Review

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Exploring the Pathogenesis of Alzheimer's Disease and Revolutionary Treatment Strategy Based on Nanotechnology

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Alzheimer's disease (AD), a catastrophic disorder that commonly affects the elderly, causes extracellular plaques to form in the hippocampus, leading to slow, progressive loss of brain function. The Blood Brain Barrier poses a significant challenge for conventional drug delivery in AD therapeutics. Therefore, introducing novel strategies such as nanotechnology-based drug delivery offers promising potential. This paper highlights the significance of nanotechnology based drug delivery in AD with respect to its pathophysiology and discusses the current situation and future prospects of the same in diagnosis and therapy. Data collection involved scientific databases such as PubMed, Science Direct, and Google Scholar. The keywords searched were AD, neurodegenerative, nanotechnology, Amyloid-beta protein, tau protein and patents. A total of 146 papers were obtained. The pathophysiology of AD with respect to the Amyloid- and tau hypotheses were found to have significant therapeutic potential. It was also found that nanotechnology systems were able to offer enhanced site-specific action, offering a low toxicity profile in areas where conventional drug delivery systems had difficulty to act on. Delivery systems that were found to have potential were nanoparticles (NPs) including inorganic NPs and magnetic NPs, Quantum Dots, liposomes, dendrimers, Micelles, etc. Thus, our work suggests that NP-based drug delivery systems are able to overcome the challenges faced by conventional systems to achieve therapeutic efficacy with substantial levels of evidence, initiating the much-needed discussions on their potential use in AD therapeutics.

Keywords: Alzheimer's disease; neurodegenerative; nanotechnology; Amyloid-beta protein; patents

Introduction

Alzheimer's disease (AD) is a slowly progressing neurodegenerative disorder characterized by the presence of Amyloid-beta plaques and neurofibrillary tangles and it is a common type of dementia. Patients suffering from AD are not only affected by the adverse effects of the disease, but also facing financial burden and decrease in their Quality of Life (QoL) [1]. Statistics from World Health Organization (WHO) have shown that 55 million people around the world suffer from dementia, in which 60% of them are from low and middle-income countries [2]. Gender analyses also reveal that women are more affected by related disabilities and mortality. Moreover, 10 million cases arise yearly with AD, a predominant contributor to dementia cases worldwide [3].

The pathophysiology of AD with respect to the brain anatomy involves the presence of plaques and Neuro Fibrillary Tangles (NFT), as aforementioned. The former results from the Amyloid-beta hypothesis that encompasses protein accumulation due to derangement in its synthetic and metabolic pathway, while the latter focuses on the tau hypothesis [4]. The development of intraparenchymal haemorrhage is yet another anatomical manifestation due to the Amyloid-beta hypothesis deposition in the capillaries, causing leakage and occlusion of the blood flow [5].

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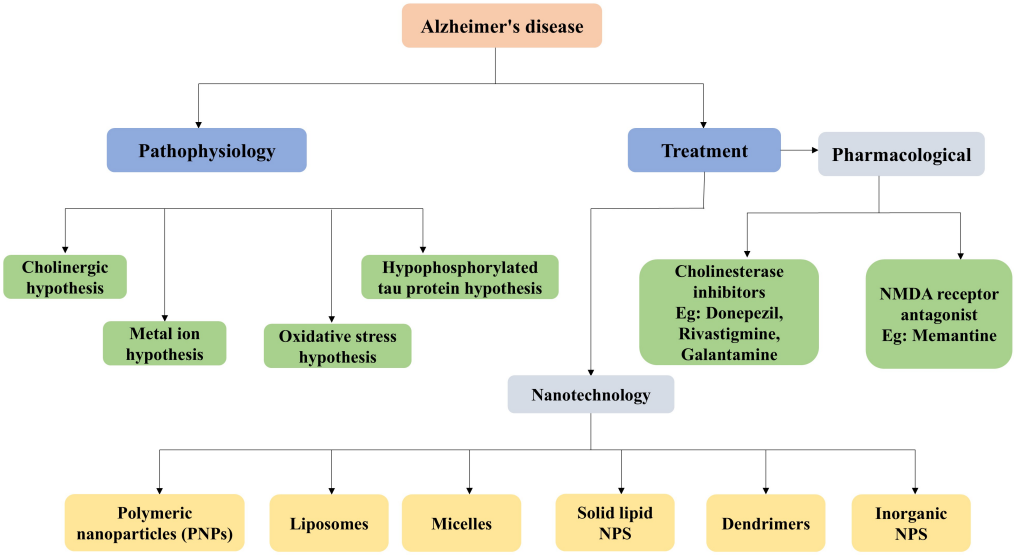

Graphical Abstract.

When it comes to the diagnosis of AD, standardized organizations have classified the disease as probable, characterized by progressive memory loss, aphasia and decline in daily activities, which can be assessed by neuropsychological tests, requiring histopathologic assessment through biopsy [6]. However, the National Institute on Aging-Alzheimer's Association have revised the criteria by adding clinical biomarkers, opening doors for new diagnostic methods. They have included Amyloid-based markers that can be identified through Positron Emission Tomography and cerebrospinal fluid (CSF) analysis and neuronal degeneration markers such as tau proteins, Fluorodeoxy Glucose (FDG) monitoring and magnetic resonance imaging (MRI) [7].

Conventional therapy aims to slow down the severity and progression of the disease. The pharmacological agents used include cholinesterase inhibitors such as galantamine, donepezil and rivastigmine, which work on the cholinergic hypothesis by increasing the levels of Acetylcholine in the brain [8]. Meanwhile, memantine focuses on glutamate regulation and it is combined with cholinesterase inhibitors [9]. When behavioural symptoms are involved, antipsychotic medications would find their utilization but they have no direct linkage with the disease pathology. However, FDA-approved monoclonal antibodies like Lecanemab and Donanemab were expected to hit the market in 2023 [10].

Even though these therapies have been used for a long time, they offer numerous disadvantages in mitigating the disease. The first one is the limited effectiveness of the drug, as they focus only on symptomatic management than targeting the molecular pathophysiology [11]. Since they require longer usage, precipitation of adverse effects is a common instance affecting patient's QoL [12]. With behavioural anomalies and weakness with the progression, patients have exhibited reduced compliance towards complex therapy [13]. Furthermore, the usage of antipsychotics has raised certain ethical concerns [14]. Even though the monoclonal antibodies would counter these limitations to an extent, the complex infrastructure, difficulty in ensuring compliance, screening difficulties for drug administration and precipitation of side effects remain as major concerns. This calls for an introduction of novel nanoparticle-based therapeutic strategies with substantial safety and efficacy profiles [15].

Moreover, it has been observed that conventional therapy overlooks mostly the concept of tau pathology, rendering it unexplored while concentrating on the Amyloid-beta hypothesis and cholinergic hypothesis. Due to the current resources, AD research has made sufficient advancements in tau pathology. The latest advances in Alzheimer's disease research encompass the identification of a tau-centric indicator that monitors the development of tau aggregates, a primary pathological feature indicative of dementia and Alzheimer's disease. This discovery provides biomarkers to specifically track the progression of tau tangles, which is a significant step towards early prediction and intervention of AD [16]. Another study has stated that earlier onset of AD is associated with tau pathology in brain hub regions and facilitated tau spreading. The application of innovative tau tracers to analyse and quantify tau pathology holds relevant significance in designing therapeutic modalities with respect to the same [17]. The study also has proposed Braak stages of tau pathology to illustrate how Alzheimer's disease-related tau begins in the transentorhinal cortex and eventually extends to other areas of the brain. Furthermore, contemporary research has identified that tau pathology prompts epigenetic reconfiguration of neuron-glial communication in Alzheimer's disease, facilitating the

advancement of neurodegeneration. These new revelations are indeed necessary for proper mitigation of AD [18].

The application of novel nanoparticles (NPs) in AD is an evolving yet promising concept. The significance lies in the intrinsic properties of NPs that can be moulded and integrated into AD therapeutics. This concept would include targeted drug delivery to target specific sites where plaque deposition is present, retaining the stability of the drugs inside the neural complex, smoother penetration into Blood Brain Barrier (BBB) by imparting necessary lipophilicity. It would also reduce toxicity profile with the additional advantage of reducing the toxicity of certain drugs and imaging abilities, which can help in brain imaging and subsequent therapeutic monitoring. Such an array of functions can create a significant beneficial therapeutic application, countering the disadvantages of conventional therapy. Liposomes, Polymeric NPs, dendrimers etc. offer the potential for clinical application [19].

Therefore, this review focuses on the pathophysiology and risk factors associated with AD and, thereby, the potential therapeutic targets, pharmacokinetic parameters related to conventional therapy and the significance of novel NPs as well as different types of novel NPs with potential for usage in AD and reinforces them with a discussion on related studies and contemporary research.

Pathogenesis

AD mostly affects the basal forebrain, amygdala, cerebral cortex, and hippocampus, thereby covering the brain's limbic structures. These areas are mainly accountable for learning, reasoning, memory, emotions, and behaviour [20]. The build-up of Amyloid plaques/tau proteins is highly correlated with deteriorating cognition and brain atrophy, especially hippocampal atrophy [21]. Two hypotheses have been put forth to explain the pathophysiology and aetiology of AD. The first hypothesis focuses on Amyloid cascade neurodegeneration that forms neurofibrillary tangles while the second hypothesis discusses the cholinergic system failure caused by metal-mediated toxicity, tau aggregation and inflammation (Fig. 1) [22].

Amyloid-Beta Hypothesis

The Amyloid hypothesis is one of the most prominent hypotheses that is believed as the cornerstone principle of AD, which describes the accumulation of Amyloid-β (Aβ) aggregates [23].

The parent protein, Amyloid Precursor Protein (APP), belongs to the class of Type 1 membrane protein with two marked components: one large extracellular region and a short cytoplasmic arm, which has its origin from the gene splicing on chromosome 21 [24]. Among the three isoforms present, APP 770 and APP are processed through o-glycosylation through the Golgi complex [25]. In the homeostatic state, non-amyloidogenic process would occur, where alpha-secretase cleaves through the portion between Leu 16 and 17, thereby preventing the formation of Amyloid-beta peptides. Moreover, the process releases soluble ectodomain, which confers neuroprotective roles and maintains normal function and homeostasis. The enzymatic processing of APP into Aβ involves three enzymes: alpha, beta, and gamma-secretase [26]. Among these, the alpha-secretase plays a major role in APP formation, while the beta-secretase acts only on 10% of the total APP present. Alpha-secretase belongs to the protein family of disintegrin and metalloproteinase (ADAM) that consists of a prodomain, metalloproteinase domain, disintegrin domain, an epidermal growth factor region, and a cysteine region, all of which are involved in various signalling pathways [27]. Among them, ADAM 10 and 17 constitute of alpha-secretase, which contributes significantly to the formation of APP. 90% of APP apart from those processed by beta-secretase, are processed by them. The cleavage of alpha-secretase produces sAPP-alpha, the soluble ectodomain and C-terminal fragments-alpha (CTF-alpha) with 83 amino acids. Following that, the gamma-secretase would act on them to release a small p3 fragment into the extracellular space while the unprocessed APP remains in the cytoplasm [28].

In the amyloidogenic pathway, APP is processed by beta and gamma-secretase, which results in the production of sAPP-beta ectodomain, and Beta-CTF, which comprises of 99 amino acids (and therefore, can be called C99) [29]. Furthermore, gamma-secretase cleavage on numerous sites produces various isoforms of Aβ protein such as Aβ 37, 38, 39, 40, 42, and 43. Among these, Aβ 40 and 42 are prominently deposited in the brain. Even though they are both soluble, Aβ 42 contributes to significant aggregation owing to its hydrophobicity. Thus, Aβ 42 is the major factor in triggering plaque formation [30].

From the monomers formed, they are clubbed together to form diverse oligomeric species, forming short protofibrils on further aggregation. They grow to form insoluble fibrillar groups. Oligomeric Amyloid-beta species can elevate the N-methyl-D-aspartic acid receptor (NMDAR) levels, producing excitotoxicity. The resulting inhibition of the hippocampal causes post-synaptic depression, potentiating long term-depression and related aspects [31].

Amyloid-beta assemblies would accumulate in the brain mitochondria, as they are the best source of Reactive Oxygen Species (ROS). Amyloid-beta would induce more ROS production, causing the release of cytochrome c and apoptosis-inducing factor, leading to mitochondrial dysfunction, followed by cell death. The process is depicted in Fig. 2 [32].

Tau Hypothesis

Tau protein is encoded by the microtubule associated protein tau (*MAPT*) gene that is located on chromosome 17, splicing at different positions such as exons 2,

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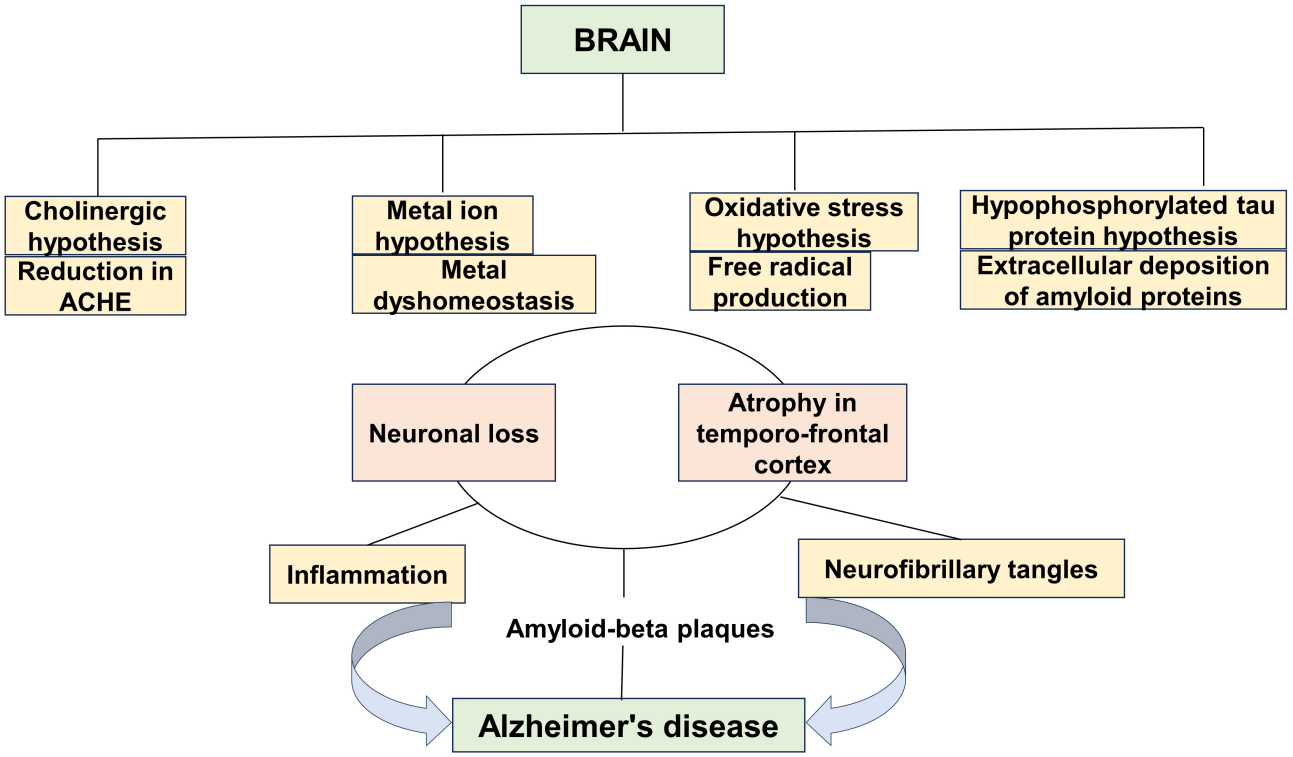

Fig. 1. Pathophysiology of Alzheimer's disease (AD). Figure was created with MS Powepoint.

3, and 10 to produce 6 different isoforms of the protein. They differ from the sequence of amino acid insertions and microtubule-binding regions. Normal homeostasis marks the presence of 3R, and 4R isoforms, in which their imbalance has been observed in different tau-marked etiologies of AD cases. In most cases observed in AD Brains with NFT, 4R has the upper hand compares to 3R [33].

The main objective of tau proteins is to retain the stability and integrity of microtubules, as they would bind to the microtubules with their binding regions with the function of axonal transport to the brain [34]. The structural and functional integrity of the tau proteins are maintained by various post-translational modifications such as:

Phosphorylation: Hyperphosphorylation causes the detachment of protein microtubules and, thereby, aggregation. The reasons are considered to be tau kinases and protein phosphatases and disruptions in their processing [35].

Lysine-based modifications: Undergo acetylation, sumoylation, ubiquitination, methylation, etc., with their respective enzymes. E.g., in acetylation at 174, 274, 280, and 281, lysine residues are commonly seen in AD, indicating that acetylation causes tau detrimental. Sumoylation is said to enhance tau phosphorylation, but not much evidence exists on correlation [36].

Truncation: Tau proteins can be cleaved by caspases, calpains, thrombins, cathepsins, ADAM 10, etc. Downregulation of all these enzymes can lead to tau aggregation [37].

Glycosylation: N- and O- glycosylated tau are seen in AD brains. e.g., the downregulation of O-GlcNAcase causes decreased glycosylation, leading to hyperphosphorylation [38].

The correlation of tau with AD begins from the formation of tau aggregates. tau as monomers are highly soluble and harmless. However, under the circumstances, they would aggregate into associated oligomers, fibrils, and further NFTs. This is due to the occurrence of mutation on *MAPT* genes, which was observed in transgenic mice due to the imbalance in the 3R:4R ratio [39].

Liquid-liquid phase separation (LLPS) forms another factor in modulating and overseeing tau aggregation. As tau exists as liquid droplets to help the binding of tubulin into the microtubule-binding domain, they would undergo LLPS, resulting in subsequent aggregation [40].

NFTs formed due to the aggregation are initially seen in the entorhinal cortex during the onset of AD with progression to the hippocampus [41]. Study on different strains of mice showed that tau seeding by injection in the form of fibrils led to rapid development and progression of the distal to the injection site, from which the tau propagation hypothesis is based on. This also further highlights that tau aggregates can be exchanged between cells [42].

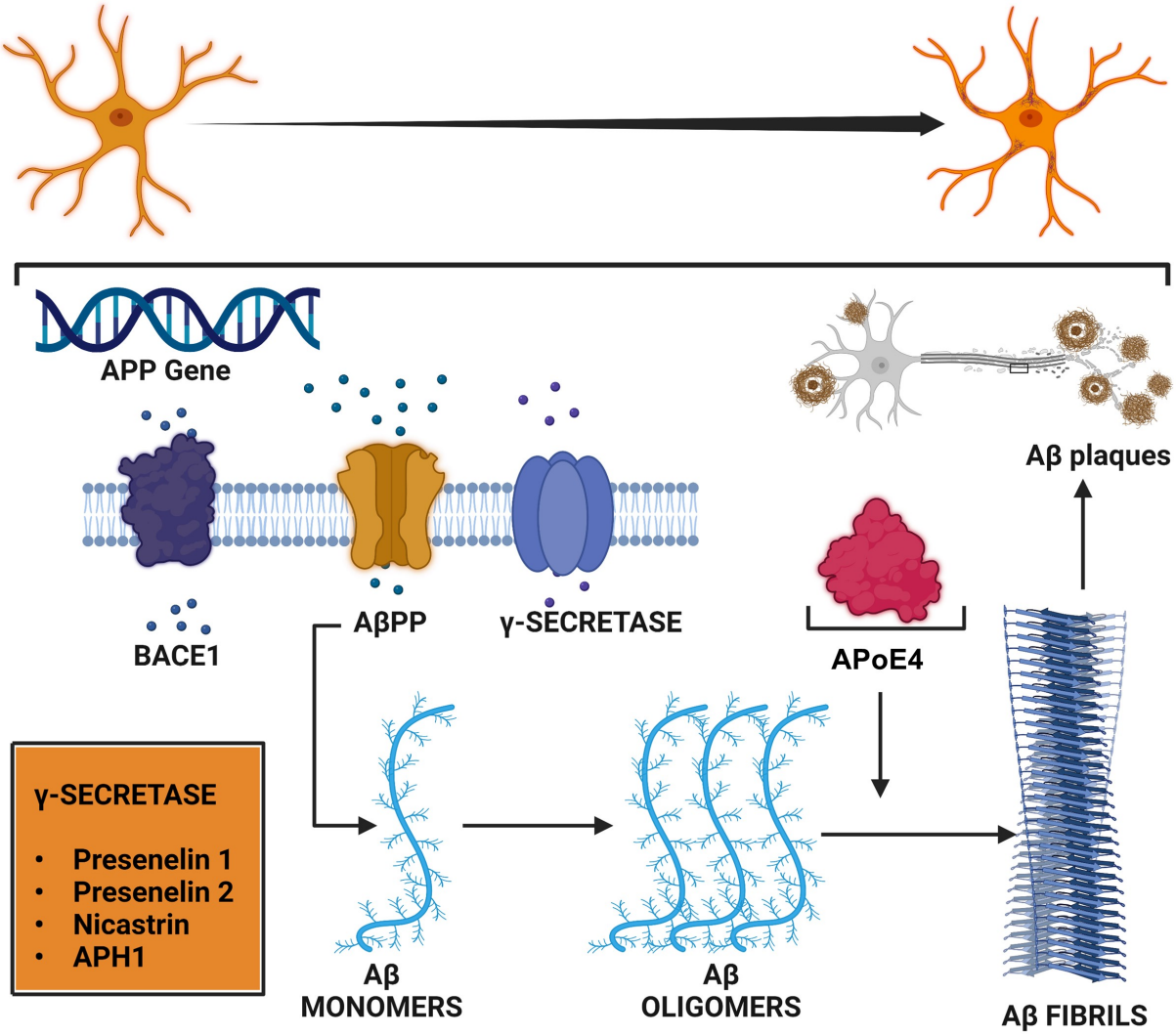

Fig. 2. Depiction of the Amyloid-beta hypothesis. Processing of Amyloid Precursor Protein (APP) by α, β and ϒ secretase, generation of Amyloid-beta (Aβ) and their deposition as senile plaques. BACE1, beta-site Amyloid Precursor Protein cleaving enzyme 1; APP, Amyloid Precursor Protein; ApoE, Apolipoprotein E; APH1, anterior pharynx-defective 1. Figure was created with BioRender.com.

As discussed above, exosome-associated taus can undergo phosphorylation or truncation to form oligomers and follow pathways. They can enter neighbouring cells via micropinocytosis, endocytosis, phagocytosis, etc. Even though there are different internalization mechanisms available, endocytosis is primarily favoured than others Neuronal cell uptake is controlled by Heparin Sulfate Proteoglycans (HSPGs) therefore, downregulating them can be marked as a promising therapeutic strategy [43].

Moreover, the pathogenically harmful tau can disrupt the integrity of microtubular assembly, axonal transport, and pre-and post-synaptic functions, leading to cell death (Fig. 3) [44].

Cholinergic Hypothesis

In the brain of Alzheimer's disease carriers, there will be a synaptic loss, atrophy, and deficiency in the central neurotransmission. The hypothesis states that the cognitive and non-cognitive symptoms in AD patients are due to the loss of central cholinergic transmission and degeneration of cholinergic neurons in the basal forebrain. Additionally, the acetyltransferase concentration, which is necessary for the production of Acetylcholine in the cortex and hippocampus, will significantly drop. This hypothesis also confirms the theory that the lack of Ach, noradrenaline, and serotonin is due to the malfunction and cell death of neurons necessary to maintain certain communication systems [45].

Acetylcholine is a major neurotransmitter, which rules our system from the most basic to complex physiology with actions in the cortex, basal ganglia, and forebrain [46]. The presence of cholinergic lesions is a characteristic of early AD, which occurs in the pre-synaptic region due to the destruction of NBM neurons and axons that traverse the cerebral cortex. Further loss of nicotinic and muscarinic recep-

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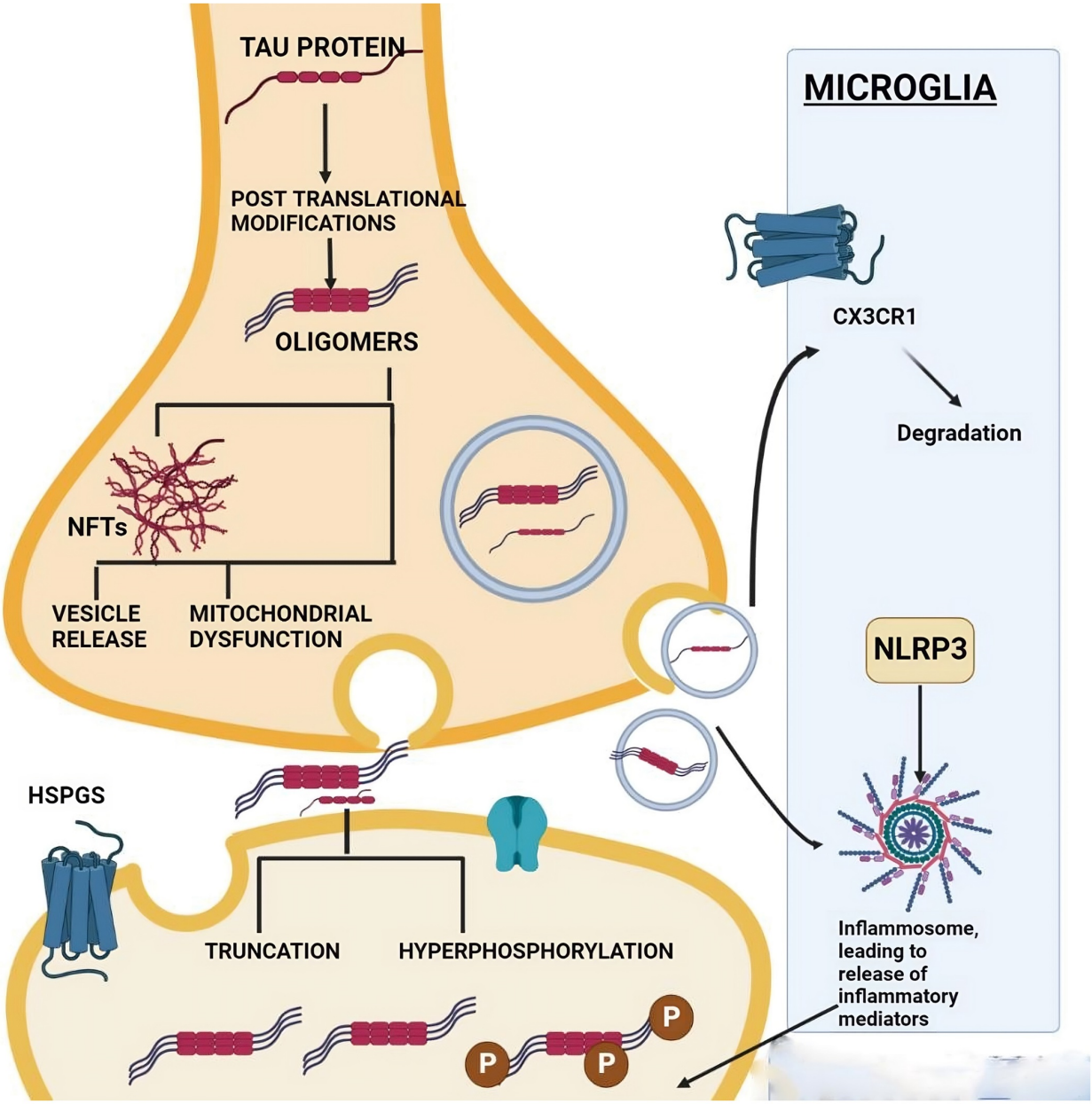

Fig. 3. Tau hypothesis-Post translational modifications undergone by tau proteins and further aggregation from tau monomers. NFTs, Neuro Fibrillary Tangles; CX3CR1, CX3C motif chemokine receptor 1; NLPR3, NLR family pyrin domain-containing protein 3; HSPGs, Heparin Sulfate Proteoglycans. Figure was created with BioRender.com.

tors is also a characteristic that must be considered, especially in the cerebral cortex [47]. In the case of muscarinic receptors, the specific loss can be seen in M2 receptors, with chances of a dysfunctional M1 assembly. The scenario marks anterograde cortical cholinergic differentiation of the hippocampus, cerebral cortex, and amygdala. This altered distributional pattern of the receptors would disrupt major functions of the cerebral cortex and limbic systems [48]. The key results are:

➢ Decreased cortical cholinergic innervation;

➢ Reduced glutamatergic neurotransmission through the cortical pathways;

➢ Loss of coupling of muscarinic receptors;

➢ Decreased production of sAPP-alpha;

➢ Increased phosphorylation of tau proteins;

➢ Reduced glutamate production (Fig. 4) [49].

Associated summary of the pathogenesis of AD is illustrated in (Fig. 5) [50].

Cell Types Involved in AD

The following cell types have a direct impact from the detrimental effects of AD pathophysiology, resulting in subsequent clinical manifestations:

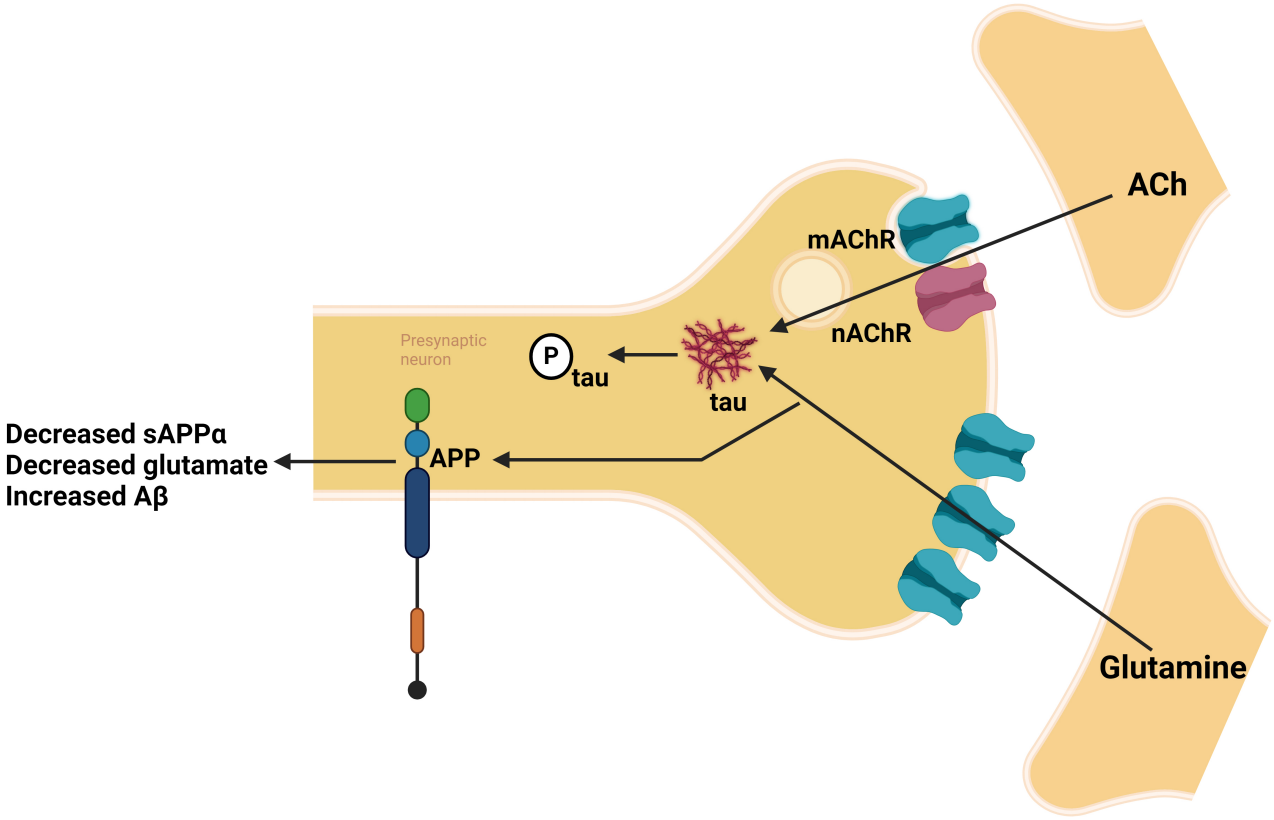

Fig. 4. Cholinergic derangements and their results according to the hypothesis. ACh, Acetyl Choline. Figure was created with BioRender.com.

➢ Neurons: Neurons are the primary victims in AD, directly impacted by the pathological hallmarks of the disease: Amyloid-beta plaques and tau tangles, as accumulation of the Amyloid proteins lead to neuronal death.

➢ Astrocytes: Astrocytes, a type of glial cell, provide structural and metabolic support to neurons. In the AD brain, astrocytes become reactive or activated, participating actively in the brain's inflammatory response. Their functional capacity is highly reduced in AD, leading to disease progression.

➢ Microglia: Microglia serve as the brain's innate immune cells, scanning for and responding to infections and neuronal damage and they are activated in the inflammatory pathway associated with AD. Their ability to clear Amyloid-beta plaques is crucial, yet impaired in AD, contributing to plaque accumulation and associated neurotoxicity.

➢ Oligodendrocytes: Oligodendrocytes are responsible for the production and maintenance of myelin, a fatty substance that insulates nerve fibers, facilitating efficient signal transmission. Demyelination and disruption of the oligodendrocytes can lead to substantial cognitive decline.

➢ Endothelial Cells: Endothelial cells lined the blood vessels in the brain and they are pivotal in maintaining the integrity of the Blood Brain Barrier (BBB). In AD, the BBB's function is compromised, allowing the entrance of immune cells and potentially harmful substances into the brain parenchyma. This breach contributes to inflammation, neuronal damage, and the progression of AD [51].

Etiology

The abnormal sediments of proteins surrounding the brain cells usually cause the occurrence. Deposits of amyloid proteins would develop plaques all around the brain cells while the accumulation of tau proteins would lead to the appearance of tangles within the brain cells. When brain cells are affected, it results in a significant decline in chemical messengers (neurotransmitters) responsible for transmitting signals between the brain cells. Furthermore, the levels of Acetylcholine would reduce in people affected with AD. Different sites of the brain, especially those that can affect memory, will begin to shrink over time [52].

Risk Factors

Patients who are older than 65 years of age are at risk of developing Alzheimer's disease, which doubles every five years. However, it would be early- or young-onset AD for those around the age of 40. The genetic defect that stands as the reason for Down's syndrome can also lead to the build-up of Amyloid plaques in the brain over

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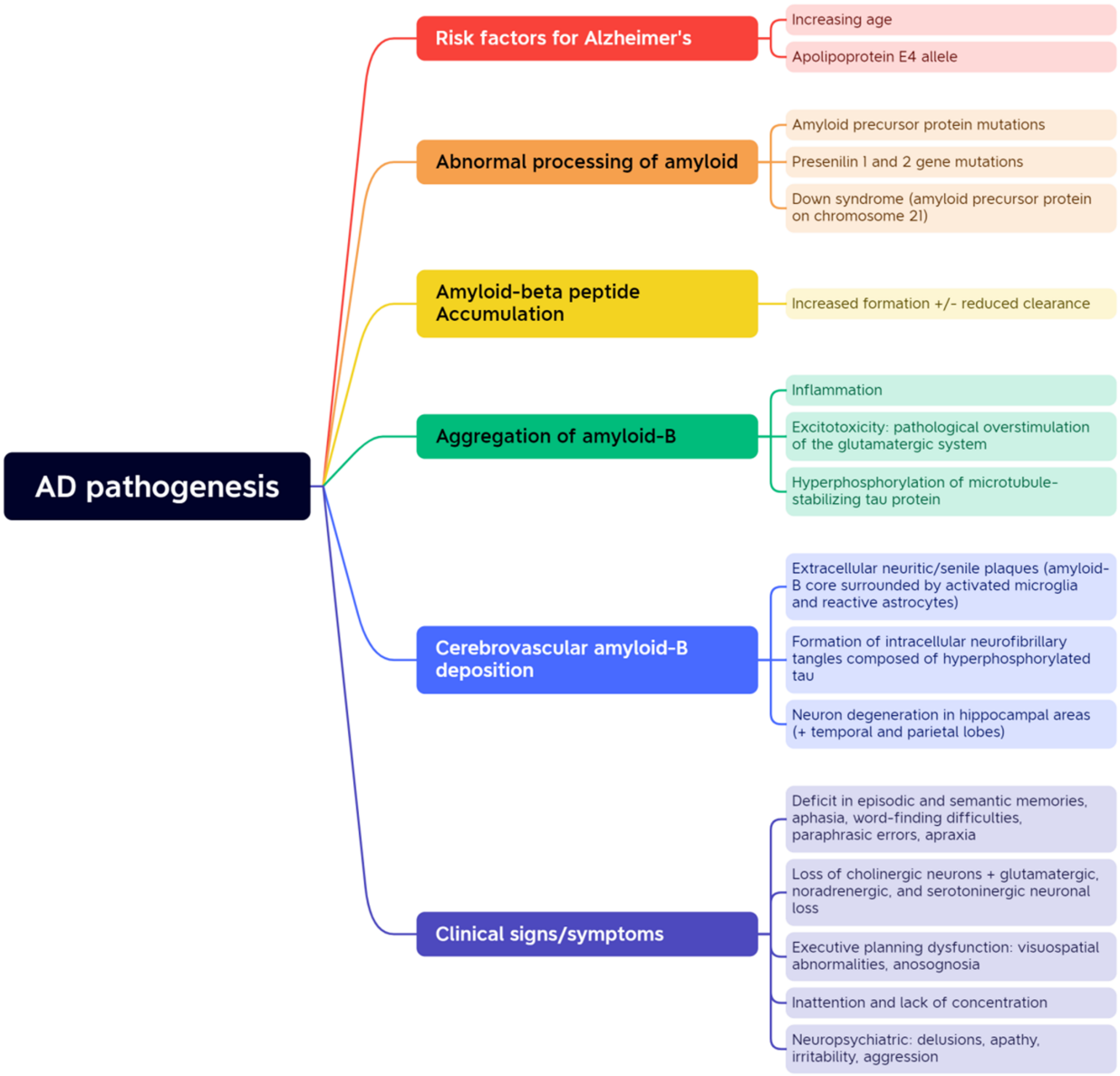

Fig. 5. Summary of the pathogenesis and resulting clinical implications of AD. Figure was created with xmind.ai.

time, thereby indicating family history as a risk factor. Not only that, people who have serious head injuries also may develop AD. Conditions related to cardiovascular diseases such as smoking, diabetes mellitus, high cholesterol, hypertension and obesity, can attenuate the risk of AD (Fig. 6) [53].

Pharmacological and Non-Pharmacological Therapy

Cholinesterase inhibitors show improvement in cognitive function and memory in most patients through the utilisation of donepezil, Galantamine and Rivastigmine. The utilisation of Tacrine is rare due to its hepatotoxic effect. Donepezil is the drug of choice as it has once-daily dosing and it is highly tolerated. The usual dose is 5 mg orally once daily, given for 4–6 weeks. It is then titrated to 10 mg once daily. This treatment resumes if any functional improvement is noticeable within months. Memantine is an NMDAR antagonist that enhances functional and cognitive ability in patients experiencing moderate to severe AD. The recommended dose is 5 mg orally once daily, which is then titrated to 10 mg orally twice daily for 4 weeks. To obtain the best results, it should be used along with a cholinesterase inhibitor [54].

The effect of Selegiline [Monoamine oxidase (MAO) inhibitor] remains unclear as of now. The latest trials do not encourage using Estrogen to treat or prevent cognitive decline. There is also no conclusion drawn regarding the role of vitamin E in preventing AD. Apart from that, non-

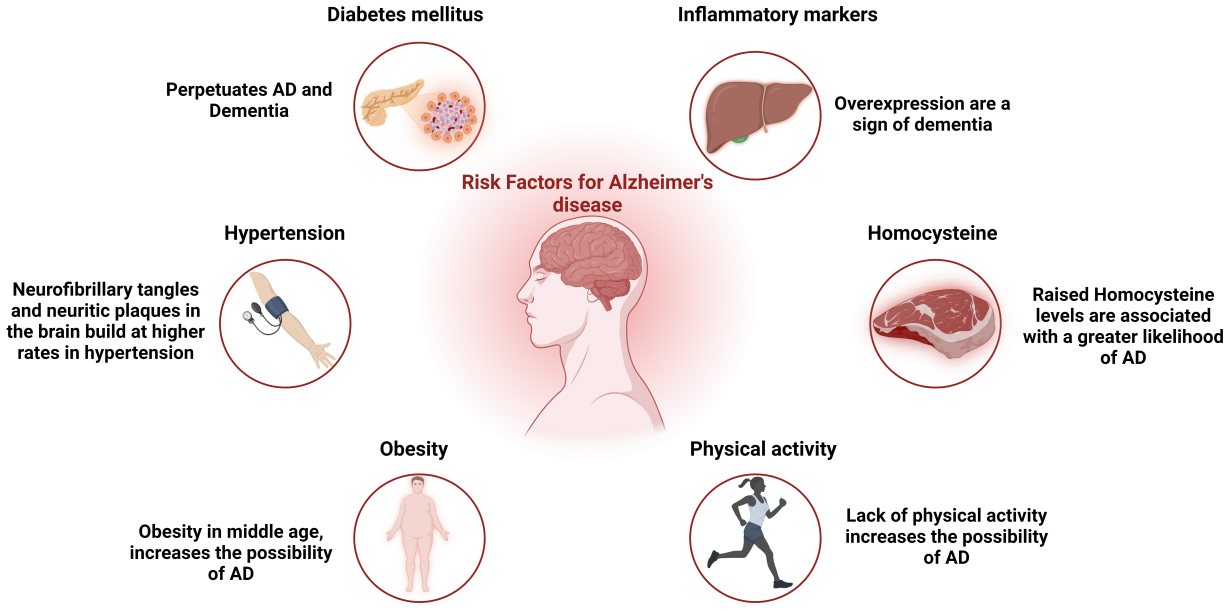

Fig. 6. Risk factors associated with the onset of Alzheimer's disease (AD). Figure was created with BioRender.com.

steroidal anti-inflammatory drugs (NSAIDs) are not utilised due to lack of evidence and the appearance of side effects. Lipid-lowering agents like Pravastatin and Lovastatin are rarely used. However, national formularies in Germany and France have approved using the dietary supplement ginkgo biloba extract, EGb761, for AD [55]. Clinical trials using investigational drugs that targeted Amyloid-beta peptide accumulation were proven inefficient [56,57]. In order to reduce potential toxicity, side effects and increase drug bioavailability primarily due to the Blood Brain Barrier, there are constraints that must be investigated further; therefore, making the nanotechnological approach as the most recent approved therapeutic modality. The pharmacokinetic parameters of conventional AD drugs are listed in Table 1 (Ref. [58–60]).

Limitations of Existing AD Therapies

The limitations of current therapies in AD present significant obstacles towards effective management and treatment of the condition. These challenges highlight the urgent need for innovative approaches in drug development and delivery, with nanotechnology offering a promising avenue for breakthroughs.

Current therapeutic strategies for AD primarily focus on symptom management and decelerating the progression of the disease, rather than offering a definitive cure. The medications available today may offer temporary improvements in cognitive and functional abilities but fail to target the root causes of AD. This limitation underscores the critical demand for more potent treatments [61].

A pivotal challenge in treating AD lies in the delivery of drugs to the brain. The Blood Brain Barrier (BBB) serves as a formidable obstacle, significantly restricting the bioavailability of therapeutic agents. This barrier is highly selective, preventing nearly 98% of small molecule drugs and 100% of large molecule biologics from reaching the brain tissues affected by AD. The difficulty in breaching the BBB does not only hamper the effectiveness of current treatments but also represents a major hurdle in the development of new drugs. Despite extensive research and development efforts, the struggle to surmount the BBB has contributed to a stagnation in the approval of new AD therapeutics [62].

Both small molecule and biologic drugs face minimal penetration through the BBB following systemic administration, severely limiting their therapeutic potential against AD. This singular challenge underscores the necessity of innovative solutions to enhance drug delivery to the brain [63].

Drugs targeting neuroinflammation, a key aspect of AD pathology, also encounter limitations due to their unidirectional therapeutic approaches and the BBB's obstructive properties. These challenges necessitate re-evaluations of current strategies and the exploration of alternative methods to improve drug delivery and efficacy [64].

In response to these limitations, nanotechnology emerges as a promising frontier. By leveraging the unique properties of nanomaterials, researchers are developing innovative strategies to enhance drug delivery across the BBB. Nanotechnology offers the potential to design therapies far more effective in interacting with brain cells and biomolecules, providing new pathways to treat AD. The exploration of nanotechnology-based therapies represents a hopeful direction in overcoming the current limitations of AD treatments, offering a new hope in advancing care for individuals affected by AD [65].

Table 1. Pharmacokinetic parameters of AD drugs [58–60].

Drug	Bioavailability (%)	Protein binding (%)	Vol of distribution (L/Kg)	Hepatic metabolism	T_{max} (h)	C_{max} (mcg/L)	Half-life (h)	Clearance (L/Hr/Kg)	Log BBB value
Donepezil	100 (Relativeoral bioavailabilty)	96	12–16	CYP2D6, CYP3A4	3–5	97.3–24.4	60–90	0.13–0.19	0.123
Rivastigmine	40	40	1.8–2.7	Non-hepatic	0.8–1.7		2	1.5	0.123
Galantamine	85–100	19	2.9	CYP2D6, CYP3A4	0.5–1.5	20.78–30.14	5–7		0.094
Tacrine	17–37	75	3.7–5.0	CYP1A2, CYP2D6	0.5–3	<15–24	1.3–7.0	2.42	–0.354
Memantine	100	45	9–11		3–7	12–17.4	60–80	4.15	0.123

BBB, Blood Brain Barrier.

Table 2. Nanotechnology based systems used in AD therapy [76–80].

Nanotechnology based systems	Active ingredients or drug	Route of administration	Major application
Polymeric nanoparticles	Rivastigmine	IV	Huge concentrations can be obtained in the brain
	Tacrine	IV	Achieve high bio-availability thereby reduction in dose
	Fibroblast growth factor	IV/IN	Increased Choline acetyltransferase
	Peptides TGN and QSH	IV	Amyloid plaque oligomer specific action
	Unloaded polymeric nanoparticles	*In vitro*	Disaggregation of β Amyloid plaques

TGN, TGNYKALHPHNG; QSH, QSHYRHISPAQV, quadrupole superparamagnetic ferrite.

Nanotechnological Approach

Nanotechnology entails developing or modifying desirable materials with structures ranging in size from 1 to 100 nanometers [66]. Nanomaterials are promising drug delivery mediums, particularly for managing cancer and Alzheimer's disease as they are stronger, smaller, faster, lighter and more durable than other materials. The broader surface area with an increased surface volume ratio is extremely beneficial because it has a substantial impact on their composition [67]. These nanotechnologies include liquid crystals, nanostructured lipid carriers, solid lipid nanoparticles, polymeric nanoparticles, and microemulsions. Each of them offers the potential to deliver therapeutic agents to the brain in several ways, particularly intranasally. On the other hand, the controlled release of medications into disease sites is a crucial component in the development of nanomedicine [68–70].

Utilizing drug delivery methods based on nanotechnology can improve the efficacy of treatment. These kinds of nanosystems could effectively distribute and transport medications and other neuroprotective chemicals into the brain in the circumstance of AD treatment [71]. Novel drug delivery systems include liposomes, polymeric and solid lipid nanoparticles (SLNs), hydrogels, microemulsions (MEs) etc. The physicochemical properties of drugs, such as their lipophilicity or hydrophilicity, ionization, poor bioavailability, extensive metabolisation, high molecular weight and unfavourable outcomes, can result in treatment failure [72]. Moreover, intranasal administration also offers good BBB permeability [73].

Similarly, oral and topical formulations can be altered with novel strategies targeted to the brain. They can pass through the Blood Brain Barrier to increase their bioavailability and pharmacodynamic properties and reduce their side effects to maximise the pharmacotherapy in AD patients [74,75]. Table 2 (Ref. [76–80]) lists the emerging platforms that seek to enhance the pharmacokinetics, pharmacodynamics, and bioavailability of medications while minimizing their negative effects [81].

The structural organization of a nanosystem depends on its core elements. For example, nanospheres offer a matrix-based structure for polymeric chains. At the same time, nanocapsules allow their oily or watery cores to be encased in thin polymer membranes due to their compartments within them (Fig. 7). Such use of lipid/polymeric NPs can aid in potentiating the pharmacokinetic properties and, thereby, the pharmacological effects of the used drug.

The rate at which the drug is delivered through endocytosis or lipophilic transcellular pathways can be enhanced by employing the endothelial cell-binding affinity of lipid-soluble NPs. Additionally, the adsorptive property of nanoparticles is beneficial as they can adhere to the BBB's blood capillaries and facilitate penetration. This alternation on NPs associated with significant receptors can also improve their permeability through BBB with improved transport [82].

The application of nanoparticles in targeting the hippocampus for the treatment of Alzheimer's disease (AD) represents a promising frontier in the battle against this neurodegenerative disorder. Nanoparticles can be engineered to penetrate the BBB effectively, a critical obstacle in neurotherapeutics. Once they have crossed the BBB, these particles can be designed to accumulate in the hippocampus—the brain region pivotal for memory and cognition which is significantly impacted in AD. This targeted delivery promises a higher concentration of therapeutic agents directly to the affected site, potentially increasing treatment efficacy while minimising the systemic side effects [83]. Nanoparticles also can be specifically tailored to bind to CD44-expressing cells, which are prevalent in inflamed regions of the brain, such as the hippocampus, in AD patients. This specificity not only ensures the nanoparticles are retained longer in the target region but to deliver therapeutic agents to every cell actively involved in the disease process, offering a targeted approach to modulate inflammation and disease progression [84]. Polymeric Nano Particles offer the flexibility to be customised in terms of size, charge, and surface characteristics, enabling them to effectively cross the BBB and reach the brain parenchyma. This customisation allows the fine-tuning of nanoparticle formulations to optimize their delivery to the hippocampus, enhancing the delivery of therapeutic molecules specifically designed to treat AD [85].

Polymeric Nanoparticles (PNPs)

PNPs are solid carriers made from naturally occurring or synthesized polymeric materials that contain colloidal organic molecules at the nanoscale. Recently, a wide range of polymers has been researched to develop PNPs that can carry drugs to specific sites for the therapy of AD. Poly(lactic-co-glycolic acid) (PLGA) is the most extensively studied polymer due to its sustained and controlled release capabilities, biocompatibility and minimal toxicity with tissues and cells. PLGA is permitted to be utilised in vaccinations, drug delivery, and tissue engineering by the European Medicine Agency (EMA) and the United State Food and Drug Administration (US FDA) [86]. PLGA stands for polylactic acid and polyglycolic acid (PGA) copolymers. They are removed from the body by numerous biological processes after being hydrolysed in the body to form monomeric components.

Recent explorations had found phytol encapsulated within the nanoparticles made of PLGA fabricated as a mitigator of Amyloid-beta peptide clustered in Alzheimer's disease. Due to the weak solubility of phytol in biological fluids, its use is restricted. Drug-loaded polymeric NPs were effectively created with a 92% encapsulation ef-

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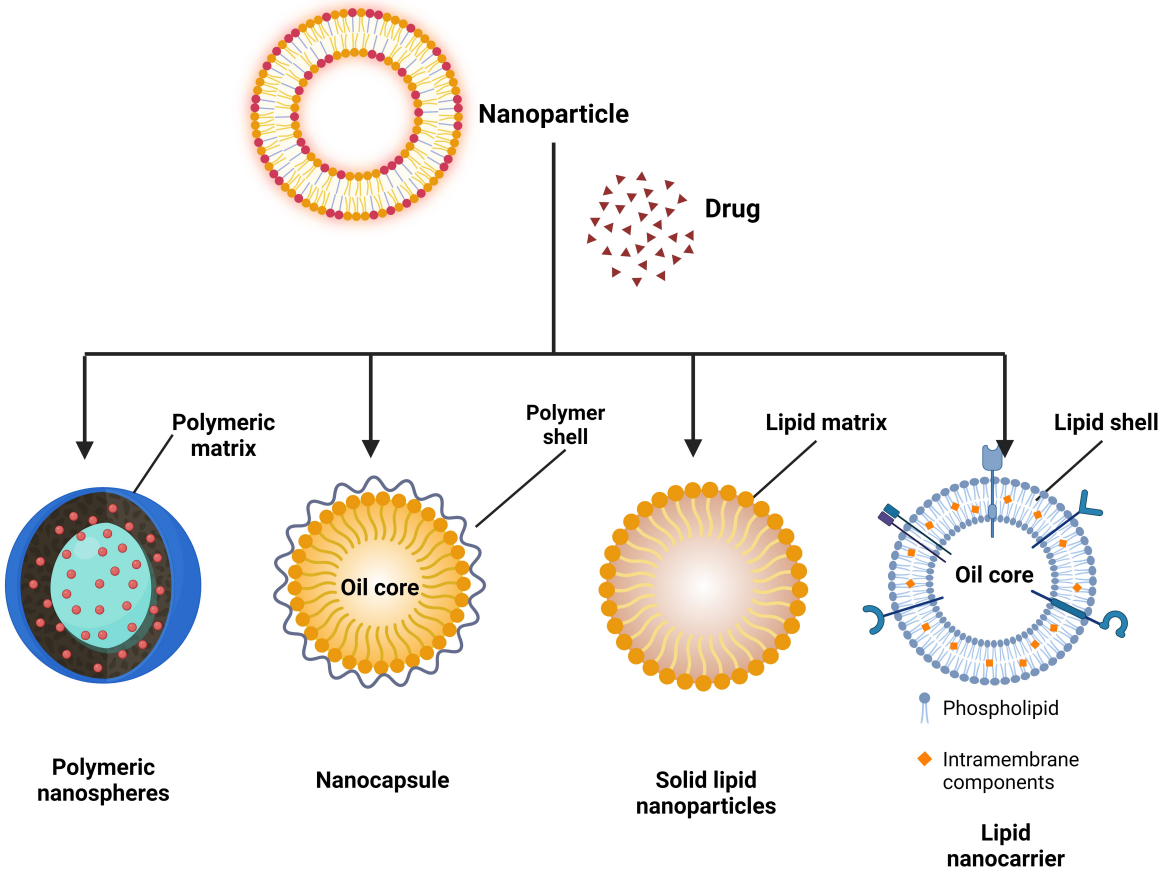

Fig. 7. Incorporation of drug into or onto a nanoparticle. Figure was created with BioRender.com.

ficiency at a drug-to-polymer ratio of 1:4. These drug-loaded NPs maintained drug release for up to 120 hours. Fresh experimentation transpired within test tubes utilizing phytol-infused PLGA microparticles and unattached phytol to evaluate their antioxidant skill, anti-clumping and clump-splitting ability of Aβ25–35, endurance, and sheltering influence, which in contrast to Aβ25–35 had prompted harmfulness in Neuro-2a cells. In contrast to the donepezil drug, the potency of the drug-loaded PLGA and the free drug were marginally improved. Through this study, it is possible for these NPs to be utilized as a novel strategy. In a different study, galantamine-loaded PLA/PLGA hybrid nanoparticles were generated, and intranasal administration of the drug was successful in AD-induced mouse models. Galantamine-loaded liposomal NP had a higher zeta potential (49 mV) than PNP (17 mV), indicating that they were less likely to aggregate. Furthermore, galantamine-loaded PNPs have a size of 200 nm, which is bigger than galantamine-loaded liposomes with a size of 100 nm. According to studies done, the neuroprotective effects of Pioglitazone (PGZ) make it an effective therapeutic agent for AD. Studies had used the solvent displacement approach with a poly lactic acid-co-glycolic acid-polyethylene glycol (PLGA-PEG) carrier to penetrate the BBB and revealed that AD-stimulated transgenic mice had decreased Amyloid-beta deposition and memory impairments.

Chitosan is another biocompatible and biodegradable polymer that is considered as a potential PNP-based drug delivery vehicle. Chitosan NPs are special due to their mucoadhesive properties and intrinsic bioactivity that help the drugs to enter the brain by the olfactory pathway and work as Alzheimer's therapies in and of themselves [87]. Galantamine-loaded thiolated chitosan PNPs administered intranasally had significantly improved amnesia-affected mice's recovery, showing beneficial results with underlying mechanisms marked as enhanced memory and decreased activity of acetylcholinesterase. The mucoadhesive characteristics of the nanoparticles eased protein channel transport, increased the permeability of Galantamine at the nasal mucosa and enhanced its bioavailability, which is crucial for Alzheimer's therapy [88]. Additionally, some investigations have shown that chitosan is a powerful chelating agent that can compete with histidine or Aβ for copper binding as their interactions serve as potential therapeutic targets for these diseases [89]. A significant finding with respect to Chitosan PNPs with high positive charge den-

sity has stated that they would be able to cross the Blood Brain Barrier (BBB) easily, facilitating the respective action. In lieu to this, Chitosan PNPs have been used to deliver Amyloid-beta peptides and caspase inhibitors for AD therapeutics [90]. Therefore, the penetration is based on the surface modifications completely. Apart from that, increasing the positive charge density also can facilitate absorptive-mediated endocytosis while the utilization of surfactants would promote receptor-mediated endocytosis [91].

Liposomes

The significance of liposomes, which were first identified in the 1960s, can be attributed to their distinctive characteristics such as non-immunogenicity, low toxicity, flexibility, biocompatibility and biodegradability [92]. Liposomes are novel drug-delivery vehicles, which are used to carry hydrophilic molecules. Investigators have developed cell-penetrating peptide-modified liposomes and rivastigmine liposomes to improve their bioavailability. As such, its pharmacodynamics have improved when they are administered intranasally. Through this, adverse side effects can be reduced as well. Based on a study done, the modified liposomes improved brain transport and increased pharmacodynamics across BBB when they were employed through the nasal olfactory route into the brain. A cell-penetrating Trans-Activator of Transcription (TAT) peptide was also successfully used to functionalize liposomes in a different manner [93]. Moreover, another study had developed metformin-loaded phosphatidylserine-based liposomes, which were more effective than free metformin in treating learning, memory impairments and reducing neuroinflammation in AD-induced rat models. Glutathione-targeted PEGylated liposomes improved Amyloid-targeting antibody fragment transport over the BBB into the brain [94].

The use of monoclonal antibodies (mAb) in liposomes containing curcumin analogue and liposomes loaded with curcumin was also investigated. MAb-modified liposomes demonstrated better affinities for senile plaques. However, observations were conducted on the postmortem brain tissue of AD patients. Evidently, more curcumin was taken via the BBB cellular model.

A brand-new peptide with the sequence of HKQLPFFEED is called H102. Liposomes, which were based on it were identified to be effective in AD drug delivery. H102 had successfully transported to the brain after intranasal treatment, and its liposomal Area under the curve (AUC) was 2.92 times greater than that of the peptide solution group when analyzed in the hippocampus area. Liposomal H102 reduced spatial memory impairment, enhanced the activities of insulin-degrading enzyme (IDE) and choline acetyltransferase (ChAT), and inhibited plaque deposition. The composition also showed no damage to nasal mucosa [95]. Additionally, Amyloid protein aggregation in AD also has been identified using liposomes. In one study, the researchers mounted multiple dye units on a vesicle's surface, enhancing the binding of fibrils that facilitated the pathogenesis, thereby featuring diagnostic implications [96].

Specific Mechanism on AD

Liposome-based drug delivery mostly focuses on inhibiting Aβ formation by blocking the production/accumulation of senile plaques [97].

Multifunctionalization of Liposomes

mApoE-PA Liposomes. Balducci *et al*. [98] (2014) had examined the potential of multifunctional liposomes in inhibiting Amyloid-beta plaques. The integration of Apolipoprotein E (ApoE)-derived peptide (mApoE) imparts had enhanced BBB permeability while phosphatidic acid acted as the ligand for Aβ, thereby increasing the target affinity. This system was able to disintegrate Aβ fibrils, making it superior to mono-functionalized liposomes. This could be attributed to the interactions between the positive charges on mApoE and negative charges on Aβ and positive charged amino acids of Aβ with negative charges on phosphatidic acid. However, *In vivo* studies on the same had limited its practical viability owing to its reduced uptake by the brain [98]. In this view, Mancini *et al*. [99] (2016) had proposed the sink effect by using a peripheral binding agent to draw Aβ out of the brain. Combining both of these concepts, mApoE-phosphatidic acid (PA)-liposomes (LIP) could be used as the peripheral agent, which can cause the former to exit the brain, as evidenced by their increased plasma levels [99].

Curcumin-Loaded Liposomes. With its intrinsic antioxidant property, curcumin can prevent Amyloid aggregate formation and disrupt the already existing pre-fibrils [100]. From a SAR point of view, those with C-4 substitution have potentiated activity [101]. However, the drawback of this conventional system is its poor bioavailability, providing scope for liposomal preparations. Mourtas *et al*. [102] (2014) had evaluated the system with transgenic mice models elucidating their large affinity on Amyloid-beta plaques.

Effects on Neurotransmission. AD pathophysiology includes cholinergic hypothesis, as discussed earlier, that concentrates on the derangements in neuronal transmission due to the loss of cholinergic neurons and reduces Acetyl Choline (ACh). Acetyl Choline Esterase Inhibitors that prevent the degradation of ACh are the treatment option for the same, which includes Rivastigmine [103]. Disadvantages of oral rivastigmine such as low bioavailability and poor stability can be overcome by using respective liposomal formulations. Yang *et al.* [104] (2013) had designed such a system using a PEGylated version of polyarginine cell-penetrating peptide (CPP) for improved stability, which also highlighted improved transcytosis across

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the BBB membrane, showing enhanced uptake. Nageeb El-Helaly *et al*. [105] (2017) had reported using an inducer called dodecyl methyl ammonium bromide to enforce electrostatic interactions.

Multiple Target-Based Liposomes. Since AD involves multifactorial aetiology, developing therapeutic strategies targeting different aspects or molecules would bring significant changes in the treatment of the disease. Kuo *et al*. [106] (2017) developed such systems by preventing the accumulation of Aβ at the molecular level by preventing the phosphorylation of p38 and c-Jun-N-terminal kinases, in which both had an active role in the kinase cascade involved with Aβ formation cellular signalling pathways. Wheat germ-agglutinin conjugated liposomes, it includes curcumin, Nerve Growth Factor, Cardiolipin and Wheat Germ Agglutinin (WGA) [106]. Nerve Growth Factor (NGF) would accelerate the activity of Tyrosine Kinase Receptor Type 1A thus, slowing down neuronal apoptosis. Curcumin elicits effects on the kinase cascade while cardiolipin utilises its affinity for Aβ. The rest of the constituents contribute to BBB permeation. Curcumin also modulates tau phosphorylation along with increasing cholinergic activity in neurons, as portrayed by Mandell and Banker (1996) [107].

Micelles

Micelles are amphiphilic novel vehicles for drug delivery specifically in the 5–50 nm range. The hydrophobic core would transport the therapeutic drugs, while the hydrophilic shell makes the system permeable to water, facilitating intravenous absorption. In a study, the integration of resveratrol into micelles to target neuronal mitochondria showed improvement in the cognition of mice models. Another research had synthesised thermos responsive conjugated polymer micelles (CPMs), demonstrating a remarkable ability to gather deadly Amyloid-beta oligomers at higher temperatures. Micelles however are limited by the necessity for steric stabilisation. Due to this, they are frequently blended with PEG or other polymers to produce "polymeric micelles", which have a more rigid outer shell [108].

To nurture the correlation between microglia and AD, Lu Y *et al*. [109] (2018) had developed a ROS-based polymeric micelle system coined as Ab-PEG-LysB/curcumin (APLB/CUR), which could reduce the oxidative stress and subsequent inflammation subjected to microglia that occurred in the initial stages of AD. The system offered the benefit and resolution of multiple factors and pathways, such as correcting the damaged microenvironment, offering neuroprotection, microglia regulation, decreasing Amyloid-beta plaque formations thus, potentiating the cognition of patients. This amphiphilic polymer was achieved by carrying out a reaction between phenylboronic containing structure and amino groups on Poly Ethylene Glycol-Polylysine conjugates. Following that, the hydrophobic segment was built and curcumin was incorporated via self-assembly. The process also involved dialysing the whole drug mixture through N, N-dimethylformamide. The neuroprotection conferred by the system under oxidative stress and Amyloid-beta build-up and toxicity was evaluated. It was found that cell death was prevented by scavenging the formed ROS with the polymer degradation mechanism. Moreover, the mice models showed improved cognition when fed with the drug system as they passed the water maze test with much ease compared to the control group [110]. In short, due to the additive effects of polymers and payloads, there are multiple AD pathways that can be identified and targeted according to the aetiology, offering resolution.

Solid Lipid Nanoparticles

In the AD brain, solid lipid nanoparticles are regarded as outstanding a-bisabolol transporters. The formulation has demonstrated considerable Amyloid aggregation inhibitory properties [111]. Developing therapeutic strategies on p-glycoprotein expression and protein transporters have led to targeting MC11 ligand-based methods. The expression of these proteins may be induced by the transferrin-functionalised nanostructured lipid carriers, which may represent a possible treatment approach for AD [112]. Researchers have identified novel formulations of donepezil to improve intranasal delivery [113]. In a similar work, the solvent emulsification diffusion process was used to prepare solid lipid nanoparticles and a formulation of donepezil. Comparing the results to other formulations, the treatment efficacy showed a promising improvement [114]. Curcumin-loaded lipid-core nanocapsules have recently been developed favourably. In AD mouse models, the curcumin nanocapsules demonstrated considerable neuroprotective effects against A1–42-induced behavioural and neurochemical alterations. Curcumin-based lipid carriers have also been employed to mitigate AD-related oxidative stress. Another study also had analysed the implications of nanocarriers integrated with huperzine-A [115]. Resveratrol, a polyphenolic agent with neuroprotective properties has low bioavailability, short biological half-life, poor solubility, fast metabolism and elimination. However, resveratrol in combination with SLNs had improved cognitive impairments and centres around the Nf2 pathway to alleviate oxidative stress, revealing increased efficacy [116]. To increase targeting ability and antioxidant activity of quercetin, transferrin-functionalised SLNs of the quercetin were developed, which eventually reduced AD symptoms [117].

The mechanism of action of SLNs is attributed to the enclosed drug where the role of the NP-based drug delivery system lies in potentiating the same, ensuring a site-specific delivery at enhanced concentration etc., while rendering a reduced adverse effect profile. A study by Meghana

Goravinahalli Shivananjegowda *et al.* [118] (2023) had utilised Memantine Hydrochloride (HCl) and Tramiprosate. The former is an N-methyl-D-aspartate (NMDA) antagonist that renders neuroprotection by reducing the production of Amyloid-beta levels and their accumulation in AD, thereby reversing progression. The latter binds to Amyloid-beta monomers, resulting in their stabilisation and thereby preventing the formation of oligomers. Based on the study, the analysis on spatial memory of the rats found positively increased results with respect to NP-based systems. Further quantification of the Amyloid-beta plaques also showed decreased levels in the SNP-based drug-administered rats, thereby indicating their effects on the Aβ plaques and cognition, which in turn could be attributed to their ability to enhance the core drug efficacy [118,119].

Dendrimers

Dendrimers are often referred as the "polymers of the twenty-first century". Studies have shown that dendrimers can act as drug carriers for AD and able to solubilise soluble medications sparingly in aqueous solutions. Nanoscopic macromolecular branching structures constitute dendrimers. The structural constitutions include a core, dendritic portion and the outer functional surface, which can be altered according to the requirement. Due to their specific structural characteristics, dendrimers have sparked interest among researchers. The combination of low-generation dendrimers and lactoferrin for novel memantine formulations has favoured brain-specific delivery. A recent work revealed that the mice in the target group experienced a considerable influence on memory impairment [120]. According to a recent study, the novel dendrimer PPARα/γ (peroxisome proliferator-activated receptor) dual agonist compound (D-tesaglitazar) stimulated macrophage Aβ phagocytosis and caused an M1 to M20 phenotypic transition. It is indeed interesting to note that the toxicity of the positively charged dendrimers, poly-l-lysine, poly(propylene imine) (PPI) and polyamidoamine (PAMAM) was dose-dependent. However, dendrimers with an overall negative or neutral charge conferred less toxicity. Another example that can change the amyloidogenesis process and prevent the buildup of tau proteins is a cationic phosphorus-type dendrimer [121].

A study by Liu *et al.* [122] (2015) showed that graphene-based Quantum Dots (QDs) had substantial potentialagainst AD as they prevented accumulation, especially in the Aβ (1–42) region. Xiao *et al.* [123] (2016) used a combination of graphene QDs and glycine-proline-glutamate, a neuroprotective agent in a transgenic mice model, which also showed inhibitory activity on the accumulation of Aβ (1–42) fibres along with an improvement in the cognition and memory. Tang *et al.* [124] (2018) also reported the same results with quantified evidence from the detection level. Moreover, QDs could also contribute to the diagnostic part, as they were proven successful in detecting Apolipoprotein E (ApoE) with utmost sensitivity and accuracy [125]. Based on the data gathered, it can be concluded that QDs, especially graphene-based QDs, have their mechanism of action centred around the accumulation of Aβ (1–42).

Inorganic NPs

Numerous materials, including gold, silver, aluminum, and silicon dioxide are included in the category of inorganic nanoparticles. When compared to the organic materials, they are extraordinarily stable, hydrophilic, biocompatible, and non-toxic. Preclinical research has demonstrated their prospective role in both diagnostic and therapeutic applications, countering the disadvantages of the conventional system.

Magnetic NPs (MNPs)

The magnetic properties of MNPs are produced by the metal core, which is typically made up of elements with unpaired electrons (Iron, Nickel, Cobalt, Chromium or Gadolinium). Iron oxides are the most prevalent cores used in nanomedicine because they can be removed via the endogenous iron metabolic process and possess lesser toxicity. The iron oxide state provides greater stability than the elemental iron. Polymers, peptides etc., can be used for coating of the core. In addition to shielding the magnetic core from chemical species, the coating regulates the pharmacokinetics and toxicity of the drug. Fluorophores and/or radionuclides can be introduced to the MNP's surface to provide additional properties for image probes [126–128]. Recently, a study developed anti-biofouling polymer magnetic nanoparticles that were based on iron oxide. The nanoparticle contributed to AD by including polyethylene glycol-block-allyl glycidyl ether (PEG-b-AGE) to detect tau protein and Aβ peptides in AD. The developed IONPs also specifically led to products with increased sensitivity and specificity. Magnetic NPs can also be used in the case of liquid biopsy in AD [129].

Superparamagnetic iron oxide NPs (SPIONs) were identified to have a beneficial role in Aβ fibrillation and, thereby, AD therapeutics which could provide more detail into its mechanism, supporting their use. Mahmoudi *et al.* [130] (2013) found that size, charge and surface were deterministic factors in eliciting their effects in which they would be able to express a dual-faceted action due to their variability. For example, higher concentrations would enhance Aβ fibrillation while lower concentrations would inhibit it, necessitating careful dosage considerations during usage. Non-magnetic NPs also exhibit similar results as discussed earlier with respect to dendrimers. Moreover, positively charged SPIONs would enhance Aβ fibrillation and bind to Aβ, producing conformational changes, while negatively charged particles would downregulate the process.

Therefore, the use of these NPs is subjected to significant formulation considerations, which have been reported

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in recent studies. As the surface of the NPs is coated by biological molecules, Aβ would interact with these coatings initially for protein. Study showed that such protein-coated NPs had an inhibitory effect on Aβ fibrillation compared to bare NPs [131].

Gold NPs (AuNPs)

The elemental essence of AuNPs that are attached firmly through chemical means to an organic exterior is to refine its interactive abilities or aim its trajectory and provide the appellation the material is known for. The configurations may be manifold, as nano globes or nanocylinders contingent on their photonic and charged characteristics. Their harmlessness is considerable and its passage beyond the BBB into the central nervous system (CNS) proves undemanding.

According to the latest study, administering maize tetrapeptide-anchored gold nanoparticles could enhance the function of the central cholinergic system and decrease the acetylcholinesterase levels, indicating the possibility to employ the new tetrapeptide as a neuroprotective treatment to ward off AD [132]. Another study also found that administering AuNPs to AD rats greatly reduced neuroinflammation and altered mitochondrial functioning, reversing the symptoms of AD [133].

Size Effect. Protein-NP interactions are the milestone events in AD therapeutics, especially their interaction with the Amyloid protein, as they are the therapeutic target. Size is one of the significant determining factors that can influence Aβ aggregation, as evidenced by studies examining the effect of varying sizes [134]. The adjustable size makes it a suitable platform for incorporating aggregation inhibitors [135]. Gao *et al*. [136] (2017) showed that larger-sized AuNPs would enhance fibrillation while smaller sizes inhibited them, similar to the dual effect discussed before. Thus, smaller NPs exhibited better performance, attributing their effect on protein folding, which was adsorbed by NPs. Moreover, smaller NPs showed large BBB permeability, thereby resolving the site-delivery challenge for aggregation inhibitors [137].

Antioxidant Effect. Antioxidants can alleviate the oxidative stress faced by the neurons, owing to their chelating activity and their usage has been approved in the therapy of AD. In addition to overcoming the BBB permeability challenges and acting as an effective drug carrier, they have intrinsic antioxidant properties [138]. Studies have evidence of the same with their effect on dermal and muscle injury models [139].

Anti-Amyloidosis Potential. As discussed earlier, they inhibit Aβ aggregation under both intracellular and extracellular conditions. Apart from this, they can also dissolve and remove toxic Amyloid plaques from the brain tissues [140]. Sanati *et al*. [141] (2019) reported their ability to improve spatial learning and memory in mice models. Thus, AuNPs have a big potential in AD therapy.

The Chiral Status. Chiral AuNPs possess the same advantages as discussed above but hold additional importance due to the absence of internalization by the brain cells, as seen in some instances in small AuNPs, thereby eliciting their full potential [142]. Due to this, they are able to protect the neurons from induced cytotoxicity. Extensive study also showed that L-AuNPs exerted their cytotoxic effect on healthy cells, which can be resolved by the use of D-AuNPs with their inhibition ability and selective toxicity [143].

Quantum Dots (QDs)

QDs are 1.5–10 nm-diameter nanocrystals of semiconducting particles. These NPs exhibit special features such as superior photostability, size-dependent optical characteristics, large extinction coefficient, and a high Stokes shift and brightness. In a recent study, graphene QDs had been developed from the flower of the *Clitoria ternatea* (ctGQDs) plant. These QDs had revealed better acetylcholinesterase inhibition than donepezil and had successfully lowered AD symptoms in rodents [144].

Although nanoparticles have the capacity to penetrate the BBB, approximately only 5% of the drugs would hit the brain. The rest of the drug can elicit adverse effects as they remain in the systemic circulation, leaving behind no beneficial effects [145]. However, it has been demonstrated that intranasal drug administration makes it easier to transport drugs to the central nervous system (CNS) directly through the trigeminal and olfactory nerves of nasal cavity [146]. Additionally, intranasal delivery is safe and non-invasive, and the drug can bypass hepatic first-pass metabolism and drug degradation, increasing its bioavailability [147,148].

A study by Liu *et al*. [122] (2015) showed that graphene-based QDs had a great potential against AD as they prevented accumulation, especially in the Aβ (1–42) region. Xiao *et al*. [123] (2016) used a combination of graphene QDs and glycine-proline-glutamate, a neuroprotective agent in a transgenic mice model, which also showed inhibitory activity on the accumulation of Aβ (1–42) fibres along with an improvement in cognition and memory. Tang *et al*. [124] (2018) also reported similar results with quantified evidence from the detection level.

Moreover, QDs could also contribute to the diagnostic part, as they were proven successful in detecting Apolipoprotein E (ApoE) with utmost sensitivity and accuracy [125]. Therefore, it can be concluded that QDs, especially graphene-based QDs, have their mechanism of action centred around the accumulation of Aβ (1–42).

Table 3. Study evidences on different nanomedicines in practical applications, animal models on which they were tested, clinical outcomes and identified concentration.

Nanocarrier Type	Modifications	Therapeutic Agent	Used Model	Clinical Outcomes/Mechanism of Action	Identified Concentration	Reference
Dendrimers	Maltose-modified PPI dendrimers	Not applicable	Neuronal neuroblastoma and Neuroendocrine cell models	Prevents Amyloid-beta peptide fibrillization.	2 micro M (plasma level)	[149]
	PAMAM dendrimers	N-acetyl-L-cysteine	Rabbit models	Alleviates inflammation and subsequent oxidative stress.	-	[150]
	Cysteine dendrimer	KLVFF peptide	Fibrillar samples	Prevents aggregation of Amyloid-beta peptide.	-	[151]
Polymer NP	Polysorbate 80 coated PBCA	Rivastigmine	Rat model	Increased brain accumulation of rivastigmine.	Liver concentration: 273.0 ± 18.1 ng/mL (free) 408.2 ± 42.1 ng/mL (drug bound)	[152]
	Polysorbate 80 coated PBCA	Nerve Growth Factor	Scopolamine-induced amnesia mice model.	Potentiates cognition and memory function with the aid of growth factors.	490 ± 150 pg/mg	[153]
	polyethylene glycol-poly lactic acid-co-glycolic acid (PEG-PLGA)	Fibroblast growth factor	Rat Alzheimer's disease model	Increases the amount of fibroblast growth factor with enhanced effects on cognition.	523.55 ± 25.51 9 µg/kg (highest blood levels)	[154]
Liposomes	PEG coated liposomes	Anti-Amyloid-beta monoclonal antibodies	Post-mortem Alzheimer's disease brain samples	Binds to Amyloid-beta monomers.	1.6 nM	[155]
	Cell-penetrating peptide modified liposomes	Rivastigmine	Endothelial cell mice model	Enhanced BBB permeation.	5 mg/mL	[104]
Micelles	Ab-PEG-LysB/curcumin (APLB/CUR)	curcumin	APP/PS1 mice models	Target the microglia and control its hyperactivity causing less damage to neurons. Synergistic effect of polymer and cargo caused elimination of extracellular ROS and removal of Amyloid-β (Aβ).	500 µg mL^{-1}	[109]
	polyethylene glycol-poly lactic acid (PEG-PLA)/C3/TPP	Reservatrol	Mice models	Targeted delivery of antioxidants by reversing mitochondrial dysfunction.	3.48 µg mL^{-1}	[156]
Quantum Dots	Selenium based Quantum Dots	-	Mice models	Aggregation of Aβ peptides.	200 µg mL^{-1}	[157]

PPI, poly(propylene imine); PAMAM, polyamidoamine; ROS, Reactive Oxygen Species; KLVFF, amino acid residues 16–20; PBCA, polybutylcyanoacrylate.

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Table 4. Limitations of nanoparticles.

Solubility	Temperature variations can have an impact on how NPs and drugs interact [158].
Bioavailability	Enzymes found in the nasal cavity have a significant impact on a drug's bioavailability which requires increasing the drug dosage when giving, and this induces unpleasant reactions in the nasal mucosa [159].
Blood Brain Barrier	It is necessary to assess the effectiveness of these ligand-modified NPs since they still need a long blood-residency time before they can cross the BBB and enter their target site [160].
Toxicity	Quite a few of its constituents, including proteins, peptides, nucleic acids, and antibody fragments, can act as antigens, increasing immunotoxicity [161].
	Long term build-up of nanoparticles in brain can cause brain injuries with associated neurotoxicity and cytotoxicity [111].
Cost	It needs optimal conditions, specific ingredients, and instruments [162].

Table 3 (Ref. [104,109,149–157]) discusses a few studies using nanocarriers in different models and their safety profiles, outcomes, and identified concentrations. Despite these advantages, nanoparticles have a few limitations, as discussed in Table 4 (Ref. [111,158–162]).

Recent Updates on Patents of Alzheimer's Disease Treatment

Depending on the nanocarrier systems, several patents have been concurred in this field, including those listed in Table 5 (Ref. [163–183]) for multiple dosage forms, solid lipid nanoparticles, liposomes and nanoemulsion. Table 6 (Ref. [104,109,117,121,137,141,144,145,156,184–221]) highlights the current usage of nanoparticles in AD and the recently used formulations in applications [222].

Limitations and Challenges of Nanomedicines

Even though nanomedicines offer numerous advantages in drug delivery in achieving specific and precise actions, there are several challenges when it comes to implementing them [223]. They are as follows:

Practical Measures with Commercial Viability

The concept, production, as well as the use of nanomedicine should be practically feasible to all patients. Therefore, the new product should offer more benefits to its precursor regarding clinical benefit, safety, efficacy, compliance, achieving serum drug concentrations, etc. Such benefits can only justify its placement in the market [224]. However, the commercial viability among the consumers and retailers remains a question, as the cost to convert a simple tablet formulation into an advanced nanoformulation product is 10 times higher of its precursor. So a humongous array of advantages should be presented to counter the commercial disadvantage offered [225].

Clinical Development Process

As a novel therapy, the clinical development associated with the drug should include specific variables that affirm the safety and efficacy of the drug and prove its superiority among the existing standards. Alas, more effort, time, and capital are needed to determine such variables [139]. Other than that, the inclusion criteria would go beyond the limits of the research. If the variables are to be proven accurately without any compromise, the remaining way to cut down costs is to reduce the sample population. This would affect the study in terms of reliability and significance, as the therapy aims to reach a larger population, which requires sufficient evidence. Not only that, the biomarkers that must be monitored during and after patient administration must be identified and assessed for viability [226].

Gap between Pre-clinical Data and Clinical Implementation

It is a known fact that data from animal studies would not be 100% compatible with the ones obtained from clinical studies. Due to this, there is a fine line that researchers must tread carefully while giving importance to positive preclinical data, as there are variabilities that can overturn the results. As this system focuses more on the pharmacokinetics and inter-individual variability, a generalised prediction model is impossible. Integrating them into personalized therapeutic approaches is both a need and a disadvantage, as future outcomes are more or less uncertain [227].

Gap between Preclinical Data and Patient Safety

Nanomedicines offer safety issues in three contexts: with the different biodistribution patterns and uptake that can result in organ damage, the toxicity of the excipients they use, and their immunological responses. It is difficult to predict the immunological reactions and they also can cause hypersensitivity or related issues. Therefore, referring to or employing cell interaction assays and complement binding studies *In vitro* are important to obtain closely specific data [228].

Manufacturing and Quality Control

It is important to note that when it comes to nanomedicines, the nanomaterial that confines the drug within would impart every pharmacokinetic process such as biodistribution, bioavailability and drug concentration [229]. Even though quality checking is necessary for every drug, here it confers additional load, as the nanoformulations and excipients must be checked for quality, which

Table 5. Patents on AD therapeutics.

Ref	Patent no	Filing country	Drug/active ingredient	Findings	Invention's field	Filled year	Granted year	Anticipated expiration/Status
[163]	US5888536	USA	Selegilin [(-)-N-α-dimethyl-N-(2-propynylphenylethylamine)] along with phospholipids	Enhanced permeability in the case of transdermal administration for AD therapy and improved targeting once administered parenterally. The preparation can be administered by orally, transdermal form or parentally.	Treatment of AD, motion sickness, Parkinson's disease, myelitis, depression, or stroke	1995-10-20	1999-03-30	2015-10-20
[164]	US20060018839A1	USA	Cholinesterase inhibitors that is donepezil hydrochloride	Cholinesterase inhibitors (ChEIs) are delivered via a variety of delivery methods, including the nasal and ocular routes. Improves site-specific targeting. The novel formulation can be administered through nasal.	Treatment of dementia, cognitive impairments, and other disorders	2004-11-16	2006-01-26	Abandoned
[165]	US20120035187A1	USA	Novel compound prepared by the general formula 1	The novel compounds formulated have improved anti-neurodegenerative efficacy by stimulating neurocytes and accelerating neurite outgrowth.	Apply for the treatment of neurodegenerative diseases.	2010-01-25	2012-02-09	Abandoned
[166]	US8017147B2	USA	Nutritional synergistic supplement using different plant extracts	Vitamins and nutritional compositions made with the aid of microfluidizers to enhance the well-being of AD patients. It can be used as food/drink/supplement/drug /cosmetic/hygienic product.	Used as molecular nutrition, nano-dispersion, nano-emulsion, nano-encapsulation and nutrigenomics for the prevention of cardiovascular, AD and lowering blood sugar	2009-10-02	2011-09-13	2028-07-08
[167]	US9427405B2	USA	Model drug, and liposomes prepared using cholesterol and sphingomyelin	Liposome based with high binding with beta Amyloid peptide in "monomer" and "oligomer" and reduce Aβ plaques.	It is used for the therapy and diagnosis of diseases due to large quantities of beta Amyloid peptide in body	2009-06-10	2016-08-30	2030-07-29
[168]	EP2332570A1	Europe	Glatiramer acetate (GA) as a submicron emulsion or a nanoemulsion	Nano-emulsion and proteosomes for GA to reduce neuroinflammation in AD.	Treatment of neurodegenerative disorders	2005-06-27	2011-06-15	Withdrawn
[169]	US20110045050A1	USA	Multiple therapeutic agent containing single or blended oil and vitamin E	Bioavailability of several drugs can be enhanced by prepared nanoemulsion.	The poorly water-soluble drug is administered by microporous devices for controlled intraluminal delivery locally	2009-08-24	2011-02-24	Abandoned
[170]	US8349293B2	USA	Nanoparticle of metallic ions	Magnetic resonance imaging (MRI) using metal-based nanoparticles to diagnose Alzheimer's disease.	It can be used for the diagnosis of the AD	2008-03-21	2013-01-08	2029-04-13
[171]	WO2014076709A1	WIPO	Peptide drugs	Liposome based systems conjugated with peptide for improved recognition of peptide.	Used for the recognition of Apolipoprotein peptide and short Amyloid beta peptide	2013-11-19	2014-05-22	No details

Table 5. Continued.

Ref	Patent no	Filing country	Drug/active ingredient	Findings	Invention's field	Filled year	Granted year	Anticipated expiration/Status
[172]	US8877207B2	USA	Cerium oxide coated with polyethylene glycol	Aβ specific antibody conjugated with polymeric nanoparticles based on Cerium oxide, and improved the therapeutic efficacy for AD.	It can be used for the treatment of the AD	2011-07-18	2014-11-04	2031-07-18
[173]	EP2550020B1	Europe	Metal ions and lipids	Metal ions and several lipids for improved targeting following principles of micellar system. It is administered orally.	It is utilized in the pharmaceutical and dietetic fields	2011-03-24	2015-07-08	2031-03-24
[174]	US9192644B2	USA	Curcuminoid	The mixture comprises curcuminoid solid lipid nanoparticle (SLN) and attenuates site-specific concentration. The preparation can be administered using capsule, gel, and liquid.	The novel formulations are used for the treatment and prevention of age-related diseases	2007-03-06	2015-11-24	2030-03-02
[175]	US10662226B2	USA	Synthetic beta Amyloid peptides	The generated Aβ peptides have the ability to aggregate into stable, soluble oligomers that can be used to better understand, diagnose, and treat AD. It is discussed how similar antibodies (specific to oligomeric Aβ) are developed.	It is used to bind specifically target soluble Amyloid-beta oligomers	2017-10-26	2020-05-26	2037-10-26
[176]	WO2018081460A1	WIPO	Anti Amyloid-beta antibody combined with beta-site Amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor	The new antibody composition is used to treat, prevent, and/or delay the start and/or progression of AD.	It is administered for the treatment of AD	2017-10-26	2018-05-03	Details not available
[177]	WO2018197383A1	WIPO	Idalopirdine, Baclofen and Acamprosate	Based on their respective prodrugs and salts, this combinatorial therapy produces improved therapeutic efficacy for AD.	It is a novel combinatorial therapy and used for the treatment of AD	2018-04-23	2018-11-01	Details not available
[178]	WO2018148821A1	WIPO	Ginseng green tea, catechin, and ginsenosides	Ginseng and ginsenosides combined actively to enhance brain cell bioavailability and cognition.	Increases the bioavailability of ginseng or ginsenoside by complexing with phospholipid	2018-02-16	2018-08-23	Details not available
[179]	US10485766B2	USA	Bryostatins	This innovation involves the development of Bryostatin-1 oral nanoparticles that promise to quickly improve cognitive function. The formulation can be administered orally.	It is used for the treatment of Hutchinson Disease, Down's syndrome, Parkinson's disease and AD	2015-05-18	2019-11-26	2032-12-19
[180]	EP2994160B1	Europe	IgG and/or anti beta Amyloid monoclonal antibody	The current study suggests treating AD (in those having the apolipoprotein E4 (ApOE4) allele) for two weeks with therapeutically effective doses of pooled immunoglobulin G. Based on monoclonal antibodies against Amyloid-beta.	Used for the treatment of AD	2014-05-05	2019-07-03	2034-05-05

Table 5. Continued.

Ref	Patent no	Filing country	Drug/active ingredient	Findings	Invention's field	Filled year	Granted year	Anticipated expiration/Status
[181]	US20210324056A1	USA	Anti-Aβ protofibril antibody	Anti-Aβ protofibril antibody BAN2401 significantly decreased the Amyloid level in brain and improved the therapeutic efficacy.	Appliedfor the treatment of AD	2019-07-23	2021-10-21	Pending
[182]	US10828276B2	USA	Bryostatin-1 and Retinoic acid	Bryoid and a Retinoid combination to increase alpha-secretase production and decrease the development of Amyloid-beta plaque. It can be delivered in the form of tablets, capsules, ointment, creams, suppositories etc.	Treatment of AD, Parkinson's disease, Hutchinson Disease, Down's syndrome, virus latency and cancer	2013-11-26	2020-11-10	2033-11-26
[183]	CN110559454B	China	Nano composite medicine	The therapeutics utilizes peptides that home in on cathode ray tubes (CRTs) and quadrupole superparamagnetic ferrites (QSHs). Nanosphere based antibodies against Aβ.	It can be used for diagnosis and treatment AD	2019-09-29	2022-04-01	2039-09-29

Table 6. Recent updates on the application of nanomedicines in AD therapeutics.

Drug	Loaded substance	Ligand	Route of Administration	Dose	Used Model (*In vitro*/*In vivo*)	Results	References
Liposome							
Metformin	Phosphatidyl serine	-	Intraperitoneal	50 mg/kg	Adult male Wistar rats	Decreased neuroinflammation. Potentiated cognition.	[184]
-	Chitosan	pApoE2	Intravenous	1 mg/kg	bEnd.3 cells C57BL/6 mice	Cell viability reduction. Phospholipid concentration increased *In vivo*: Higher expression of *ApoE* gene.	[185]
Osthole	-	Transferrin	intravenous	10 mg/kg	hCMEC/D3 cells and APP-SH-SY5Y cells APP/PS-transgenic mice	Increased drug penetration, pH controlled release.	[186]
	Glutathione-PEGylated (GSH-PEG)	VHH-pa2H Glutathione (GSH)	IV bolus	5 mg/kg	APP/PS1dE9 transgenic mice	Increased uptake values in the blood.	[187]
Galantamine hydrobromide (HBr)	Soya Phosphatidylcholine	-	Oral and intranasal	3 mg/kg	PC-12 cell, male SD rats	Enhanced drug penetration and bioavailability.	[188]
Donepezil	1,2-distearyl-sn-glycero-3-phospholine (DSPC)	-	Oral and intranasal	1 mg/kg	Male Wistar rats	Enhanced drug penetration and bioavailability (75.5% drug release).	[189]
Rivastigmine	Egg Phosphatidylcholine (EPC), Cholesterol, 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol-cell-penetrating peptide (DSPE-PEG-CPP)	cell-penetrating peptide (CPP)	Intranasal and intravenous	1 mg/kg	male SD rats	Potentiated encapsulation and release.	[104]

Table 6. Continued.

Drug	Loaded substance	Ligand	Route of Administration	Dose	Used Model (*In vitro*/*In vivo*)	Results	References
Micelles							
Resveratrol	polyethylene glycol-poly lactic acid (PEG-PLA)	C3 peptide	Intravenous, 10 mg/kg		HT22 cells, APP/PS1 transgenic mice	Enhanced accumulation and targeting. Potentiated cognition. Inhibits Aβ.	[156]
Curcumin	PEG	Aβ peptide	Intravenous		SH-SY5Y, APP-swe/PS1dE9 transgenic mice	Improvement in memory. Inhibit Aβ.	[109]
-	Linoleic acid	Lactoferrin	Oral, 4 gm/mL		Adult male Wistar rats	Inhibits Aβ aggregation and oxidation.	[190]
	PMO-block-polymerizing with butyl methacrylate (PMO-b-PBM), POEG-b-PBM and PF	-	-		PC-12 cells	Inhibits Aβ aggregation and fibrillation. Showcases cytotoxicity.	[191]
Solid-lipid NPs							
galantamine HBr	Glyceryl behnate, pluronic F-127, tween 80	-	Oral route, 2.5 mg/kg		Adult Wistar rats	Enhanced drug entrapment and release. Increased action.	[192]
Rivastigmine	Campritol 888 ATO	-	-		Franz diffusion cell, goat nasal mucosa	Enhanced drug diffusion.	[193]
Donepezil	Stearic acid, oleic acid, lecithin, sodium taurodeoxytaurocholate	-	Transdermal		-	Enhanced permeation and delivery.	[194]
Rivastigmine	Glyceryl monostearate (GMS), castor oil	-	Transdermal		Albino Wistar rats	*In vitro*/*In vivo*: Non-irritant. Enhanced bioavailability.	[195]
Erythropoietin	GMS, span 60, span 80, tween 80	-	Intraperitoneal, 1250 IU/kg and 2500 IU/kg		Albino male Wistar rats	Resolved memory issues and potentiated efficacy.	[196]
Nicotinamide	Stearic acid, phospholipon 90G, sodium taurocholate	Phosphatidylserine	Intravenous or intraperitoneal		BCES, SH-SY5Y, adult male Sprague-Dawley rats	Neuroprotection. Enhanced bioavailability.	[197]
Resveratrol	Lecithin	-	Oral, 10 mg/kg		Male Sprague-Dawley rats	Ensures sustained release.	[117]

Table 6. Continued.

Drug	Loaded substance	Ligand	Route of Administration	Dose	Used Model (*In vitro*/*In vivo*)	Results	References
Resveratrol and grape extract	Cetyl palmitate, tween 80, tween 20	Anti-transferrin receptor mAb (OX26 mAb)	-		HBEC	Reduced Aβ aggregation.	[198]
Quercetin	-	-	Intravenous, 4.41 mg/kg		Male Wistar rats	Enhanced BBB crossing and cognition.	[199]
Lipid NPs							
Quercetin	-	Transferrin	-		hCMEC/D3 cells	Less cytotoxicity to BBB.	[200]
Curcumin	Phosphatidylcholine (PC), cholesterol oleate, glycerol trioleate	Lactoferrin	Intravenous, 10 mg/kg		BCECs, SD rats	Enhanced activity and permeation.	[201]
Polymeric-NPs							
Galantamine	PLA-PLGA	-	Intranasal, 3 mg/kg		Wistar rats	Good drug-carrier stability and bioavailability.	[202]
Donepezil	PEG-PLGA	-	-		HBMEC and HA cell	Decreased neuroinflmmation. Destabilizes beta-fibrils.	[203]
Rivastigmine	L-Lactide-depsipeptide	-	-		-	Sustained Release.	[204]
Resveratrol	Methoxy PEG-caprolactone	-	-		*Caenorhabditis elegans*, N2, CF1553, CL4176, and CL1175	Antixidant properties with radical scavenging and lipid peroxidation.	[205]
Curcumin	PLGA-PEG	B6 peptide	Intraperitoneal, 25 mg/kg		HT22 cells/APP/PS1 transgenic mice	Improvement in spatial learning and memory. Reduced Aβ aggregation.	[206]
ECG	PLGA, PEG, ascorbic acid, tween 80	-	Oral, 40 mg/kg		BMVECs, APP/PS1, C57BL/6 mice	Reduced neuroinflammation. Positive effect on spatial learning.	[207]
Pioglitazone	PLGA-PEG, tween 80	Anti-Aβ antibody	Oral, 10 mg/kg		HBEC, hCMEC/D3 cell line, APP/PS1 transgenic mice	Decreases concentration of Aβ peptide.	[208]
Quercetin	PLGA, polyvinyl alcohol (PVA)	-	Intravenous, 20 mg/kg		SH-SY5Y cells, APP/PS1 mice, BALB/c nude mice	Offer low toxicity sand high viability, Enhanced efficacy.	[209]

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Table 6. Continued.

Drug	Loaded substance	Ligand	Route of Administration	Dose	Used Model (*In vitro*/*In vivo*)	Results	References
-	PEG-PLA	B6 peptide	Intravenous, 1 mg/kg		bEnd.3 cells, male ICR mice	Enhaced BBB penetration and cognition.	[210]
Galantamine	Thiolated-chitosan NPs	-	Intranasal 4 mg/kg		Swiss albino mice	Enhaced ACh activity.	[211]
Memantine	Polyamidoamine (PAMAM) dendrimer	Lactoferrin	Intraperitoneally, 2 mg/kg		Swiss albino mice	PAMAM-MEM maximum release concentration was 77.14 ± 6.0% after 6 h. Improved ACh activity.	[121]
Nanoemulsions							
Memantine	-	-	Intranasal, 5 mg/kg		Neuro 2a, Sprague-Dawley rats	*In vitro/In vivo*: 98% cell viability and sustained its antioxidative potential. Increased bioavailability.	[212]
Donepezil	Labrasol (10%) as oil, cetyl pyridinium chloride (CPC) (1%) as surfactant in water (80%), glycerol (10%) as co-surfactant		Intranasal, 0.45 mg/kg		Neuro 2a, Sprague-Dawley rats	*In vitro/In vivo*: Maximum drug release of 99.22% in 4 h in PBS. Non-toxic. Effective drug delivery.	[213]
Huperazine A	Capryol 90 (oil phase), cremophor EL & labrasol (surfactant & co-surfactant) & lactoferrin (targeting ligand)	Lactoferrin	Intranasal		hCMEC/D3 cells, adult Wistar rats	*In vitro/In vivo*: No nasal mucosal toxicity. Effective BBB penetration. Enhanced activity.	[214]

Table 6. Continued.

Drug	Loaded substance	Ligand	Route of Administration	Dose	Used Model (*In vitro*/*In vivo*)	Results	References
Quantum Dots							
-	Graphene Quantum Dots (QDs)	-	-		Adult male Wistar rats	*In vitro*/*In vivo*: Enhanced penetration across BBB. Improved learning and memory. Reduced level of lipid peroxide and nitric oxide.	[145]
-	Black phosphorous QDs	-	-		PC12 cells	*In vitro*: Low cell toxicity. Inhibited insulin and Aβ aggregation.	[215]
-	Selenium-doped carbon QD	-	Intravenous		PC12 cells, adult male Wistar rats	*In vitro*/*In vivo*: High cell viability. Inhibited Aβ aggregation. Improved memory and cognitive function of an AD rat model.	[216]
Curcumin	Graphene QD & indium-tin-oxide Electrode	-	-		-	*In vitro*: High sensitivity on detection of ApoE4 DNA. Enhanced efficacy.	[217]
Gold nanoparticles							
-	-	L and D Glutathione	Intravenous, 25 mg/kg		SH-SY5Y cells, C57BL/6 mice	*In vitro*/*In vivo*: Effective BBB penetration. Improved behavioral performance.	[137]

Table 6. Continued.

Drug	Loaded substance	Ligand	Route of Administration	Dose	Used Model (*In vitro*/*In vivo*)	Results	References
AuNP	-	-	Intraperitoneal,	2.5 mg/kg	Male Wistar rats	*In vivo*: Normalize tau phosphorylation. Prevented oxidative stress and neuroinflammation.	[144]
AuNP	-	Bucladesine	Intrahippocampal, intraperitoneal		Male Wistar rats	*In vivo*: Better acquisition and retention of spatial learning and memory. Improved neuron survival.	[141]
-	3D-Au-PAMAM, electro grafted p-aminobenzoic acid (PABA)	CAb-GA conjugate	-		-	Detection: Effective detection of tau protein. LOD value of 1.7 pg/mL.	[218]
Magnetic Nanoparticles							
Quercetin	superparamagnetic iron oxide nanoparticles (SPIONs)	-	Oral,	50 and 100 mg/kg	Male Wistar rats	*In vivo*: Increased penetration. Enhanced Bioavailability.	[219]
-	Sialic acid (SA)-modified selenium (Se) NPs	B6 peptide	-		PC12 cells and bEnd.3 cells	*In vitro*: Effective in crossing BBB. Inhibitory effects on Aβ peptide.	[220]
siRNA	PEGylated magnetite NPs	OmpA	-		HFF-1 cells and SH-SY5Y cells	*In vitro*: Reduced cell toxicity. Enhanced activity. Silencing of *BACE1* gene in HFF-1 cells.	[221]

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Table 7. Summaries of the application of different nanotechnology-based approaches in the treatment of AD, their advantages and disadvantages.

Nanoparticle Type	Advantages	Limitations	References
Liposomes	• Biocompatible • Encapsulate both hydrophobic hydrophilic drugs • Proven safety in clinical applications	• Stability issues in the bloodstream • Rapid clearance by the reticuloendothelial system	[231]
Micelles	• Solubilize poorly water-soluble drugs • Dynamic and self-assembling structure	• Lower drug-loading capacity • Stability issues *In vivo*	[232]
Solid-Lipid Nanoparticles	• Improved drug stability • Sustained drug release	• Drug expulsion during storage • Limited to lipophilic drugs	[233]
Lipid Nanoparticles	• High bioavailability • Suitable for RNA/DNA drug delivery	• Complex production process • Stability concerns	[234]
Nanoemulsion	• Improved drug solubility and bioavailability • Suitable for oral, topical, and parenteral delivery	• Stability issues over time • Phase separation concerns	[235]
Quantum Dots	• Bright and photostable fluorescence for imaging • Multi-functionalization possibilities	• Potential toxicity due to heavy metals • *In vivo* clearance challenges	[236]
Magnetic NPs	• MRI contrast agents • Can be guided for targeted drug delivery	• Potential biocompatibility issues • Overheating in magnetic hyperthermia	[237]
Dendrimers	• Well-defined molecular structures • Ease of functionalization	• Potential cytotoxicity • Complex synthesis	[238]
Polymeric NPs	• Controlled/sustained drug release • Surface modifications for targeting	• Potential toxicity depending on the polymer • Production scalability challenges	[239]

is a sophisticated method. Moreover, drug release and action depend on particle size, charge, pH, drug encapsulation, etc., which must be considered in manufacturing. Therefore, proper adherence to GMP rules is necessary. Precise and careful designing are also needed, as the process of reformulation is both tedious and expensive [230]. The practical advantages and limitations of the specified nanotechnological approaches for AD are listed in Table 7 (Ref. [231–239]).

Toxicity Profile of Nanoparticles

The core of nanotechnology has sparked a technological revolution in various domains, from medicine and pharmacy to energy and environmental science. Their unique properties, including their surface area, volume ratio and Quantum effects have made them instrumental in addressing numerous contemporary challenges. However, the promising facets of nanoparticles are entwined with concerns regarding their potential toxicity and environmental implications [240].

In terms of toxicity, nanoparticles' size and surface characteristics have a profound impact on their biological interactions. When these particles reduce to the nanoscale, their high surface reactivity and ability to penetrate biological barriers can lead to unforeseen toxic effects [241].

A central area of concern with nanoparticles is their capacity to induce oxidative stress. Potential toxicity arises from the increase in Reactive Oxygen Species (ROS) owing to the NP administration. Such ROS-mediated injuries could potentially incite chronic inflammatory responses, induce genomic alterations, and stimulate programmed cell death (apoptosis), culminating in the manifestation of pathological conditions such as neoplasia, neurodegenerative ailments, and cardiovascular disorders [242].

Bio-persistence is another pivotal concern with nanoparticle toxicity. Unlike larger particles, nanoparticles are able to resist the body's clearance mechanisms, leading to their accumulation over time. Their persistence can enhance the possibility of prolonged exposure to tissues and organs, inflicting chronic toxicity [243].

Immunotoxicity is another aspect of its toxicity profile, owing to its interactions with the nanoparticles in the immune system of the physiological system. The reactions however would vary with the shape, size and other pharmacokinetic characteristics of the system under application [244].

Nanoparticle cytotoxicity, governed by their physicochemical properties, is also a significant area of concern. Experimental investigations performed in controlled laboratory conditions had revealed that specific nanoparticles possessed the ability to impede normal cell function, inflicting harm to the cell membrane, causing degeneration of intracellular constituents, and precipitating cell mortality. Additionally, nanoparticles might perturb the stability within cells, instigating modulated cellular responses that could ultimately lead to cell malfunction or demise [245].

Therefore, despite nanoparticles have provided substantial advancements in multiple fields, their potential tox-

icity cannot be overlooked. Meticulous exploration on nanoparticle toxicity is an absolute necessity to fully capitalise on the immense potential of nanotechnology, while safeguarding both human health and environmental integrity. In tandem, it is essential to ensure that legislative frameworks and directives guidance on the utilisation of nanoparticle and waste management are continually revised, reflecting the advancing insights into nanoparticle toxicological effects.

Current and Future Perspectives

By actively controlling different routes in targeted places, nanocarriers appear to offer promising potential among the present and futuristic therapeutic modalities. Prior to the introduction of nanomedicines for AD in the clinical context, a few challenges in targeting and drug distribution on the site must be considered. The aim should be to target not only the BBB but also the affected site to avoid distribution throughout the brain. Besides the current increase in the registration of patents relating to nanotechnologies, further research is essential to assess the clinical efficacy and possible toxicological effects of nanotechnology-based systems in humans. It is also necessary to pay close attention to the stability and safety of different polymers used as nanocarriers in terms of biological retention, exposure period, nanocarrier dose, size and metabolites. The evaluation of the adequacy and safety of suitable nanocarriers through human clinical research might bring the push it requires to develop the much needed cost-effective AD therapies [246,247].

The exploration of nanotechnology in Alzheimer's disease (AD) thus far illuminates a pathway towards addressing some of the most persistent challenges in diagnosis, treatment, and understanding of the disease. As we stand on the threshold of significant advancements, the integration of current applications with forthcoming innovations could redefine our approach in managing AD.

Current applications have laid a robust foundation, particularly in the realms of targeted drug delivery and early diagnosis. Nanoparticles' ability to cross the Blood Brain Barrier (BBB) and target pathological hallmarks of AD directly offers a promising alternative to conventional methods, which often fall short in specificity and effectiveness. Similarly, the development of nanotechnology-based diagnostic tools has started to facilitate earlier and more accurate detection of AD, essential for timely intervention [248].

Looking forward, the horizon of nanotechnology in AD is vast and varied, offering exciting prospects. Future research should aim to develop nanoparticles that not only target and mitigate the hallmark lesions of AD such as Amyloid-beta plaques and tau tangles, but also address other pathological factors including inflammation and oxidative stress. This holistic approach could significantly improve the efficacy of treatments [249]. Nanotechnology holds promise in regenerative medicine, potentially enabling the repair of neuronal damage and the promotion of neurogenesis through the delivery of stem cells or growth factors. Nano-scaffolds could support the integration of new neurons, offering hope in restoring cognitive functions lost to AD [250]. The application of nanotechnology might bring us to more sophisticated BCIs and offer novel solutions to cognitive impairments in AD patients. This direction not only aims to mitigate symptoms but also to enhance the quality of life and independency of individuals with AD [251]. The future of nanotechnology in AD leans heavily towards precision medicine, with treatments tailored to individual patients based on genetic, biomarker, and phenotypic profiles. This approach promises more effective, personalised care plans, optimising therapeutic outcomes based on real-time data [252].

As we navigate this promising landscape, it is imperative to rigorously assess the long-term safety and ethical implications of integrating nanotechnology into AD care. Continuous research and dialogue among scientists, clinicians, ethicists, and patients are crucial to ensure these innovative approaches are safe, effective, and equitably accessible [253].

Conclusion

Recent evidence suggest that the exposure to risk factors during midlife is associated with vascular cognitive impairment, which directly depends on the duration of exposure. Limiting vascular brain injury can inhibit the development of this disease and overt dementia.

Memory changes have become a concern to many old age patients since scientists and doctors started to focus their attention mainly on AD and dementia. According to an estimation, 10% to 25% of risk factors could possibly reduce 3 million cases of AD worldwide, and a reduction in all risk factors would have the greatest impact on the prevalence of dementia. Half of the cases of AD are believed to be avoidable based on modifiable risk factors. Lack of clarity regarding the mechanisms underlying the pathophysiology and pathogenesis of memory loss is a major challenge in its treatment. Current paradigms of drug design for AD have changed by targeting multiple disease aspects rather than a single-target approach (Amyloid-centric). Preventive strategies at the initial stages are more effective than treatment during later stages.

Current management strategies include repurposing drugs to treat and manage various conditions including neuronal protection, anti-inflammation, and neurogenesis. Different epigenetic approaches are under the pipeline for treating Alzheimer's condition. Its key characteristics are the buildup of Aβ peptides and associated neurodegeneration. They are also based on tau proteins and the characteristics include hyperphosphorylation and accumulation of NFTs. As mentioned, the presently available treatment for AD pri-

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marily focuses on reducing symptoms due to the drug's inability to cross the BBB. Because of its many benefits, therapy based on nanotechnology has the ability to overcome this particular obstacle. Therefore, nanotechnology should be the new preferred mode of treatment for AD to ensure enhanced and site-specific drug delivery. The use of nanotechnology has been extended to bioimaging and proteomics. Research on translational animal models has gained popularity, ranging from transgenic mice to non-human primates, and these ongoing advances may unwind potential and effective treatment paths. Even then, the cost-related challenges in the field remain the same, which needs to be addressed and countered.

Availability of Data and Materials

All data included in this study can be obtained by contacting the first author if needed.

Author Contributions

SCN, AD and AJ designed this study. ABK, AD, AJ, SCN, AS, HAAG, SR, ES, JK, SHK and RKS performed the data collection and formal analysis. AD, ABK, SR, AJ, RKS and SCN contributed to the writing—original draft. AD, SR, AS, HAAG, SHK, ES, RKS and JK contributed to the review and editing. All authors contributed to important 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

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Conflict of Interest

The authors declare no conflict of interest.

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