

DENDRIMERS IN ALZHEIMER'S DISEASE: CURRENT STATE AND FUTURE DIRECTIONS

Abstract

Alzheimer's disease (AD), neuronal death, and synaptic loss are all characterized by extracellular amyloid-(A) plaques and neurofibrillary in the intracellular milieu, all of which lead to progressive cognitive impairment. The prevalence of AD exponentially rises after age 65, making age the most major risk factor for the disease. It is expected that during the next 20 years, the overall prevalence of AD will double as the average lifespan in emerging nation's increases. Ideal drug delivery systems depend on the pharmacokinetics and pharmacodynamics of many innovative formulations to achieve the following characteristics: efficient drug transport to the target tissue, consistent therapeutic drug concentrations, a reduction in dose quantity and frequency, and increased patient compliance. Various dendrimers-based formulations, include orally disintegrating tablets, extended-release capsules, and numerous attempts to develop alternative delivery systems, including Three basic components make up a typical dendrimer molecule: a central core composed of at least two identical functional groups on an atom or molecule; branching units that emerge from the central core; and various peripheral surface functions, such as drug delivery, a nose-to-brain delivery system, and nano formulations with various nano-carriers for the treatment of AD. Fate of all the novel formulations depends on the Pharmacokinetics and Pharmacodynamic behavior of the drug substances. Pharmacokinetics (PK) studies the disposition of drug molecules in the body, including their concentration patterns and AUC last, T_{max} , C_{max} , and AUC in values Pharmacodynamic (PD) assessment looks at how a drug affects the body includes variations in E_{max} , EC_{50} , in an E_{max} - model

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parameter. A drug must cross the blood brain barriers and be absorbed by the specific tissues in order for it to be effective in treating an Alzheimer patient (as measured by PK studies). To successfully alter the target protein activity in the body (as determined by PD studies), this is required. This chapter will focus on the various novel formulations Targeting AD and its Pharmacokinetics and Pharmacodynamics behaviour.

Keywords: Dendrimer, Pharmacokinetic, Pharmacodynamics, Alzheimer's disease (AD), blood–brain barrier

I. INTRODUCTION

Alzheimer's disease (AD) is a condition that results in a decline in cognitive function and a loss of independence in daily activities. This condition is primarily caused by a complex illness known as AD, which brings about the deterioration of brain cells. The two primary causes of AD are cholinergic and amyloid, although other risk factors primarily target symptoms rather than underlying causes. This chapter aims to explore the available drugs on the market as well as potential therapeutic options for AD, including disease-modifying therapeutics (DMT), chaperones, and natural compounds [1]. Dendrimers are a type of three-dimensional, nanoscale, artificial macromolecules with a well-defined globular architecture. The monodispersity, biocompatibility, and good biodegradability of dendrimers make them special [2]. A typical dendrimer molecule has three fundamental parts: a central core made up of an atom or molecule with at least two identical functional groups, branching units that come from the central core, and various peripheral surface functions [3]. As a result, dendrimers are made up of repeating branching shells; each branching shell is referred to as a generation [4-5]. Dendrimers have been effectively used in preclinical delivery of a number of medicinal compounds with various pharmacological properties, including anti-inflammatory, hypolipidemic, antibacterial, antifungal, and anticancer [6]. Psychiatric conditions, other neurodegenerative illnesses, such as fronto-temporal dementia other disorder that cause dementia [7]. When chronic (lasting for months), these encephalopathies are considered in the differential diagnosis of dementia [8]. Toxic-metabolic encephalopathies are the outcome of several insults that might impair cognitive function [9].

The biological cause of dementia is chronic disease that modifies or destroys brain-related nerve cells and synapses [10]. For the most prevalent neurodegenerative diseases of aging that lead to dementia, there are currently no viable treatments to prevent or reverse the underlying disease process [11]. The number of elderly people suffering from dementia is increasing, as are the resources and expenditures connected with their care [12]. This is due to longer life expectancies. People of all ages are susceptible to dementia. A person must have had a higher level of intellectual ability before a drop in order to be classified as demented, per definition. More dementias strike people who have lived long enough to acquire intellectual skills before losing those [13]. Because diagnosing and documenting dementia cases in the poor world is challenging, it is challenging to acquire estimates of the incidence and prevalence of dementia globally [14]. The illnesses that are classified as dementia and the types of dementia that should be included in these surveys also differ between studies [15]. Numerous textbooks claim that degenerative dementias are the most frequent causes of dementia, with AD being the most prevalent in that category [16].

Following AD, considerable percentages of dementia cases (perhaps 10–20%) are caused by disorders like frontal lobe dementia and dementia of the Lewy body type [17]. But it is becoming better acknowledged that people with so-called vascular dementia frequently experience a mixed overlapping pattern with AD [18]. Additionally, vascular abnormalities including amyloid angiopathy and arteriosclerosis are frequently seen in AD patients [19]. Independent life is impacted by the dementia syndrome of cognitive impairment or cognitive decline [20]. Every four seconds, a new case of dementia is reported globally [21].

II. PATHOGENESIS AND CLINICAL FEATURES IN AD

Alzheimer's disease is a neurodegenerative condition that progresses and is quite complex. It is one of the main contributors to dementia cases worldwide. The neuropathological characteristics of AD entail the presence of neurofibrillary tangles (NFTs) that are composed of hyper phosphorylated microtubule-associated proteins and plaques that accumulate extracellularly, as depicted in figure1. The accumulation of $A\beta$ in the locus coeruleus, transentorhinal, and entorhinal regions of the brain leads to tangle formation, and various *in vivo* studies targeting AD have been investigated, as illustrated in table 1. They explained the cause, pathophysiology, and elements involved in the course of AD because $A\beta$ and NFTs are thought to be the main players in the illness [22].

Table 1: Studies Conducted *in Vivo* Targeting Alzheimer's disease have been Examined

Polymer	Target site	Drug used	<i>Invivo model</i>
Polymer	Target site	Drug used	Invivo model
Chitosan	$A\beta$	Cannabidiol	$A\beta$ 1-42 peptide-induced AD rat model
PLGA	$A\beta$	-	C57 mice
PLLA and PLGA	AChE	Galantamine	Wistar rat
PLGA	$A\beta$	-	5xFAD AD mice
Chitosan	$A\beta$, oxidative stress	Tanshinone IIA	Caenorhabditis elegans model of AD
Prussian blue,	$A\beta$, oxidative stress	--	APP/PS1 transgenic mice

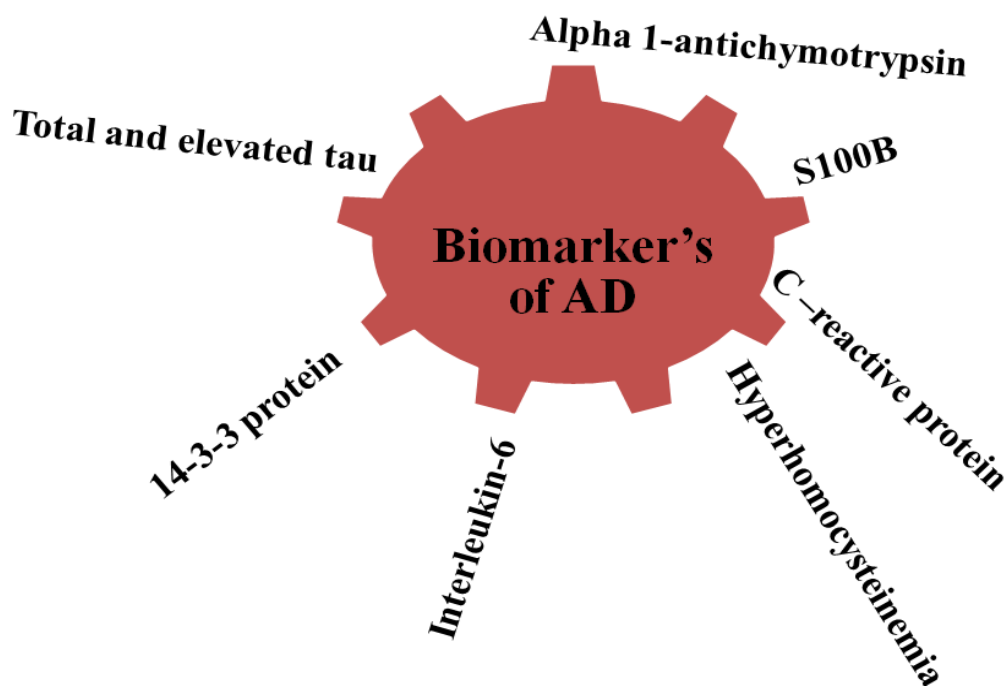


Figure 1: The Histopathological features of AD

1. **Amyloid Plaques:** The anomalous buildup of amyloid-beta (A β) peptides in the brain results in the emergence of amyloid plaques, which have detrimental effects on neurons and impede cellular communication.
2. **Neurofibrillary Tangles:** Inside nerve cells, tau proteins aggregate and form neurofibrillary tangles, causing disruptions in the cell's internal transport system and eventual cell death.
3. **Neuronal Loss:** Over time, the accumulation of amyloid plaques and neurofibrillary tangles leads to the progressive loss of neurons and brain tissue.
4. **Inflammation:** Chronic inflammation in the brain, caused by the body's immune response to amyloid plaques, can further damage neurons.
5. **Oxidative Stress:** Increased oxidative stress contributes to cellular damage and accelerates the degeneration of brain cells.
6. **Genetic Factors:** Certain genes, such as the APOE ϵ 4 allele, are associated with an increased risk of developing AD.
7. **Environmental Factors:** Environmental factors, such as lifestyle choices and exposure to toxins, may also influence the development of AD.
8. **Clinical Features of Alzheimer's Disease:** AD typically progresses through several stages, each characterized by specific clinical features:
 9. **Preclinical Stage:** In the early preclinical stage, there are no apparent symptoms, but there might be subtle changes in the brain related to amyloid deposition and neurodegeneration.
 10. **Mild Cognitive Impairment (MCI):** This stage is characterized by mild memory and cognitive deficits that are noticeable to the individual and their close associates, but not severe enough to interfere significantly with daily activities. Some individuals with MCI may progress to AD, while others may remain stable or even improve.
 11. **Mild Alzheimer's Disease:** As the disease advances, individuals experience more pronounced memory loss, confusion, and difficulty with problem-solving. They may have trouble finding the right words and frequently misplace items. Challenges with managing finances and navigating familiar places may also arise.
 12. **Moderate Alzheimer's Disease:** In this stage, cognitive decline becomes more severe, and individuals require more assistance with daily activities. Behavioral and psychological symptoms, such as agitation, restlessness, and aggression, may appear.
 13. **Severe Alzheimer's Disease:** In the final stage, individuals lose the ability to communicate coherently, become dependent on others for all aspects of care, and may experience difficulty swallowing. Physical and functional decline is significant, and patients are vulnerable to infections and other complications.

III. RECENT ADVANCES IN ALZHEIMER'S DISEASE ETIOLOGY

Alzheimer's disease (AD) is commonly linked with the elderly population, however, roughly 10% of cases are identified prior to the age of 65, referred to as early-onset AD (EOAD), and these cases are up to 100% genetically caused. The remaining 90% of patients, referred to as late-onset AD (LOAD) or sporadic AD are affected by AD.

- 1. Amyloid Hypothesis:** The amyloid hypothesis is a prominent theory that seeks to explain the underlying cause of Alzheimer's disease (AD), a progressive neurodegenerative disorder that primarily affects memory and cognitive function. It proposes that the accumulation of amyloid-beta ($A\beta$) protein in the brain plays a central role in the development and progression of Alzheimer's disease.
- 2. Tau Hypothesis:** Tau is a multifaceted protein that stabilizes microtubules, and its role in AD has been the subject of research. In AD, tau becomes excessively phosphorylated and loses its ability to bind microtubules.
- 3. Neuroinflammation Hypothesis:** Researchers widely concur that there is a close relationship between neuroinflammation and the pathogenesis of Alzheimer's disease (AD), with one being the underlying cause or the consequence of the other, regardless of which triggers.
- 4. Oxidative Stress:** Under ordinary circumstances, the levels of reactive oxygen species (ROS) in the body are controlled by natural antioxidant defenses such as detoxifying enzymes (superoxide dismutase, catalase and glutathione peroxidase). When this protective capacity diminishes, however, an inequity in ROS levels generates oxidative stress, causing harmful effects on the redox chain such as a decrease in ATP production. The brain has high energy and oxygen consumption, There exists a hypothesis that oxidative stress induced by metal.
- 5. Mitochondrial Dysfunction:** The electron transport chain in mitochondria provides ATP and accounts for 90% of endogenous ROS generation. Mitochondrial quality control (MQC) mechanisms can repair ROS-associated damage under normal conditions, but if these processes fail, symptoms of AD may manifest more quickly. In fact, biopsies of AD patients have revealed the presence of a substantial number of structurally damaged mitochondria in their brains.

IV. FABRICATION OF DENDRIMERS

The creation of novel dendrimers with unique features for use in biomedical applications is of great interest. A variety of PEPE dendrimers with various topologies were made generations. For instance, Dhanikula and Hildgen combined convergent and divergent strategies to synthesise a new polyester-co-polyether (PEPE) dendrimer with a hydrophilic interior/cavity. Novel dendrimers have been designed with biocompatibility, amphiphilicity, and biodegradability as their primary design objectives for drug delivery applications. To address these different techniques such as, synthetic techniques, natural procedures, mechanical procedures, and dynamic procedures have all been used in the development of medicinal dosage forms [23]. Because of its affordability, absence of significant environmental hazards, and biological reduction, the natural synthesis of nanoparticles (NPs)

was selected an appealing alternative to chemical methods [24]. The distribution of the drug is the most crucial component of any dosage unit, and different polypeptide molecules are utilized to ensure focused on effective drug administration at the right site [25]. A particular class of nanocarrier known as dendrimers is named from the Greek word dendron, which translates to "branching of a tree." Having a set shape and specificity, dendrimers are globular, branching, symmetrical polymeric structures as per figure 2.

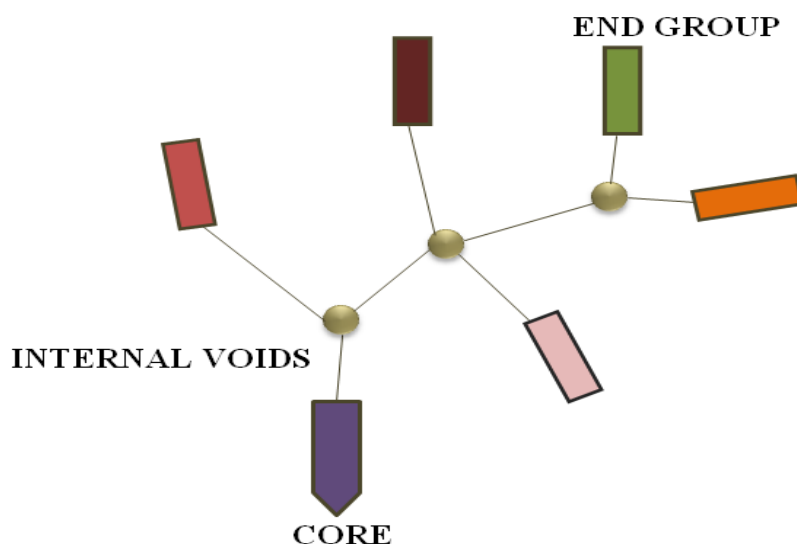


Figure 2: Structure of Dendrimer

By applying various dendritic patterns to the surface, the dendritic approach enhances pharmacological activity, enabling a specific functional molecule to significantly outperform the sum of its individual entries. The synergistic effect produced by dendrites is what causes the increased activity [26]. The main purpose of dendrimers is to change and improve bioavailability in pharmaceuticals by changing pharmacokinetic with pharmacological characteristics of the API (active pharmaceutical ingredient) [27]. Dendrimers are an attractive family of nano-vectors for brain targeting and monodisperse in comparison to conventional polymer nanovehicles [28]. Dendrimers' unique structural characteristics also give them the flexibility to carry medicinal medicines via covalent conjugation or electrostatic adsorption [29].

Drug molecules may be trapped inside the cavities of a dendrimer due to the open nature [30]. Lower generation is typically patulous and amorphous [31]. Hydrophobic and hydrogen bond interactions, electrostatic interaction, straightforward physical entrapment, and encapsulation are all types of interactions [32]. Due to these interactions, dendrimers may be able to integrate irregular or insoluble medicines, improving their water solubility and bioavailability while also regulating their release [33]. However, due to steric restriction and option for electrostatic attachment results in a significant increase in drug solubility [34]. While the core was made of the biocompatible component anetetra carboxylic acid and aspartic acid and it was demonstrated that the dendrimers successfully surround guest molecules with loadings of 15.80 and 6.47 percent weight-for-weight for rhodamine and beta-carotene, respectively (models of hydrophilic and hydrophobic substances). P-amino benzoic acid and polyethyleneglycol (PEG) are frequently combined to generate the conjugation

through amide or ester bonds [35]. It was discovered that ester bonding allows for the regulation of drug release by hydrolysis, whereas amide bonding is more stable [36].

In contrast to liposomes, Poly (amidoamine) (PAMAM), Poly (propylene imine) (PPI), Polyether-copolyester (PEPE), PEGylated (polyethylene glycol), and peptide dendrimers are examples of dendrimers, have a small size range (1–15 nm) and a high water solubility, making them an unique drug delivery mechanism [37]. In 1978, Fritz Vogtle reveals hyperbranched fragments; in the early 1980s, Donald Tomalia and his helper; and in the same year, but separately, George R. Newkome. Arborols, from the Latin for "trees," are the name given to the second class of synthesised macromolecules. Although this word is less well-known than "dendrimers," dendrimers are occasionally referred to as "cascade molecules". Drug solubility is a key factor in the blood-brain barrier (BBB) transit of endogenous substances. Due to their inadequate solubility, absorption, distribution, metabolism, excretion, and other unachieved physical qualities, the newer medications (drugs in the preclinical phase) are experiencing difficulties that adversely affect their pharmacokinetics and therapeutic efficacy [2]. This restricts the advancement of novel neurotherapeutics. Genes and about 98% of big protein molecules with molecular weights more than 400–600 Da are unable to penetrate the BBB. The conveyed therapeutic candidate's lipophilicity attests to its successful crossing of the BBB. The majority of active pharmaceutical ingredients (APIs) are insufficiently soluble in water, which hinders the development of new therapeutic strategies [38].

By maximizing their aqueous solubility and systemic bioavailability, pharmaceutical businesses have rejected about 40% of drug candidates that are subjected to further research into successful formulation [39]. Despite the undisputed use of NPs to enhance drug delivery to the brain via multiple modes of administration, particles larger than 250–300 nm in size indicate ineffective drug delivery in the brain due to poor penetration transport across intracellular and paracellular areas [40]. These drawbacks can be resolved by using nanocarriers, which result in effective drug transport across BBB. Due to their desirable size (less than 10 nm), dendrimers were chosen for this study because they served as effective drug carriers for the CNS delivery of medicines with low hydrophilicity as per figure 3. Dendrimers are created through an interactive, step-by-step synthesis that has a core in their distinctive nanostructure [41]. The engineering of "important nanoscale design parameters" and nanoparticles has been driven by the exclusive enormous range and surface qualities. Cells and connections in the nervous system that are essential for movement, coordination, strength, sensation, and cognition are gradually damaged as a result of neurodegenerative illnesses.

The two neurodegenerative illnesses with the highest prevalence are Alzheimer's. The term "dementia" is specifically used to describe the brain's diminished functionality. Alzheimer's disease is characterized by problems with thinking, remembering, and making decisions; these problems can differ from person to person. Dendrimers are innovative nanotechnology for drug delivery across blood brain barrier [42]. Enhancing stability, BBB delivery, targeted delivery, dummy and carrier for formulations, nanoparticles, nanodrugs, hydrogel for ocular drug administration, transdermal drug delivery, Medical Applications (drug delivery in the body that is directly related to pharmaceutical therapy and also deals with diagnostic perspectives like gene therapy, cancerous drugs, magnetic resonance imaging contrast agents, etc.), Other Applications (like in the field of cosmetics for controlled release of film forming agents and also extend shelf life of the cosmetics product). For dendrimers in

hair care, skin care, and nail care products, L'Oreal Unilever and The Dow Chemical Company hold patents [43].

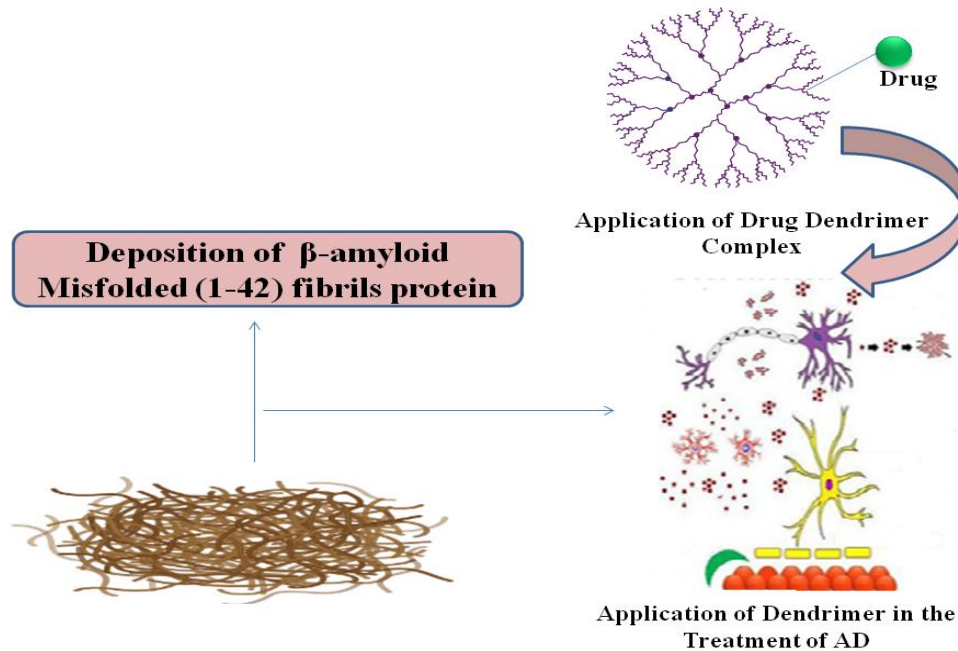


Figure 3: Application of Dendrimer in the Treatment of AD

Few intrusive techniques, such the direct administration of drug-loaded nanocarriers or reversible rupture of the BBB, are successful but have issues with patient compliance and other issues. Dendrimers have drawn a lot of attention from researchers because of non-invasive technique with several functional groups that can be altered to have a specific function. Dendrimers have several noteworthy benefits, including biocompatibility, the ability to infused pharmaceuticals [44].

Dendrimers have two primary mechanisms for preventing the production of amyloid fibrils and dissociating aggregates that have already formed as part of their anti-amyloid action. Dendrimers, on the other hand, are most likely the most promising substances that have been linked to anti-amyloid action [45]. Temozolamide (TMZ) distribution in the brain can be enhanced by using chitosan-coated polyamidoamine (PAMAM) dendrimers. The bioavailability of TMZ in the brain *in vivo* was increased by twofold following intraperitoneal administration utilising a chitosan-PAMAM dendrimer-based formulation [9]. Additional "onion peel" glycodendrimer uses that are being researched include those as galectin-antibodies, vaccine delivery systems, and drug-targeting nanoparticles [10]. Sialic acid the first conjugate and it provided positive results against the haemagglutinin of the flu virus. Furthermore, these kinds of dendrimers act as antibacterial (for gastrointestinal, pulmonary, or urinary tract disorders) and the main mechanisms of endocytosis and passive diffusion, employed improve medication. As the primary internalization mechanism, endocytosis has also been shown to exist.

The goal of dendrimer systems is to penetrate biological membranes and eukaryotic cells engage in a process called endocytosis. Most cells have pinocytosis, which can be mediated by receptors. Internalization cationic PAMAM dendrimers occurs and assert that

the medicine is retained in cells, tissues, and/or organs more effectively when complexed to the dendrimer through electrostatic or hydrophobic interactions. With a similar drug release profile, the therapeutic effectiveness of the medication may be seen. Drugs covalently attached to dendrimers, such as dendrimer prodrugs, may demonstrate greater cell retention in addition to delayed release and extended blood circulation periods. The production of β -amyloid peptides linked to Alzheimer's disease may be inhibited by glycodendrimers. Antiamyloidogenic, the corresponding substances have been studied in this context. Low intrinsic toxicity has been shown for maltosylated PPI dendrimers are shown to lessen the toxicity of the β -amyloid peptide, which is linked to Alzheimer's disease [11].

Despite the promising potential of dendrimers in AD research, it is essential to address concerns related to their biocompatibility, toxicity, and clearance from the body. Further research and development are needed to optimize dendrimer formulations for safe and effective use in the diagnosis and treatment of Alzheimer's disease.

- 1. Drug Delivery Systems:** Dendrimers can encapsulate drugs within their interior or chemically conjugate them on their surface. This property makes them promising carriers for delivering therapeutic agents across the blood-brain barrier (BBB) to the brain, where the target site of action for AD is located. They can enhance drug solubility, stability, and bioavailability, and they allow for sustained and controlled release of drugs, potentially reducing the frequency of drug administration.
- 2. Amyloid-Beta ($A\beta$) Aggregation Inhibition:** One of the hallmarks of AD is the accumulation of amyloid-beta ($A\beta$) peptides, leading to the formation of plaques in the brain. Some dendrimers have shown the ability to bind to $A\beta$ peptides and inhibit their aggregation into toxic forms, potentially slowing down the progression of AD.
- 3. Tau Protein Stabilization:** Dendrimers have been investigated for their ability to stabilize tau proteins, which are involved in the formation of neurofibrillary tangles in AD. By preventing the abnormal aggregation of tau, dendrimers may help to preserve the structure and function of neurons.
- 4. Metal Chelation:** Some dendrimers have metal-chelating properties, which could be beneficial in AD as metal ions have been implicated in the aggregation of $A\beta$ and tau proteins. By chelating metal ions, dendrimers may reduce their toxicity and the subsequent damage to brain cells.
- 5. Imaging and Diagnostics:** Dendrimers can also be functionalized with imaging agents, such as fluorescent dyes or radioactive markers. These modified dendrimers can be used for early detection and diagnosis of AD-related pathological changes in the brain, enabling better monitoring and understanding of disease progression.

V. CLINICAL TRIALS FOR AD

Advances in amyloid therapy have been made since the monoclonal antibody aducanumab was approved. The pipeline for AD drugs is well-represented by therapies for tau abnormalities, inflammation, and synaptic dysfunction in addition to other amyloid approaches. Notwithstanding the difficulties brought on by the present pandemic, there have been a few more clinical trials. Clinical trials are becoming increasingly informed by

biomarkers, including their use in diagnosis and as outcomes. More sensitivity to the effectiveness of the treatment is provided by new clinical outcome measures, particularly composite scales and scores. Given the significant time sacrifices individuals and their families make during trial participation, the discovery of drugs for AD depends on strong partnerships with these groups. As of January 25, 2022, there were 172 clinical studies analyzing 143 medications for AD. The pipeline included 30 drugs undergoing 31 Phase 1 trials, 82 agents in 94 Phase 2 trials, and 31 agents in 47 Phase 3 trials. Of the agents being evaluated, disease-modifying therapies comprised the majority with 83.2%, while neuropsychiatric symptom treatments accounted for 6.9% and symptomatic cognitive enhancing therapies for 9.8%. Almost all CADRO categories were targeted by the pharmacological agents being studied. Notably, 37% of the candidate compounds were modified versions of medications that had already received approval for other purposes. The recruitment process necessitated 50,575 participants to meet the required standards. DMTs have been the subject of extensive study, with 119 drugs (representing 83.2% of all drugs in trials) falling into this category. Of these, 16.8% are symptomatic drugs, with 9.8% aiming to improve cognitive function and 6.9% targeting neuropsychiatric and behavioral symptoms. Biologics comprise 33.6% of DMTs, while small molecules account for 66.4%. Amyloid is the primary mechanistic target for 16.8% of DMTs, followed by tau (10.9%), inflammation (19.3%), and synaptic plasticity/neuroprotection (16%). When focusing solely on DMTs, 67.8% of agents are in Phase 3, 86.6% are Phase 2 medications, and 90% are Phase 1 agents. Currently, there are 53 agents being repurposed for development in the treatment of AD. Despite the amyloid hypothesis, many international pharmaceutical companies have failed to produce a medication that clears amyloid. This failure poses the question of the hypothesis's plausibility. The ADAS-Cog 11 changes serve as the primary outcome indicator, and trials are expected to run until February 2020. The MINDSET clinical trial's third phase investigated the effects of intepirdine on mild to moderate AD patients receiving a daily dose of 5 or 10 mg of donepezil. The MINDSET study began in October 2015 and ended in September 2017. The primary outcome measures in the study were alterations in ADAS-cog 11 and ADCS-ADL 23 scores. Despite the study's primary objectives not being met, a noteworthy improvement in clinician interview-based perception of change and carer interview was observed as a secondary outcome with statistical significance.

VI. CURRENT TREATMENT AVAILABLE MANAGEMENT OF AD

The US FDA has approved the first DMT for the treatment of AD and its name is aducanumab and others are enlisted as in table 2. The other DMT, edaravone, is used to treat amyotrophic lateral sclerosis, and it is the second DMT that has been licenced in the US for any neurodegenerative condition [46]. A quick regulatory process based on evidence of amyloid plaque reduction that was thought to reasonably anticipate clinical benefit was utilised to approve aducanumab [47]. Future research may qualify more biomarkers as surrogate outcomes that predict clinical benefit [48]. Drug development is aided by surrogate results. After glucuronidation and excretion in the urine, DZ is metabolised by the CYP 450 isoenzymes 2D6 and 3A4 into four key metabolites [49]. Researchers have recently shown a great deal of interest in the idea of medications more effectively entering the brain when they are able to penetrate the blood-brain barrier [50]. The goal of the current method is to test the hypothesis that the conjugation strategy can improve donepezil (DZ) transport to the brain when used with polyamidoamine (PAMAM) dendrimers. Tacrine (TAC) was approved for medical usage, however because oral administration led to hepatotoxicity, it is critical to minimise side effects. Both drug delivery systems and standalone nanodrugs can be made

using PAMAM dendrimer generation 4.0 and 4.5 (DG4.0 and DG4.5). In the convergent method, Hawker and Fréchet defined synthesis as the reaction between dendrimers with a multifunctional core and many dendrons, which leads to dendron fixing and a final hyperbranched product. Dendrimers are simple to create, and the final reaction product is purified with precise positioning, which is the technology's key advantage. Drug giants can be discovered covalently bonded to functional groups on dendrimer surfaces or as non-covalent complexes with functional group-containing dendrimers in the perimeter and few defects. These molecules bind amine or amide groups on the outside and have an ethylenediamine (C₂H₈N₂) or ammonia (NH₃) core. PAMAM dendrimers having carboxylic groups at the ends are half-generation dendrimers.

Table 2: Pharmacokinetic data of drugs are widely used for AD

Drug	Formulations	Outcomes of Pharmacokinetic study	Drug Description
Donepezil	Penetration enhancing nano gel formulation	C _{max} = 1930 µg AUC= 39160 µg*h	An acetylcholinesterase inhibitor used to treat the behavioral and cognitive effects of Alzheimer's Disease and other types of dementia.
Rivastigmine	Nasal liposomal and PLGA nanoparticle formulations	AUC= 35,921.75 ± 9559.46 C _{max} = 1489.5 ± 620.71 half-life= 30.92 ± 8.38 min	Inhibits both acetyl and butyryl cholinesterase.
Curcumin	Solid Lipid Nanoparticle and Nanostructured lipid carrier	C _{max} 105 µg/ml, T _{max} 2 h, Kel,0.23/h, and 1 AUC 629 µg.hr/ml)	It inhibits COX-2.
Bacopa Extract	Phospholipid complex	The bioavailability experiments conducted in rats indicated the presence of bacopaside I and II in the serum. In the case of the basic extract (BE), the peak serum concentration was rapidly reached within the first hour, with values of 10.41 µg/ml and 10.38 µg/ml for bacopaside I and II, respectively. However, when a Phytosome preparation was used, higher serum concentrations of bacopasides were observed.	It inhibits Aβ aggregates.

		<p>The peak concentrations for bacopaside I and II were 12.21 µg/ml and 12.28 µg/ml, respectively, and these levels were reached within the first hour. These results indicate that the phytosome preparation led to improved serum concentrations of bacopasides compared to the basic extract (BE).</p>	
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VII. BIOMEDICAL APPLICATIONS

Dendrimers have shown great promise in various biomedical applications due to their exceptional properties. Some significant applications include:

1. **Drug Delivery:** Dendrimers can encapsulate drugs within their interior or conjugate drugs onto their surface. This controlled drug delivery system allows for targeted and sustained release of therapeutic agents, reducing side effects and improving treatment efficacy.
2. **Imaging Agents:** The surface of dendrimers can be functionalized with contrast agents or fluorescent molecules.
3. **Gene Delivery:** Dendrimers have been explored as non-viral vectors for gene delivery. They can condense and protect nucleic acids, facilitating their transport into cells for gene therapy applications.
4. **Antimicrobial Agents:** Some dendrimers exhibit antimicrobial properties and have been investigated as potential alternatives to traditional antibiotics.
5. **Cancer Therapeutics:** Dendrimers can be used to target cancer cells selectively, delivering anticancer drugs or therapies with reduced damage to healthy tissues.
6. **Tissue Engineering:** Dendrimers play a role in tissue engineering as scaffolds or carriers for growth factors and cells to support tissue regeneration.
7. **Diagnostic Tools:** Dendrimers can be modified to bind specifically to biomarkers, enabling sensitive detection of diseases and infections.
8. **Enhanced Permeability and Retention (EPR) Effect:** Dendrimers, especially those in the nanometer size range, can take advantage of the EPR effect in tumors. This effect allows them to accumulate preferentially in tumor tissues due to their leaky vasculature, providing a basis for targeted drug delivery to cancer cells.

- 9. Multivalency:** Dendrimers possess a high density of functional groups on their surface, allowing for multivalent interactions with biological targets. This multivalency can enhance binding affinities, making dendrimers useful in applications like targeted drug delivery and diagnostics.
- 10. Dendritic Vaccines:** Dendrimers have been investigated as components of vaccines. By coupling antigens to dendrimers, they can improve immune responses and aid in the development of novel vaccine strategies.
- 11. Blood-Brain Barrier (BBB) Delivery:** Dendrimers can be engineered to cross the BBB, which is a significant challenge for drug delivery to the central nervous system. This capability opens up possibilities for treating neurological disorders and brain tumors.
- 12. Biological Imaging:** Dendrimers can serve as contrast agents for various imaging modalities, including MRI, CT, PET (positron emission tomography), and SPECT (single-photon emission computed tomography).
- 13. Inflammation and Autoimmune Diseases:** Dendrimers have been explored as potential therapeutics for inflammatory and autoimmune conditions, either by delivering anti-inflammatory agents or modulating immune responses.
- 14. Biosensors:** Dendrimers have been incorporated into biosensor platforms, allowing sensitive detection of analytes in various biological samples.
- 15. Dendrimer-Polymer Hybrids:** Dendrimers can be combined with other polymers to create hybrid materials with unique properties, expanding their potential applications in biomedicine.
- 16. Regenerative Medicine:** Dendrimers are being studied for their ability to promote tissue regeneration and wound healing through controlled release of growth factors and bioactive molecules.
- 17. Biocompatible Coatings:** Dendrimers can be used to modify the surface of medical devices, enhancing biocompatibility and reducing the risk of adverse reactions in patients.
- 18. Theranostics:** Dendrimers are increasingly being used in theranostic applications, where a single system combines both therapeutic and diagnostic functions, enabling personalized medicine approaches.

VIII. CONCLUSION

Alzheimer's disease (AD), a neurological ailment that deteriorates over time, leading to impaired memory, cognition, and behavior, currently has no known cure, and available treatments only address the symptoms. Nonetheless, multiple novel formulations are under investigation, targeting the underlying pathophysiology of AD. These formulations use advanced drug delivery systems, including development, characterization, production, and application. Some of the innovative technologies being explored are liquid crystals, dendrimers, nanostructured lipid carriers, Nano emulsions, solid lipid nanoparticles, and polymeric nanoparticles. These sophisticated techniques show promise for enhancing

therapeutics in AD treatment. Currently, there is no known cure for AD, and available therapies merely address the symptoms. However, ongoing research is actively exploring new formulations that target the underlying pathophysiological processes of AD. The objective is to improve treatment options by focusing on the development, characterization, manufacturing, and utilization of diverse drug delivery systems. Technologies such as liquid crystals, dendrimers, nanostructured lipid carriers, Nano emulsions, solid lipid nanoparticles, and polymeric nanoparticles are being investigated as potential methods for drug administration. These innovative AD formulations aim to slow down or halt the disease's progression by tackling its underlying pathophysiology.

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