been associated with increased A β production in the brain. A β can affect APOE internalization and control it [183,184]. Particularly, either APOE3 or APOE4 binds to LDL receptors in the presence of A β , undergoes conformational changes, and exerts substantial internalization. This results in greater APOE4 than APOE3 binding to hippocampal neurons and an overall rise in A β absorption by neurons mediated by APOE4 [183].



Fig. 5. A summary of how APOE4 affects the mechanistic pathways. The APOE gene has three isoforms: APOE2, 3, and 4. Neurodegeneration is more likely to occur along APOE4 routes, while APOE2 and APOE3 offer protection. Function declines and increases, especially in APOE4 carriers. Loss of phagocytosis, a decline in glucose absorption, autophagy, long-term potentiation (LTP), a rise in phosphorylated tau, proinflammatory microglia, excessive mitochondrial activity, and intense amyloid binding causes plaques are some of the symptoms. Reductions in LTP, autophagy, aggressive amyloid binding that culminates in plaques, phosphorylated tau, proinflammatory microglia, excessive mitochondrial activity, and mitochondrial respiration. The glucose transporter protein type-4 (GLUT4), mammalian target of rapamycin (mTOR), pAkt, pERK, and pTau are acronyms for specific proteins (phosphorylated tau), and all stand for "phosphorylated tau" [182].

The significance of APOE4 in $A\beta$ pathology remains explored as a possible target for disease-modifying therapy, even though the focus of AD. research has shifted away from the amyloid cascade theory and toward inflammation, metabolism, and hyperactivity in recent years. Before the onset of clinical symptoms, a deposition may be recognized in the brain, and pinpointing the interval between the deposition and the onset of the illness opens the door to therapeutic intervention [185]. By increasing LRP1 expression or altering its function, prospective future treatments may be able to lessen APOE/A β competition or boost A β clearance by directly targeting amyloid with antibodies or aiming to lower plaque burden itself [186].

5.1.2 APOE and Neurofibrillary Tangles

The creation of neurofibrillary tangles (NFTs), which are a hallmark of AD and other neurodegenerative illnesses, is caused by abnormal tau protein phosphorylation. Excessive tau phosphorylation is thought to interfere with regular neuronal function and cause neuronal death [175].

According to in vitro research, different APOE isoforms may affect tau pathology differently. In the presence of sodium dodecyl-sulfate (SDS), APOE3 but not APOE4 forms a stable complex with tau. Tau's association with APOE3 is inhibited by phosphorylation, proving that APOE3 only interacts with non-phosphorylated tau. This implies that APOE3 may inhibit aberrant tau phosphorylation and maintain the cytoskeleton of neurons [187]. Increased tau phosphorylation has been shown in studies using transgenic mice that express human APOE4 but not in astrocytes. This suggests that APOE4 has a neuron-specific impact on tau phosphorylation. Additionally, in APOE mutant mice fed a high-cholesterol diet, hyperphosphorylated tau accumulated intraneuronally. This finding suggests a connection between dietary cholesterol and APOE function in promoting tau disease [188].

The amino-terminal domain of APOE3 is assumed responsible for the protein's interaction with tau. Furthermore, research has shown that carboxyl-terminally shortened APOE promotes tau phosphorylation and the development of intracellular NFT-like inclusions. It is still unclear how APOE gains access to the cytoskeleton of neurons. The regulation of tau kinases and phosphatases is another potential method by which APOE isoforms may contribute to tau hyperphosphorylation. To completely comprehend the molecular processes underlying the connections between APOE isoforms and tau pathology in AD, it is significant to stress that more investigation is required [189]

5.1.3 APOE, Cholesterol, and Synaptic Repair

The main function of APOE is to redistribute lipids and keep the body's cholesterol levels in check. APOE4 is less effective than APOE2 and APOE3 at facilitating cholesterol uptake in laboratory studies using cultured neurons. APOE4 is less effective at encouraging cholesterol clearance from astrocytes and neurons. The structural changes between various APOE isoforms may cause these functional variations [190]. There is a decline in brain cholesterol levels in AD, and mounting research indicates that cholesterol may have a role in the onset of AD. Clinical and epidemiological studies show that those with high plasma cholesterol levels are more likely to develop AD [191]. Statins, which stop the production of cholesterol, have also been demonstrated in numerous studies to slow the onset and progression of AD. Other genes related to the transport and metabolism of cholesterol have also been linked to AD risk and APOE [192].

An increased risk of developing AD has been linked to genetic variations in cholesterol uptake receptors like the low-density lipoprotein receptor-related protein (LRP) and very-low-density lipoprotein (VLDL) receptor as well as enzymes that break down cholesterol like cytochrome-46 (Cyp46) [193]. Additionally, the data point to cholesterol as a regulator of amyloid-beta (A β), a protein linked to AD. Known as lipid rafts, the cell membrane contains enzymes necessary for generating A β , such as β -secretase and γ secretase [194].

The location of APP and the location of the enzymes that cleave it can be affected by the amount or distribution of cholesterol in the membrane. $A\beta$, on the other hand, can affect how cholesterol is made and distributed in neurons [195]. Additionally, research has demonstrated that cholesterol can counteract the negative effects of $A\beta$ on calcium signaling and neurotoxicity in various animals. These results demonstrate the intricate relationships between cholesterol and $A\beta$ and imply that the APOE genotype may influence these relationships [196].

The nervous system's growth, regeneration, and synaptic plasticity depend on interactions between neurons and glial cells. A crucial part of these processes is the redistribution of lipids that APOE promotes. The limbic system and neocortex both experience severe neuronal loss in AD, and the synaptic disruption that results impairs the survival of neurons. It has been suggested that various APOE isoform variations contribute to synaptic plasticity and repair processes to variable degrees. Mice deficient in APOE as well as those that express APOE4 but not APOE3, have been shown to have impaired synaptic plasticity [197]

These variations in APOE isoforms have also been observed in humans, where those with the APOE4 variant demonstrate less regenerative change in the same brain regions than those without and who show inadequate compensation for the neuronal loss. These results imply that APOE4 performs less functionally in synaptic regeneration than other APOE isoforms. This deficit probably also has an impact on synaptic activity. Studies have shown that mice expressing APOE4 exhibit less long-term potentiation (LTP), a process linked to synaptic strength and plasticity, compared to animals of the wild-type and mice expressing APOE3 [198].

5.1.4 APOE and Cholinergic Dysfunction

AD is well known for affecting cholinergic signal transduction. Comparatively to non-carriers, those with the APOE4 variation and AD show more pronounced impairments in cholinergic activity in the cortex and hippocampus [199]. Additionally, they have fewer cholinergic neurons overall, and markers of cholinergic function, such as nicotinic acetylcholine receptor binding and choline acetyltransferase activity, are reduced. However, the amounts of muscarinic receptors in AD patients with various APOE genotypes do not differ noticeably [200].

Studies conducted in vitro have shown that different APOE isoforms affect the signaling cascade triggered by muscarinic acetylcholine receptors differently. In response to carbachol stimulation, APOE4 affects phosphoinositide hydrolysis, whereas APOE3 does not. Additionally, APOE3, but not APOE4, has demonstrated the capacity to fend off disruption brought on by the amyloidbeta protein fragment A β (1-42) [201]. The modulation of cholinergic impairments resembling AD depends on the particular APOE isoform, $A\beta$ overproduction, and the animal's age rather than plaque deposition, according to recent research using a double transgenic mouse model. The research showed synaptic and cholinergic impairments in mice carrying human APP/APOE4 before plaques developed. The synaptic and cholinergic deficits in aged mice harboring human APP/APOE4 and human APP/APOE3 were strikingly similar, despite differences in plaque load [202].

These findings imply that APOE4 directly impairs cholinergic signaling, which may explain why cholinergic replacement therapy is less effective in APOE4-associated AD patients. AD is well known for affecting cholinergic signal transduction. Comparatively to non-carriers, those with the APOE4 variation and AD show more pronounced impairments in cholinergic activity in the cortex and hippocampus [202]. Additionally, they have fewer cholinergic neurons overall, and markers of cholinergic function, such as nicotinic acetylcholine receptor binding and choline acetyltransferase activity, are reduced. However, the amounts of muscarinic receptors in AD patients with various APOE genotypes do not differ noticeably [203].

Studies conducted *in vitro* have shown that different APOE isoforms affect the signaling cascade triggered by muscarinic acetylcholine receptors differently. In response to carbachol stimulation, APOE4 affects phosphoinositide hydrolysis, whereas APOE3 does not [204]. Additionally, APOE3, but not APOE4, has demonstrated the capacity to fend off disruption brought on by the amyloid-beta protein fragment A β (1-42). The modulation of cholinergic impairments resembling AD depends on the particular APOE isoform, A β overproduction, and the animal's age rather than plaque deposition, according to recent research using a double transgenic mouse model [205]. The research showed synaptic and cholinergic impairments in mice carrying human APP/APOE4 before plaques developed. The synaptic and cholinergic deficits in aged mice harboring human APP/APOE4 and human APP/APOE3 were strikingly similar, despite differences in plaque load. These findings imply that APOE4 directly impairs cholinergic signaling, which may explain why cholinergic replacement therapy is less effective in APOE4-associated AD patients.

5.1.5 APOE and Signaling

Numerous signaling pathways, some of which are pertinent to AD, have been demonstrated to be modulated by APOE. APOE has shown isoform-specific impacts on various signaling cascades in vitro studies. Different APOE isoforms activate calcium channels in different ways, which causes varying degrees of intracellular calcium rise [200]. APOE also has an isoform-specific impact on the actions of numerous proteins involved in signaling pathways, including PKC, GSK-3, pAkt, ERK, JNK, and CREB. Recent microarray studies employing hippocampus samples from AD patients have found significant variations in gene expression patterns between APOE4 carriers and non-carriers. Individuals with the APOE4 gene tend to express tumor suppressors and negative regulators of cell development more frequently, which could promote APOptosis. On the other hand, they have decreased expression of genes linked to mitochondrial energy metabolism, neuronal outgrowth, synaptic plasticity, and neurotransmitter receptors [206].

A person with APOE4 may develop resistance to several pharmacological treatments because of changes in neurotransmitter receptors and downstream signaling pathways. Additionally, it appears that APOE4 carriers experience both a loss of function in cell defense mechanisms and a gain in function in pathways leading to the formation of $A\beta$, a key pathological feature of AD, and tau phosphorylation. These are two additional effects of disrupting multiple signaling pathways mediated by APOE4 [207].

5.1.6 APOE and Neurotoxicity

By toxically impacting neurons, APOE may also directly contribute to neurodegenerative processes. Vitro studies have demonstrated that APOEderived fragments and lipid-free APOE, notably APOE4, are hazardous to neurons [208]. However, this toxicity is prevented when APOEcontaining lipoproteins, which are more physiologically relevant, are utilized instead of delipidated APOE. APOEcontaining lipoproteins have shown that they can, in an isoform-specific manner, enhance cell survival and neurite outgrowth (APOE3 being more advantageous than APOE4) [209].

APOpE3/E3 mice are more protected against ageinduced neurodegeneration than APOE4/E4 animals, according to *in vivo* studies employing transgenic mouse models expressing human APOE3, APOE4, or both. This shows that APOE4 acts as a major negative component, interfering with APOE3's positive function and offering less neuroprotection than APOE3 [210].

The neurotoxic effects of APOE have been attributed to its numerous proteolytic fragments, with studies demonstrating that both the N- and C-terminal fragments cause neurodegeneration and impair neuronal function. Importantly, APOE C-terminal fragment levels were greater in AD patients' brains than controls, especially in conjunction with neurofibrillary tangles. The neurotoxicity and aggregation of APOE may be influenced by the susceptibility to cleavage and the existence of lipid-bound or lipid-free APOE [188].

According to recent studies, APOE aggregates into soluble fibrils *in vitro*. The aggregation rate varies amongst isoforms, with APOE4 having the highest propensity. It has been discovered that these APOE fibrils are more hazardous to cultured neuronal cells than APOE tetramers. Nevertheless, further research is still needed to determine whether APOE fibrils and isoform-specific differential fibrillation exist in the AD brain. Gaining knowledge of the role of APOE in neurodegenerative processes requires understanding both the elements that lead to APOE neurotoxicity (such as lipid association, proteolytic cleavage, and fibrillation) as well as its neuroprotective properties [204].

It can activate several routes for downstream kinase signaling, resulting in dephosphorylation in Thr231, Ser235, and Ser396. Although the link between APOE and phosphorylation has been proven, more research into the isoform-specific effects of APOE on protein is still needed. Because APOE can influence regulation and modulate AD pathophysiology positively and negatively, Future studies should concentrate on how each APOE isoform regulates activity, causing microtubular and cytoskeletal instability that aids in disease development [211].

6. Nanomedicine

Nanotechnology studies and manipulates matter with dimensions ranging from one to one hundred nanometers. Materials create unique phenomena at these dimensions, allowing for novel uses that have only recently been investigated in research and medicine [212]. Nanotechnology is not new; this discovery was the impetus for developing nanomedicine. It is a relatively new field focusing on all human biological systems and their detection, control, creation, repair, defense, and improvements [212]. Nanotechnology is not new; evidence reveals that Egyptians, Greeks, and Romans used nanocrystal-contain hair colors [213].

Nanotechnology is a comprehensive science that involves manipulating atoms, electrons, protons, and neutrons in various ways to provide new insights into how materials might be developed to tackle numerous problems in numerous fields [31]. Nanotechnology has emerged as one of the most promising science-related technologies. Nanotechnology involves studying materials at the nanoscale and developing system architectures, devices, and materials with distinct properties and functions that arise from their nanoscale dimensions and characteristics [212]. Nanotechnology-produced metal nanoparticles (NPs) have gotten much attention because of their wide range of uses in the medicinal and agricultural industries [214]. The application of microorganisms and plants in synthesizing metal nanoparticles has gained substantial attention as a sustainable and efficient method of utilizing these organisms as practical nano producers [215].

Nanotechnology focuses on producing nanomaterials with a range of forms (from 1 to 100 nm) and their applications in numerous industries [214]. A DNA double helix has a diameter of roughly 2 nm, and the length of a C-C bond is approximately 0.12 nm [214]. Pharmaceutical interests were already shifting due to the potential usage of multiple biological sources for nanoparticle manufacturing and application. Silver is the most preferred metal for producing NPs because it has specific antibacterial, antifungal, anti-inflammatory, anti-angiogenic, and anti-permeability properties, among others [33].

Nano-medicine [216] applies nanotechnology in medicine, focusing on nano systems for treatments, diagnostics, and imaging [212]. Synthesizing nanoscale particles to sizes compatible with biological molecules such as proteins and nucleic acids can be utilized as potential probes, delivery platforms, carriers, and devices. This presents new opportunities for disease detection, therapy, and prevention [217]. Moreover, NPs can potentially improve the pharmacokinetic and pharmacodynamics profiles of well-studied treatments, making them appealing carriers for classical anti-cancer drugs [218]. Nano medicine has recently led to the creation of nanoparticle carriers for drug/gene delivery [219], imaging [220], and theranostics (diagnostics and therapies) [217].

6.1 Liposomes

Liposomes, specifically their phospholipid bilayer, are a potential solution for transporting medication across the BBB, but the BBB is not easily penetrable. Therefore, numerous surface modifications have been made to enhance the transport of liposomal carriers across the BBB [221]. The BBB surface contains proteins, peptides, antibodies, and other ligand receptors, which can aid in transcytosis. Ligands present in these compounds facilitate the movement of cationic liposomes through the BBB. To enhance their movement throughout the body, glucose and other nutrients are incorporated into the liposomes [222]. The passive diffusion mechanism is started by the brain's passive efflux when the liposomes reach the brain [222]. The substance releases at the same rate as before. New tactics have been developed that adapt to changes in the patient's physiological parameters and control the drug's release. pH changes, changes in enzyme activity, or changes in glutathione levels can all cause liposome drug release



[223]. Acetylcholine (ACh) is bound by amyloid peptides, causing the dissolution of amyloid plaque and reduction of inflammation in the brain. This supports the preservation of healthy neurons and serves as a treatment option for AD once it has developed. To facilitate active internalization, liposomes can be modified with ligands due to the negative charge of the BBB and the occurrence of electrostatic forces [224].

To improve the pharmacokinetic profile of liposomes, PEG11 or polysaccharides can be added to the particles' surface, extending their circulation time and improving their distribution into the brain by inhibiting rapid clearance via the reticuloendothelial system (RES). However, there is no guarantee that liposomes will cross the BBB, even with "stealth" liposomes that can significantly reduce circulation time. Several emerging strategies to enhance the stealth liposomes include incorporating peptides, antibodies, or small molecules that specifically bind to receptors or transporters overexpressed on brain endothelial cells. Among the various methods of delivering liposomes to the brain, receptor-mediated transcytosis is the most efficient and commonly used approach due to the precise interactions between receptors and ligands [225].

The transmembrane glycoprotein TfR13 is a frequently targeted receptor due to its high concentration in brain endothelial cells. However, the binding of endogenous Tf inhibits the binding of TfR-targeting ligands to the receptor. To overcome this, experiments involving Tf14functionalized liposomes have utilized antibodies that bind to unique sites on the TfR receptors to reduce ligand antagonism and enhance the effectiveness of the liposomes in crossing the BBB [226,227]. A different approach, mammalian iron-binding glycoprotein lactoferrin, has also functionalized liposomes. Lactoferrin interacts with Lf15 receptors and is widely dispersed throughout the BBB. Using receptor-mediated transcytosis, lactoferrin-modified liposomes were developed as modified nanocarriers for BBB crossing [228].

To determine whether combining the two BBBpiercing peptides may have a synergistic effect and whether curcumin interfered with the activity of the BBB-targeting ligands, the previous research was coupled with curcumin and two BBB-invading peptides [229].

The surface of multifunctional liposomes is modified by introducing two BBB-binding ligands and a curcumin derivative, which targets transferrin and LDL receptors. Researchers studied the inhibitory effects of these surface-modified liposomes on $A\beta$ in hCMEC/D3 cells. The ability of these liposomes to target the BBB and bind amyloid was investigated while examining the effects of one or more modifications [229,230]. To develop a nanomedicine for Alzheimer's disease, PEGylated immunoliposomes were created by combining two monoclonal antibodies (mAbs) targeted at the transferrin receptor and $A\beta$ peptide. The surface of the liposomes was bound with transferrin receptors antibody (OX26), an antitransferrin receptor mAb, and 19B8, which were conjugated to maleimide and streptavidin-biotin. When administered intravenously to male Wistar rats, these immunoliposomes were absorbed by porcine brain capillary endothelial cells and crossed the BBB effectively *in vivo*. The persistent BBB breach caused by the disease allowed 19B8 to cross the BBB, and it was found that using immunoliposomes with two ligand-targeting antibodies was an effective treatment for Alzheimer's disease [231].

6.2 Gold (Au) NPs

Gold nanoparticles (GNPs) have several advantages over other metal NPs, including chemical inertness, biocompatibility, and lack of cytotoxicity. Humans have been using gold internally for 50 years [232]. The nano size, surface area, and photothermic nature directly impact the antibacterial activity of GNPs [233]. Another accepted theory is that GNPs connect intracellularly to the Sulphur base found in cells as the thiol group in enzymes, causing an abrupt disruption of the respiratory chain by forming many free radicals in death. GNPs, on the other hand, lower Adenosine tri-phosphate (ATP) activities by reducing t-RNA and ribosome interaction [234]. GNPs also decrease bacterial growth by blocking transmembrane hydrogen efflux; yet, at lower concentrations, GNPs can reduce bacterial growth by 250-fold. Because GNPs are smaller than bacterial cells, they attach to pathogen cell walls and cause cell death by delaying cell processes [234].

GNPs apply to several industries, including electronics, energy, optical, and health care. GNPs are studied for multiple purposes, like ultra-sensitive biomarkers [235], targeted heat therapy, and drug delivery vectors [236]. Gold has a higher radio density compared to contrast agents already in use. GNPs have exhibited more potent contrast qualities than those now used as a contrast agent for CT scanning. GNPs can also be used as a drug delivery vector for various reasons. For example, the same GNPs can be linked to several functional groups, enabling customized drug delivery [234]. Nanoscale particles are particularly well suited to this purpose due to their high surface area to volume ratio; additionally, light absorption by the plasmon of GNPs can be exploited to induce the heat-sensitive release of medicinal chemicals. The plasmonics of GNPs also enables localized heat therapy through the absorption of specific wavelengths of light [237]. The absorbed energy is then diffused onto the surrounding region. Combining this method of cancer tumor attack with the production of heat-sensitive anti-carcinogens is wildly successful [238].

GNPs have been investigated to boost the efficiency of solar panels in energy technology, and their utility is also derived from their plasmonic characteristics. Specific wavelengths of light are required for solar panels to function. Nevertheless, as the plasmon of NPs can be altered through regulated synthesis, Developing NPs that can both absorb light at frequencies that the solar panel cannot use and release light at those frequencies is possible [238]. Other metallic NPs have been studied using similar methods. Another notable application of GNPs is wiring in nano-circuitry [238]. Since the formulation of Moore's law in 1965, there has been a lot of interest in making circuits smaller and smaller, eventually leading to courses on the nano-scale [239].

6.3 Antibody (Ab)-Decorated NPs

The administration of immunotherapy doses to target amyloid plaques for Alzheimer's disease treatment results in significant adverse outcomes, including meningoencephalitis [240]. Nanoparticles coated with antibodies that target specific proteins can detect and dissolve protein clumps in brain cells, potentially reducing the harmful side effects of immunotherapy for Alzheimer's disease. One technique to accomplish this is using metal oxide nanoparticles coated with antibodies that bind to AD-associated proteins, which can be detected using secondary ion mass spectrometry [241]. Polyethylene glycol (PEG) nanoparticles coated with specific antibodies can degrade A β -42. In Alzheimer's disease, A β fibrils cause neurotoxicity, but this can be significantly reduced by covering the surface of poly (lactic-co-glycolic acid) (PLGA) nanoparticles with monoclonal A β 83-14 [242].

6.4 Iron NPs

Iron oxide nanoparticles (NPs) are commonly used in biomedical research, and there is ongoing research to explore the possibility of creating new theranostic drugs for Alzheimer's disease using ultra-small superparamagnetic iron oxide nanoparticles and a phenothiazine-based nearinfrared (NIR) fluorescent dye. These particles have the potential to offer NIR fluorescence and magnetic resonance imaging of A β plaques in the brains of mouse models with Alzheimer's disease and also prevent the plaques from aggregating [242]. Protein-capped (PC) cadmium nanoparticles and PC-Fe₃O₄ coated with proteins may be a promising strategy for inhibiting tau aggregation in AD cells and developing anti-tau aggregation drugs. These iron oxide nanoparticles may also have applications in diagnosing and treating neurological diseases such as AD [243].

6.5 Quantum Dots

A β peptides consisting of 39–42 amino acids are mainly present in humans, with A β -1-40 and A β -1-42 being the most abundant. These peptides can form A β plaques due to their ability to form fibrils. The accumulation of A β peptides, including soluble oligomers and mature fibrils, is associated with the development of AD [244]. However, only a few authorized medications may be used to treat AD due to the related toxicity and emergence of resistance [245]. Peptides, organic compounds, and synthetic peptides have shown promising results in preclinical studies in AD

S. No	Nanoparticles	Combinations	Effects	References
1.	Liposomes	Curcumin + liposomes (Liposomes inner \rightarrow hydrophilic core (phosphatidylcholine) and outer \rightarrow lipophilic phospholipid bilayer)	curcum in-loaded liposomes $\rightarrow {\rm A}\beta$ inhibition	[221,229]
2.	GNPs		${\rm A}\beta$ fibrils are dissociated and ${\rm A}\beta$ aggregation is hindered	[248]
3.	Antibody Decorated NPs	W20/XD4-SPIONs are composed of a super- paramagnetic iron oxide nanoparticle, a class $A\beta$ scavenger receptor activator, and an $A\beta$ oligomer-specific scFv antibody	W20/XD4-SPIONs preserved the anti-A β capabilities of W20 and XD4 in addition to their diagnostic utility by suppressing A β aggregation, reducing AO-induced cytotoxicity, and boosting microglial phagocytosis of A β	[249]
4.	Iron Oxide Nanoparticles (IONPs)	Anti- A β antibodies + IONPs	used for imaging-based detection of amyloido- genic plaque or fibril depositions on the sur- face of cells	[250]
5.	Quantum Dots	Tramiprosate (aminosulfonate compound) linked covalently with GQDs	shown synergistic inhibition of $A\beta$ aggregation in AD	[251,252]

Table 4. Some nanomedicines for AD.

*NPs, Nanoparticles; GNPs, gold nanoparticles; GQDs, graphene quantum dots.

by either preventing the formation of aggregates or removing them. However, their effectiveness is limited due to poor *in vivo* stability, limited BBB penetration, and inferior efficacy, making them inefficient in treating AD [246]. The effectiveness of modern AD therapies is attributed to the use of quantum dots (QDs), which potently inhibit the formation of A β plaques and protect cells against the harmful effects of A β oligomers. This is due to their small size (2– 10 nm) and low cytotoxicity. Additionally, A β -1-42 peptides and carbon materials can interact hydrophobically to prevent A β plaque formation, reducing negative surface potential and enhancing the inhibitory properties of QDs [247] (Table 4, Ref. [221,229,248–252]).

Tramiprosate covalently coupled with graphene quantum dots (QDs) decreased A β accumulation in AD synergistically [253]. The coupling of glycine-proline-glutamate (Gly-Pro-Glu, GPE) and GQDs resulted in the creation of glycine-proline-glutamate (GQDG) nanomaterial, which showed a reduction in A β -1-42 fibril aggregation when administered intravenously in APP/PS1 transgenic mice (Fig. 4, Ref. [50]). The small size and large surface area of GQDG allowed it to pass through the Madin-Darby Canine Kidney (MDCK) cell monolayer and selectively interact with the hydrophobic group of A β 1-42 protein, leading to increased inhibition and improved memory and learning in mice treated for AD [254].

The distinct characteristics of QDs make them an attractive alternative to traditional imaging techniques and dyes. QDs can detect $A\beta$ aggregation states *in vivo*, enabling early identification of AD. To achieve this, fluorescent QD probes and an anti-A β antibody are injected into transgenic mice carrying human APP695swe and APP717 mutations via the intracerebroventricular route [255].

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6.6 Gene Therapy Using Nanoparticles

In gene therapy, which was initially proposed in the 1960s, the barrier of gene delivery is overcome due to NPs. These challenges include cell-specific targeting, protecting genetic cargo from deterioration, preventing reticuloendothelial system (RES) clearance, and lysosomal and endosomal escape [256].

Inorganic NPs can be engineered to enhance gene delivery effectiveness. An ideal gene delivery method should possess the following characteristics: the capability to enter the cell's plasma membrane, disrupt the endosomal membrane, bind and condense genetic material, safeguard the nucleic acid cargo, ensure specific delivery to the intended target, remain stable in the bloodstream and evade immune system detection [256,257]

Extensive research into the underlying disease mechanisms of neurodegenerative disorders has identified specific genetic abnormalities that play a crucial role in disease onset. Gene therapy offers a means to deliver various types of genetic material, including messenger RNA (mRNA), small interfering RNA (siRNA), guide RNA (gRNA), and microRNA (miRNA). Scientific investigations have shown that RNA interference (RNAi), a technique that reduces the production of specific mRNA molecules using siRNA and miRNA, is highly effective for silencing genes involved in disease progression [258].

Synthetic double-stranded siRNAs, approximately 21–25 nucleotides long, are highly precise for targeting specific mRNA sequences and silencing genes within human cells [259]. The advent of RNAi has revolutionized the field of therapeutics, providing a new pathway for treating a wide range of diseases, including cancer and neurological disorders [260]. However, to practically implement siRNAmediated gene silencing in medicine, it is crucial to have an

Table 5. Since 2017, Researchers studying neurological disorders have used nanotechnology.

NPs	Disease	Therapeutic	Therapeutic effect	Cell entry	References
Gold	PD	Nerve growth factor (NGF) and ex- ogenous interfering RNA (RNAi) were integrated into the pDNA	substantia nigra striatum dopamin- ergic neuronal death and PC12 cell inhibition	Endocytosis of nerve growth factor (NGF)	[268]
Gold	AD	L- and D-glutathione at 3.3 nm	preventing A β -42 aggregation	Crossing of the BBB via chiral nanoparticle endocytosis	[267]
Silver	PD	Citrate cap	Increased production of $\mathrm{H}_2 S$ and $\mathrm{Ag}_2 S$ reduces neurotoxicity	Silver's organic characteristics en- ter the brain	[269]
Silver	AD	Plant extract- from Lampranthus coccineus - and Malephora lutea - F. Aizoaceae	As a plant-based anti-Alzheimer medication, anticholinesterase and antioxidant action	Silver's organic characteristics en- ter the brain	[270]
Selenium	AD	Curcumin-loaded nanospheres	Amyloid- plaques in AD lesions are less prevalent	Curcumin forms intermolecular hy- drogen bonds with $A\beta$ and iron in plaques without additional chemi- cal linkers	[271]

pRNA, packaging RNA; BBB, blood-brain barrier.

efficient and safe delivery method, preferably a nanocarrier, to transport the siRNA to the desired site effectively. Recent advancements in gene therapy, such as genome editing, hold significant promise in specifically targeting abnormal genetic modifications in diseased areas [261].

The accumulation of misfolded proteins, such as amyloid-beta oligomers and alpha-synuclein, is a key factor in various diseases. These proteins lead to endoplasmic reticulum (ER) stress and trigger ER-associated degradation, making them potential targets for gene therapy [262]. When these proteins aggregate within the ER lumen, they disrupt ER calcium homeostasis and disturb the unfolded protein response (UPR) signaling. As a result, neurons undergo apoptotic cell death through pro-apoptotic reactions [263,264]. In the context of diseases like Parkinson's disease (PD), it has been possible to improve protein folding and preserve dopaminergic neurons' survival and motor function through gene therapy. Specifically, gene therapy has been employed to suppress the overexpression of the BiP gene, also known as glucose-regulated protein 78, which is associated with a reduction in the unfolded protein response. In such cases, gene silencing techniques can effectively address the pathology [265].

In AD, PD, and Huntington's disease (HD), aberrant signaling of the rapamycin (mTOR) pathway has been noted in addition to the deregulation of epigenetics, autophagy, and dysfunctional microglia and astrocytes. As the situation worsens, specific types of dysfunction are displayed by each disease mechanism. Therefore, to provide the best care, it is essential to pinpoint the precise mechanism underlying how a patient present with these disorders. Gene therapy is a viable strategy for treating neurodegenerative diseases because it has effectively treated various problems. This is especially noteworthy given the findings on genetic anomalies in PD and AD patients [266]. Between 2017 and 2020, numerous nanoparticles were used in central nervous system (CNS) gene therapy, as shown in Table 5 (Ref. [267–271]). Our knowledge of targeting particular genes that are defective or aggregated proteins linked to neurodegenerative illnesses has greatly benefited from these investigations. Approaches for safe and efficient delivery using nanoparticle-based gene therapy are particularly promising in overcoming biological barriers like the BBB. The natural synthesis of NPs offers several advantages besides gene therapy, mainly when using certain extracts that can work together with therapeutic genes [267].

6.7 Challenges

Applications for diagnosing and treating AD using nanotechnology are promising. Targeting particular ADrelated biomarkers with functionalized nanoparticles enables non-invasive imaging approaches for early detection and diagnosis [272]. By encapsulating therapeutic chemicals and boosting their stability, bioavailability, and targeted distribution to the brain, nanoparticles can help improve drug delivery and targeted therapy [273,274]. Additionally, functionalized nanoparticles can support neuroprotection and regeneration by providing neurotrophic factors and reducing neuroinflammation and oxidative stress [275].

However, there are challenges to overcome in translating nanotechnology into AD.

Biocompatibility and safety: To assure the long-term safety of nanomaterials, thorough studies are needed to evaluate their possible toxicity and clearance pathways [276].

Blood Brain Barrier: Effective distribution of nanoparticles across the BBB is still difficult. To increase BBB penetration, strategies like surface alterations, functionalization with targeted ligands, and focused ultrasonic techniques are being investigated [277].

Scalability and manufacture: For clinical translation, scalable and repeatable synthesis and manufacturing processes for nanoparticles are required [278].

7. Phyto-Pharmaceuticals.

Various foods, such as fruits, whole grains, nuts, and vegetables, contain phytochemicals. These phytochemicals offer tremendous therapeutic promise for treating a variety of ailments, either individually or in combination [34]. Phytochemicals with nutraceutical properties contained in food are crucial due to their favorable effects on human health. Cancers, coronary heart disease, diabetes, high blood pressure, inflammation, microbial, viral, and parasitic infections, depression, anxiety, erratic circumstances, ulcers, osteoporosis, related disorders, and other diseases are all protected by them [279].

7.1 Curcumin

Curcumin, found in the rhizome of turmeric (Curcuma longa), is used in Indian cuisine to add flavor and preserve food [280] (Fig. 6). An intriguing observation is that the incidence of AD among individuals aged 70-79 in India is four times lower than that in the United States, implying that a diet high in curcumin among older Indians could be accountable for the reduced risk of AD [281]. The anti-amyloidogenic, anti-inflammatory, and anti-oxidative properties of curcumin have been backed by robust in vitro and in vivo studies, which suggest that it can potentially prevent Alzheimer's disease [35]. Curcumin and its derivative rosmarinic acid exhibit anti-amyloidogenic properties *in vitro*, inhibiting the formation of neurotoxic $A\beta$ fibrils and preventing their elongation from fresh A β . Additionally, they can break down preformed $A\beta$ fibrils and regenerate A β monomers [36]. Curcumin has been identified as a potential therapeutic agent for treating and preventing AD because of its ability to target $A\beta$ fibrilization primarily. The inhibition of $A\beta$ fibril formation has been proposed as a practical therapeutic approach for AD treatment. The unique structure of curcumin, composed of two 3,4-methoxyhydroxyphenyl rings connected by a short carbohydrate chain, enables it to bind specifically to free $A\beta$, preventing the formation of $A\beta$ fibrils. However, the exact mechanism underlying curcumin's anti-amyloidogenic effect is unclear. Additionally, curcumin may bind specifically to $A\beta$ fibrils, disrupting their β -sheet-rich structure [36].

Curcumin, a substance that can target amyloid pathology, has drawn much attention for its potential as a treatment for AD. Its use in diagnostics using imaging techniques is one area of focus. When human neuroblastoma SK-N-SH cells were subjected to H_2O_2 , using biodegradable PLGA-curcumin nanoformulations demonstrated both safety and protective effects against oxidative damage. This





Fig. 6. Structure of curcumin.

formulation protects neurons against oxidative stress, a typical occurrence in AD, by inhibiting the activation of the redox-sensitive transcription factor nuclear factor erythroid 2–related factor (Nrf2) in the presence of H₂O₂ [282]. It has been shown that curcumin formulations with different modifications can prevent amyloid-beta (A β) from aggregating and protect against its harmful effects. These formulations include nanoliposomes, lipid-conjugate liposomes, biodegradable poly (alkyl cyanoacrylate), biotin-coupled poly (ethylene glycol) (PEGylated), PEG liposomes with anti-transferrin, and click chemistry. These alterations have demonstrated the potential of curcumin-based formulations to stop the aggregation of A β and protect cells from its damaging effects [283,284].

Athymic mice fed with the NanoCurcumin formulation showed decreased levels of H2O2 and increased levels of glutathione in their brains. Furthermore, the activity of the cell death-related enzymes caspase 3 and 7 dropped. These results demonstrate the promise of this therapy for AD, indicating a favorable cellular environment with enhanced redox balance. Another unique method uses curcumin-loaded polymer nanoparticles coupled to APOE3 and constructed of PBCA (poly butyl cyanoacrylate). This method has proven effective in reducing the cytotoxicity caused by A β in AD [285,286]. Curcuminfunctionalized gold nanoparticles have shown successful interactions with amyloid protein/peptide. These nanoparticles can prevent the development of amyloid fibrils and even break up already-formed fibrils. They help to stop the aggregation of amyloid proteins and encourage their disaggregation by acting as synthetic molecular chaperones [287].

In male Lacca mice, an oral curcumin lipid nanoformulation has demonstrated encouraging results in correcting the adverse effects of aluminum (AlCl₃) exposure. The effectiveness of this therapy was shown by the 97% restoration of membrane lipids and a 73% recovery of acetylcholinesterase function. Additionally, PLGA-based curcumin nanoformulations have shown promise in reversing the neurotoxicity brought on by acrolein. The restoration of -glutamylcysteine synthetase levels and a decline in reactive oxygen species (ROS) and reactive nitrogen species were credited with this reversal. The drop in glutathione levels, known for their neuroprotective role, was unaffected by this treatment, which is crucial to highlight [288].



Fig. 7. Structure of GX-50 molecule.

7.2 GX-50

The compound N-[2-(3,4-methoxyphenyl)ethyl]-N-[2-(3,4-methoxyphenyl)ethyl]-3-phenylacrylamide, also known as GX-50, has been found in Sichuan pepper (Zanthoxylum bungeanum) and has been recognized as a potential therapeutic agent for AD [289]. Furthermore, in vitro studies showed that GX-50 can disintegrate $A\beta$ oligomers, prevent A β -induced neuronal apoptosis and apoptotic gene expression, and minimize neuronal calcium toxicity [290,291]. Furthermore, GX-50 can inhibit microglial migration toward $A\beta$ aggregates by activating the TGF-1-Smad2 signaling pathway and decreasing CCL5 chemokine production [292]. However, GX-50 is linked to neuroinflammation, and its anti-inflammatory properties have not been fully explored. Toll-like receptor 4 (TLR4) expression is increased in activated microglia and the brains of AD patients, resulting in the activation of the NF- κ B and MAPK pathways and the production of proinflammatory cytokines.

The possibility of treatment approaches that target this receptor for treating the condition is highlighted by the function of TLR4 in the onset of AD. Numerous studies have shown that blocking TLR4 can halt the course of AD. The clearance of $A\beta$ and the induction of neurotoxic cytokines during neuroinflammation are two distinct functions of TLR4 signaling in AD. As a result, individuals with AD may experience both good and bad outcomes from TLR4 activation. TLR4 activation can be harmful because it is frequently used in trials to produce a state that resembles AD and is characterized by neuroinflammation and memory deficits [293,294]. TLR4 inhibition and the subsequent decrease in pro-inflammatory cytokines may be the underlying molecular mechanisms for these effects. It has been demonstrated in studies employing the APP/PS1 animal model, which has cerebral amyloid deposition, that lowering TLR4 levels enhances cognitive function. The injection of TAK-242, a particular inhibitor of TLR4, improved cognitive performance, reduced A β formation, and prevented neuronal death in these animal models. Similar to what was seen with TLR4 inhibition, baicalin has also shown neuroprotective effects in this mouse when acting through the TLR4/NF- κ B signaling pathway [295,296]. A Sichuan pepper extract known as GX-50 as shown in (Fig. 7) has anti-inflammatory properties, particularly in the brain regions afflicted by AD. TLR4 is suppressed as part of its mechanism of action, which then lessens the recruitment of MyD88 and TRAF6. As a result, the critical signaling pathways involved in inflammation—NF- κ B nuclear translocation and MAPK phosphorylation are suppressed. In the setting of AD, GX-50 demonstrates its antiinflammatory capabilities via modulating various molecular pathways [297,298].

The possibility of GX-50 inhibiting A β -42, a protein linked to AD, is being studied. When GX-50 and gold nanoparticles (AuNPs) are used together, A β -42 is dramatically inhibited compared to GX-50 alone. The potential use of the GX-50-AuNPs complex in treating AD has been further verified by molecular docking studies, systems biology, and time course simulation [299].



Fig. 8. Structure of resveratrol.

7.3 Resveratrol

Resveratrol, a polyphenolic phytoalexin found in berries, grapes, and red wine, has been associated with several biological and pharmacological effects [280]. Numerous epidemiological studies have reported an inverse association between wine consumption and the development of AD, indicating that resveratrol may contribute to wine's beneficial effects in treating Alzheimer's patients. Resveratrol as shown in (Fig. 8), like curcumin, can readily penetrate the intact BBB and enter the brain tissue [300]. Recent research has demonstrated that resveratrol possesses considerable neuroprotective properties in vivo and in vitro experiments. It has been found to hinder neuronal cell death and reduce brain damage caused by ischemia/hypoxia, trauma, and excitotoxicity [301,302]. In various cell lines expressing the Swedish mutant APP695, resveratrol has been demonstrated to have anti-amyloidogenic properties by decreasing the secretion or intracellular accumulation of A β peptides; however, it does not affect the enzymes in-



volved in A β production, such as β - or γ -secretase. The reduction of A β levels by resveratrol was inhibited by selective proteasome inhibitors and siRNA-mediated knock-down of the proteasome subunit β 5, suggesting that resveratrol modulates proteasome activity to lower A β levels [303].

Resveratrol-Selenium Nanoparticles (RSV-SeNPs) demonstrated a potent anti-inflammatory and antioxidant impact against neurotoxicity. Additionally, because RSV-SeNPs have an anti-amyloidogenic capability, they improve the clearance of misfolded proteins. RSV-SeNPs affect several signaling pathways implicated in AD development, alleviate cholinergic deficiencies, and enhance neuropathology and neurocognitive functions. RSV-SeNPs may be utilized to treat AD in general. However, more research is needed to pinpoint the precise underlying pathways [304].

8. Current Medicines Used

8.1 Acetylcholinesterase Inhibitors

Acetylcholine (ACh) is well known for playing a critical part in memory and learning processes. A negative feedback loop that controls $A\beta$ production has been suggested due to the interplay between the cholinergic and $A\beta$ systems [305]. This feedback loop is broken by abnormal $A\beta$ buildup, affecting cholinergic transmission, especially through alpha-7 nicotinic acetylcholine receptors [306].

Based on this knowledge, cholinesterase inhibitors are efficient AD treatments, supporting Davies and Maloney's (1976) original concept on the role of cholinergic deficiencies in AD pathology. Tacrine, Donepezil, Rivastigmine, Galantamine, Xanthostigmine, Para-aminobenzoic acid, Coumarin, Flavonoid, and Pyrroloisoxazole analogs are only a few of the drugs that have been created and explored for the treatment of AD [307,308]. Drugs like Rivastigmine, Donepezil, and Galantamine that have received Food and Drug Administration (FDA) approval improve cholinergic function by preventing the activity of acetylcholinesterase, which breaks down acetylcholine. The brain's ACh levels rise as a result of these drugs. Acetylcholinesterase inhibitors are often well tolerated except for tacrine; side effects are typically dose-dependent. A monoamine oxidase A and B inhibitor called Ladostigil (TV3326), currently in phase II clinical studies, also exhibit antidepressant benefits [309,310].

8.2 N-Methyl-D-Aspartate Receptor (NMDA) Antagonist

It is generally known that glutamate-induced excitotoxicity causes cells to become overloaded with calcium, experience a mitochondrial malfunction, produce more nitric oxide, and make a lot of oxidants, all of which contribute to neuronal apoptosis. However, NMDA receptor antagonists like memantine can lessen the harmful effects of glutamate. Memantine, which the FDA licensed in 2003 for use in patients with moderate-to-severe AD, has demonstrated some modest cognitive advantages in mild-to-moderate AD [311,312].

Memantine protects neurons by inhibiting the activity of glycogen synthase kinase-3 (GSK-3), which lowers tau phosphorylation. Memantine is an acetylcholinesterase inhibitor that functions as a noncompetitive antagonist of the glutamatergic NMDA receptor. It can be used alone or in conjunction with other medications. It's important to remember, though, that as compared to monotherapy, combination therapy may not result in as many positive changes [307,313].

8.3 Secretase Inhibitors

The APP cleavage by α -secretase or β -secretase enzymes is followed by processing by γ -secretase. The creation of inhibitors that target this amyloidogenic pathway was prompted by the theory that aging causes "overactivation" of secretases or reduced α -secretase processing [314].

The α -secretase activity of specific metalloproteinases, such as ADAM10 and matrix metalloproteinase 9 (MMP-9), has been investigated. Melatonin, gemfibrozil (a PPAR α -agonist), and serotonin 5-HT4 receptor agonists have all been suggested as ways to stimulate ADAM10 and inhibit the production of A β [315]. Additionally, it has been demonstrated that overexpressing MMP-9 prevents cognitive abnormalities in transgenic mice models of AD [316].

Inhibitors have been developed to target the transmembrane protease BACE1, although early attempts based on molecular docking techniques to target the enzyme's inaccessible catalytic core failed. Compared to other ADAM proteases, BACE1 inhibition has fewer adverse consequences [317,318].

A multisubunit protease complex called γ -secretase is involved in the proteolysis of several signaling proteins. γ -secretase inhibitors have been examined; however, due to suppressing other signaling pathways, particularly the Notch system, they frequently cause serious side effects, such as gastrointestinal problems and an increased risk of skin cancer. Although notch-sparing inhibitors have been developed, the findings of their clinical trials have not been very encouraging. It has been noted that γ -secretase complex modulators have more promising outcomes than inhibitors [308].

To stop the production of $A\beta$ peptides, both β secretase and γ -secretase must be active. Dietary modifications and antioxidants that activate the ADAM proteases may compensate for the reduction in γ -secretase activity that comes with aging. PSEN-1 and PSEN-2 genetic deficiencies in -secretase are recognized risk factors for familial AD. As a result, early trials of γ -secretase inhibitors were unsuccessful; now, modulators that target this complex show more potential [319].

The effects of γ -secretase inhibitors on other cleaved receptors, like the Notch receptor, are linked to their toxicity. Contrarily, γ -secretase modulators only affect the A cleaving site, not the complex's other sites [320]. Furthermore, the regulation of A β synthesis may be influenced by cholesterol and its derivatives, such as cholesterol acid, which function as γ -secretase modulators. These endogenous metabolites' dysregulation may contribute to AD linked to metabolic syndrome, dyslipidemia, and obesity [321].

8.4 Anti-A β Aggregation Compounds

Significant research efforts have been made in recent years to create cures that aim to stop the development and aggregation of the $A\beta$ peptide. Small molecule inhibitors have been studied in clinical trials to prevent $A\beta$ aggregation, including tramiprosate (in phase III), clioquinol (in phase II), scylloinositol (in phase II), and epigallocatechin-3-gallate (in phase II/III). These medications have considerable adverse effects, even though they can stabilize $A\beta$ monomers [322].

Another strategy uses artificial peptides called "sheet breakers" generated from the iA5p sequence. Zetidine-2carboxylic acid, 3-phenyl azetidine-2-carboxylic acid, proline, and sulfonyl proline are a few peptides that have demonstrated promise in reducing the cellular harm brought on by A β exposure. They accomplish this by inhibiting the development of fibrils and successfully improving spatial memory [323,324].

Additionally, stemazole has demonstrated defense mechanisms against $A\beta$ -induced toxicity in SH-SY5Y cells *in vitro*, lowering $A\beta$ -aggregation. The efficacy of substances like curcumin, T718MA, and SK-PC-B70M to protect neurons against $A\beta$ -induced toxicity has also been proven. These results imply that these substances may be able to reduce the harmful effects of $A\beta$ on neuronal cells [323].

8.5 Tau Therapies

Neurofibrillary tangles, which are collections of hyperphosphorylated tau protein in the form of paired, helicaltwisted filaments, are one of the therapeutic targets in treating them. Axon's Alzheimer's Disease vaccine (AADvac1) was the first vaccination evaluated in clinical immunotherapy trials; currently, trials for ACI-35, another vaccine based on liposomes, are being conducted [308].

It has been investigated to prevent tau proteins from becoming phosphorylated, which is a factor in the aberrant aggregation of these proteins. However, testing of tideglusib, an irreversible inhibitor of the protein kinase GSK-3 (which is implicated in tau phosphorylation), failed to produce any statistically significant advantages. Cyclindependent kinase 5 (CDK5), which is similarly involved in tau hyperphosphorylation, is a potential therapeutic target [309].

Several compounds are being tested in clinical studies for their potential to prevent tau aggregation. One such example is the ability of methylene blue (MB) and its metabolites azure A and azure B to enhance protein degradation and inhibit the activities of caspase-1 and caspase-3 [325]. Additionally, in mouse models genetically modified to express tau mutations associated with AD, leucomethylthioninium with a suitable counterion (LMTX, in phase III clinical trials) and methylthioninium chloride, or MTC (in phase II clinical trials) have demonstrated the capacity to decrease tau aggregation and reverse behavioral deficits [326]. Additionally, they can reduce the course of the disease in AD patients. LMTX and MTC have been shown to have neuroprotective effects *in vivo*, although the precise mechanisms by which they do so are still not well known. N-phenylamines, anthraquinones, phenyl thiazolyl-hydrazides, rhodanines, benzothiazoles, and phenothiazines are further interesting tau aggregation inhibitors [327,328].

9. Future Direction

Delivery of therapeutic medicines into the brain is a significant barrier to treating neurodegenerative disorders because of the BBB obstructive nature [329,330]. Different methods have been formulated to release medication into the brain effectively. Chemical drug and prodrug modification, temporary disruption of BBB, local distribution into the brain by nanoparticle-mediated transport. However, osmotic pressure causes the BBB to open when tight junctions are temporarily disrupted. In general, using NPs for drug delivery has numerous benefits, including being non-invasive, inexpensive, having strong biodegradability and long-term stability, being simple to make, having high targeting effectiveness, and having high controllability to load and release conjugated pharmaceuticals across the BBB. Conjugating these phytochemicals may have promising therapeutic effects against diseases such as AD. Evidence suggests nanoparticle assisted medication transport across the BBB is a relatively effective technique [331].

Numerous *in vivo* studies have investigated how nanoparticle size affects the biodistribution of those particles in mice. Because differing GNP sizes impact how well they are cleared from the blood, insulin-targeted gold nanoparticles (INS-GNPs), which can target BBB insulin receptors, are a successful *in vivo* technique for imaging and therapeutic purposes. Eliminating nanoparticles by renal excretion is preferred since it involves less catabolism, largely excretes the particles in their original state, and minimizes the risk of adverse effects.

10. Conclusion

AD is one of the leading causes of dementia in many individuals worldwide. The pathophysiology of AD is explained by many ideas. Although precise causes of the disease have not yet been discovered. Patients with AD's most severe form won't be able to carry out even the most basic physical duties, and they'll be forced to rely on others for practically all of their daily activities. They could even struggle with simple tasks like swallowing when the illness is severe. As a result, caring for an AD sufferer is quite expensive. Usually, 20 years after the A plaques started to aggregate, patients with AD started to show apparent cognitive problems. As a result, most people suspected of having AD have suffered significant neuronal damage. This makes a mechanism for AD early detection extremely important. The detection techniques should also be capable of picking up on changes in the course of the disease. Thorough testing while the medicine is administered would allow researchers to expedite the discovery of drugs for AD. There is currently no treatment for AD. Even though there is a wealth of knowledge about this complex condition, there are few alternatives for managing it. Unfortunately, the therapy options currently available (AChEIs and memantine) only address the symptoms of the disease rather than its root cause. So, there is now more optimism for cutting-edge treatments that tackle the underlying causes of the disease and have the potential to halt the steady buildup of $A\beta$. While targeting $A\beta$ synthesis by inhibiting β -secretase is a potential strategy, only a few compounds have been studied and put through clinical trials.

We suggested GX-50 and curcumin conjugated with GNPs would be a potential candidate medication for AD treatment. It investigated the impact of GX-50 on A β neurotoxic effects. Therefore, we believe that GX-50 may prevent A β oligomerization and eventually encourage primary preventive medicine before the clinical phenotype of AD. Curcumin will destabilize the plaques and is suitable for inflammation which is caused due to aggregation of A β -plaques. It is also possible to target γ -secretase, another enzyme involved in forming $A\beta$ oligomers. Still, the danger of toxicity associated with inhibition prevents using such drugs to treat AD patients. By the five hypothesized pathways, nanomedicines outperform traditional anti-AD medications as a possible weapon against AD. Some apolipoprotein-based nanomedicines could preferably bind to $A\beta$ and increase the elimination of $A\beta$; nanomedicineinduced autophagy could be aided to increase the elimination of $A\beta$; nanomedicine-induced inhibition of tau aggregate may inhibit high-titer anti-A β antibodies, and many other undesirable pharmaceutical characteristics of conventional anti-AD drugs may be significantly overcome by nanomedicine. We suggested GX-50 as a potential candidate medication for the treatment of AD. It investigated the impact of GX-50 on A β neurotoxic and cellular and molecular neuroprotective effects of GX-50. Therefore, GX-50 prevents A β oligomerization and eventually encourages primary preventive treatment before the clinical phenotype of AD.

Availability of Data and Materials

The data is available inside the manuscript. There is no other data. generated nor used.

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Author Contributions

KM, MTK, MSL, DW Conceived and designed the study. MM, DW collected data. DW, KM, ZL, MM completed the data analysis and interpretation. MM, MTK drafted the article. KM, DW, MSL modified content. DW, ZL completed editing and data validation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10. 31083/j.fbl2810258.

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