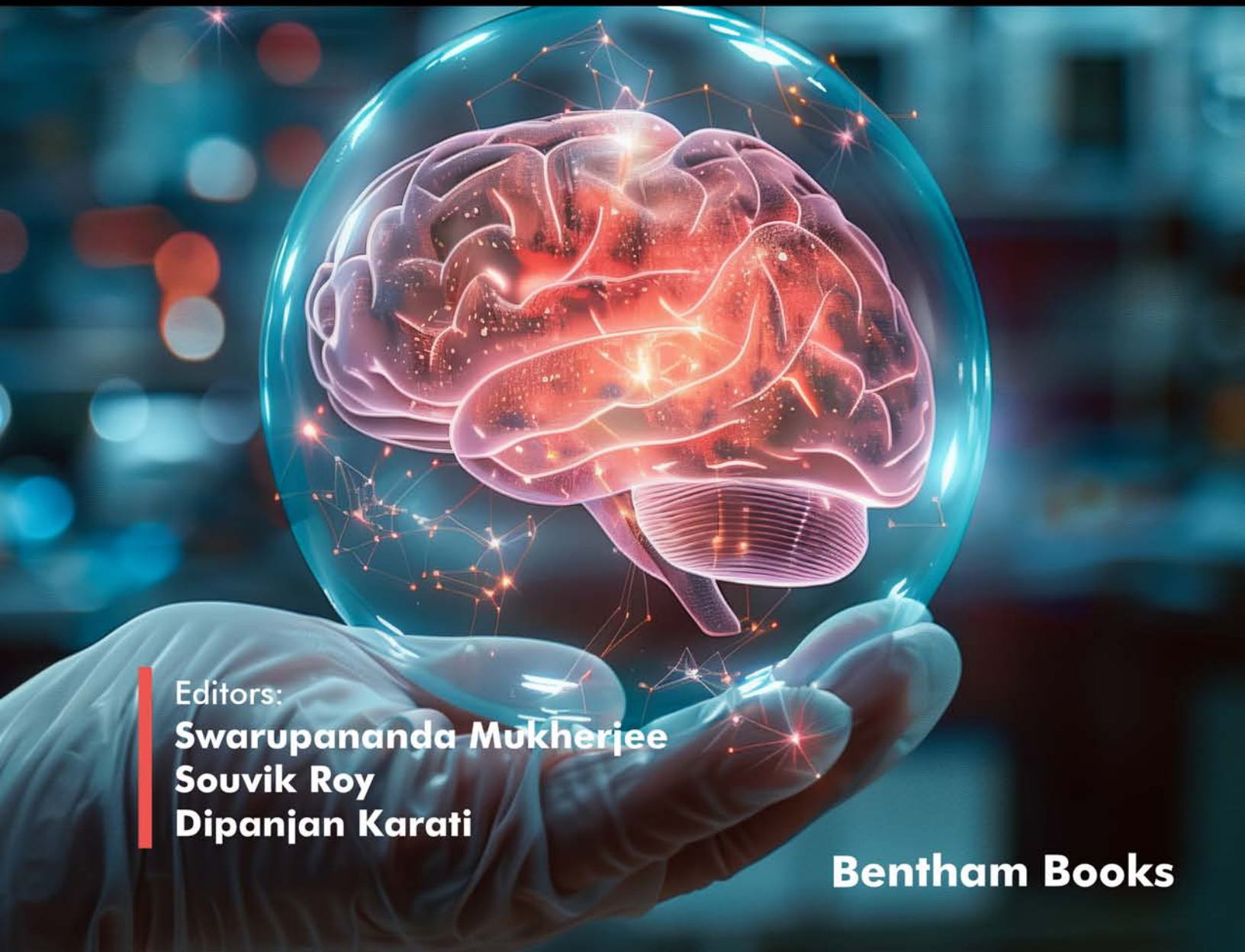
# MOLECULAR TARGETED THERAPY FOR ALZHEIMER'S DISEASE



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# Molecular Targeted Therapy for Alzheimer's Disease

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**Molecular Targeted Therapy for Alzheimer's Disease**

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# FOREWORD

Alzheimer's disease continues to challenge scientists, clinicians, and caregivers alike as one of the most complex and devastating neurodegenerative disorders of our time. Despite decades of research, effective long-term treatments remain elusive. However, recent advances in molecular biology, pharmacology, and neuroimmunology have begun to reshape our understanding of the disease's underlying mechanisms, offering hope for new and more effective therapeutic strategies.

This timely and compelling book, "Molecular Targeted Therapy for Alzheimer's Disease," provides a comprehensive and forward-looking exploration into the evolving landscape of Alzheimer's research. It brings together emerging perspectives on the pathophysiology of the disease, highlighting innovative molecular targets, cutting-edge drug development, and integrative therapeutic approaches that extend beyond the traditional amyloid- and tau-focused paradigms.

The chapters, authored by experts in the field, offer readers a deep dive into critical areas such as neuroinflammation, mitochondrial dysfunction, axl kinase disregulation, tau protein hyperphosphorylation, miRNA, and biopolymer-based therapeutic approaches. This book not only elucidates the science behind these developments but also discusses the translational challenges and future directions necessary to bridge laboratory findings with clinical practice.

Whether you are a researcher, clinician, student, or stakeholder in neurodegenerative disease care and policy, this book serves as an invaluable resource. It encourages a multidisciplinary approach and fosters a renewed sense of urgency and innovation in tackling one of the most pressing public health concerns of the 21st century.

In a field that is rapidly evolving, "Molecular Targeted Therapy for Alzheimer's Disease" stands as a testament to the resilience and ingenuity of the scientific community. It is with great admiration and hope that I commend this work to all readers who are committed to making a difference in the battle against Alzheimer's disease.

**Debasis Bagchi**
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# PREFACE

Due to the loss of mental faculties, millions of individuals worldwide are deprived of their right to cognitive freedom by Alzheimer's disease (AD), a neurodegenerative illness of exceptional magnitude. Despite significant advances in understanding and devising therapeutic management, existing medications give only limited symptom relief and fail to arrest or reverse the process of the disease. The glaring treatment barriers prompted scientists to focus on the molecular basis of Alzheimer's, leading to the development of more accurate and possibly revolutionary approaches to treatment.

Its central goal of Molecular Targeted Therapy for Alzheimer's Disease is to provide a thorough analysis of innovative methods of research in order to analyse and intervene into key molecular pathways of AD. The book covers a great number of key areas such as the role of amyloid-beta and tau proteins, neuroinflammation, oxidative stress, and synaptic dysfunction.

This book aims to assist researchers, clinicians, graduate students, and healthcare specialists who participate in the study of Alzheimer's disease, which is characterized by numerous complex mechanisms. Suggesting a comprehensive review of molecular targets and associated possibilities for therapy, we enable new directions for further research and interdisciplinary collaboration in the treatment of this difficult disorder.

To all those who contributed detailed knowledge and devoted their labor to this volume, we offer our heartfelt thanks. We hope that this compilation will become an indispensable guide, an inspiration for future improvement and development in new therapeutics aiming at a molecular-level treatment for Alzheimer's disease.

Sincerely,

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# CHAPTER 1

# Unveiling the Role of Glutamate and NMDA Receptors in Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is a neurological condition that affects people as they age. Clinically, this illness is typified by changes in behavior, personality, and overall cognitive impairment, including memory loss. The hippocampus and neocortex, two delicate brain regions involved in memory and cognition, have been linked to a progressive decline in form and function as AD progresses. N-methyl-D-aspartate receptor (NMDAR)-mediated excitatory glutamatergic neurotransmission is essential for neuron survival and synaptic plasticity. However, increased NMDAR activity leads to cell death and excitotoxicity, which may be the mechanism behind the neurodegeneration that occurs in AD. Research suggests that regionalized receptor activity, followed by diverse downstream signaling pathways, is responsible for the various NMDAR-mediated responses. Synaptic NMDAR activation promotes cell survival and initiates plasticity. On the other hand, memantine, an AD medication that specifically inhibits the activity of extrasynaptic NMDARs, can prevent the activation of extrasynaptic NMDARs, which causes cell death and hence contributes to the etiology of AD. This chapter aims to outline the role of glutamate and NMDA receptors in AD.

**Keywords:** Alzheimer's disease, Glutamate, Memantine, N-methyl-D-aspartate receptor (NMDAR), Neurodegeneration.

## INTRODUCTION

Named after the German psychiatrist Alois Alzheimer, Alzheimer's disease (AD) is the most prevalent form of dementia. Neuritic plaques and neurofibrillary tangles are the hallmarks of this condition, which is brought on by the build-up of

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amyloid-beta peptide (Aβ) in the brain's most affected regions, the medial temporal lobe and neocortical structures [1]. As AD progresses, these brain areas undergo significant degeneration, leading to the cognitive and functional impairments associated with the disease. AD shows results in abnormalities in the pulmonary and circulatory systems, low oxygen levels in the blood, vitamin B12 insufficiency, nutritional deficits, and others, which lead to a progressive loss of cognitive functions [2, 3]. The AD is predicted to impact 131.5 million people by 2050 if no new treatments are found [4].

The development of AD has been attributed to cholinergic deficiency [5], tau protein hyperphosphorylation [6], amyloid beta (Aβ) toxicity [7], synaptic dysfunction [8], oxidative stress [9, 10], and neuroinflammation [11]. Synapse loss was found to have a substantial correlation with cognitive impairment in AD when compared to other biochemical measures, such as senile plaques and neurofibrillary tangles (NFTs) [12]. By 2050, there will be 12.7 million people in the US living with AD dementia, up from the present 6.2 million. Apart from persons with AD in the advanced stages of dementia, around 10 million Americans suffer from moderate cognitive impairment (MCI), with 5 million of them having MCI as a result of AD. There are 11.2 million people in the US who have MCI from AD and AD dementia, which are symptomatic manifestations of the disease [13]. $355 billion was projected to be spent on Alzheimer's disease and related dementias (ADRD) care in 2021. By 2050, the number of people affected by AD dementia worldwide will triple from 50 to 150 million, with the majority residing in low- and middle-income nations [14]. AD is categorized as: (i) late-onset AD (LOAD) or sporadic, and (ii) early-onset AD (EOAD) or familial [15]. Their pathophysiologies are remarkably similar [16, 17]. Approximately 5–6% of AD patients have an early-onset disease (EOAD) before the age of 65 [18], and a significant proportion of these patients show severe language or visuospatial deficits. Significant non-cognitive neuropsychiatric symptoms (NPS) (apathy, sadness, anxiety, agitation, violence, and psychosis) are also brought on by AD, regardless of the age at which symptoms first appear [19, 20].

Neurotransmission is the process by which a signal is sent from one neuron to another using endogenous signalling chemicals called neurotransmitters [21]. After being released from the axon terminal of a neuron, neurotransmitters cross the synaptic cleft and bind to receptors on the dendrites of another neuron, then convert those receptors into electrical impulses. The tripartite structure of the synapse, or neuronal junction, is composed of presynaptic and postsynaptic nerve terminals as well as the intimate association of glial cells [22]. Through a feedback mechanism, glial cells—particularly astrocytes—play a significant role in controlling neurotransmission [22]. Signals are transmitted between neurons by

neurotransmitters binding to certain postsynaptic receptors [21]. Postsynaptic receptors are characterized as ionotropic receptors, which function as ligand-gated channels, and metabotropic receptors, which act by signal transduction [23]. There are various types of neurotransmitters, such as cholinergic and monoaminergic neurotransmitters. Critical cholinergic neurotransmitters in AD pathogenesis include acetylcholine (ACh) and gamma-aminobutyric acid (GABA), while critical monoaminergic neurotransmitters include histamine, dopamine (DA), and serotonin (5-HT) [24, 25]. Neurotransmitter inhibitors, including acetylcholinesterase inhibitors (AChEI) donepezil, rivastigmine, memantine, and galantamine, have a well-established treatment promise in AD [23]. As AD progresses, pathological alterations include reduced GABA levels, monoaminergic neuron loss, glutamatergic neuron dysfunction, and cholinergic neuron loss. Dopaminergic and 5-hydroxytryptaminergic monoaminergic neurons are subtypes of monoaminergic neurons. Neurotransmitters send messages to the following neuron by binding to postsynaptic membrane receptors [26]. Neuronal dysfunction can be brought on by modifications to the synthesis, storage, transport, and breakdown of neurotransmitters, which can lead to AD-related dementia (Fig. **1**).

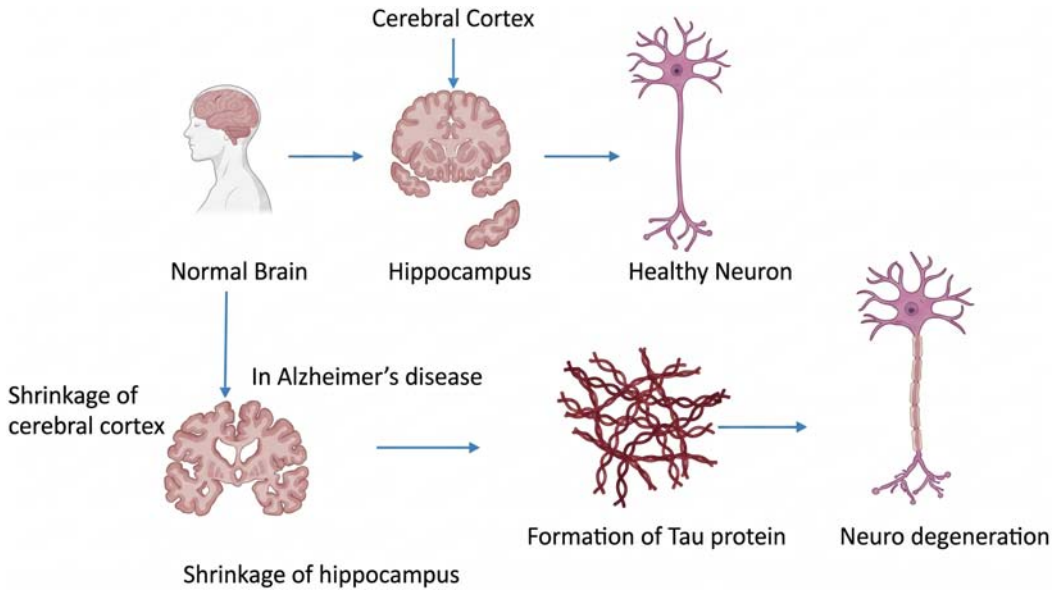


**Fig. (1).** Neuronal physiology in healthy brains versus brains with AD.

CHAPTER 2

# Tau Protein in Alzheimer's Disease

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**Abstract:** In Alzheimer's disease (AD) and other tauopathies, tau, a protein linked to microtubules, creates insoluble filaments that form as neurofibrillary tangles. Compared to the healthy human brain, tau is around three to four times more hyperphosphorylated in the brain of an AD patient. In this hyperphosphorylated condition, tau polymerizes into paired helical filaments mixed with straight filaments to create neurofibrillary tangles. During development, anesthesia, and hypothermia, tau is hyperphosphorylated; however, not to the same extent as in the brain of an AD patient. The potency of the abnormally hyperphosphorylated tau in AD brain to sequester healthy tau, microtubule-associated protein 1 (MAP1), and microtubule-associated protein 2 (MAP2), break microtubules, and self-assemble into PHF/SF, differentiates it from hyperphosphorylated tau. Due to oligomerization, the cytosolically hyperphosphorylated tau is sedimentable and loses its capacity to sequester normal MAPs during self-assembly into PHF/SF. For AD and associated tauopathies, inhibition of dysfunctional tau hyperphosphorylation will serve as a possible therapeutic target in the near future.

**Keywords:** Alzheimer's disease, Microtubule-associated protein 1, Neurofibrillary tangles, Neurodegenerative disorder, Tau protein.

## INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder associated with age progression and affects the thoughts, memory, and behavioural pattern of a person [1, 2]. Approximately 40-44 million people suffer from dementia, among them 60-80% of cases are due to AD [3, 4]. Considering the present-day demographic condition, 10% individuals in the age range above 65 years suffer from AD, and that increases to 32% over the age bar of 85 years. Gender based study indicates two-thirds of AD patients are women, this may be due to the higher life expectancy of women in comparison to men [5]. Predictive data suggests that

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approximately 65.7 million people may suffer from dementia in 2023, and projections are high in the case of 2050, which is around 115.4 million [4].

A complex relationship exists between proteins and AD. AD is characterised by two hallmarks. Firstly, amyloid plaque formation by accumulation of Amyloid-beta (Aβ) peptide, and secondly, from intraneuronal neurofibrillary tangles (NFTs) due to hyperphosphorylation of Tau protein [1, 6, 7]. Tau is a key microtubule-associated protein (MAP) found in ocular neurons and the central nervous system (CNS), and it stabilizes neuronal microtubules [2]. Microtubules (MTs) play a crucial role in the functioning of intracellular signal transduction and the structural maintenance of neurons.

In normal physiologic conditions, the tau protein is moderately phosphorylated, whereas in abnormal conditions, the tau protein is hyperphosphorylated [8]. In this hyper phosphorylated tau first tends to detach from MTs, followed by aggregation in the form of Paired Helical Filaments (PHFs), leading to NFTs formation [8, 9]. This abnormal aggregation of tau protein subsequently causes breakdown of MTs and neuroinflammation, ultimately leading to neuronal degradation [10]. This suggests that the presence of tau does not cause AD; rather, in atypical conditions, it helps in the formation of plaques and tangles in the brain to spawn AD.

After identifying the pivotal role of the Tau protein in AD, researchers are finding various ways to control AD by utilizing the Tau protein. From a diagnostic reference point, tau imaging is now used for early diagnosis of AD [11, 12]. In AD treatment, tau targeting is also gaining significant focus as a potential therapy, with methods like Tau aggregation inhibitors [13], phosphorylation modulators [14, 15], and immunotherapy [16, 17], showing promising future applications.

## STRUCTURE AND ACTIVATION OF TAU

### Structural Elucidation of the Tau Protein

Tau is an abundant neuronal protein that is linked to microtubules. Tau is a protein that aids in maintaining the internal framework of neurons, which are nerve cells. Nutrients and other necessary materials pass through this tube-like structure to reach different areas of the neuron.

The microtubule-associated protein tau (MAPT) gene mutation, which is responsible for frontotemporal dementia with Parkinsonism associated with chromosome 17 (FTLD-17), was a groundbreaking discovery. It came up with genetic proof that demonstrated tau dysfunction was sufficient to initiate neurodegeneration, even in the absence of ß-amyloid peptide (Aß) [18]. The tau

proteins with a molecular weight of 50,000-68,000 are found in the adult brain, while the fetal brain only contains one band with an apparent molecular weight of 48,000 [19]. Tau is mostly in axons. It is a highly soluble protein, generally an unfolded protein that interacts with tubulin to promote microtubule assembly and helps in the stabilization of microtubule structure under proper physiological conditions. The latest research suggests that tau has other functions, for example, by sustaining ß-catenin, phosphorylation of tau allows neurons to avoid apoptotic death [20]. Additionally, tau regulates the anterograde transport by kinesin and the retrograde transport by dynein, which is crucial for maintaining the equilibrium of microtubule-dependent axonal transport of organelles and biomolecules [21].

Six isoforms of tau are expressed in the adult human brain. These isoforms are formed by alternative splicing of the MAPT gene, which is found on chromosome 17q21 [22]. The splicing of exons 2 and 3 can be altered to produce variants with zero (0N), one (1N), or two (2N) embeds at the N-terminus. Furthermore, tau proteins with three (3R) or four (4R) C-terminal microtubule-binding domains are generated based on the presence or absence of exon 10, where 3R tau isoforms bind microtubules less firmly than 4R tau. A total of six tau isoforms are reported, and these are 3R0N, 3R1N, 3R2N, 4R0N, 4R1N, and 4R2N. The ratio of 3R to 4R tau expression levels is 1:1 in the human brain. The alterations in the 3R:4R tau ratio are a hallmark of many tauopathies. For example, a higher proportion of 4R tau is located in some mutated exon 10 with FTDP-17 families, which elevates the ability of tau to interact with microtubules [18, 22].

Tau is modulated by a number of posttranslational changes, such as nitration, glycosylation, ubiquitination, glycation, and oxidation, during both normal homeostasis and stress-induced reactions. Phosphorylation is the posttranslational change that has been studied the most. About 2–3 residues of tau are phosphorylated in a healthy human brain. The level of phosphorylation of tau is higher, with around nine phosphates per molecule in AD and other types of tauopathies. Tau may become hyperphosphorylated at serine, threonine, and tyrosine when the activity of tau kinases and tau phosphatases is interrupted. Although the exact effects of this event are still being studied, it decreases the affinity of tau for microtubules. It increases tau's susceptibility to neutral proteases activated by calcium and the ubiquitin-proteosome pathway, which degrades tau [22]. The fibrillization and aggregation into neurofibrillary tangles are controlled by tau hyperpolarisation. Glycogen-synthase kinase-3ß (GSK3ß), cAMP-dependent protein kinase (PKA), mitogen-activated protein kinases (MAPK), cyclin-dependent protein kinase 5 (CDK5), calcium-calmoduli--dependent kinase-II (CaMK II), and microtubule affinity-regulating kinase (MARK) are a few significant tau kinases. According to research on transgenic mice models of AD, inflammation, poor brain glucose metabolism, and Aß with

**CHAPTER 3**

# Axl Kinase in Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is a debilitating neurodegenerative disorder characterized by progressive cognitive decline, neuroinflammation, and the accumulation of amyloid-beta plaques and neurofibrillary tangles. These pathological features result in significant neuronal loss and impaired brain function, underscoring the urgent need for effective therapeutic interventions. Axl kinase, a member of the TAM receptor family, has emerged as a promising target due to its neuroprotective properties. Activation of Axl by its ligand, growth arrest-specific protein 6 (Gas6), modulates several critical signaling pathways that are integral to reducing neuroinflammation, promoting neuronal survival, and enhancing the clearance of amyloid-beta and hyperphosphorylated tau. Additionally, Axl influences ApoE metabolism, further impacting amyloid-beta clearance. The strategic modulation of Axl-mediated pathways supports an anti-inflammatory environment and bolsters microglial phagocytic activity, thereby mitigating the progression of AD. Current therapeutic strategies range from plant-based small molecule inhibitors to recombinant Gas6, focusing on the selective activation of Axl kinase to ensure optimal blood-brain barrier penetration and minimal off-target effects. Critical information regarding the structural aspects of Axl kinase, along with its protective role in the central nervous system (CNS), its capability to modulate hallmarks of AD as well as neuroinflammation, and finally, the therapeutic regulation of Axl and Gas6 has been discussed here. As our understanding of the molecular mechanisms underlying Axl signaling in the CNS deepens, the development of Axl-targeted therapies promises a hopeful trajectory towards effective and sustainable treatments for Alzheimer's disease, ultimately improving patient outcomes and quality of life.

**Keywords:** Alzheimer's disease, Axl kinase, Gene expression, Microglia, Neurodegeneration.

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## INTRODUCTION

Alzheimer's disease (AD), a progressive neurodegenerative disorder, has emerged as a critical global health concern, particularly in the context of an aging population [1]. AD accounts for 60-80% of dementia cases worldwide, currently affecting approximately 50 million people, with projections suggesting this figure could triple by 2050 [2] (World Health Organization, 2020). The pathogenesis of AD involves the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau proteins, which disrupt neuronal communication and function, ultimately leading to neuronal death [3]. In the quest for effective treatments, kinase-targeted therapies have garnered significant attention due to their role in modulating various signaling pathways implicated in Alzheimer's disease.

Among the kinases, the TAM (Tyro3, Axl, and MerTK) receptor tyrosine kinase family plays a pivotal role in the regulation of immune responses and cellular debris clearance in the central nervous system (CNS) [4]. Analysis of TAM gene mutations in mice led to the discovery of the function of TAM receptors within the mouse immune system. Chronic inflammation was also observed in mice deficient in all three of the TAM receptors [5]. Numerous published studies have demonstrated that TAMs control a variety of microglial processes, such as phagocytosis, the removal of apoptotic cells, and the clearance of cellular debris [6, 7]. It was recently found that neurodegenerative disorders are associated with a subtype of disease-associated microglia (DAM) [8]. In this subtype, they found evidence of brain injury in the guise of neurodegeneration-associated molecular patterns or NAMPs, which they linked to the activation of a defense mechanism through pattern recognition receptors (PRRs) [9]. In contrast to the control population, Axl was significantly elevated inside the DAM of the AD model, indicating that TAM receptors may be involved in degenerative disorders [9].

Axl kinase, structurally characterized by its extracellular domains that facilitate ligand binding and its intracellular kinase domain, is instrumental in the phagocytosis of apoptotic cells and the suppression of inflammatory responses [10]. Studies have shown that Axl is upregulated in response to amyloid-beta, suggesting a compensatory mechanism aimed at mitigating amyloid burden and inflammation [11]. The activation of Axl is primarily mediated by its ligand growth-arrest-specific gene 6 (Gas6), which binds to the extracellular domain of Axl, leading to receptor dimerization and autophosphorylation of the intracellular tyrosine kinase domain. This activation triggers a cascade of intracellular signaling pathways, including the PI3K/Akt, MAPK/ERK, and NF-κBpathways, which are crucial for cell survival, autophagy, and inflammatory response modulation. Axl activation enhances the phagocytic activity of microglia, the

brain's resident immune cells, facilitating the clearance of Aβ and apoptotic neurons [12].

A connection has been found between microglial function and innate immune responses in up to 50% of AD gene variations [12]. Positron emission tomography (PET) has directly demonstrated increased microglial activity in the brains of AD patients [13]. Thus, the microglial-expressed Axl kinase may be at the nexus of neuroinflammation as well as neurodegenerative illnesses. The purpose of our study is to delve into the molecular pathways involving Axl, evaluate the therapeutic potential of targeting Axl, and assess the outcomes of preclinical and clinical studies. By including a comprehensive analysis of activation and regulation of Axl kinase, protective role, real-world studies, therapeutic potential, and future directions, this chapter aims to provide a thorough understanding of Axl kinase's role in AD and its potential as a therapeutic target. Our study emphasizes the importance of continuing research to develop targeted therapies that can effectively mitigate the progression of Alzheimer's disease.

## AXL RECEPTOR TYROSINE KINASE: AN OVERVIEW

### Structure and Biological Function

Axl kinase is a receptor tyrosine kinase that belongs to the TAM family, which also includes Tyro3 and Mer (Mertk). This family is named after the first three letters of its members: Tyro3, Axl, and Mer [4]. Axl was initially identified in chronic myelogenous leukemia cells, and its gene is located on chromosome 19q13.2 [14]. The name "AXL" means "uncontrolled," and it originates from the Greek term "anexelekto". The Axl receptor consists of an extracellular domain, a single-pass transmembrane domain, and an intracellular tyrosine kinase domain [15]. The extracellular region is composed of two immunoglobulin-like (Ig-like) domains and two fibronectin type III (FroIII) domains, which facilitate ligand binding and receptor dimerization and bear a resemblance to neural cell adhesion molecules (NCAMs) [16]. Upon ligand binding, typically by growth arrest-specific 6 (Gas6), a protein of 75kDa, Axl undergoes dimerization and autophosphorylation of its tyrosine residues within the intracellular domain [17]. This phosphorylation initiates a cascade of downstream signaling pathways, including the PI3K/Akt, MAPK/ERK, and NF-κB pathways, which regulate diverse cellular processes such as survival, proliferation, migration, and immune responses [18]. The intracellular domain of Axl kinase contains the TAM family-specific KW(I/L)A(I/L)ES sequence, which is involved in tyrosine kinase activity and shares considerable homology with Axl-relatedreceptor tyrosine kinases (RTKs) like Rearranged during transfection (RET) [19]. It controls a variety of processes, including platelet aggregation, natural killer cell differentiation, cell

# CHAPTER 4

# Role of NFAT Dysregulation in the Pathogenesis and Progression of Alzheimer's Disease

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**Abstract:** Alzheimer's Disease (AD) is a progressive neurodegenerative condition marked by cognitive deterioration, memory deficits, and neuronal degeneration. Its pathogenesis is multifactorial, involving amyloid-beta (Aβ) plaque accumulation, tau hyperphosphorylation, synaptic dysfunction, and neuroinflammation. Among these pathways, calcium dysregulation and its downstream signaling have emerged as critical contributors. Calcineurin (CN), a calcium-dependent serine/threonine phosphatase, and its downstream target, the nuclear factor of activated T-cells (NFAT), play pivotal roles in AD pathophysiology. Dysregulated CN-NFAT signaling has been linked to neuroinflammation, synaptic plasticity deficits, and enhanced Aβ production, exacerbating AD progression. This chapter elaborated on the preclinical studies, highlighting that CN-mediated NFAT activation promotes astrocyte and microglial activation, increasing pro-inflammatory cytokines like IL-6 and TNF-α. Besides, NFAT also influences amyloid precursor protein (APP) processing, augmenting Aβ generation. Moreover, excessive NFAT activation disrupts synaptic protein expression, leading to cognitive deficits. Here, we have also emphasized clinical studies implicating elevated nuclear NFATc4 levels and dysregulated NFAT signaling pathways in post-mortem AD brain tissues, highlighting their relevance in human pathology. Therapeutic strategies targeting NFAT signaling include CN inhibitors, such as FK506, to reduce Aβ deposition, neuroinflammation, and synaptic loss. Emerging selective NFAT inhibitors, including VIVIT, LxVP peptides, and novel small molecules like Q-134R, have demonstrated efficacy with reduced side effects

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compared to traditional CN inhibitors. Polyphenols, hydrogen sulfide donors, and gene therapy approaches also offer potential avenues for modulating CN-NFAT activity.

**Keywords:** Alzheimer's disease, Amyloid-beta, Cyclosporin A, Harmine, Hippocampus, Neuroinflammation, Nuclear factor of activated T-cells (NFAT).

## INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, memory impairment, and changes in executive function and disposition [1, 2]. It is considered the predominant reason for dementia and constitutes a substantial public health challenge, impacting approximately 6.9 million adults over the age of 65 in the United States in 2024 [3]. However, this figure is anticipated to increase to 13.8 million by 2060 [3], thus positioning AD as the fifth predominant reason for mortality among the geriatric community [3, 4]. The prevailing clinical treatment for AD generally encompasses symptomatic therapy aimed at decelerating cognitive deterioration with no medications to cure it [5]. The primary reason is its multifaceted pathophysiology involving amyloid-beta (Aβ) plaque accumulation, tau hyperphosphorylation, synaptic dysfunction, neuroinflammation, and neuronal loss [6, 7]. Moreover, among the several other biochemical pathways associated with AD, calcium dysregulation has been documented to hinder cognitive function and elevate susceptibility to the disease [8, 9]. Further, there are numerous reports that exhibited a direct link between the perturbed intracellular calcium homeostasis and calcium-dependent phosphatase, *i.e.*, calcineurin (CN) protein, that subsequently activates various other pathogenic hallmark proteins of AD [10 - 12]. Among these, the CN-activated nuclear factor of activated T-cells (NFAT) transcription factor has gained attention for its role in exacerbating the disease pathology. This chapter will discuss the role of CN and NFAT dysregulation in AD, drawing on preclinical and clinical evidence to highlight its contribution to the disease progression and its potential as a therapeutic target.

## CALCINEURIN

Calcineurin is a calcium/calmodulin-dependent serine/threonine phosphatase that is activated upon fluctuation in the intracellular calcium level [13, 14]. The holoenzyme of the calcium-sensing CN consists of two primary subunits, *i.e.*, a 60 kDa catalytic subunit and a 19 kDa regulatory subunit that includes four $Ca^{2+}$-binding EF-hand motifs [15]. An increase in the intracellular calcium level causes conformation changes in the calmodulin protein (CaM), thus exposing its hydrophobic binding site, which helps in binding to the regulatory subunit of CN [16]. This increases the phosphatase enzyme activity of CN, which

dephosphorylates various cellular proteins that mediate crucial cellular and molecular processes, including inflammation, apoptosis, and memory formation [17, 18]. It has been reported that NFAT is dephosphorylated in the presence of CN and CaM complexes, which largely contribute to the advancement of AD [15, 19, 20]. These cascades of events, in turn, cause the localization of NFAT inside the nucleus, resulting in the transcription of inflammation-related genes like interleukins (ILs), tumor necrosis factor (TNF-α), granulocyte-macrophage stimulating factor, and apoptotic factor FasL [21] (Fig. **1**). Furthermore, aberrant activation of CN-mediated NFAT has also been noted in various other cellular processes often associated with AD, such as astrocyte activation, Aβ production, synaptic plasticity, and cognitive inflexibility [22].

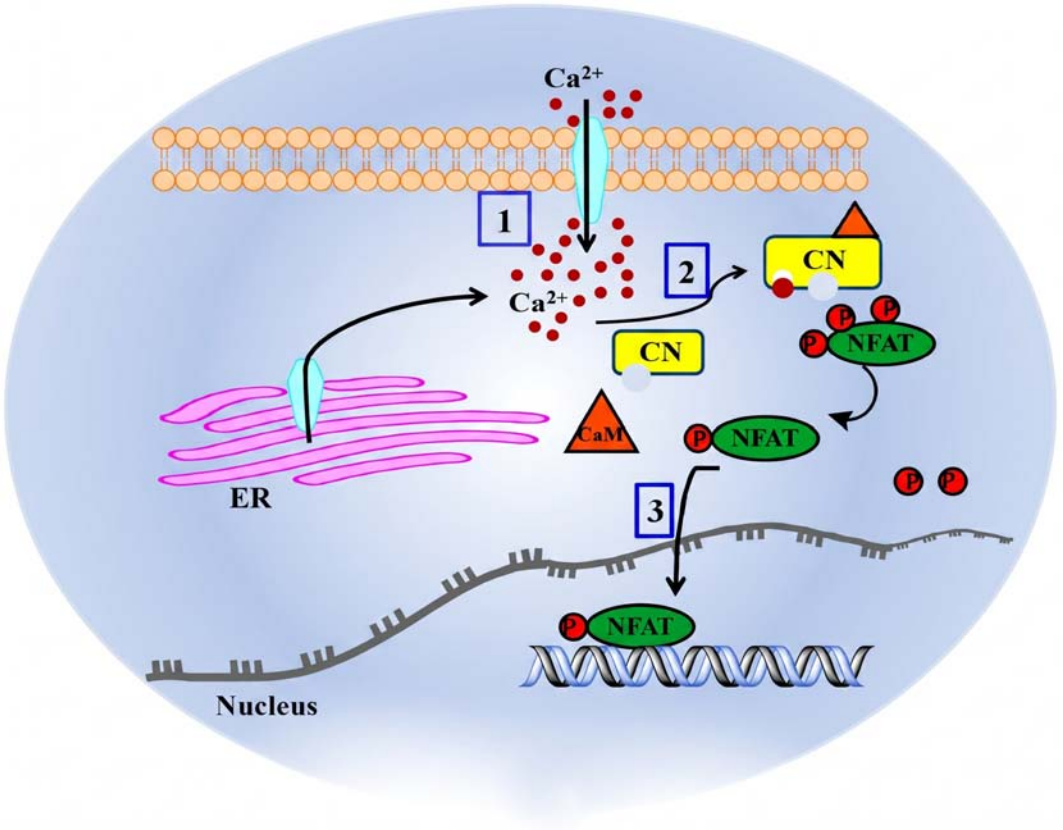


**Fig. (1).** The mechanism of activation of Nuclear Factor of Activated T-cells (NFAT) post-calcium perturbation *via* the calcium sensor, *i.e*., calcineurin (CN). This image illustrates the activation pathway of NFAT following an increase in cellular calcium levels (1). Calcium influx triggers the binding to calmodulin (CaM), a calcium-sensingprotein, which in turnactivates CN [2]. CN dephosphorylates NFAT, facilitating its translocation into the nucleus, where it modulates gene expression pertinent to immunological response, neural plasticity, and several cellular functions [3].

CHAPTER 5

# Pathophysiological Insights and Therapeutic Approaches of Oxidative Stress in Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is the leading neurodegenerative disorder responsible for dementia. Globally, AD is the leading cause of disability among those over 65. The primary pathological features of AD brains include the formation of senile plaques, loss of neurons, and neurofibrillary tangles. Amyloid beta plaque formation, aggregation, and accumulation, disturbedmetal (copper, iron, and zinc) homeostasis, metal-induced abnormal acetylcholinesterase (AChE) activity, neuroinflammation, oxidative stress, and other pathologies are all manifestations of AD, a multifactorial neurodegenerative illness. Therefore, developing treatment methods aimed at preventing AD pathogenesis requires a knowledge of the oxidative stress mechanism and degenerating synapses. The hypothesis of free radicals suggests that the buildup of certain oxidative lesions is at least primarily responsible for the slow and unavoidable process of physiological aging. Environmental risk factors are recognized as a major contributor to the development and progression of AD. Antioxidant combinations may provide an even higher potential benefit for AD, particularly if the medicines show complementary action or operate in distinct cellular compartments. Furthermore, it has been proposed that exposure to heavy metals, pesticides, and particulate matter increases the risk of Alzheimer's disease and, *via* epigenetic pathways, contributes to phenotypic variation. Therefore, gaining a deeper understanding of the mechanisms of antioxidants and biomarkers behind oxidative stress and synaptic degeneration is essential for developing therapeutic approaches aimed at preventing the progression of AD.

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**Keywords:** Alzheimer's disease, Biomarker, Intracellular neurofibrillary tangles (NFTs), Oxidative stress.

## INTRODUCTION

A progressive neurodegenerative illness, Alzheimer's disease (AD) is defined by memory and learning impairment that causes disruptions in language, perception, and planning. In 1906, German psychiatrist Alois Alzheimer made the initial discovery of AD. It is now thought that AD may impact 10% of the world's population. Millions of individuals throughout the world have been affected by this pandemicillness. By 2050, it is anticipated that the global prevalence will have quadrupled to 106.8 million [1]. Oxidative stress arises when there is an imbalance between pro-oxidants, including reactive oxygen species (ROS), and the body's antioxidant defenses. Oxidative stress is the result of an imbalance between the body's antioxidant defences and pro-oxidants, such as reactive oxygen species (ROS), with the balance shifting in favour of the pro-oxidants [2]. Memory impairment and dementia are caused by AD, which is typified by the accumulation of extracellular senile plaques, neurofibrillary tangles (NFTs), and neurodegeneration. Comprehensive efforts to study the pathophysiology of AD have not yet revealed the precise processes underlying the disease [3]. According to clinical research, persons with AD and those with moderate cognitive impairment had higher plasma cortisol levels (Fig. **1**). Because the hypothalamic-pituitary-adrenal (HPA) axis is frequently activated in physiological reactions to different stresses, causing the release of corticosteroids into the blood [4]. At the cytochrome oxidase complex, over 98% of the molecular oxygen is used by the mitochondrial electron transport chain, with the remainder being converted into superoxide and hydrogenperoxide radicals. The oxygen radical superoxide ($O_2\bullet^-$), the non-radical oxidant hydrogenperoxide ($H_2O_2$), and hypochlorousacid are formed during regular metabolism and other processes [5]. AD is characterized by the loss of synapses, build-up of extracellular amyloid beta-peptide (Aβ), and formation of senile plaques (SPs) due to amyloid precursor protein (APP) undergoing amyloidogenic transformation. Moreover, there is an increase in intracellular neurofibrillary tangles (NFTs) made up of hyperphosphorylated tau protein that stabilizes microtubules and is associated with this region [6]. Over the past ten or fifteen years, conclusive evidence has been proposed connecting AD to a rise in oxidative stress, partly due to both the enhanced production of reactive oxygen and nitrogen species (ROS and RNS, respectively) and loss of function of numerous antioxidant defence enzymes [7, 8]. Oxidative stress is recognized as a key factor in the development of AD; however, the precise mechanisms leading to redox imbalance and the origins of free radicals remain unclear. This chapter explores how the abnormal deposits of amyloid-beta (Aβ) and tau proteins contribute to oxidative imbalance and the production of free radicals. It highlights

processes such as mitochondrial dysfunction and disruptions in transition metal homeostasis as potential sources of oxidative stress. Additionally, it examines how oxidative damage enhances Aβ- and tau-driven neurotoxicity, further accelerating neuronal degeneration in AD [9].

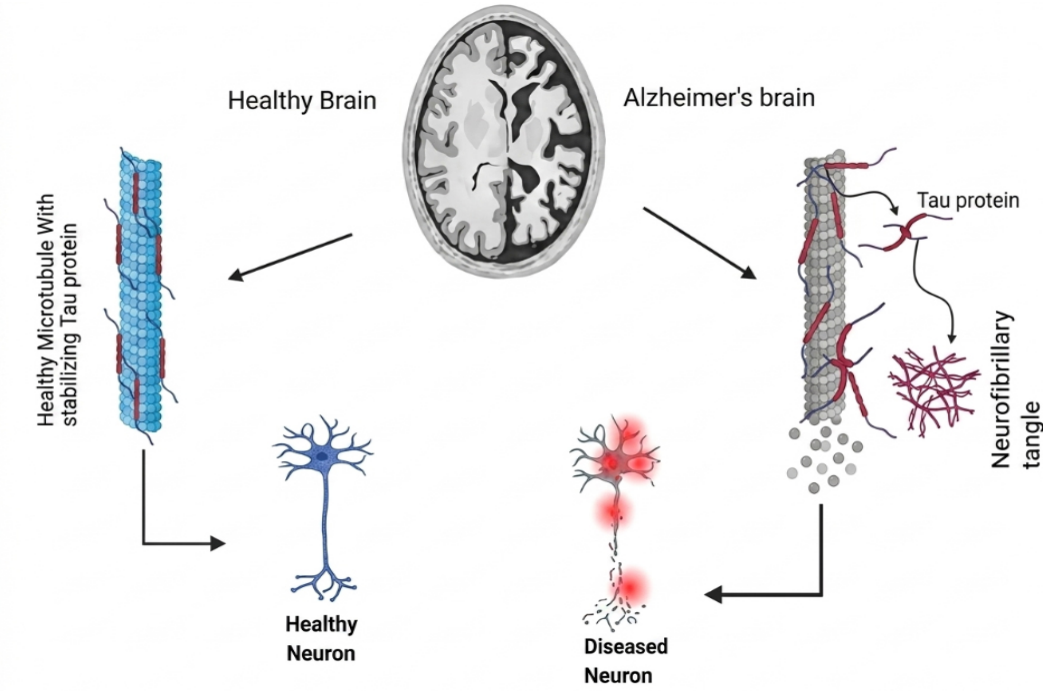


**Fig. (1).** Comparison between a normal brain and an AD-affected brain.

## PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

The study of AD pathophysiology is traced back to 1907 when Alzheimer found crucial neuropathological characteristics of the disease, such as amyloid plaques and hyperphosphorylated neurofibrillary tangles (NFTs).

Several theories have been advocated for explaining the complicated disorder on the basis of various causative elements. Some of these hypotheses are the tau hypothesis, cholinergic hypothesis, inflammation hypothesis, and amyloid-beta (Aβ) hypothesis (Fig. **2**) [10].

## AMYLOID PLAQUES AND TAU TANGLES

Beta-amyloid plaques are insoluble peptide deposits that arise as a consequence of the pathological cleavage of amyloid precursor protein (APP), whose functionis not exactly known. APP is normally processed by three enzymes: α-secretase, γ-

CHAPTER 6

# The Role of MicroRNAs in the Onset and Progression of Alzheimer's Disease: An Explicative Overview

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**Abstract:** MicroRNAs (miRs) are a class of small non-coding RNAs that harness immense potential in influencing disease pathogenesis by regulating gene expression. Given their abundance in the biological fluids, their ease of detection and quantification, miRs are being extensively studied as diagnostic biomarkers and therapeutic targets in various diseases. It is reported thatmiRs have significant roles in neuroinflammation, amyloid-β accumulation and metabolism, tau protein phosphorylation, and neuronal plasticity, which cumulatively precipitate Alzheimer's disease (AD). This chapter briefly describes the epigenetic landscape of AD, followed by the biogenesis of miRs and their major functionality in gene silencing. Furthermore, it elaborates the roles of different miRs identified in AD pathology, for developing early diagnostic markers and identifying druggable targets. Recent advances in miRNA-based therapeutics, including the use of miRNA mimics, inhibitors, and nanoparticle-mediated delivery systems, offer new possibilities for intervention. The chapter concludes by highlighting the challenges, such as targeted delivery, stability, and immunogenicity, along with the aspects for miRNA-guided drug development to transform AD treatment strategies.

**Keywords:** Alzheimer's disease, Biomarkers, RNA-binding proteins, Gene silencing, Gene expression, MicroRNAs.

## INTRODUCTION

Alzheimer's disease (AD) is a morbid condition characterized by progressive neuronal degeneration usually in the entorhinal cortex and hippocampus. It leads to dementia and cognitive decline. The incidence of AD increased more than 145% in the United States between 2000 and 2021, making it the 7th leading

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cause of death in 2021 [1]. For decades, cholinesterase inhibitors like Galantamine, Memantine, Rivastigmine, and Donepezil have been the mainstays of AD treatment. In 2023, the FDA approved a humanized monoclonal antibody (mAb), Lecanemab, as an anti-amyloid treatment that binds to soluble Amyloid β (Aβ) protofibrils, inhibiting their transformation to insoluble plaques and reducing Aβ burden in the brain. This treatment is indicated for patients with mild AD and mild cognitive impairment caused by AD [2]. However, all these interventions have limited efficacy owing to molecular complexities at different stages of the disease and significant side effects. Thus, to date, there is no cure for AD. The most important pathological characteristic and therapeutic target of AD is the deposition of Aβ plaques, Tau protein, and neurofibrillary tangles (NFT). These plaques are formed due to the imbalance in expression or non-clearance of Aβ. BACE1 (β-site amyloid precursor protein (APP) cleaving enzyme 1) is required to cleave APP to produce monomeric Aβ [3]. Functionally, SCARA-1 to 5, namely scavenger receptor class A members, are involved in the uptake of soluble Aβ, and RAGE (receptor for advanced glycated end products) is responsible for pro-inflammatory signaling following Aβ binding and microglial activation [4, 5].

Along with genetic involvement, epigenetic changes are also investigated thoroughly in recent times, and alteration of gene expression patterns influences the key pathological events like neuroinflammation, oxidative stress, and neuronal plasticity. MicroRNAs (miRNAs/ miRs) are most investigated owing to their activity involving the regulation of multiple gene expressions. Their presence in almost all biological fluids makes them an ideal candidate for diagnostic, prognostic, and therapeutic biomarkers in several neurological diseases. MiRs are non-coding, small RNAs, typically around 22 nucleotides long. They primarily function to suppress gene expression by binding to the 3′ UTR (untranslated region) of target mRNAs (messenger RNAs), but they are also capable of interacting with other regions, *i.e.*, the 5′ UTR, coding sequences, and gene promoters. With multifaceted roles, such as neuroinflammation, Aβ processing and accumulation, tau phosphorylation and synaptic functions, miRNA plays a central role in AD pathogenesis. This chapter briefly describes the epigenetic landscape of AD while focusing on microRNAs. It aims to highlight major miRs with clinical utility in the development of early disease markers and targeted therapeutic strategies.

## EPIGENETIC LANDSCAPE UNDERLYING AD

The epigenetic landscape of AD is complex, and key changes like histone modifications and non-coding RNAs are vital players in the development and progression of AD. Hypomethylation and hypermethylation of crucial genes involved in amyloid protein processing (APP and BACE) and neuronal plasticity

are observed in AD pathology [6 - 8]. In chromatin, a nucleosome is formed by DNA wrapped around histone proteins. The posttranslational modifications of histone in the amino-terminal regulate their interactions with DNA, thereby influencing gene expression. The histone tails are susceptible to undergo acetylation, ubiquitylation, methylation, glycosylation, ADP-ribosylation, and SUMOylation [9]. Histone acetylation changes memory processes and synaptic plasticity. Hyperacetylation and hypoacetylation of the cerebellum and hippocampus in AD patients were reported [10]. However, the use of HDAC (Histone Deacetylase) inhibitors was not as successful due to notable side effects and non-selective pharmacological effects [11]. On the other hand, histone methyltransferases were considerably more site-specific than acetyltransferases. This makes it more important to identify methylation on specific site and their relevance to pathology. For example, methylation of H2B K108 and H4 R55 and ubiquitination of H2B K120 were reported in the frontal cortexes of patients, which bear significance in the pathology of the disease. However, they are yet to be therapeutically targeted [12].

Tau aggregation, neurodegeneration, and reduction in autophagy that contribute to the AD neuropathology can be attributed to methylation of genes and alteration of histone methylations [13, 14]. In addition, phosphorylation of histone H3 was found to increase in the frontal cortex, and phosphorylation of Ser 47 of histone H4 (H4S47p) was a disease-specific modification, and shares a positive correlation with disease progression [6]. The ubiquitination of K120 on H2B increased by 91% in the frontal cortex of AD cases, as reported by Anderson and Turko. Dysregulated expressions of long non-coding RNA (lncRNA) have been observed post-transcriptomic analysis of brain tissues from animals and AD patients. X inactive specific transcript (XIST) is a widely investigated lncRNA that is correlated with pathological Aβ-mediated neuroinflammation and BACE expression [15, 16]. The ATP-dependent chromatin remodeling complexes are found to be dysregulated, as well as histone-modifying enzymes, leading to abnormal transcription of genes involved in AD pathology. Given that the loss of DEK (Drosophila, Erythrocyte protein band 4.1, and Kidney) protein induces brain aging-related phenotypes such as DNA damage and apoptosis [17].

## BIOGENESIS OF MIRNAS

### MiRNA Biogenesis: The Canonical Pathway

Predominantly, the canonical biogenesis pathway is utilized for miRNA biosynthesis (Fig. **1**). The pathway involves processing of the pri-miRNA, transcribed from their respective genes within the nucleus, into pre-miRNAs by a microprocessor complex. This microprocessor complex comprises DGCR8

CHAPTER 7

# Clinical Indication of the Role of Inflammation in Alzheimer's Disease

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**Abstract:** Considerable evidence gained over the past decade has supported the conclusion that neuroinflammation is associated with Alzheimer's disease (AD) pathology. Inflammatory components related to AD neuroinflammation include brain cells such as microglia and astrocytes, the classic and alternate pathways of the complement system, the pentraxin acute-phase proteins, neuronal-type nicotinic acetylcholine receptors (AChRs), peroxisomal proliferator-activated receptors (PPARs), as well as cytokines and chemokines. The microglia and astrocytes have been shown to generate beta-amyloid protein (Aβ), one of the main pathologic features of AD. Aβ itself has been shown to act as a pro-inflammatory agent, causing the activation of many of the inflammatory components. Further substantiation for the role of neuroinflammation in AD has come from studies that demonstrate patients who took non-steroidal anti-inflammatory drugs had a lower risk of AD than those who did not. These same results have led to increased interest in pursuing anti-inflammatory therapy for AD, but with poor results. On the other hand, an increasing amount of data suggests that AChRs and PPARs are involved in AD-induced neuroinflammation. In this regard, future therapy may focus on their specific targeting in the AD brain.

**Keywords:** Acetylcholine receptors, Food and drug administration, Peroxisomal proliferators-activated receptors, Non-steroidal anti-inflammatory drugs.

## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioral changes. While

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the exact mechanisms underlying AD remain unclear, a growing body of evidence highlights the auspicious role of neuroinflammation in its pathogenesis. Inflammation, typically a protective response of the immune system to injury or infection, becomes dysregulated in AD, contributing to disease progression.

In the context of AD, neuroinflammation is primarily mediated by the brain's resident immune cells, microglia, and astrocytes. These cells become activated in response to the accumulation of pathological hallmarks, such as amyloid-beta (aβ) plaques and tau protein tangles. However, instead of resolving the issue, this activation often leads to a chronic inflammatory state. This persistent inflammation exacerbates neuronal damage and synaptic dysfunction. Research also suggests that systemic inflammation, driven by comorbidities like infections, metabolic disorders, or lifestyle factors, may influence the progression of AD by breaching the blood-brain barrier and amplifying neuroinflammatory responses. Genetic factors, such as mutations in the APOE gene, further modulate the inflammatory processes associated with the disease. Understanding the role of inflammation in AD opens new avenues for therapeutic interventions [1]. AD is the most prevalent neurodegenerative disorder, currently impacting an estimated 20 to 30 million individuals globally. It comprises the majority of dementia cases diagnosed in individuals over the age of 60. In the United States alone, approximately 4 million patients are affected. The incidence of AD exhibits a significant age-related increase: around 1% to 3% of the population in their 60s are diagnosed, escalating to 3% to 12% among those aged 70 to 80, and reaching as high as 25% to 35% in older adults [2].

## INFLAMMATORY PATHWAYS IN THE AD BRAIN

A key feature of AD is neuroinflammation, which is primarily mediated by microglia and astrocytes. Here's an overview of the inflammatory pathways in the AD brain:

### Activation of Microglia and Astrocytes

Microglia and astrocytes are the primary immune cells of the central nervous system, playing crucial roles in maintaining brain homeostasis. In AD, these cells become activated in response to pathological stimuli such as amyloid-beta (Aβ) plaques and tau tangles.

Microglia are among the first responders to amyloid-beta (Aβ) deposition. Upon activation, microglia seek to clear Aβ plaques through phagocytosis. However, long-term activation can lead to the production of pro-inflammatory cytokines. Similarly, astrocytes, which support neuronal function and maintain the blood-

brain barrier, become reactive in AD. Persistent activation of these glial cells exacerbates neuroinflammation [3].

## NLRP3 Inflammasome Activation

The NLRP3 inflammasome is a multiprotein complex that is activated in response to Aβ accumulation in the AD brain. Once activated, the NLRP3 inflammasome leads to the release of IL-1β, a potent pro-inflammatory cytokine (Fig. **1**). Chronic activation of the inflammasome in microglia promotes a sustained inflammatory environment, contributing to neurodegeneration. Additionally, tau pathology has been shown to further activate the inflammasome, creating a vicious cycle of inflammation and neuronal injury [3, 4].

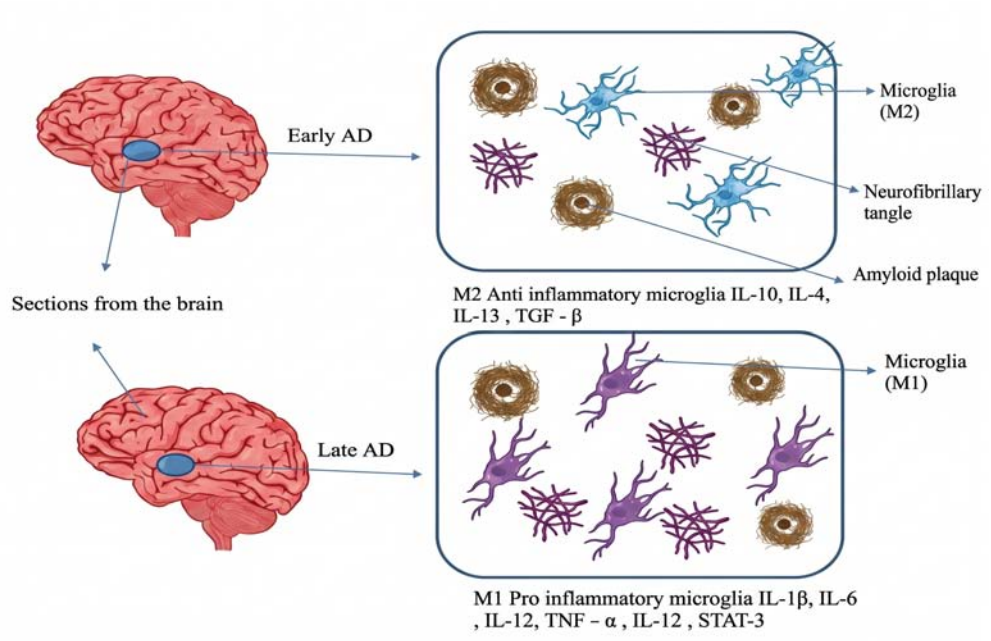


**Fig. (1).** NLRP3 inflammasome activation.

## Toll-like Receptors (TLRs)

Toll-like receptors are expressed in numerous cell types in the brain. In AD, TLRs, particularly TLR2, TLR4, and TLR9, are upregulated in response to the accumulation of amyloid-beta (Aβ) and tau protein aggregates. These receptors recognize Aβ plaques as damage-associated molecular patterns (DAMPs) and initiate an inflammatory response, which is meant to clear the pathological proteins but often leads to chronic neuroinflammation [5, 6].

# CHAPTER 8

# Nanotechnology-based Therapeutic Approach in Alzheimer's Disease

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**Abstract:** Nanotechnology-based newer therapeutic approaches can take care of the numerous shortcomings of the present treatment modalities for Alzheimer's disease (AD). Conventional therapies usually fail at targeting neuronal cells effectively and crossing the Blood Brain Barrier (BBB), leading to a poor drug delivery system and undesirable side effects. So, the use of nanomaterials and nano-carriers such as liposomes, polymeric nanoparticles, and dendrimers can rejuvenate the drug-delivery system. This optimises BBB penetration and thereby specifically targets affected neurons, reducing side effects and increasing drug stability, controlled release, and bioavailability-all of which are crucial in treating neurodegenerative disorders like AD. In this regard, significant advancements have been made in nanoparticle formulations showing great promise in improving the pharmacokinetics and pharmacodynamics of anti-Alzheimer's drugs. For example, liposomal formulations protect drugs from degradation until they reach the brain, whereas polymeric nanoparticles permit sustained drug release so that therapeutic effects can be maintained over a longer duration. Dendrimers serve as a mouldable drug-delivery system due to their hyper-branched construction, capable of co-delivering several therapeutic agents. This review discusses the pharmacological implications of the nanotechnology-based treatment of AD by providing an overview of recent developments and clarifying the mechanisms involved in Action.

**Keywords:** Alzheimer's disease (AD), Blood brain barrier (BBB), Drug delivery, Nanotechnology, Nano carriers, Neurodegenerative diseases.

## INTRODUCTION

Alzheimer's disease (AD) is one of the most difficult and debilitating neurological diseases of our day, with a substantial impact on international healthcare systems. This disorder, which mostly affects the ageing population, is characterised by a

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persistent deterioration in cognitive function, memory impairment, and significant behavioural abnormalities. As the illness worsens, people lose their freedom and quality of life, which puts a tremendous amount of emotional and financial strain on families and carers [1]. Remarkably limited is the therapy landscape for AD, despite decades of rigorous research and medical advances. The current therapies do not address the fundamental causes of the illness; instead, they provide momentary symptomatic alleviation. Patients' hope diminishes as the disease progresses because these medications are not able to stop or reverse the progression of AD [2]. The delivery of therapeutic drugs across the BBB, a barrier that selectively restricts the entry of elements into the brain, is one of the most severe obstacles to effective treatment. This has made it challenging to make significant advancements in the treatment of AD, especially in light of the systemic toxicity and restricted effectiveness of conventional medications [3]. The development of nanotechnology has created a new front in the fight against AD in light of these difficulties. With its capacity to modify materials at the molecular and atomic levels, nanotechnology presents previously unheard-of possibilities to transform medicinal strategies completely. Nanoparticles have some unique features: they are very small, have a large surface area, and can be specially designed to target certain areas of the body. These qualities make them useful for improving how medicines are delivered, especially for diseases like Alzheimer's. Scientists are using nanotechnology to find new ways to get drugs into the brain more effectively, reduce side effects, and help patients feel better. This chapter explores how nanotechnology is being used to fight Alzheimer's disease. It looks at the latest research and new materials that could lead to better, more targeted treatments. By studying these developments, we can get a clearer picture of how Alzheimer's might be treated in the future. Nanotechnology could change the way we understand and manage this complex condition [4].

## Pathophysiology of Alzheimer's Disease

Among the regions with maximum neuronal loss and/or illness are the entorhinal cortex, hippocampus, amygdala, and cortical association areas of the frontal, temporal, and parietal cortices. The subcortical nuclei such as the serotonergic dorsal raphe, the noradrenergic locus coeruleus, and the cholinergic basal nucleus are also included in this group. The first tangles are found in the entorhinal and trans-entorhinal cortex, in the hippocampus CA1 region, and in cortical association regions, mostly concerning the frontal, parietal, and temporal lobes. When the amyloid plaque is less, the DSM is more tightly linked to the location and extent of tangle formation [5]. Cognitive impairment is hugely correlated with tau protein infarctions and cerebrum shrinkage, especially in the hippocampi. Neuronal death and atrophy occur in the temporofrontal cortex with Alzheimer 's-induced inflammation; amyloid deposits, an abnormal cluster of protein

fragments, and twisted fibre bundles. This, in turn, raises the number of monocytes and macrophages in the cerebral cortex along with the activation of parenchymal microglial cells [6]. Fig. (**1**) illustrates the pathophysiology of AD, with a very detailed visual representation highlighting the processes and mechanisms that are key to the progression of the disease.

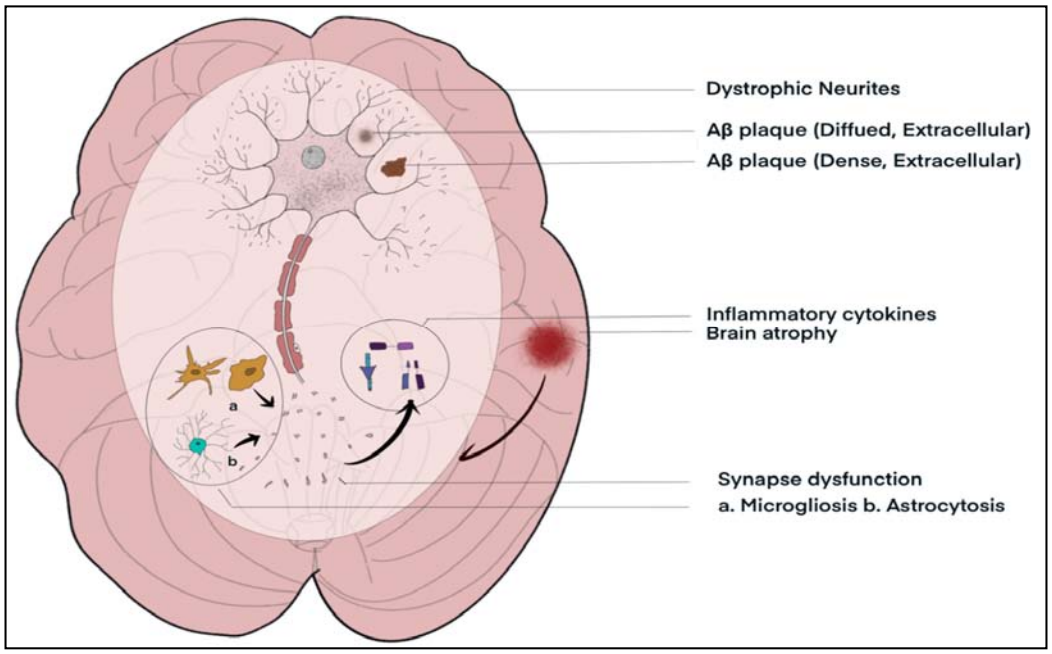


**Fig. (1).** Pathophysiology of AD

## Hyperphosphorylated Tau Protein and Amyloid β Hypothesis

The appearance of senile deposits in the human brain and such accumulations represent one of the major pathogenic features of AD, with the formation of plaques due to amyloid beta (Aβ) depositions. Being subjected to α-α-secretase, β-secretase, and γ-secretase, the amyloid precursor protein (APP) produces small soluble peptides, which are Aβ. These different toxic oligomers- fibrils, plaques, and protofibrils- are generated when there is an imbalance in either clearing or forming β-amyloid (Aβ), depending on the concentration of oligomers. While some factors influencing it include sequence, concentration, and conditions affecting stability, the genuine source of Aβ is still a mystery [7]. Numerous variables, including oxidative stress/mitochondrial dysfunctions, amyloid/tau toxicity, and cholinergic dysfunction, are implicated in the aetiology of AD [8].

# CHAPTER 9

# Treatment Using Anti-Amyloid Antibodies for Alzheimer's Disease

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**Abstract:** This chapter critically examines the latest advancements in novel antibody therapies targeting amyloid-β for Alzheimer's disease, as jointly endorsed by the European Association of Neurology and the European Psychiatric Association. Following numerous setbacks in the pursuit of disease-modifying treatments, compelling and consistent evidence now underscores the clinical efficacy of monoclonal antibodies against amyloid-β. Recent trials have not only succeeded in decelerating disease progression over several months but have also demonstrated positive secondary clinical outcomes and a reduction in amyloid-β levels, as shown through positron emission tomography scans. Collectively, these findings represent a significant breakthrough, confirming that reducing amyloid-β yields tangible clinical benefits beyond mere biomarker changes. As these new-generation drugs become more widely utilized, it remains to be seen whether their statistical efficacy will translate into clinically meaningful improvements. This could indeed mark the dawn of a new era in Alzheimer's disease therapeutics.

**Keywords:** Anti-amyloid immunotherapy, Cognitive decline treatment, Dementia, Fluid and imaging biomarkers, Mild cognitive impairment, Monoclonal antibodies.

## INTRODUCTION

Alzheimer's disease (AD), a chronic and progressive neurodegenerative disorder, is the most prevalent form of dementia, afflicting millions of elderly individuals with cognitive decline and behavioral impairments, responsible for up to 70% of all cases. Its prevalence surges with age, affecting roughly 10% of those over 65 and up to 50% of individuals past 85 [1]. The disease's hallmark pathology includes the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles,

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formed from hyperphosphorylated tau protein, which disrupts neuronal communication, ultimately leading to neuronal death and cognitive decline [2]. Historically, no treatments could modify the disease course, but in 2021, remarkable progress has been made in the treatment of AD, with the U.S. FDA approving five cognitive-enhancing drugs, one agent aimed at reducing agitation, and two disease-modifying therapies (DMTs). All approved DMTs for AD are currently anti-amyloid monoclonal antibodies (mAbs) [3]. The approval of Aducanumab (Aduhelm®), the first Aβ-targeting antibody, marked a breakthrough in AD treatment, offering a glimpse of hope in the development of disease-modifying therapies. Before this, the FDA had approved only a few drugs aimed at symptomatic relief, such as acetylcholine esterase inhibitors and NMDA receptor modulators, often discontinued due to adverse effects and limited efficacy [4]. The success of aducanumab, followed by the approval of Lecanumab (Leqembi®), a next-generation Aβ antibody, underscores the potential of Aβ-targeted therapies. The two approved therapies, Aducanumab and Lecanemab, have received approval based on their significant reduction of β-amyloid (Aβ) plaques, a hallmark of AD, as evidenced by amyloid positron emission tomography (PET). Donanemab, another promising agent, is under review for standard approval following phase II and III clinical trial data (Fig. **1**) [5]. While all anti-amyloid mAbs share a common mechanism of action—targeting high molecular weight fibrillar Aβ aggregates and inducing significant Aβ clearance—they also exhibit distinct characteristics. These differences lie in the specific amyloid species they target, as well as their pharmacokinetic profiles, including half-life, infusion frequency, and titration schedules [6]. Notably, these mAbs have been tested in populations with early AD, though the criteria for early AD, in terms of severity, vary across trials, potentially influencing patient selection for treatment. This chapter delves into the mechanisms of action of these mAbs, summarizes preclinical data, and highlights key features of their phase I, II, and III clinical trials [7]. We also explore how the similarities and differences among these agents may shape their use in clinical practice. Additionally, we discuss other drugs in development, including Remternetug, currently in a phase III trial, and Gantenerumab, whose development was halted after negative phase III results [8]. It is crucial to interpret the efficacy and safety of these drugs with caution, as direct comparisons can only be made if the agents are tested in equivalent arms within the same clinical trial, considering the variations in entry criteria, trial sites, investigators, and participant profiles [9].

## THE CHRONICLE OF AMYLOID CASCADE HYPOTHESIS

In 1984, the discovery of amyloid-beta (Aβ) as the main component of extracellular plaques marked a pivotal moment in Alzheimer's disease (AD) research, highlighting a distinct pathological hallmark of the condition [10]. This

breakthrough laid the foundation for the "amyloid cascade hypothesis," proposed by Hardy and Higgins in 1992, which posits that Aβ deposition is the initial trigger for AD pathogenesis, leading to tau tangles, neuronal loss, and cognitive decline. Since then, extensive genetic and non-genetic research has reinforced this hypothesis [11, 12]. For instance, Down syndrome, associated with APP gene triplication, and APP mutations in early-onset Alzheimer's disease (EOAD) both elevate Aβ production and alter the Aβ42/40 ratio, accelerating plaque formation and cognitive deterioration. Furthermore, key genetic risk factors for late-onset Alzheimer's disease (LOAD), such as APOE and Clusterin (CLU), have been found to significantly influence Aβ aggregation and clearance [13].

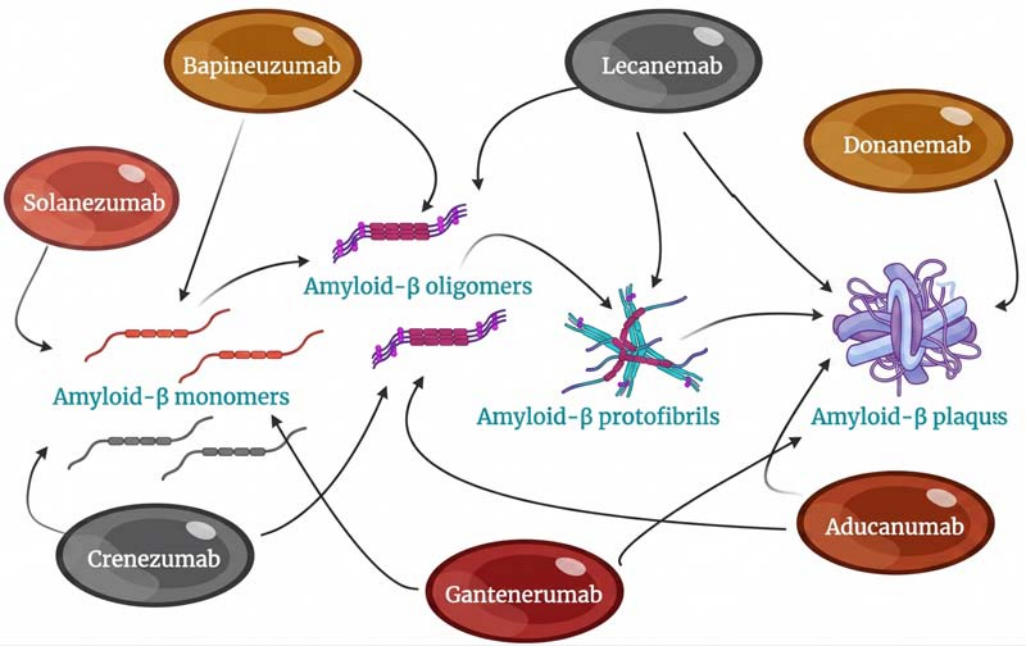


**Fig. (1).** Advancements in Alzheimer's therapies: mechanisms, trials, and implications of anti-amyloid monoclonal antibodies.

## Aβ Aggregate Morphology

Amyloid-beta (Aβ) aggregation is a pivotal event in the pathogenesis of Alzheimer's disease (AD). After its secretion, Aβ transitions from soluble forms into structured cross-β-sheet fibrils, ultimately forming amyloid plaques [14]. These plaques manifest in two distinct types: classical and diffuse. Classical plaques feature a dense Aβ core surrounded by a clear zone and a corona comprising degenerating neurites, reactive astrocytes, and microglia. In contrast, diffuse plaques are more scattered, lacking a concentrated core, and their Aβ

CHAPTER 10

# Small Molecules as Anti-Alzheimer's Scaffolds

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**Abstract:** Alzheimer's disease (AD) remains one of the most common diseases in our society. Its prevalence is increasing gradually, particularly in advanced nations, because life expectancy is increasing, and it presents a major worldwide economic burden. Throughout the last decades, all efforts to the development of newer diagnostic and therapeutic approaches have invariably met with failure, understanding that AD is currently irremediable and emphasizing the urgent requirement for innovative strategies. Recently, small molecules have emerged as an optimistic avenue for the cure of AD. These compounds can simultaneously provide diagnostic insights and therapeutic effects, enabling the evaluation of molecular activity, therapeutic responses, and pharmacokinetics. This dual functionality makes them highly promising for advancing AD drug research and their integration into personalized medicine. The small molecule theranostic compounds are the subject of this review article as a possible resource for the development of innovative therapeutic and diagnostic strategies for AD, which may highlight their noteworthy and advantageous influence in upcoming clinical applications.

**Keywords:** Alzheimer's disease, Dementia, Neurodegeneration, Pathophysiology, Small molecule theranostic agents.

## INTRODUCTION

Dementia is a general term used to describe a collection of symptoms linked to cognitive impairment, including memory loss, changes in mood and behavior, difficulty solving problems, and the inability to do daily tasks. Alzheimer's disease (AD) has drawn more attention than other dementia symptoms because of its high incidence (60–80%), which can result in the development of Lewy body disease, hippocampus sclerosis, Parkinson's disease, frontotemporal lobar degeneration, and cardiovascular disease [1]. The most common multifactorial neurodegenerative disease is AD, which is typified by a progressive decline in

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brain neuronal function. Currently, it is estimated that around 57 million people are affected worldwide, representing a considerable burden. It was predicted that AD will progress markedly to exceed 150 million cases in 2025 [2], demonstrating that AD is a debilitating condition that affects not just patients but also their family members and caregivers, and attesting to its significant influence on our society.

Clinically, AD manifests as cognitive impairment, including mood swings, depression, apathy, behavioural changes, and memory loss with difficulty recalling recent knowledge, leading to the display of physical disabilities with difficulties in speaking, working, and ultimately death [3]. These manifestations appeared in a slight way over a long duration of time, where three stages are generally discriminated, such as moderate cognitive impairment (slight symptoms that do not interfere with everyday work), dementia (symptoms that interfere with daily performance), and asymptomatic or preclinical AD. The asymptomatic symptoms in the preclinical stage do not reveal severe pathogenic mechanisms, while they can be observed in two decades prior to the onset of the symptoms, which is highly significant to search for therapeutic tools for early diagnosis of AD [4, 5]. Despite the numerous studies on AD, the cause of AD progression remains unclear. A few pathways have been found to efficiently target the onset and development of AD. The formation and accumulation of misfolded protein leads to the triggering of the induction of neurodegenerative disorder, which subsequently causes neuronal death. Tau and β-amyloid proteins are two important hallmarks associated with the initiation of AD pathophysiology, and both proteins have an important role in protein misfolding. Additionally, neuroinflammation, oxidative stress, imbalance in cholinergic and glutamatergic transduction, and mitochondrial dysfunction also participate in the progression of AD [6]. Furthermore, some risk factors are also involved in AD pathogenesis, including intrinsic factors, such as genetic factors associated with the amyloid protein precursor APP, γ-secretase – PSEN1 / PSEN2, and apolipoprotein E), aging, diseases like traumatic brain injury, cardiovascular disease, obesity, and diabetes, and external factors, like unhealthy lifestyle, smoking, exposure to metals – aluminium, lead, and cadmium [7, 8].

Only a few medications are authorized to treat AD as acetylcholinesterase inhibitors (AChE), rivastigmine, tacrine, galantamine, and donepezil block the route that suppresses the effects of acetylcholine (ACh). Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, comes in fifth. Additionally, a human IgG1 anti-Aβ monoclonal antibody *i.e.*, Aducanumab (Aduhelm), was authorized by the Food and Drug Administration (FDA) in 2021for treating AD, especially to target β-amyloid oligomers and fibrils [9]. The previous review highlighted the relevance of the innovative therapeutic and diagnostic approaches

for the treatment of AD. Moreover, the most pertinent developments for the treatment of AD in relation to small-molecule theranostic drugs are critically reviewed in this paper.

## PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Neurons in vertebrates share a critical physiological process involving the production and turnover of amyloid-beta (Aβ) (Fig. **1**). Several studies have shown that Aβ monomers play an important role in regulating synaptic activity [10, 11]. Preserving the homeostasis of synaptic Aβ monomer ratios is crucial and requires a very complex procedure. The interaction of the metastable hydrophobic peptide with lipids, vesicles, and membranes is what gives rise to this intricacy. It is difficult to quantify the amounts of metastable Aβ monomers in living animals because intrinsically disordered proteins (IDPs) can take on their structure during extraction. While some progress has been made in characterizing intermediate Aβ species in APP transgenic mice by combining synchrotron-based Fourier transform infrared microspectroscopy with nondenaturing gel electrophoresis [12], it is still very challenging to evaluate nascent Aβ monomer concentration in-vivo. According to certain theories, disruptions in the processes of Aβ synthesis and metabolism are likely the first signs of pathology [12].

Given the importance of preserving physiological Aβ levels at synapses, disruption of the Aβ turnover pathway leads to the early development of misfolded neuropathogenic species. If the proper monomer concentration at the synapse is crucial, losing Aβ monomers necessitates quick replacement. The only ways to restore this are to upregulate BACE and increase Aβ synthesis *via* APP processing. Because of the increased synthesis and turnover of Aβ monomers, this positive feedback loop raises the possibility of Aβ misfolding. Elevated BACE levels in the presynaptic endings of transgenic AD models [13] and the cerebrospinal fluid (CSF) of AD patients [14, 15] are among the most obvious markers of this effect. Mild cognitive impairment (MCI) patients exhibit early biochemical abnormalities in Aβ physiology, such as decreased CSF levels of Aβ42 monomers, even before severe neuronal loss in the advanced stages of AD [16]. Monomeric Aβ is a physiological cofactor that is necessary for the synaptic vesicle cycle (SVC) process and is considered a harmless pre-amyloid peptide.

Presynaptic terminals within the SVC have a significant concentration of Aβ production, which is acknowledged as the major site of Aβ generation [17]. Thus far, the conversation surrounding the function of Aβ monomer in SVC turnover has mainly centred on the pathophysiological function of APP or the precursor molecule itself. Compared to research on synuclein, considering the variations within pathological and physiological isoforms have been better recognized [18],

CHAPTER 11

# New Insights into Drug Development and Immunotherapy for Alzheimer's Disease

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**Abstract:** Alzheimer's disease, the most prevalent form of dementia and a chronic neurodegenerative disorder, accounts for 60-80% of all cases, which poses a significant challenge to healthcare systems worldwide. According to the Global Burden of Disease Study, approximately 57.4 million people were living with dementia in 2019, a number projected to rise to 152.8 million in 2050. The underlying pathophysiology of AD includes the buildup of β-amyloid plaques outside cells and the formation of neurofibrillary tangles due to tau protein accumulation within cells. Acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists are the main drugs used for diagnosis and treatment right now. Moreover, these treatments can temporarily mitigate dementia symptoms but do not halt disease progression or prevent symptom emergence. In this period, there is an urgent need for newer strategies to address AD effectively. Recently, immunotherapies have gained attention as a promising therapeutic avenue for treating AD by leveraging the immune system to downregulate several pathological protein expressions in the brain. In this review, we discuss the pathophysiological mechanisms of AD, newer strategies for drug development, and the potential of immunotherapies to prevent or manage AD.

**Keywords:** Alzheimer's disease, Current treatment strategies, Immunotherapy, Neurodegenerative disorder, Pathophysiology.

## INTRODUCTION

Alzheimer's disease, a neurodegenerative disorder characterized by a progressive decline in cognitive function that mainly affects the elderly population globally, was expected to be the predominant form of dementia, and in 2025, it will affect more than 100 million people worldwide [1]. Therefore, the WHO classifies AD

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as a public health priority. The global burden of Alzheimer's disease is underscored by its escalating prevalence, incidence, and mortality rates that remain estimated due to the widespread underdiagnosis of AD [2]. Clinically, AD is characterized by progressive loss of memory and development of cognitive impairments. The mild cognitive impairment caused by AD can subsequently promote AD dementia, which estimates the etiology among patients at 40% to 75%, depending on the population studied and whether the diagnosis has been made clinically or in combination with biomarkers [3]. The epidemiological study of dementia and AD in Portugal stated that both occurrence and prevalence rates are dramatically increased with age, replicating tentatively every 5 years [4]. The risk of AD dementia is significantly escalated as cognitive function declines, commencing with normal cognition and no amyloid-beta accumulation, advancing to early neurodegenerative alterations, and eventually progressing to mild cognitive impairment (MCI). The pathogenesis of AD is typically characterized by the aberrant accumulation of toxic protein fragments in the nervous system, including β-amyloid deposition within senile plaques and outside neurons, intracellular accumulation of hyperphosphorylated tau protein associated with microtubules, oxidative stress, inflammation, and depletion of central cholinergic neurotransmitters [5, 6].

Numerous researchers have developed effective drug molecules that cure this fatal disease, but these investigations remain stopped due to their numerous adverse effects. Recently, there are five marketed drugs, including acetylcholinesterase (AChEIs) inhibitors—Donepezil, Tacrine, Rivastigmine, and Galantamine—and N-methyl-D-aspartate (NMDA) receptor antagonist Memantine, that have been approved by the Food and Drug Administration (FDA) for AD treatment. Moreover, these marketed drugs could substantially inhibit the progression of AD and alleviate symptoms, while they may not eventually cure the disease [7, 8]. Hence, there is an urgent need for the advancement of AD treatment, which can significantly prevent and downregulate AD progression. New drug development in AD is remarkable due to the growing global burden of the disease and the limited efficacy of existing therapies. As AD progresses, it leads to the deterioration of cognitive ability, memory loss, and subsequently death. Despite extensive research, most existing therapies exclusively manage symptoms without reversing the underlying neurodegeneration. The complexity of AD pathophysiology, including β-amyloid plaques, tau protein tangles, neuroinflammation, and synaptic dysfunction, requires the development of innovative therapeutic strategies for AD treatment [5]. Developing new drugs could address AD etiology and pathogenesis, which are comprehensive and multidimensional, essential to slowing disease progression, improving quality of life, and potentially offering a cure. Recent advances in precision medicine, biomarker identification, and neuroprotective strategies open new avenues for

drug discovery. However, drug development in AD faces several challenges, including the high failure rate in clinical investigations due to the heterogeneity of the disease [9, 10]. Nonetheless, continued efforts in exploring novel targets, such as neuroinflammation, synaptic plasticity, and autophagy pathways, hold promise for transformative therapies that could address the unmet needs of AD patients.

Recently, immunotherapies have been at the forefront of controlling AD pathogenesis by immunological modification. Immunotherapy refers to the immunological arena, which primarily aims to identify target sites by activating, suppressing, and inducing immune responses [11]. Intriguingly, immunotherapy in AD management is a relatively novel strategy for non-infectious diseases. Currently, antibody-mediated passive immunotherapy that targets β-amyloid and tau proteins, aimed at obstructing β-amyloid peptide fibrillization and tau protein phosphorylation, and disrupting pre-existing fibrils, has become a dominant one in AD immunotherapy due to the repeated failures of active immunotherapy for AD [12, 13]. The most rational and safest strategies will focus on targeting toxic molecules without provoking an excessive immune response, thereby facilitating therapeutic benefits and improving the efficiency of clinical trial design. This review provides a concise overview of novel insights in drug development and encompasses immunotherapeutic strategies, including active and passive immunotherapy in AD management.

## PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Despite the cumulative knowledge about the molecular, biochemical, and cellular mechanisms of the disease, the accurate etiology and pathogenesis of AD remain unclear. Therefore, the development of innovative, effective, disease-modifying drugs faces significant challenges. The pivotal pathological hallmarks are a significant accumulation of β-amyloid to form plaques, neurofibrillary tangles, and loss of neuronal function. Despite a genetic predisposition, several lines of evidence indicate that AD pathogenesis involves inflammation, gliosis, an imbalance in the production and clearance of reactive oxygen species (ROS), excessive metal ion accumulation, and mitochondrial dysfunction (Fig. **1**) [6, 14, 15]. The following discussion highlights the most relevant pathophysiology of AD and putative drug targets for the AD therapeutic arsenal.

### β-amyloid Plaques

The proteolytic fragment of amyloid precursor protein (APP) cleavage produces -amyloid, a key factor of AD pathogenesis, and localizes it in the somatodendritic and axonal compartments of neurons, as highlighted by the -amyloid cascade [16]. APP is a single-pass type-I membrane protein, which consists of a single transmembrane domain with a large extracellular domain and a small cytoplasmic

# CHAPTER 12

# Natural Products as Effective Treatment Approach for Alzheimer's Disease: *In silico* Justification

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**Abstract:** Despite its complicated pathology and the lack of predefined curative treatments, Alzheimer's disease (AD) is still a challenge to this day. This chapter has focused on modern medical drug design for the use of natural products as therapeutic tools by providing a range of bioactive compounds in their spectra against which more than one pathological pathway in AD could be targeted. *In silico* approaches have provided powerful tools in evaluating the efficacy of these compounds in a cost-effective and time-efficient manner. This chapter discusses the current utility of *in silico* approaches like molecular docking, molecular dynamics simulations, and absorption, distribution, metabolism, elimination, and toxicity (ADMET) predictions towards confirming the application of naturalproducts as potential therapeutic alternatives for AD treatment. Some of the bioactive compounds originate from natural sources and encompass polyphenols, alkaloids, and terpenoids that display strong potential to inhibit fundamental pathological pathways such as Aβ aggregation, AChE inhibition, oxidative stress, and neuroinflammation. The computational assessment of such compounds predicts favourable pharmacokinetic profiles and drug-likeness. Such will pave the way for further investigations of these new chemical entities through *in vitro* and *in vivo* studies. Thus, *in silico* methodologies are a solid justification for developing natural products as effective therapeutic agents in AD.

**Keywords:** Alzheimer's disease, Amyloid-β aggregation, Acetylcholinesterase inhibition, Admet, *In silico*, Molecular docking, Natural products, Neuroinflammation, Oxidative stress.

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## INTRODUCTION

Alzheimer's disease (AD) is a worsening neurodegenerative illness affecting mental activity, function, and personality, with 25 million cases globally. It progresses from preclinical to dementia, and a rise in dementia cases is expected over the next 30 years. Understanding the illness process is crucial for improved patient treatment and preparedness [1, 2]. Symptoms include difficulty recalling events, uncertainty about time and location, and problem-solving challenges. The National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association established the criteria in 1984 for AD, stating that dementia develops gradually and no other brain disorders can explain memory loss and cognitive impairments [3]. Histological confirmation of clinical diagnosis is the only way to diagnose AD definitively. Advances in understanding pathogenic variants and presymptomatic individual clinical investigations have led to advancements in monogenic AD. An estimated 6.7 million Americans 65 and older are thought to be affected by Alzheimer's disease, and by 2060, that figure is predicted to rise to 13.8 million [4, 5]. With COVID-19 exacerbating the trend, the disease is now the sixth most common cause of death in the United States. More than 11 million relatives and unpaid carers gave 18 billion hours of care in 2022, worth $339.5 billion. Family carers now face higher expenses due to the lack of paid healthcare professionals [6]. Medicare and Medicaid pay three times as much per person on average for services provided to people with dementia as they do to people without the condition. In 2023, the total amount paid for hospice services, health care, and long-term care is expected to reach $345 billion [7, 8].

The amyloid cascade theory states that an accumulation of amyloid-beta peptides in the brain sets off degenerative processes that ultimately result in neurodegeneration. The cost of more recent monoclonal antibody treatments makes them less accessible, and patient noncompliance can reduce the effectiveness and tolerability of the treatment [9, 10]. Limited therapeutic methods exist for AD, but physical activity improves cognitive performance, reduces inflammation, boosts brain health, and encourages neurogenesis while addressing lifestyle, reducing symptoms, and managing cardiovascular risk factors. Acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate antagonists (NMDA) are approved therapies for AD [11, 12]. These drugs reduce the overactivation of the NMDAR glutamate receptor, restoring regular activity. However, they only treat AD symptoms. AChEIs increase ACH levels in the synaptic cleft but are often ineffective due to poor solubility and bioavailability [13]. However, due to poor solubility, limited bioavailability, and inability to penetrate the blood-brain barrier (BBB), acetylcholinesterase inhibitors are often ineffective as a therapeutic approach. The BBB is crucial for treating disorders

and AD pathophysiology, but few drugs can cross it, necessitating effective BBB techniques, understanding of BBB transportation, and therapeutic agent transfer [14, 15].

AD has no effective treatment. By blocking the synthesis of Aβ-peptides, encouraging Aβ breakdown, blocking AChE, lowering oxidative stress, and lowering neuroinflammation, these substances can combat AD in many ways [16, 17]. Additionally, several beneficial herbs can be utilized to treat AD and lessen dementia. Natural substances like curcumin, resveratrol, and Ginkgo biloba extract have antioxidant properties, which can lower oxidative stress, reduce brain inflammation, and maintain neuron health and cognitive capacity. However, further clinical research is needed to assess the effectiveness, ideal doses, and long-term safety of these compounds [18, 19]. The use of natural components in treating AD is examined in this chapter, highlighting their effectiveness and potential benefits. It emphasizes the need to understand their pharmacokinetics, bioavailability, and safety characteristics, as including natural ingredients could enhance patient outcomes and advance neurodegenerative treatments. Physical activity improves cognitive performance in the elderly, reduces inflammation, and promotes neurogenesis. Advances in understanding pathogenic variants and presymptomatic clinical investigations have led to advancements in monogenic AD. *In-silico* justification of natural products offers a new therapeutic approach without side effects, inhibiting Aβ-peptide production and reducing oxidative stress.

## COMPREHENSION OF ALZHEIMER'S DISEASE

### Pathogenesis of Alzheimer's Disease

AD is a worsening neurological condition causing dementia in senior populations, leading to behavioral abnormalities, loss of functional independence, and cognitive deterioration, primarily in memory. This chapter explores the disease's pathophysiology (Fig. **1**), molecular processes, and potential treatment options [20 - 22].

### Core Histopathological Features of Alzheimer's Disease

AD is characterized by some hallmark traits that exacerbate the neurodegenerative process:

- AD is a condition distinguished by the accumulation of two key proteins, tau and amyloid-beta (Aβ), which form the pathological lesions that define the disease.

# CHAPTER 13

# Biopolymer-based Therapeutic Approaches as Effective Treatment Methods for Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is a complex neurodegenerative disorder marked by progressive cognitive decline, memory impairment, and neuroinflammation, with no curative therapies currently available. The complexity of its pathogenesis, which involves amyloid-beta (Aβ) plaques and tau protein aggregation, presents significant challenges to effective therapeutic development. Despite advances in pharmacological interventions, the lack of curative therapies highlights the need for innovative approaches. Biopolymers, owing to their unique properties such as biocompatibility, biodegradability, and the ability to cross the blood-brain barrier (BBB), have emerged as promising candidates for therapeutic applications in AD. These materials enable targeted delivery of therapeutic agents, sustained release, and enhanced bioavailability, minimizing off-target effects. This chapter delves into the potential of biopolymers as innovative tools for addressing AD's therapeutic challenges. It categorizes biopolymer systems into polysaccharides, proteins, peptides, and nucleic acids, exploring their ability to encapsulate drugs, ensure sustained release, and achieve targeted delivery across the blood-brain barrier (BBB). Emphasis is placed on their capacity to modulate critical AD mechanisms, including Aβ aggregation, tau pathology, oxidative damage, and neuroinflammation. Strategies such as nanoparticle engineering, targeted delivery, and phytochemical-based therapies are discussed, emphasizing their potential to overcome existing challenges in drug delivery and therapeutic efficacy. Novel nanocarrier-based drug delivery systems highlight the transformative potential of these approaches, though challenges related to biodegradation, stability, and regulatory compliance remain. By synthesizing cutting-edge research, this chapter highlights biopolymer-based therapies as transformative strategies poised to address the unmet clinical needs of AD, paving the way for novel, targeted, and patient-centric treatment paradigms.

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**Keywords:** Alzheimer's disease, Biopolymer, Blood-brain barrier, Nanoparticles, Tau protein.

## INTRODUCTION

Alzheimer's disease (AD) is one of the most devastating neurodegenerative disorders, characterized by progressive memory loss, cognitive decline, and behavioral impairments [1]. Despite extensive research efforts, the complexity of AD pathogenesis—which encompasses amyloid-beta (Aβ) plaques, tau protein aggregation, oxidative stress, and chronic neuroinflammation—continues to pose significant challenges to effective treatment development [2]. Current pharmacological approaches provide only symptomatic relief, leaving an unmet need for innovative and holistic therapeutic strategies that target the disease's multifactorial nature. Biopolymers have garnered increasing attention in recent years for their potential to revolutionize the therapeutic landscape of AD [3]. These natural polymeric materials, such as polysaccharides, proteins, peptides, and nucleic acid-based systems, offer remarkable versatility in addressing key challenges in drug delivery and therapeutic targeting [4]. Biopolymers are not only biocompatible and biodegradable but also capable of encapsulating, protecting, and delivering therapeutic agents directly to the brain. Their tunable properties allow for advanced functionalities, including sustained drug release, precision targeting, and the ability to cross the blood-brain barrier (BBB) [3].

This chapter delves into the transformative potential of biopolymers in Alzheimer's disease therapy. It highlights their unique ability to overcome critical barriers, such as crossing the blood-brain barrier (BBB), delivering therapeutics with precision, and enabling sustained release of bioactive agents. The focus shifts to innovative biopolymer-based systems, classified by their origin and function. Polysaccharide-based systems like chitosan and hyaluronic acid offer solutions for drug encapsulation, while protein-based formulations, including collagen and silk fibroin, enable targeted delivery to brain cells. Peptide-based polymers and nucleic acid delivery platforms further expand the toolkit for combating amyloid-beta aggregation, tau pathology, and other neurodegenerative mechanisms with unprecedented specificity and efficacy. These systems, optimized for size, surface characteristics, and ligand targeting, exemplify the strides made in enhancing bioavailability and therapeutic precision. Moreover, innovative nanocarrier-based combination therapies are discussed, showcasing how biopolymer systems can synergize with other modalities to enhance therapeutic efficacy. A comprehensive exploration of biopolymer-based strategies in AD treatment is presented here, emphasizing their promise in overcoming current therapeutic barriers. By addressing challenges such as stability, biodegradation, and regulatory concerns,

it sets the stage for advancing these systems toward personalized and precision medicine approaches for Alzheimer's disease.

## BIOPOLYMERS IN DRUG DELIVERY

Biopolymers are an extensive and highly adaptable class of compounds originating from biological systems or synthesized using biological precursors. Similar to other polymers, biopolymers are constructed from repeating structural units, or monomers, linked in sequence [5]. Their unique features, including biodegradability, accessibility, and customizable physicochemical properties, make them attractive for advanced formulations. As the global emphasis shifts toward sustainability, biopolymers have become pivotal in designing systems aligned with environmental preservation. Recently, their utility in drug delivery systems (DDS) has garnered significant interest [6]. DDS refers to strategies for incorporating therapeutic agents, ensuring their precise delivery to specific diseased locations while minimizing systemic side effects. The ideal DDS enables both targeted delivery and controlled drug release, safeguarding drugs from premature degradation within the body before they reach their intended target. Moreover, these systems leverage biocompatibility and biodegradability to reduce adverse effects while optimizing therapeutic outcomes [7].

Both natural and synthetic polymers have shown potential in DDS development. While natural polymers excel in biocompatibility and biodegradability, their limited mechanical strength, thermal stability, and solubility often restrict their broader applications [8]. To address these challenges, functionalization and blending techniques are employed, creating advanced materials that exhibit enhanced properties derived from the parent polymers [7, 8]. Such hybrid systems combine complementary attributes, minimizing drawbacks and enhancing the efficiency of DDS [9]. The development of polymeric nanobiocomposites often involves combining polymers with fillers like metal nanoparticles, hydroxyapatite, or organic and inorganic clays. This approach enables high drug-loading efficiency while minimizing the quantity of carrier material used. Drug incorporation into nanocomposites is achieved through two main methods: impregnation, which involves incubating nanocomposites in a drug solution, and integration, where drugs are encapsulated during the material's synthesis (Fig. **1**) [10].

Polymer–drug complexes typically form through interactions such as hydrogen bonding, hydrophobic forces, electrostatic attractions, or van der Waals forces. To improve mechanical strength and system stability, cross-linking agents are often introduced, providing robust structural integrity. In certain applications, supramolecular aggregates with cavity-like structures are required to host guest

# CHAPTER 14

# Integrative Molecular Approaches in Targeted Therapy for AD: Bridging Complex Mechanisms and Future Innovations

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**Abstract:** Alzheimer's disease (AD) is an extremely complicated neurodegenerative disease that results in memory loss and a progressive deterioration in cognitive function. While significant strides have been made in understanding its underlying mechanisms, the intricate molecular pathways of AD pose substantial challenges in developing effective treatments. This chapter explores the potential of integrative molecular approaches in targeted AD therapy, with a focus on the current pharmacological treatments available. Additionally, it highlights research into natural products related to the disease. By examining the interconnected network of molecular signalling pathways, we delve into emerging genetic innovations such as gene editing technologies, neuroinflammation modulation, and targeting amyloid-β and tau proteins. As our understanding of AD continues to deepen, integrative approaches hold the promise of not only enhancing treatment options but also fostering a more holistic approach to managing the disease. The future of AD treatment lies in combining molecular insights with innovative therapies, paving the way for more effective and personalized care for patients.

**Keywords:** Alzheimer's disease, Amyloid-β, Acetylcholine, Natural products, NMDA receptor antagonists.

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**Swarupananda Mukherjee, Souvik Roy & Dipanjan Karati (Eds.)**

## INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia and the most prevalent neurodegenerative disorder. It is characterized by a deterioration in short-term memory and cognitive function, which affects daily activities. The number of Americans affected by AD is rapidly increasing. In 2024, approximately 6.9 million people aged 65 and older are living with Alzheimer's, with nearly 73% of them being 75 or older [1]. This means that roughly 1 in 9 people in this age group, or 10.9%, have the disease. Women make up almost two-thirds of those diagnosed, and older Black and Hispanic Americans are disproportionately affected, with Black Americans being about twice as likely, and Hispanics one and a half times as likely, to develop Alzheimer's or other dementias compared to older Whites. As the U.S. population continues to age, the number of people living with Alzheimer's is expected to grow significantly, potentially reaching 12.7 million by 2050, unless significant medical breakthroughs are made to prevent or cure the disease [1].

The complexity of AD is reflected in the intertwining of these various factors, where genetic predispositions may set the stage for the disease, but environmental and lifestyle factors may influence its progression and severity. Understanding these interconnections is crucial for developing more effective prevention and treatment strategies.

There are several hypotheses that attempt to explain the underlying mechanisms and causes of AD. These hypotheses are based on the observed pathological features of the disease and the factors that might contribute to its development [2]. The major ones have been illustrated in Fig. (**1**).

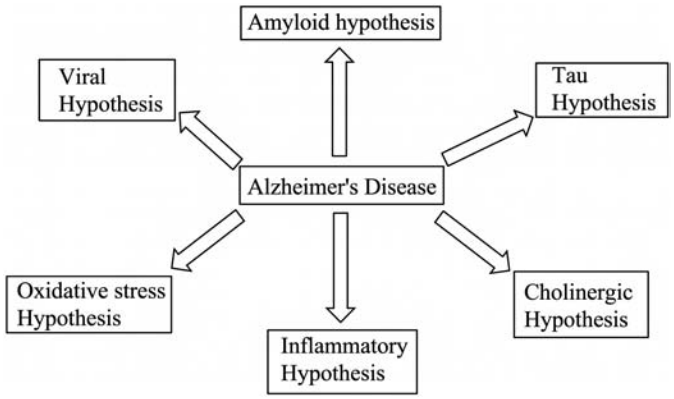


**Fig. (1).** Predominant hypotheses of Alzheimer's disease.

## PHARMACOLOGICAL TREATMENT LANDSCAPE

Traditional AD medications are generally classified into two main groups: acetylcholinesterase inhibitors (AChEIs) and NMDA receptor antagonists [3]. The AChEIs—such as tacrine, donepezil, rivastigmine, and galantamine—work by elevating the concentration and prolonging the duration of acetylcholine (ACh) activity at the synapse, which helps improve cognitive and behavioral symptoms in patients [4]. Tacrine, the first AChEI approved for the treatment of AD in 1993, was taken off the global market in 2013 mainly because its usage was linked to liver toxicity. Despite this, tacrine remains of interest in research, particularly in the development of multitarget-directed therapies [5 - 7].

Second-generation acetylcholinesterase inhibitors (AChEIs), such as donepezil, rivastigmine, and galantamine, are more selective than their predecessors [8, 9]. These drugs tend to have fewer side effects and enhanced pharmacokinetic properties, making them the preferred choice for treating AD. Despite their widespread use, current research is dedicated to refining aspects such as optimal dosing, formulation, administration methods, and development of combination therapies in order to reduce side effects and lead to the improvement of patient adherence to treatment [10 - 12]. In 2022, the FDA approved the donepezil transdermal patch, Adlarity, for the treatment of mild, moderate, and severe AD-related dementia [13]. This patch, which is applied weekly, proved to be bioequivalent to the oral version taken daily at the same dosage, while also resulting in significantly less gastrointestinal side effects compared to oral administration. Moreover, using a combination of suitable cholinesterase inhibitors like donepezil and galantamine, or pairing AChEIs with some other neurological medications, metal chelators, or potent antioxidants, can result in unexpected benefits in managing cholinergic drugs for AD therapy, including improved efficacy, safety, and tolerability [11, 14].

Memantine, an NMDA receptor antagonist approved by the FDA, is used to treat moderate to severe AD. By regulating glutamate transmission and dopamine receptors, it has shown effectiveness in enhancing cognitive function, daily living skills, and behavior in patients [15, 16]. Namzaric, a fixed-dose combination of extended-release memantine and donepezil, offers an additional therapeutic option for individuals with moderate to severe AD [17]. Medications like these mainly work by adjusting the neurotransmitter levels, though they do not alter the progression of the disease [15, 18]. This limitation has helped guide the development of new treatments. In 2017, a review [19] introduced the concept of "disease-modifying therapy for AD, which seeks to target the core physiological mechanisms of the disease to stop its progression and provide lasting benefits for patients.

# SUBJECT INDEX

## G



## H



## I



## K



## L



## M



## N



## O

## P



## Q



## R



## S



## T



## V



## X

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