Ageing Research Reviews 109 (2025) 102775

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

Advances in Alzheimer's therapy: Exploring neuropathological mechanisms to revolutionize the future therapeutic landscape

Vrashabh V. Sugandhi [a,1], Dnyandev G. Gadhave [a,b,*,1], Akanksha R. Ugale [a], Nilesh Kulkarni [c], Sopan N. Nangare [d], Harshal P. Patil [c], Seepra Rath [e], Rahul Saxena [f], Amol Lavate [b], Apeksha T. Patel [g], Ashish Jadhav [b], Keshav Raj Paudel [h,**]

[a] College of Pharmacy & Health Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY 11439, USA
[b] Department of Pharmaceutics, Dattakala Shikshan Sanstha's, Dattakala College of Pharmacy (Affiliated to Savitribai Phule Pune University), Swami Chincholi, Daund, Pune, Maharashtra 413130, India
[c] Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule, Maharashtra 425405, India
[d] Department of Pharmaceutics, Krishna Vishwa Vidyapeeth (Deemed to be University), Krishna Institute of Pharmacy, Karad, Dist-Satara, Maharashtra, 415539, India
[e] Center for Dermal Research, Rutgers, the State University of New Jersey, 145 Bevier Road, Piscataway 08854, USA
[f] Graduate Programs in Molecular Biosciences, Rutgers, the State University of New Jersey, Piscataway 08854, USA
[g] Department of Quality Assurance, Navinta III INC, Boca Raton, FL 33487, USA
[h] Centre for Inflammation, Faculty of Science, School of Life Science, Centenary Institute and University of Technology Sydney, Sydney 2007, Australia

ARTICLE INFO

Keywords:
Alzheimer's disease
Cellular mechanisms behind AD
Blood-brain barrier
Neurodegeneration
Gene therapy
Clinical trials

ABSTRACT

Alzheimer's disease (AD) is still an excessively complicated neurological disorder that impacts millions of individuals globally. The ideal defensive feature of the central nervous system (CNS) is the intimate junction of endothelial cells, which functions as a biological barrier to safely control molecular transport throughout the brain. The blood-brain barrier (BBB) comprises tightly locked astrocyte cell junctions on CNS blood capillaries. This biological barrier shields the brain from hazardous toxins by preventing the entry of polar medications, cells, and ions. However, it is very challenging to provide any treatment to the brain for neurodegenerative illnesses like Alzheimer's. Different causative mechanisms, such as amyloid-β (Aβ) plaques, tubulin-associated unit (Tau) tangles, and neuroinflammation, cause neuronal dysfunction, leading to dementia and memory loss in the subject. Several treatments are approved for AD therapy, whereas most only help treat related symptoms. Disappointingly, current remedies have not been able to control the progression of AD due to associated side effects. Specific pathogenic mechanisms are involved in the initiation and development of this disease. Therefore, the expected survival of a patient with AD is limited and is approximately ten years. Hence, the pathogenic mechanism behind AD progression must be understood to better comprehend and improve the overall survival rate. This review highlighted the recent insights into AD pathogenesis, molecular mechanisms, advancements in theragnostic techniques, the existing updates of clinical trials, and emerging innovations for AD medicinal development. That has helped researchers develop other strategies to address the shortcomings of traditional medications.

1. Introduction

The most prevalent type of neurodegenerative illness, Alzheimer's disease (AD), can be recognized by the intracellular accumulation of neurofibrillary tangles (NFTs), which are made of hyperphosphorylated Tau, and the extracellular aggregation of amyloid-β (Aβ) plaques (DeTure and Dickson, 2019; Y. Zhang et al., 2023). Further, AD is accompanied by the destruction of neurons and synapses (Griffiths and Grant, 2023). Since Alois Alzheimer's first discovered AD at the beginning of the 20th century, it has become a significant healthcare concern

* Corresponding author at: College of Pharmacy & Health Sciences, St. John's University, 8000 Utopia Parkway, Queens, NY 11439, USA
** Correspondence to: Centre for Inflammation, Centenary Institute and University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, NSW 2007, Australia.
E-mail addresses: dnyanraj24@gmail.com (D.G. Gadhave), Keshavraj.paudel@uts.edu (K.R. Paudel).
[1] Both authors contributed equally

https://doi.org/10.1016/j.arr.2025.102775
Received 12 December 2024; Received in revised form 7 May 2025; Accepted 16 May 2025
Available online 20 May 2025

because, currently, no appropriate treatment exists.

1.1. Clinical signs and manifestations of AD

AD demonstrates a variety of neurological signs, primarily expressed as early amnestic mental retardation and trouble with short-term memory (Tarawneh and Holtzman, 2012). In AD, neurological symptoms frequently arise in addition to cognitive impairment, especially in the beginning stages when detachment, depression, and anxiousness are common (Botto et al., 2022; Gadhave et al., 2024c). As the illness becomes more severe, patients may have hallucinations, illusions, aggression/agitation, and lability/irritability, among other symptoms (Cerejeira et al., 2012). In previous decades, the diagnosis of AD was restricted to the dementia stage, which was indicated by neurobehavioral manifestations that were sufficient to significantly impede daily functioning or by considerable, cumulative cognitive impairment throughout numerous domains (Liss et al., 2021). Many molecular pathways, such as neuroinflammation, tubulin-associated unit (Tau) tangles, and amyloid-β (Aβ) plaques, are employed to diagnose AD (Gadhave et al., 2024b). Fig. 1. demonstrates the neurological features of Alzheimer's disease. Jack et al. (2018) state that Aβ and phosphorylated Tau are necessary for diagnosing AD (Jack Jr. et al., 2018). AD is identified as a separate neurodegenerative illness from other mental conditions, which causes dementia; however, the primary factors behind AD are Amyloid-β, Tau, and Neurofilament Light (ATL), which play a crucial role in the diagnosis of the disease (DeTure and Dickson, 2019). According to pathogenesis, initially, AD is in an asymptomatic form; subsequently, at a Mild cognitive impairment (MCI) stage, it turns into prominent dementia (Tahami Monfared et al., 2022). In people who are at risk for AD, Aβ dysfunction starts 15–20 years before significant memory impairment is expected to manifest (Sperling et al., 2014). Increased Tau concentrations in cerebrospinal fluid (CSF) indicate neuronal damage and correlate with the disease's severity (Constantinescu et al., 2011). In individuals with AD, 18fluorodeoxyglucose (18FDG)-positron emission tomography (PET) is a valid indicator of synaptic damage linked to neurodegeneration (Gadhave and Kokare, 2019; Guedj et al., 2021). Even in the most severe stages of the illness, structural magnetic resonance imaging (MRI) measures brain shrinkage as neurons and synapses degenerate (Veldsman, 2017). That is consistent with post-Tau tangle pathology, which is highly connected with the degree of mental impairment.

1.2. Prevalence and global impact of AD

Around 60 % and 80 % of dementia patients have AD. Globally, around 57.4 million people had dementia in 2019 (Collaborators, 2022). Approximately 145 % more fatalities were caused by AD in 2019 compared to 2000, making it the sixth most prevalent cause of mortality in the US. The symptoms that appear autosomal- dominant AD subtype account for around 1 % of instances of AD; late-onset sporadic AD accounts for the other 99 % (Rujeedawa et al., 2021; Van Cauwenberghe et al., 2016). The majority of people with autosomal-dominant AD begin to exhibit symptoms in their 40 s and 50 s, with symptoms usually appearing before the age of 65 (Gadhave et al., 2024b). The physiological mechanisms of AD are greatly influenced by hereditary factors, which are thought to be responsible for between 58 % and 79 % of incidents (Breijyeh and Karaman, 2020; Xiao et al., 2021). Autosomal-dominant AD is associated with rare presenilin-1 (PSEN1), presenilin-2 (PSEN2), and amyloid protein precursor (APP) mutations (Cai et al., 2015). The apolipoprotein E (APOE) gene is a major genetic risk factor for sporadic AD. Apolipoprotein E epsilon 4 allele (APOEε4) was found in 66 % of individuals with AD-type dementia and 64 % with MCI (DiBattista et al., 2016; Yamazaki et al., 2019). A single APOEε4 allele increases the risk 3.4 times, whereas having two alleles increases the risk 9.15–15.5 times (Raulin et al., 2022). According to estimates, 18.1 % of people over 65 have AD, and that number jumps to 33.2 % for people over 85. Furthermore, among those over 65 in the US, AD affects 11.6 % of males and 21.1 % of women (Aggarwal and Mielke, 2023). Twelve potential risk factors have been recognized by the Lancet Commission on Dementia Prevention, and taken together, they could be responsible for almost 40 % of cases of dementia globally (Livingston et al., 2024). A lack of education, high blood pressure, hearing loss, smoking, obesity, depression, lack of exercise, diabetes, and little social contact are some of these causes (Livingston et al., 2020). As reported in 2020, over 55 million individuals were affected worldwide with dementia (Shin, 2022). As predicted, this number will double in 20 years, reaching 78 million in 2030 and 139 million in 2050 (Prabha et al., 2024; Tiwari et al., 2023). Fig. 2. illustrates the current global preponderance of AD. More than 121,499 individuals died in 2019 due to AD (Gadhave et al., 2024b). Nowadays, Finland ranks first in deaths

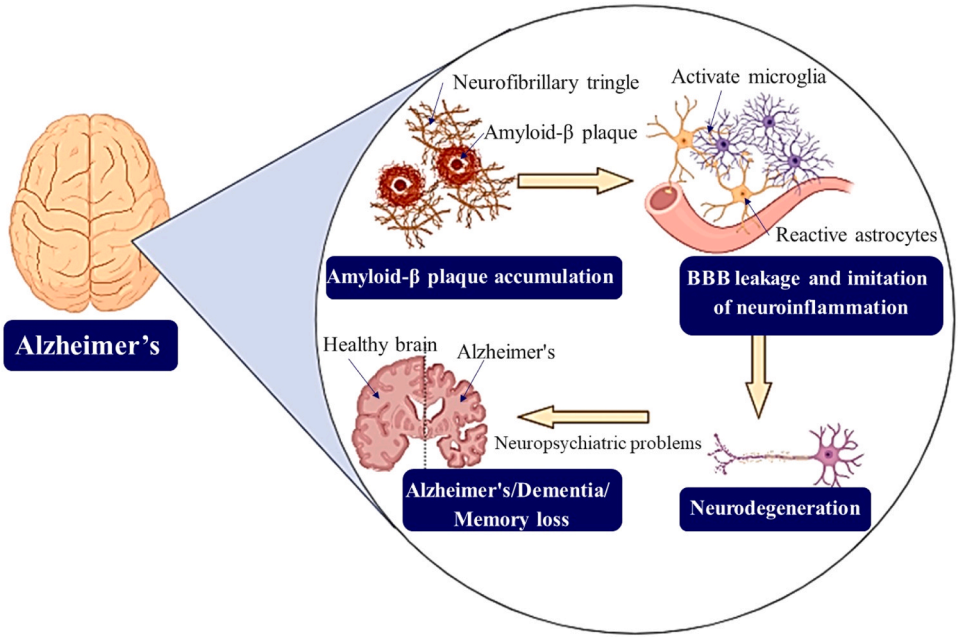

Fig. 1. Illustration of neurological features of Alzheimer's disease.

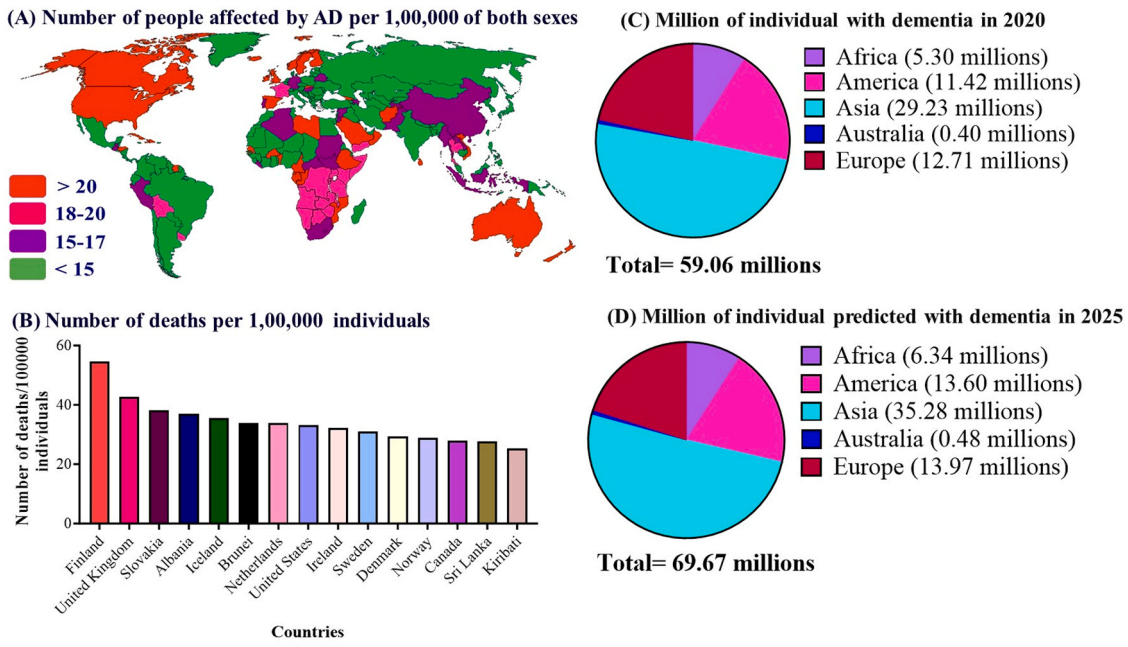

Fig. 2. **(A)** Map depicting regional severity of AD prevalence and the number of people affected per 1,00,000 individuals by country. According to the key, scores of > 20, 18–20, 15–17, and < 15 people influenced among 1,00,000 are demonstrated in red, pink, violet, and green colors, respectively. **(B)** A statistical representation of the top 15 countries with high mortality rates worldwide due to AD. **(C)** Millions of individuals suffered from AD in 2020, and **(D)** Millions of people are predicted to suffer from AD in 2025.

associated with AD, with almost 54.65 patients amongst 1,00,000 individuals; however, the United Kingdom poses second (42.70/100,000 deaths). Further, the United States of America stands in the eighth position, where 33.26/100,000 deaths were observed. Hence, Europe, America, Canada, and Australia have more AD prevalent than other countries (Li et al., 2022).

1.3. Purpose of the review

There are many approved treatments available for AD, but the majority assist in treating its symptoms (Yiannopoulou and Papageorgiou, 2013). Due to several obstacles, including the blood-brain barrier (BBB) and several adverse reactions to available treatments, the existing medications have not been able to control the progression of AD (Pardridge, 2009), which has resulted in a lower survival rate (Gadhave et al., 2022; Kokare et al., 2020). Several studies have underscored the potential of nanotechnology approaches to treat CNS ailments, including AD (Gadhave et al., 2021; Srikanth and Kessler, 2012). Biomaterials have the potential to be very selective and effective in enabling targeted drug administration, molecular detection, treatment monitoring, and neurodegeneration (ND) diagnosis, according to several recent papers (Takallu et al., 2024). Additionally, by pinpointing the exact mechanism behind AD initiation, novel therapeutic approaches may improve the therapeutic efficacy against AD (Yu et al., 2021).

The current review focuses on the inadequacies of conventional therapies, the precise mechanism of AD initiation, the development of biomaterials in treating Neurodegenerative disorders (NDS), and their clinical significance (Gadhave et al., 2024c). The work emphasizes new opportunities for enhancing the therapeutic features of AD shortly.

2. Neuropathological understandings of AD

2.1. Neurofibrillary tangles and tau pathology

Intracellular aggregates of hyperphosphorylated tau protein, also known as neurofibrillary tangles (NFT), are implicated in neurodegenerative diseases like Alzheimer's disease (AD) and related tauopathies (Boutajangout et al., 2011). In AD, the limbic system, hippocampus, and neocortex are gradually affected as NFTs initially form in layer II of the entorhinal cortex (Halliday, 2017). Tauopathies are proposed to progress through three stages: (i) the preclinical high-risk stage, (ii) the mild cognitive impairment stage, and (iii) the disease manifestation stage (Rawat et al., 2022). AD develops due to the inability of tau protein to stabilize microtubules. Tauopathies are linked to the accumulation of amyloid beta (Aβ), α-synuclein, or Huntingtin proteins in patients. Elevated tau levels are associated with its accumulation as NFTs and paired helical filaments (PHFs), contributing to the progression of AD pathogenesis (Iqbal et al., 2010). Tau degradation occurs through two primary mechanisms: the ubiquitin-proteasome system and the autophagy-lysosome pathway (Lee et al., 2013). Pathological tau is primarily cleared by the ubiquitin-proteasome system, while the autophagy-lysosome pathway becomes involved in tau degradation during the advanced stages of NFT development. Impairment in tau degradation pathways is a key factor contributing to its accumulation and deposition. When tau becomes hyperphosphorylated, it interferes with the transport of peroxisomes by kinesin, heightening cellular susceptibility to oxidative stress and ultimately causing neuronal degeneration (Alavi Naini and Soussi-Yanicostas, 2015). In cultured fibroblasts, tau protein effectively blocks the movement of cellular components, causing mitochondria to migrate back toward the cell center, where the minus ends of microtubules are anchored. When mitochondria and the endoplasmic reticulum are absent in the outer regions of axons, it can disrupt glucose and lipid metabolism, reduce adenosine triphosphate (ATP) production, and lead to calcium imbalance (Matuz-Mares et al., 2022; Peruzzo et al., 2020). Studies suggest that mitochondrial dysfunction may lead to phosphorylated tau (p-tau) accumulation, breakdown of microtubules, and the development of pathology resembling NFTs (Cheng and Bai, 2018). Research from Reddy's lab showed that p-tau interacts with the mitochondrial fission protein, Dynamin-related protein 1 (Drp1), increasing Drp1's Guanosine Triphosphatase (GTPase) activity (Manczak et al., 2016). This interaction results in excessive mitochondrial fragmentation and impaired mitochondrial function in AD. Tau hyperphosphorylation and detachment from microtubules cause tau to mis-localize from axons to the

somatodendritic region, disrupting the structure of axonal microtubules and leading to synaptic dysfunction (Rawat et al., 2022). Phosphorylation changes tau's interactions with various partners, such as the cytoplasmic membrane, Deoxyribonucleic acid (DNA), and Fyn kinase, interfering with tau's role in multiple signaling pathways as shown in Fig. 3.

2.1.1. *Hyper-phosphorylation of tau protein*

A hallmark of AD is the formation of NFTs, which arise from the excessive phosphorylation of the microtubule-associated tau protein. NFTs are composed of paired, helically twisted protein filaments that accumulate within the neuronal cytoplasm and extend into neuronal processes (Moloney et al., 2021). The tau protein contains a microtubule-binding region that enables it to assemble with tubulin, contributing to the formation of stable and mature microtubules (Mietelska-Porowska et al., 2014). The tau protein stabilizes microtubules by forming cross-links between adjacent microtubules, creating a stable network to support cellular structure. However, in the presence of elevated amyloid-beta (Aβ), tau encounters activated kinases that induce its hyperphosphorylation, leading to tau oligomerization (Kadavath et al., 2015; Mandelkow and Mandelkow, 2012). This modification destabilizes the microtubules as tau dissociates, causing microtubule subunits to disassemble. The resulting tau fragments aggregate into large NFTs- fibrillary, rigid structures within the neuronal cytoplasm and extensions. These NFTs disrupt neuronal communication, impair signal transmission, and eventually trigger apoptosis in neurons. Studies have shown that soluble Aβ regulates both the cleavage and phosphorylation of tau, contributing to the formation of NFTs (Zhang et al., 2021). Additionally, tau phosphorylation is controlled by multiple kinases, with Glycogen Synthase Kinase 3β (GSK3β) and Cyclin-Dependent Kinase 5 (CDK5) playing major roles when activated by extracellular amyloid-beta (Aβ) (Mietelska-Porowska et al., 2014). While GSK3β and CDK5 are primary drivers of tau hyperphosphorylation, other kinases, such as Protein Kinase C, Protein Kinase A, extracellular signal-regulated kinase 2 (ERK2), as well as the serine/threonine kinases caspase 3 and caspase 9—also significantly contribute, often triggered by Aβ presence (Zhang et al., 2021).

2.1.2. *Propagation and impact of tau tangles in neurodegeneration*

In tauopathies like AD, tau aggregates into NFTs within neurons and glial cells. In AD, most tau pathology appears as neuropil threads or dystrophic neurites (Gibbons et al., 2019; Vogels et al., 2020). These tangles disrupt cellular functions by causing both a loss of normal tau activity and toxic gains-of-function. Hyperphosphorylated tau forms aggregates, impairing axonal transport, loss of synapses, and eventual neurodegeneration (Fig. 4) (Gendron and Petrucelli, 2009; Ittner and Ittner, 2018). Tau tangles contribute to neurodegeneration by disrupting axonal transport, which is essential for synaptic function and cellular health. Studies show that stabilizing microtubules with drugs like paclitaxel can mitigate these effects, indicating the significance of maintaining tau's normal function (Afsar et al., 2023). While the extent of NFTs correlates with cognitive decline, it remains debated whether their impact stems from direct physical obstruction or from sequestering essential proteins, amplifying cellular dysfunction (Theofilas et al., 2018). The propagation of tau pathology involves the spread of hyperphosphorylated tau across neurons, leading to early disruptions in axonal transport, synapse loss, and inflammation. These early changes set the stage for neurodegeneration, with fibrillary tau tangles appearing as a later manifestation that further disrupts cellular processes and exacerbates the disease by interfering with normal protein functions (Rajmohan and Reddy, 2017). Although it's challenging to separate toxic gains from loss-of-function effects, both mechanisms likely contribute to the progression of AD and related disorders (Medeiros et al., 2010).

2.2. *Amyloid-beta pathology*

Aβ is a peptide, produced as a byproduct of brain function. It is produced through the proteolytic processing of a transmembrane protein, Amyloid Precursor Protein (APP), by β- and γ-secretases (Chen et al., 2017; Hampel et al., 2021). Although the precise function of Aβ has not been identified, it is thought to be involved in neuroprotective, trophic, and adhesive functions. However, Aβ accumulation in the brain is proposed to be an early toxic event in the pathogenesis of AD (Gulisano et al., 2018; Y. Zhang et al., 2023). The dementia in AD is defined by neurotoxic plaques forming Aβ peptides in the brain (Hampel

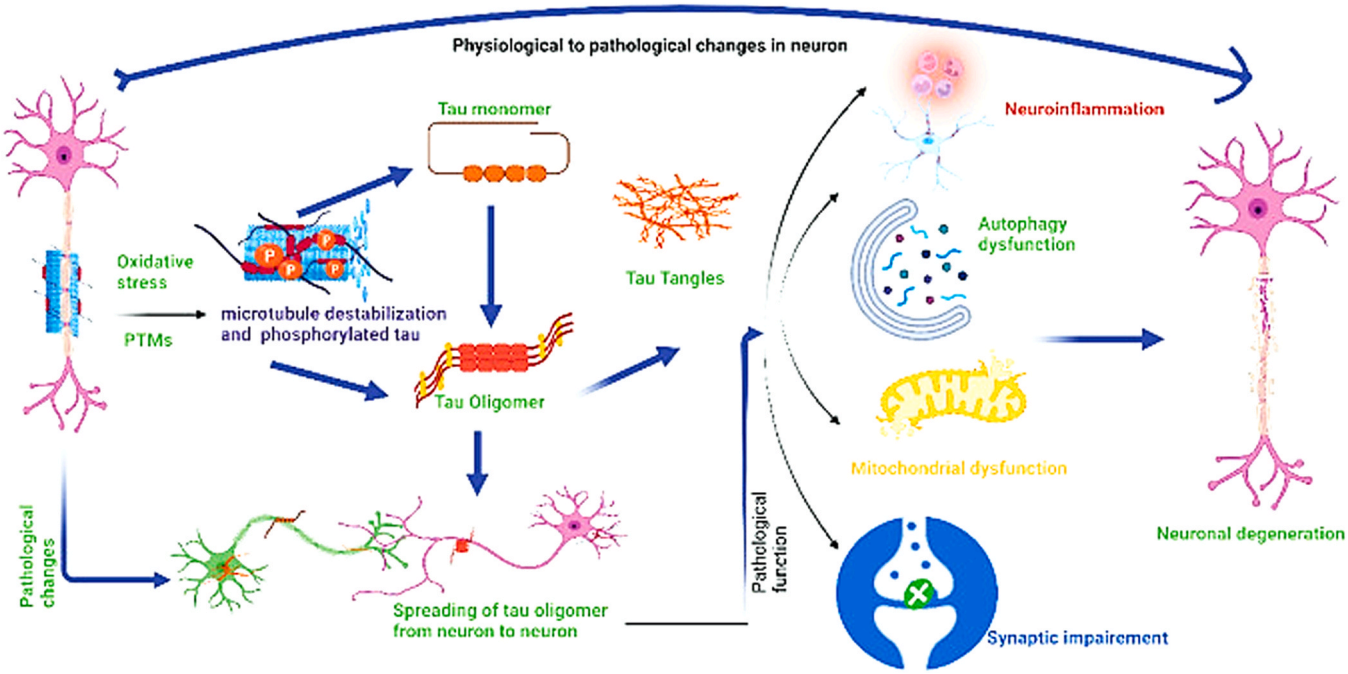

Fig. 3. Schematic representation of neurons undergoing physiological to pathological changes.

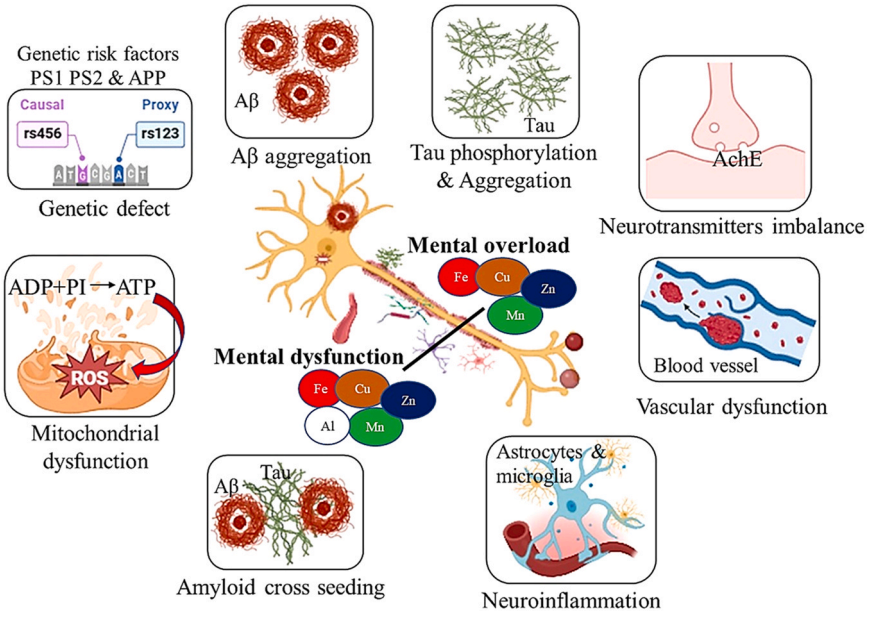

Fig. 4. Molecular mechanisms and etiological factors involved in the progression and development of Alzheimer's disease.

et al., 2021). These peptides can trigger the aggregation of neurofibrillary tangles, resulting in neurodegeneration and subsequently leading to progressive and irreversible cognitive decline. Aβ accumulation is estimated to begin 15–20 years prior to the appearance of clinical symptoms. A genetic mutation in presenilin (PS) leads to elevated levels of extracellular Aβ42(43), which is directly linked to the development of AD (Kakuda et al., 2021; Newman et al., 2007). Aβ42(43) accumulates early and specifically in the senile plaques, a characteristic of AD. Research indicates that mutations associated with familial AD contribute to the disease by raising Aβ42(43) levels and promoting its deposition (Hurley et al., 2023; Quan et al., 2023). This supports the hypothesis that the buildup of Aβ in the brain plays a crucial role in the onset and progression of AD **(**Fig. 4**).** Although reduction of Aβ concentration and prevention of Aβ deposition may seem to be quite attractive as therapeutic targets in AD treatment, the pathological changes resulting from elevated Aβ levels and/or Aβ deposition may also prove to be promising therapeutic targets (Sehar et al., 2022). This is essentially because the utility of preventing any pathological changes in AD depends on its function in the development of dementia and not the stage of the disease.

2.2.1. *Mechanism of amyloid-beta plaque formation and AD progression*

Aβ plaques are formed when Aβ proteins accumulate and clump together in the brain. These plaques are a key feature of AD. There is an imbalance between the production and clearance of Aβ, resulting in the accumulation of plaques (Gholami, 2023; Hampel et al., 2021). The formation of Aβ plaques may be triggered by various factors, including overproduction of Aβ, perturbed clearance, aggregation of Aβ proteins, which tend to aggregate and form oligomers, which may eventually develop into large plaques (Fig. 4) (Abelein, 2023; Azargoonjahromi, 2024).

2.2.2. *Clinical relevance and controversies about the amyloid theory*

The amyloid hypothesis suggests that Aβ, in various forms, initiates a chain reaction that damages synapses and eventually neurons, resulting in the characteristic features of AD, such as Aβ plaques, tau tangles, synapse degeneration, and neurodegeneration, which contribute to dementia (Nasb et al., 2024; Zhang et al., 2022). It is believed that the buildup of Aβ begins the pathological process of AD by disrupting synapses, promoting the formation of neurofibrillary tangles, and ultimately inducing neuronal loss (Azargoonjahromi, 2024). It is often quipped that "the amyloid hypothesis, like certain banks, may have become too big to fail". Concerns about the hypothesis have been raised due to factors such as the weak correlation between Aβ deposits and AD, significant differences between familial and sporadic forms of the disease, pathological findings suggesting that certain lesions, proteins, and cascades are secondary, challenges in replicating soluble species in the lab, and the lack of relevance of synaptic assessment for pathological interpretation (Wells et al., 2021; J. Zhang et al., 2024). Morris et al., outlined the various steps in the current amyloid hypothesis and highlighted the inconsistencies (Morris et al., 2018).

2.3. *Neurodegeneration due to synaptic dysfunction*

In healthy neurons, tau is mainly confined to the axons. However, during pathological states, tau detaches from its usual position on axonal microtubules and shifts to presynaptic and postsynaptic regions (Robbins et al., 2021). This mis-localization disrupts normal synaptic function by hindering vesicle movement and limiting the release of neurotransmitter-filled vesicles at the presynaptic terminal (Bonnycastle et al., 2021; Longfield et al., 2024). Tau is also present in various cellular structures, including the Golgi apparatus, rough endoplasmic reticulum, autophagic vesicles, neuronal plasma membranes, and synapses, where it plays a role in protein transport and secretion (Cui et al., 2022). Tau can contribute to cellular toxicity by binding to synaptic vesicle proteins, which interferes with the release of neurotransmitter-filled vesicles at synapses (Chen et al., 2024). Within synapses, tau primarily associates with components like actin, microfilaments, the scaffolding protein postsynaptic density protein 95 (PSD-95), N-methyl-D-aspartate receptors (NMDARs), and the kinase FYN, forming a network that influences synaptic function. In AD, hyperphosphorylated tau accumulates within the somatodendritic regions of neurons (Duman et al., 2022). This abnormal presence of tau in dendritic spines can disrupt glutamate receptor transport, leading to impaired synaptic function. Damage caused by tau within the synaptic compartment is a leading factor in synaptic loss and has the potential to propagate from one neuron to neighboring neurons, affecting widespread areas of the brain (Fig. 4) (Rawat et al., 2022).

2.3.1. *Destruction of synaptic network*

Synaptic degeneration is a key feature of AD, associated with cognitive decline. The pathology of AD is driven by the accumulation of

amyloid-β (Aβ) and tau proteins, both of which exhibit direct synaptotoxic effects (Griffiths and Grant, 2023; Rajmohan and Reddy, 2017). Soluble oligomeric forms of these proteins disrupt synaptic function and propagate through neural circuits, amplifying synaptic dysfunction and degeneration (Liu et al., 2024). Aβ induces synaptic damage primarily through calcium dysregulation, mitochondrial impairment, and disruption of synaptic vesicle recycling (Rajmohan and Reddy, 2017). Binding of Aβ to receptors such as NMDARs and metabotropic glutamate receptors (mGluR5) facilitates excessive calcium influx, triggering signaling pathways that contribute to synapse loss. Tau, typically an axonal protein, becomes mis-localized to dendritic compartments in AD, where it interacts with synaptic components and disrupts the stability of microtubules (Sinsky et al., 2021). This interaction leads to the loss of synaptic vesicle pools and impaired neurotransmission. The mis-localization and hyperphosphorylation of tau are critical to the breakdown of synaptic architecture, further exacerbating cognitive deficits (Wu et al., 2021). Glial cells, particularly microglia and astrocytes, play an active role in synaptic degeneration (Griffiths and Grant, 2023). Microglia, in response to Aβ plaques, are often driven to a reactive state in which they engage in phagocytosis of synapses (Miao et al., 2023). This process is mediated by the complement system, where synapses tagged by complement proteins such as C1q and C3 are targeted for elimination (Gomez-Arboledas et al., 2021). Although this system is protective under normal circumstances, in the context of AD, it becomes misregulated, leading to the loss of functional synapses (Nimmo et al., 2024). Astrocytes, too, contribute to this process by engulfing synaptic elements and participating in the maintenance of a reactive inflammatory environment, further driving synaptic degeneration (Fig. 4).

2.3.2. *Effect of neuronal degeneration on mental functions*

In AD, neuronal degeneration primarily disrupts memory and cognitive processes due to the progressive loss of neurons and synaptic connections, particularly in the hippocampus and cortex (Rao et al., 2022). This degeneration leads to impaired communication between brain regions, manifesting as deficits in short-term memory, language skills, and executive functions like decision-making and problem-solving (Cipriani et al., 2020). Age-related factors, including oxidative stress and chronic inflammation, contribute to the aggregation of toxic proteins, leading to synaptic dysfunction and subsequent neuronal death (Dash et al., 2024). These processes collectively disrupt neural circuits, exacerbating cognitive decline and affecting daily activities, such as planning, organizing, and recalling information. It has been observed that direct infusion of homocysteine into substantia nigra or striatum accelerated neuronal degeneration and motor dysfunction (Kim et al., 2022). Homocysteine endangers hippocampal neurons by increasing their vulnerability to excitotoxic and oxidative injury (Bhattacharjee et al., 2016). Early-stage AD may present as subtle memory lapses, but as neuronal degeneration advances, patients experience significant difficulties with spatial orientation, language, and complex tasks. This progressive impairment underscores the need for early intervention to slow the decline in cognitive functions and maintain quality of life for as long as possible.

2.4. *Genetic and Environmental Aspects*

AD is influenced by a complex interaction between several genetic and environmental factors. Genetic variants, lifestyle factors, diet, smoking, physical activity, and epigenetic mechanisms are implicated in the development and progression of this disease (Athanasopoulos et al., 2016). Several studies have verified that aging is the strongest risk factor in the development of AD, and its occurrence increases with age, especially in patients over 65–70 years of age (Tsalenchuk et al., 2023). Over the years, more than 80 genetic areas associated with AD have been identified. Understanding their role may prove to be instrumental in identifying and developing newer methods to prevent or treat AD related dementia (Van Cauwenberghe et al., 2016).

The apolipoprotein E (APOE) gene increases the risk of AD. It helps transport cholesterol and other lipids in the bloodstream and also aids in repairing injuries in the brain. In humans, the APOE gene exists in the form of three polymorphic alleles (i.e., ε2, ε3, and ε4) (Liu et al., 2013). The prevalence of the ε2 allele is the lowest (8.4 %), followed by ε4 (13.7 %) and ε3 (77.9 %). Individuals possessing the APOE ε2 allele may not develop the disease (Mick et al., 2024). The chances of developing AD earlier in life in individuals possessing this allele are lower than those possessing the APOE ε4 gene (DiBattista et al., 2016). The majority of the population possesses APOE ε3 allele, which has no discernible effect on AD. However, APOE ε4 increases the risk for AD, with approximately 40 % of the patients with AD showing the presence of this gene, implicating its role in the disease. Roughly 2–5 % of the people possessing this allele carry two copies (Pires and Rego, 2023). Carrying two copies of APOE ε4 has been linked to a higher risk of AD. However, some people carrying the APOE ε4 allele may never develop the disease ε3. Approximately 95 % of clinical cases of AD are those of late onset AD (LOAD) which affects people over 65 years of age (Yamazaki et al., 2016). Although the mutations in the APOE gene are one of the major risk factors, there is no conclusive explanation for the LOAD pathogenesis.

Interestingly, ~33 % of the AD cases indicate that low educational status, lack of cognitive activity, and comorbidities such as diabetes mellitus, depression, hypertension and obesity are major risk factors that may contribute to the development of AD (Raulin et al., 2022; Santos et al., 2017). It has been noted that risk factors such as diet, lifestyle, alcohol, smoking, and pollutants can result in epigenetic modifications of key genes and pathways linked to AD. Elevated levels of homocysteine in the body may significantly increase the risk of AD (Athanasopoulos et al., 2016; Liu et al., 2022). Folic acid and vitamin B6 and B12 supplementation have shown to decrease the blood levels of homocysteine (Fig. 4) (Olaso-Gonzalez et al., 2022). A mentally and physically active lifestyle may facilitate neurogenesis, thereby providing some protection against developing neurodegenerative disorders.

2.4.1. *Influence of Different Genes such as PSEN1, PSEN2, and APOE*

Although majority of AD cases are LOAD, several patients develop a disease phenotype when they are younger. Manifestation of the disease below the age of 65 is referred to as early-onset AD (EOAD) and represents 1–5 % of the cases. Although most EOAD patients present with disease phenotypes after 40 years of age, earlier onset in the 20 s has also been documented (Mendez, 2019; Reitz et al., 2020). EOAD is generally inherited in an autosomal dominant pattern, but in some instances, it can also follow an autosomal recessive inheritance pattern. Three causative genes have been associated with autosomal dominant familial AD, viz., amyloid precursor protein (APP) on chromosome 21, presenilin-1 (PSEN1) on chromosome 14, and presenilin-2 (PSEN2) on chromosome 1 and 1 genetic risk factor (APOEε4 allele). Modifications to these genes result in the production of abnormal proteins associated with AD (Bekris et al., 2010; Hoogmartens et al., 2021). The occurrence of these mutations is rare with ~ 1 % of the cases carrying APP mutations, ~ 6 % carrying PSEN1 mutations, and < 1 % carrying PSEN2 mutations. PSEN1 mutations have been identified as the most common causative factor for EOAD, where the disease progresses rapidly. Currently, over 300 mutations have been identified in PSEN1 (Bonvicini et al., 2019; Lanoiselée et al., 2017).

2.5. *Neuroinflammation*

Neuroinflammation is a key pathological feature in AD, primarily triggered by the accumulation of toxic proteins like amyloid-β (Aβ) and tau (Y. Zhang et al., 2023). In AD, these proteins form plaques and tangles, which activate the brain's immune cells—especially microglia and astrocytes. In response to Aβ and tau, microglia, the central nervous system's primary immune cells, adopt a pro-inflammatory M1

phenotype and release cytokines such as IL-1β, TNF-α, and IL-6, causing neuronal damage and advancing disease progression (Fakhoury, 2018; Gao et al., 2023). Initially meant to protect the brain, this inflammatory state becomes chronic, creating a harmful cycle that further intensifies neuroinflammation. Astrocytes, another crucial cell type in the CNS, also become reactive in AD (Gao et al., 2023). They respond to inflammation by hypertrophying and upregulating glial fibrillary acidic protein (GFAP), and in their reactive state, they disrupt blood-brain barrier integrity (Bhatt et al., 2024). This dysfunction allows peripheral immune cells to infiltrate the brain, worsening neuroinflammation and contributing to neurodegeneration. Astrocytes in AD are often found in an atrophic state, especially in brain regions such as the entorhinal cortex, which impairs their ability to support synapses and maintain glutamate balance, both essential for cognitive function (D'Egidio et al., 2024; Gao et al., 2023). Further amplifying this inflammatory cascade is the NLRP3 inflammasome, an innate immune protein complex activated by Aβ. Once activated, the NLRP3 inflammasome triggers the release of additional pro-inflammatory cytokines, further aggravating tau pathology and neurodegeneration in AD (Feng et al., 2021). Chronic neuroinflammation not only affects neurons but also impacts oligodendrocytes, leading to myelin disruption and cognitive deficits, making it a crucial target for therapeutic strategies aimed at mitigating the inflammatory damage without compromising the brain's defense mechanisms (Fig. 4) (W. Zhang et al., 2023).

2.5.1. Impact of Activated Microglia and Astrocytes in AD Advancement

Glial cells are non-neuronal cells in the central and peripheral nervous systems that offer support and protection to neurons. Astrocytes are star-shaped glial cells that play a crucial role in supporting neurons by maintaining the blood-brain barrier, regulating blood flow, providing nutrients, and aiding in brain repair and immune responses (Gadhave et al., 2024b; Gradisnik and Velnar, 2023). During the progression of AD, activated resident microglia enhance the ability of resting astrocytes to transform into reactive astrocytes, which in turn accelerates neurodegeneration. Reactive astrocytes can disrupt the integrity of the blood-brain barrier, allowing harmful substances to enter the brain, further worsening the inflammatory response (Deng et al., 2024; Gao et al., 2023). They can disrupt synaptic plasticity and function, impairing neuronal communication and contributing to cognitive decline (Chowen and Garcia-Segura, 2020). The activation of microglia can further stimulate astrocyte activation, creating a vicious cycle that perpetuates neuroinflammation (Fig. 4) (Cornell et al., 2021).

Alzheimer's disease is characterized by the buildup of hyperphosphorylated tau that forms amyloid-beta plaques and neurofibrillary tangles, which causes synaptic dysfunction, neuronal degeneration, and cognitive decline. The disease is influenced by environmental and genetic factors (APOE, PSEN1/2, APP), as well as chronic neuroinflammation that is fueled by activated microglia and astrocytes.

3. Existing Therapies for AD

3.1. Symptomatic Therapies

Alzheimer's disease is a neurological disorder that worsens over time, comprises functional impairments, the decline in cognition, and an increased risk of neuropsychiatric symptoms. Neuroinflammation, epigenetic modifications, vascular anomalies and synaptic disorder coexist with these alterations (Cornell et al., 2021). This can lead to neuron degeneration in neurotransmitter systems. Alzheimer's disease (AD) disease modifying approaches are still in need of substantial investigation. The therapeutic monitoring of AD can be primarily categorized into disease-modifying therapies and symptomatic treatments (Passeri et al., 2022; Yang et al., 2023). All existing approved therapies for AD are symptomatic agents intended to improve behavioral and cognitive symptoms without altering the underlying progressive illness. At present, most of the AD treatment strategies emphasize symptomatic therapies, comprising N-methyl-D-aspartate (NMDA) receptor agonist, in addition to three inhibitors of cholinesterase, which are intended to enhance cognitive function and counteract neurotransmitter disorders (Passeri et al., 2022). These therapies aim to reduce neuropsychiatric disorders while providing modest improvement in overall behavior and mental functioning.

3.1.1. Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (AChEIs) play a crucial role in prohibiting the acetylcholinesterase from functioning, which initiates a breakdown of ACh in the synaptic cleft. These AChEIs alleviate cholinergic transmission by inhibiting ACh breakdown to compensate for the deficit of cholinergic neurons which helps in improving the thought processes and cognitive decline in patients with Alzheimer's disease (AD) (Chen et al., 2022; Motebennur et al., 2023). Also, it improves the inadequate cholinergic neurotransmission in the brain. Furthermore, AChEIs might also interact with amyloid-beta, to promote the peptide's deposition into insoluble plaques, which makes AChEIs inhibitors act as a disease-modifying agent (Chen et al., 2022). AChEIs agents can be categorized as reversible, irreversible, and pseudo-irreversible depending on how much the enzyme is inhibited (Čolović et al., 2013; Lenina et al., 2020).

3.1.1.1. Mechanism of Acetylcholinesterase Inhibitors in AD. AChEIs addresses a particular feature of AD, the deletion of presynaptic cholinergic neurons in the cortex and amygdala, yet maintaining postsynaptic neurons in the same regions. Due to this preservation, AChEIs can increase cholinergic activity in the brain, which significantly promotes cognitive abilities such as memory and learning. And the key element of this process is the nucleus basalis of Meynert, which transmits cholinergic input to vital regions of brain (Chen et al., 2022; Teralı et al., 2024).

3.1.1.2. Donepezil. Donepezil is a selective, reversible, less competitive AChEIs. Donepezil is authorized to treat modest to serious AD (Table 1). This drug is approved for every phase of AD (Rogers et al., 1998). Donepezil crosses the blood-brain barrier, improves cognitive function by enhancing acetylcholine levels in the brain (Marucci et al., 2021; Ongnok et al., 2021). It has high selectivity for acetylcholinesterase against butyrylcholinesterase, decreasing the peripheral side effects. This drug has a widely recognized pharmacology in terms of absorption, metabolism and drug elimination (Čolović et al., 2013; Liston et al., 2004). It has a long half-life of seventy hours, making it a once-daily dosage and after 3 months of administration, the drug's plasma concentration stabilizes and stays at that level over time (Correll et al., 2021). In two independent 6 months trials enrolling 473 patients and 818 individuals diagnosed with moderate to serious AD, donepezil administered at 5 and 10 mg/day showed a slight enhancement in cognition and functioning parameters (Tamargo et al., 2015). Four clinical investigations comprising 599 participants (218 on donepezil and 318 on placebo). In this study, donepezil did not significantly lower hippocampus diminution in individuals with mild cognitive impairment (MCI) with respect to placebo ($P > 0.05$) (Rogers et al., 1998). Despite this, there was a substantially lowered hippocampus shrinkage in individuals with Alzheimer's disease at twenty-four to fifty weeks ($P < 0.001$), even though there was no discernible enhancement in neuropsychological function (Cummings, 2019). The clinical effectiveness of donepezil studies showed that individuals who received treatment exhibited statistically significant improvement on standardized cognitive scales like the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (La Joie et al., 2013; Levine et al., 2021). The common side effects involve nausea, diarrhea, bradycardia, muscle cramps due to peripheral cholinergic effects and elevated cholinergic activation.

Table 1
Symptomatic therapies for Alzheimer's disease.

Therapeutic class	Drugs available	Selectivity	Indication	Dosage forms available	Clinical efficacy	References
Acetylcholinesterase inhibitor (AChEIs)	Rivastigmine	AChEI, Butyrylcholinesterase (BuChE)	For mild to moderate AD. Enhanced cognitive benefit and improved gastrointestinal tolerability	**Patches** (4.6–9.5 mg) and **Capsule** (6 mg, 12 mg)	Shown to be effective in maintaining cognitive stability for a long duration	(Li et al., 2019)
	Donepezil	AChEI	All stages of AD. (mild, moderate, severe improvement in cognitive activities).	**Tablet** (5–10 mg)	Donepezil showed an improvement of 1–3 points on the ADAS-Cog scale in comparison to placebo.	(Li et al., 2019)
	Galantamine	AChEI and nicotine receptor modulator	Treatment of mild to moderate AD	**Tablet** (12–24 mg)	The short-term efficacy improved the cognitive score by approximately 1.5–3 points compared to placebo, and the long-term efficacy was up to 36 months.	(Jiang et al., 2015)
NMDA receptor antagonist	Memantine	NMDA antagonist	Modest improvement in cognition and behavior in moderate to severe AD.	**Extended-release capsule** (7,14,21,28 mg), **Tablet** (5–10 mg) and **Oral solution** (2 mg/mL)	Demonstrated improvement on the Mini-Mental State Examination (MMSE) and Severe Impairment Battery (SIB) scales.	(Dou et al., 2018)

3.1.1.3. Rivastigmine. Rivastigmine is a noncompetitive, carmate cholinesterase and pseudo-irreversible suppressor of both acetylcholinesterase and butyrylcholinesterase (Jann, 2000). It is a synthetic physostigmine based derivative and approved by FDA in 1997 as an anticholinesterase inhibitor in AD management (Eskander et al., 2005). It has other multiple benefits such as inhibition of amyloid-beta aggregation, reactive oxygen species (ROS) scavenging activity **(**Table 1**)**. The marketed formulation is available in oral and transdermal form (Singh et al., 2024). Rivastigmine is approved to treat moderate to serious AD. Rivastigmine has a shorter plasma half-life compared to donepezil, but it showed prolonged inhibition due to the formation of a covalent bond with the enzyme (Bullock et al., 2005). Rivastigmine has a favorable propensity to inhibit the G1 isoform of AChE enzyme than G4 form (Onor et al., 2007). Rivastigmine possesses an excellent blood-brain barrier penetration and is metabolized via cholinesterase-mediated hydrolysis and is eliminated through the kidneys. The transdermal patch formulation enhanced steady drug delivery (Kandiah et al., 2017). The oral formulation of the drug gets rapidly absorbed, about ninety percent of the total administered dose (Hossain et al., 2002). It's time to peak concentration varies from 0.8 to 167 hours. The oral dose of 6–12 mg/day twice daily showed improvement in the MMSE scale and cognitive ability.

3.1.2. NMDA Receptor Inhibitors

In the brain, glutamate is an integral excitatory neurotransmitter. N-methyl-D-aspartate is one of the receptors which is activated by glutamate, and it is essential for functions including memory and learning (Zhou and Danbolt, 2014). Over-activation of NMDARs is proven to cause injury to neurons, which can lead to both acute and long-term disorders of the nervous system, such as Alzheimer's dementia (Liu et al., 2019; Zhang et al., 2016). Memantine is an NMDA receptor inhibitor that is approved for mild to severe AD **(**Table 1**)**. It modifies the glutamatergic neurotransmission by suppressing excessive NMDA receptor activity, which has been observed to be associated with impairment in cognition and neurotoxicity (Olivares et al., 2012; Parsons et al., 2007). In brain cells, the NMDAR functions as a gate that facilitates specific charged molecules. Magnesium typically blocks this gate and prevents the charged molecules from passing through. The magnesium leaves the brain when it is activated, unlocking the gate and permitting calcium to enter to promote the effective functioning of the brain cells (Iacobucci and Popescu, 2024; Zhang et al., 2016). This gate becomes hyperactive and remains open for an extended period in Alzheimer's disease. Memantine works mainly by closing the gate and protecting the brain from becoming saturated. Memantine is a non-competitive antagonist that binds to NMDA receptor-associated ion channels, which limits excessive calcium influx while maintaining regular synaptic activity without any detrimental impact on physiological neurotransmission. This inhibition might shield neurons from excitotoxicity (Pichardo-Rojas et al., 2023; Tang et al., 2023). Knight, R. et al., showed that memantine and other Cholinesterase Inhibitors (ChEIs) improve cholinergic signaling and help Alzheimer's patients with their acetylcholine imbalance (Knight et al., 2018). The assessments of the Mini-mental state examination (MMSE) for ChEIs over a six-month period were shown to be more favorable than memantine, reported in a study that compiled data from eighty trials. Also, demonstrated to be effective are memantine and ChEIs. Yaghmaei, et al., showed that administration of memantine and donepezil in combination therapy may substantially improve the 5-year survival rate of Alzheimer's patients (Yaghmaei et al., 2024). The study showed that the outcomes are reliable and unlikely to be affected by any unmeasured confounded variable.

3.1.3. Limitations of Existing Therapies

Even though symptomatic therapies are widely used, they have an insignificant overall effect on the progression of the disease. Usually, the advantages are marginal and short term, and most patients eventually continue to degrade cognitively (Baryakova et al., 2023; Preethy H et al., 2024). Blood-brain-barrier can be a limitation for drug delivery. The underlying neuropathological effects of AD, such as Tau pathology and Aβ deposition, are not addressed by current therapeutics. Individual differences in effectiveness can be attributed to hereditary factors, gender, disease level, metabolic disorders, dyslipidemia and multiple medical conditions (Maggiore et al., 2024). All existing therapies only provide short-term symptom stabilization, and as the disease progresses, their effectiveness usually diminishes (Chen and Zhong, 2013). In addition to this, cholinesterase inhibitors have various adverse effects involving diarrhea, vomiting, nausea, and gastrointestinal adverse effects.

3.2. Challenges in AD Therapeutic Development

3.2.1. Issues with Clinical Trial Strategies

The absence of effective therapies, such as medications that can prevent the development of Alzheimer's disease, is still unknown, although a comprehensive investigation is underway. New curative strategies are urgently required since the majority of treatments only manage the symptoms without influencing the disease condition (Arafah et al., 2023). The lack of early diagnosis biomarkers prohibits timely intervention and effective treatment (Passeri et al., 2022). The neurological inflammation and metabolic syndrome such as insulin resistance

and reduced glucose metabolism are intricately associated with Alzheimer's disease. This connection elevates the possibility of therapeutic outcomes, but it also increases the complexity in recognizing the effective treatment (Jha et al., 2017). Additionally, the limited efficacy of available drugs such as NMDA antagonists and acetylcholinesterase inhibitors essentially controls symptoms without changing the disease development which ultimately affects the efficacy of disease modifying treatment (Chvojkova et al., 2024; Singh et al., 2024). Alzheimer's disease progresses slowly, and the clinical trials are time-consuming and expensive, and the treatments that are promising in the initial phase of the disease may not be effective later, which makes the approval more challenging (Boxer and Sperling, 2023).

3.2.2. Safety Issues of Amyloid-targeting Therapies

Amyloid-beta plaque buildup, along with Tau protein excessive phosphorylation, results in synaptic impairments, tangled neurofibrillary cells, neurological inflammation, and an increase in oxidative stress, which are contributing factors for the pathogenesis of Alzheimer's disease (Roy et al., 2023). Treatments that focus on amyloid- beta plaques are lacking in demonstrating therapeutic efficacy. Amyloid-Related Imaging Abnormalities (ARIA), which demonstrate oedema (ARIA-E) and hemorrhage (ARIA-H), are being clinically linked to amyloid-targeting treatments, more particularly monoclonal antibodies (Cummings et al., 2024; Hampel et al., 2023). The outcome, which can be seen on neuroimaging, is related to targeted brain oedema and hemosiderin deposition. Patients receiving amyloid targeting treatments risk developing Amyloid-Related Imaging Abnormalities (Sin et al., 2023; Sperling et al., 2011). There are various adverse effects including nausea, headache and seizures. Synaptic dysfunctioning and neurotoxicity get brought by soluble amyloid oligomers causes. Oligomers amyloids are highly toxic, and trigger synaptic damage although the target is amyloid plaques (Sengupta and Kayed, 2022; Tolar et al., 2021). These results in dementia and synapse damage. The blood-brain barrier's (BBB) functionality may be compromised by removal of amyloid plaques, exposing cerebral arteries more prone to damage. There has been tremendous variation in the safety profile and effectiveness of amyloid-targeting medicines comparing preclinical investigations and human clinical trials, as the underlying cause of Alzheimer's disease in humans is frequently not mimicked in animal models (Y. Chen et al., 2023; Zenaro et al., 2017).

3.2.3. Dissimilarities Within the Preclinical Success and Clinical Significance

The challenge of effectively stimulating human Alzheimer's disease pathogenesis in animal studies is a significant barrier (Kamatham et al., 2024a). There are some complexity factors such as human cognition, fluctuating mood and the progression of disease, that is not entirely represented by animal models, even if transgenic mice are specifically used for studying the mechanism of disease (Puzzo et al., 2014; Usai et al., 2023). Due to this, the treatments that first showed promise in preclinical phases result in a substantial failure rate in clinical trials. The translation of preclinical to clinical remains challenging. Understanding the long-term consequences of possible treatments is challenging due to the fact that the majority of preclinical investigations are cross-sectional in contrast to longitudinal (Segovia-Zafra et al., 2021; Seyhan, 2019). For assessing how early-life factors, response to certain chemicals or environmental triggers, may have an impact on Alzheimer's disease progression. According to epigenetic research, initial exposure can have major influence on the pathophysiology of Alzheimer's disease later in life, which emphasizes the importance of longitudinal data (Sharma et al., 2020). Many aggravating factors, involving the genetic heritage of animal models, ecological circumstances, augment translational challenges in preclinical research (Loewa et al., 2023). It can be challenging to investigate whether the obtained results are attributable to the treatment or other independent variables because those factors tend to greatly affect the findings (Jankovic et al., 2021; Reed et al., 2021). For animal research to produce accurate interpretable results, monitored and standardized procedures are required (Drummond and Wisniewski, 2017; Harper, 2010). Majority of animal models created for Alzheimer's disease rely on factors such as neurotoxin-induced cell death, genetic modification and severe brain injury (Cetin et al., 2022). Even though these models mimic some aspects of the disease, they frequently fall short of precisely predicting clinical efficacy in humans (Vitek et al., 2021). It is widely acknowledged that these animal studies' inadequacies create a major hurdle in obtaining confident clinical results.

Most current therapeutic approaches for Alzheimer's disease (AD) focus on symptomatic treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, which provide some cognitive benefits without changing the course of the disease. Translational gaps, safety concerns, especially with amyloid-targeting agents, and limitations in preclinical model validity continue to hinder disease-modifying approaches.

4. Future Trends in Advanced Therapeutic Approaches

The severity of Alzheimer's disease (AD) and its economic burden can be understood through the number of cases, which stood at 6.5 million in 2022 and is predicted to reach 13.8 million by 2060. AD is the fifth leading cause of death in the United States and the sixth leading cause globally (Hassan et al., 2022). In the year 2016, the caregiving cost per patient was USD 28,017 in the United States (Nandi et al., 2024), which is on the rise with the severity of the disease. Advanced drug delivery systems—although costly—are known to reduce long-term therapy costs, which could provide a significant advantage to the families of the patients suffering from AD. There are a handful of strategies available for brain targeting; these are increasing lipophilicity of molecules, intranasal administration, and Blood-brain-barrier (BBB) disruption with the help of an osmotic agent or by using a stimulus, and temporary alteration of permeability of BBB by using suitable surfactants (Gadhave et al., 2024d). However, these strategies are associated with some or other major drawbacks (Wu et al., 2023). On the other hand, nanotechnology holds the promise in delivering both small and large molecules to target sites while minimizing the potential for off-target drug accumulation(Bashir et al., 2025) (Fig. 5). The nanoformulations that has been explored for targeting in AD can be categorized as follows: lipid-based preparations, including liposomes and solid lipid nanoparticles; polymeric nanoparticles; metal nanoparticles; and dendrimers (Agraharam et al., 2022).

4.1. Nanotechnology in Alzheimer's Treatment

AD is a neurodegenerative disorder characterized by the aggregation of amyloid β peptide (Aβ) in the extracellular space of nerve cells, leading to the formation of senile plaques. Within the intracellular space of neurons, neurofibrillary tangles composed of hyperphosphorylated τ-protein develop. These neuropathological processes occur in the cortical and limbic regions of the human brain (Se Thoe et al., 2021). Conventional treatment for AD includes cholinesterase inhibitors and N-methyl-D-Aspartate receptor antagonists, which is approved by the US FDA. While this modality does not address the root cause of AD, it can enhance cognitive function in patients. Conversely, gene therapy and monoclonal antibodies (mAbs) have shown promising improvements in therapeutic outcomes. Additionally, nanoparticles are emerging as key delivery carriers for these therapeutic agents (Se Thoe et al., 2021). Various drug-targeting strategies for the brain that have been reported are aimed at pathological processes, such as amyloid generation or deposition, as well as τ-protein accumulation, or hyper-phosphorylation (Ordóñez-Gutiérrez and Wandosell, 2020), and are depicted in Fig. 5.

4.1.1. Nanoparticle-based drug delivery as a potential formulation approach to by-pass the BBB

Nanoparticles are useful carriers, especially for drug targeting to the

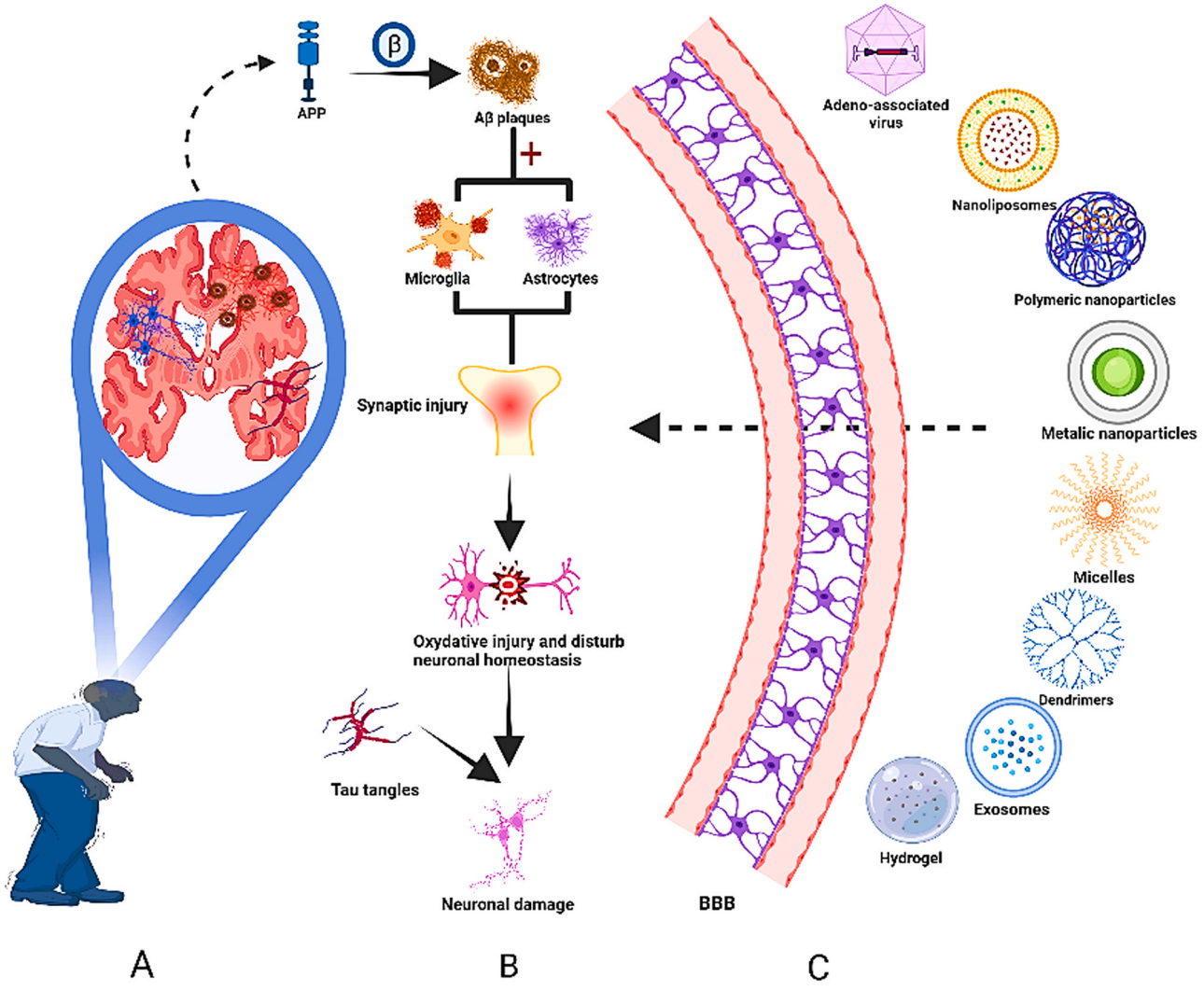

Fig. 5. The illustration depicts the pathology of AD. The amyloid precursor protein (APP) undergoes cleavage by β-secretase, producing Aβ through the "amyloidogenic" pathway. The resulting $A\beta_{42}$ is more toxic than the Aβ produced via the "non-amyloidogenic" pathway. $A\beta_{42}$ aggregation results in the formation of plaques. The deposition of Aβ around microglia and astrocytes induces inflammation, which contributes to synaptic injury. Additionally, oxidative stress and τ-protein tangles further exacerbate neuronal damage. Nanotechnology has shown significant promise in the diagnosis and treatment of AD, with various types of nanoparticles capable of efficiently crossing the BBB to deliver therapeutic effects.

brain, owing to their small size, typically in the range of 1–100 nm, and the possibility for surface modification and subsequent multi-functionalization (Gadhave et al., 2023b; Gadhave et al., 2019). Surface charge on the nanoparticles is a critical aspect from the viewpoint of safety and cytotoxicity (Gadhave et al., 2024a). It has been shown that cationic nanoparticles can induce toxicity in BBB; therefore, neutral or negative surface charge is essential for drug delivery to the brain (Wechsler et al., 2019). Ensuring adequate drug bioavailability in the brain is a primary challenge for the effective treatment of AD (Ordóñez-Gutiérrez and Wandosell, 2020). To address this issue, various nanotechnology-based approaches have been developed for targeted delivery to the brain. These approaches include:

4.1.1.1. Nanoliposomes. Larger nanoparticles encounter challenges when attempting to cross the BBB. However, it has been demonstrated that smaller nanoparticles, in the 50–100 nm range, can pass through the BBB without requiring any modifications. Nanoliposomes are advantageous for drug targeting to the brain due to their flexibility, which enables them to cross the blood-brain barrier (BBB) efficiently, as well as their biocompatibility and ability to protect the encapsulated drug cargo during transit to the desired site (Naziris and Demetzos, 2021). The micro ribonucleic acid (miRNA) is capable of controlling the expression of multiple proteins and targeting the genes, which are specific to the disease. Recently, in one of the research works, small-sized (< 200 nm) nanoliposomes have been developed for the delivery of a miRNA-195 and polyethyleneimine complex. The complex was surface modified to contain P-aminophenyl-alpha-d-mannopyranoside and a cationic-cell penetrating peptide derived from human immunodeficiency virus-1 (HIV-1) transcription activator. The liposomes were found to cross the BBB and cell membrane efficiently and attenuated signals of Aβ, Anti-Paired Helical Filament Tau (AT8), and Cluster of Differentiation 68 (CD68) in a mice model in early as well as advanced stages of the disease (Su et al., 2024). Similarly, another study reported surface-modified liposomes with Apolipoprotein (ApoE) for enhanced delivery of resveratrol and salidroside, which have shown promising therapeutic effects in AD, as evident by several clinical trials. These molecules have limited clinical applications in AD due to their poor aqueous solubility, low selectivity for targets, and insufficient permeability across BBB. The liposomal formulation concealed the drawbacks associated with the molecules and demonstrated their utility in alleviating pathological symptoms of AD (M.-H. Chen et al., 2023). Liposomes have been explored as bio-membrane models to elucidate the

mechanisms by which Aβ interacts with them and becomes neurotoxic (M.-H. Chen et al., 2023). The major drawback associated with liposomes is their poor stability and recognition by the reticuloendothelial system (RES), which reduces their circulation time. The former can be addressed by using membrane stabilizers like cholesterol, while the latter can be addressed by applying a coating of polyethylene glycol (PEG) (Agrawal et al., 2021a). There are other strategies, such as transferrin conjugation, lactoferrin conjugation, glucose modification, and glutathione modification have been reported for the brain targeting in AD (Agrawal et al., 2017).

4.1.1.2. Exosomes. Exosomes are heterogeneous extracellular bilayered vesicles produced by nearly all cell types in response to different physiological and pathological conditions. Among the other two extracellular vesicles, microvesicles and apoptotic bodies, exosomes are the smallest, with an average diameter ranging from 30 to 150 nm (X. Zhang et al., 2023). Due to their indigenous nature, exosomes can be engulfed by other cells and therefore can elicit a desired therapeutic response (Chavda et al., 2023). Exosomes have been reported to play vital role in the pathogenesis of AD by spreading Aβ and phosphorylated τ-protein between neurons. On the other hand, due to their ability to communicate between cells and the availability of protein markers on their surface they can potentially be explored for drug targeting as drug delivery vesicles. There are also evidences suggesting the presence of transferrin and insulin receptors on exosomes, which facilitates their uptake through BBB (Kandimalla et al., 2023). Qi Y. et al. reported quercetin-containing plasma exosomes for delivery to the brain, as quercetin is a potential molecule for the treatment of AD, but its therapeutic effect is limited by poor aqueous solubility. It acts by preventing τ protein-related pathological incidents and providing neuroprotection. The quercetin-containing exosomes were found to be effective for brain targeting ameliorating cognitive dysfunction in a mouse model compared to its free form (Qi et al., 2020). One of the pathological pathways in AD is characterized by the overexpression of amyloid-β precursor protein (APP). This overexpression results in the binding of the APP intracellular domain (AICD) to the Fe65 protein through the C-terminal Fe65-phosphotyrosine-binding (PTB2) domain, following proteolytic breakdown of APP by β-secretase and γ-secretase. Consequently, this process leads to the excessive release of amyloid-β, a mediator in the well-established pathogenesis of AD. Considering the importance of this interaction, and the role of Fe65 in long-term memory formation and the treatment of AD, exosomes derived from hippocampus neurons, loaded with Corynoxine-B- an autophagy inducer, targeted at APP overexpressing neuron cells, were developed. Exosomes were engineered with Fe65, which stopped the interaction between Fe65 and APP and brought about autophagy in APP-expressing neuronal cells (Iyaswamy et al., 2023).

4.1.1.3. Polymeric Nanoparticles. Due to their small size, polymeric nanoparticles can effectively cross the blood-brain barrier. They offer better stability compared to liposomes, but they fall short in terms of toxicity. Various types of nano drug delivery systems prepared by using polymers have been designed for drug targeting to the brain in AD and are discussed below.

1. *Dendrimers*

   Dendrimers can cross biological membranes such as the BBB because of their small size, while their surface functionalization assists in targeted drug delivery. A drug molecule can interact with a dendrimer molecule *via* three main mechanisms: encapsulation, electrostatic interaction, and conjugation (Dubey et al., 2020). The structure of dendrimers comprises a core and branching units, leading to various types, including polyamidoamine (PAMAM), phosphodendrimers, polypropylene-imine, carbosilane, poly-L-lysine, and triazine (Igartúa et al., 2020). Among these, PAMAM is highly explored because it features primary amine functionality in its cationic dendrimers and carboxylic acid functionality in its anionic dendrimers, which facilitates the conjugation of various moieties with them. Memantine is an N-methyl-$_D$-aspartate (NMDA) receptor antagonist approved by the US-FDA for the management of moderate to severe AD. It works by preventing $A\beta_{1-40}$ development, but has limitations due to daily administration in the form of patient non-compliance. In an attempt to increase its concentration in the brain, memantine was conjugated with lower generation PAMAM, which was further decorated with lactoferrin as a targeting moiety. The nanoscaffolds exhibited significant uptake in the brain in an animal model in addition to sustained release for 48 hours (Gothwal et al., 2019). In contrast, it was observed that, the strategies focusing only on inhibition of Aβ aggregation did not prove to be effective in patients with advanced stage of AD. Therefore, synergistic approach that brings about neuroprotection and ameliorates oxidative stress could be a more effective therapeutic modality for correcting pathological brain microenvironment. Microglia and astrocytes are the immune cells of the central nervous system (CNS); control over the mitophagy of microglia is a potential treatment option for AD. To tap this therapeutic option, Zhong. et al., reported Prussian blue/PAMAM/Angiopep-2 dendrimers; apart from good BBB permeability, dendrimers exhibited their effect through reactive oxygen species (ROS) scavenging, which restored the mitochondrial functions of microglial cells. In addition, dendrimers lowered the accumulation of Aβ aggregates and improved cognitive ability in the amyloid precursor protein and presenilin 1 (APP/PS-1) mouse model (Zhong et al., 2022). Other than therapeutic applications, dendrimers have also been explored to understand the pathology of AD (Zhong et al., 2022).
2. *Core-shell, and Matrix Type Polymeric Nanoparticles*

   These types of nanoparticles are prepared using synthetic or natural biodegradable polymers. Examples of synthetic polymers include poly ε- caprolactone (PCL), poly- (lactic-co-glycolic acid) (PLGA), and poly-(lactic acid) (PLA), among others (Sugandhi and Mahajan, 2022; Thapa et al., 2024). On the other hand, natural polymers used are- sodium alginate, chitosan, pectin, various amino acids, albumin, and gelatin (Wang et al., 2024). Various ligands are employed to facilitate the efficient traversal of nanoparticles across the BBB. These ligands engage with specific receptors and transporters present on the BBB, including insulin receptors, glucose transporters, and transferrin peptides.
3. *Micelles*

Micelles, due to their ability to self-associate and spontaneously form, provide a simple and efficient approach for preparing nanocarriers. By adjusting the hydrophilic-lipophilic balance (HLB) of the surfactant material, micelles can be formulated to accommodate both hydrophilic and lipophilic molecules. Additionally, micelles enhance the solubility of encapsulated substances, thereby improving their therapeutic efficacy in low-water environments within the human body. Micelles have been extensively studied for targeted drug delivery in the treatment of AD (Jalili et al., 2023; Wang et al., 2024).

4.1.1.4. Inorganic nanoparticles. Inorganic nanoparticles offer several distinct advantages, including high targeting efficiency, extended circulation times, and the capability to perform multiple functions simultaneously. A variety of inorganic nanoparticles have been investigated for use in AD, such as gold, silver, iron oxide, magnetic nanoparticles, and quantum dots (Ding et al., 2024). Metal nanoparticles can be categorized into two main types: 1. Nanoparticles are composed of noble metals, such as gold, silver, and platinum; and 2. Nanoparticles are made from magnetic materials, including iron, cobalt, copper, and nickel (Pantwalawalkar et al., 2022)

1. *Gold nanoparticles*

Several studies have highlighted the role of inflammation in AD. Microglia, the brain's resident immune cells, become activated in response to the presence of amyloid plaques, which further stimulates T cells within the brain's parenchyma. This activation results in the expression of pro-inflammatory cytokines in both the peripheral and central nervous systems. Additionally, the deposition of Aβ triggers the release of these cytokines. Collectively, these events lead to the activation of microglia and the subsequent expression of APP. The expression of APP further promotes the production of Aβ, which exacerbates neuronal dysfunction and ultimately contributes to cell death (Aili et al., 2023). Gold nanoparticles exhibit anti-inflammatory and antioxidant properties. They reduce pro-inflammatory cytokines, including TNF-α, IL-1β, and lower the expression of ROS. Furthermore, gold nanoparticles inhibit multi-signaling inflammatory pathways, such as mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and inhibitory kappa B kinase alpha (IKK-α/β) pathways. Additionally, they promote the polarization of microglia toward the M2 phenotype, rather than the M1 phenotype, which enhances neural restoration and regeneration (Behera et al., 2023a).

2. *Silver Nanoparticles*

Silver nanoparticles can efficiently cross the BBB. They exhibit antioxidant activity by inhibiting ROS expression and preventing the formation of reactive nitrogen species (RNS). According to the molecular imbalance hypothesis, the conversion of Aβ monomers into oligomers, and subsequently into extracellular transient oligomers, contributes to neuronal toxicity. Recent studies have reported that silver nanoparticles can dissolve Aβ fibrils when subjected to near-infrared illumination, potentially mitigating this toxic pathway (Behera et al., 2023b).

3. *Other Types of Noble Metal Nanoparticles*

There are other metal nanoparticles, such as ruthenium, cerium, selenium, and zinc, that have been explored in the treatment of AD. These nanoparticles act against Aβ aggregation and the subsequent formation of Aβ fibrils. Notably, zinc oxide nanoparticles demonstrate a range of effects in AD management, including anti-inflammatory properties, inhibition of acetylcholinesterase, and modulation of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Abd Elmonem et al., 2023; Behera et al., 2023c). However, it has also been reported that zinc oxide nanoparticles may contribute to the induction of central nervous system (CNS) inflammation (Tian et al., 2015).

4. *Magnetic Nanoparticles (MNPs)*

Superparamagnetic iron oxide nanoparticles (SPIONs) serve as effective theranostic agents owing to their biocompatibility, multifunctionality, and distinct magnetic properties. SPIONs inhibit Aβ fibrillation, a process influenced by their particle size distribution (PSD). A positive surface charge and increased surface area contribute to a reduction in the kinetics of Aβ fibrillation. However, at higher concentrations of MNPs, Aβ fibrillation is enhanced (Amiri et al., 2013). In addition, targeted MNPs have been reported for the detection of biomarkers and targeted delivery of siRNA (small interfering RNA) in AD (Lopez-Barbosa et al., 2020; Yang et al., 2011).

Functionalized magnetic nanoparticles (FMNs) can rapidly traverse the blood-brain barrier (BBB) with minimal systemic effects. When subjected to a pulsed magnetic field, they demonstrate targeted aggregation at the desired site, while avoiding the adhesion to vessel walls typically seen under a constant magnetic field. Furthermore, by conjugating specific active moieties to the FMNs, their precise localization within the hippocampus—the brain region critical for learning and memory—can be achieved, despite its deep anatomical position (Amin et al., 2017).

5. Biomaterial-based delivery systems in AD:

Biomaterials are substances of natural or synthetic origin that offer several advantages for brain delivery, including biodegradability, biocompatibility, improved solubility of APIs (active pharmaceutical ingredients), targetability (owing to their easily modifiable molecular structures for the attachment of ligands), controlled release of APIs, ability to cross the BBB, and cellular adhesion. Biomaterials are broadly categorized as of synthetic origin and of natural origin (Agrawal et al., 2021b). Biomaterial-based delivery systems to the brain can be of any type among nanoparticles, hydrogels, implantable scaffolds, and neural probe coatings (Galindo et al., 2024)

Various types of drug delivery systems to the brain are fabricated using biomaterials, which include pH-responsive systems made of natural polymers such as chitosan, cellulose, albumin, and gelatin; thermoresponsive systems targeted at Aβ aggregates or inflamed tissues (where physiological pH is often elevated) and made of polymers including chitosan, xyloglucan, and poly(N-isopropylacrylamide); and other systems made of photosensitive, electro responsive, and magnetically controlled biomaterials (Slika et al., 2025). Examples of the photosensitive biomaterials are polyaniline, Poly (3,4-ethylenedioxythiophene), and Polypyrrole (Agrawal et al., 2021b).

Drug targeting the brain is associated with limitations, including poor drug transportation across the BBB, and difficulty in achieving site-specific targeting. To overcome these issues, block polymers of biomaterials, which partly carry properties of the conjugated polymers, has shown potential, especially when converted into nano-sized drug delivery systems (Rahman et al., 2023). Examples of such polymers are PLGA-PEG, poloxamers, PLGA-PEG-PLGA, and PEG-PLA (Revdekar and Shende, 2021).

The use of stem cells in the regeneration of damaged neurons and support cells holds promise in treating AD. However, there are three major hurdles involved in their use, including cell distribution, cell viability, and host tissue integration. Biomaterials, in the form of injectable hydrogels or implantable polymer scaffolds, have shown promise in the stimulation of the extracellular matrix (ECM). As an example, hyaluronan is present ECM of CNS cells, carriers having affinity towards hyaluronic acid receptors increase the possibility of cell attachments and their subsequent survival (Prajapati et al., 2024). Especially, hyaluronic acid, and collagen containing scaffolds has shown potential for neural regeneration by creating favorable microenvironment for cellular migration, and proliferation, and enhances survival of encapsulated cells (Ranjan et al., 2025). Furthermore, recent advancements in biomaterial preparation techniques, such as inkjet, micro-extrusion, and laser-assisted bioprinting have enabled development of precisely controlled biomaterial structures in addition to better cell survival and incorporation of desired mechanical properties suitable for brain delivery (Lally et al., 2022).

4.2. Gene Therapy Strategies

Many clinical investigations aimed at treating Alzheimer's disease (AD) have been conducted, the majority of which have failed. This underscores the urgent need for more versatile therapeutic strategies, such as gene editing and modulation, targeting a broader range of molecular entities, including genes, RNA, and proteins (Grabowska-Pyrzewicz et al., 2021). Gene therapy is widely recognized as a promising and durable approach for the potential cure of various genetic and cellular disorders. Since the 1990s, the US FDA and other regulatory agencies have approved several gene therapies, each utilizing different types of vectors and targeting a broad spectrum of indications, including neurological diseases, various cancers, and even COVID-19 vaccines (Grabowska-Pyrzewicz et al., 2021). This highlights the growing and promising research landscape aimed at overcoming the challenges associated with drug delivery to the brain. Gene therapy strategies are typically categorized based on the type of delivery vector, with two main

approaches: virus-based and non-viral systems (Maguire et al., 2014). Viruses are well-known for their ability to efficiently deliver genetic material, making viral vectors a highly effective tool for gene therapy. These vectors can overcome significant barriers, such as the blood-brain barrier (BBB). For example, intravenous (IV) injection of adeno-associated virus (AAV) serotype 9 has demonstrated the capacity to bypass the BBB and facilitate effective delivery to the central nervous system (CNS) (Foust et al., 2009). Although approximately 70 % of clinical trials have utilized viral vectors for gene delivery, non-viral vectors are increasingly preferred due to their enhanced safety profile (Yin et al., 2014). Additionally, cell-based gene therapies and hybrid vector systems are emerging as promising strategies in the field of gene therapy.

4.2.1. Gene Editing Approaches in AD

Due to limitations such as the high failure rate of anti-amyloid antibody (anti-Ab) therapies in the treatment of AD, there has been a shift toward more critical and precise approaches, including gene manipulation using advanced genome editing technologies (Bhardwaj et al., 2022a). Among the three primary genome editing tools—zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)—CRISPR/Cas9 is the most widely utilized (Xu and Li, 2020). Originating as an immune mechanism in bacteria, CRISPR/Cas9 has garnered significant attention from researchers as a promising approach for treating neurodegenerative diseases. It offers high efficacy, precise target specificity, and the potential for permanent cures by accurately deleting disease-causing genes (Jiang et al., 2020; Xu and Li, 2020). Regardless of the type of gene-editing tool used, the gene-editing procedure at the cellular level can have a permanent, lifelong impact on the patient. Therefore, it is crucial to ensure maximum target selectivity and minimize off-target effects. Avoidance of off-targeting is achieved through various CRISPR/Cas9-based strategies, such as the 'Cas9/sgRNA' complex and 'Cas9 mRNA and sgRNA' systems. In these approaches, the plasmid-borne CRISPR/Cas9 system ensures that the Cas9 protein and sgRNA are expressed specifically in the targeted cells (Bhardwaj et al., 2022b). The sgRNA and Cas9 complex enhance the efficiency of CRISPR/Cas9-based genome editing by facilitating precise cleavage of targeted genetic sequences (Barman et al., 2020). Cas9 is a six-domain protein that plays a critical role in inducing targeted DNA cleavage, resulting in a double-strand break (DSB), a process guided by the sgRNA. The CRISPR/Cas9 system can be delivered via both viral and non-viral vectors. While viral vectors enable efficient delivery, they are associated with risks such as unintended mutations. Non-viral vectors, although free from such immunogenic risks, face the significant challenge of crossing the BBB (Maguire et al., 2014).

4.2.2. Modulation in Genes Related to Amyloid and Tau Pathology

Tau and amyloid-β pathology are key pathological markers associated with the progression of AD, making them prime targets for therapeutic interventions, including gene modulation approaches. Antisense oligonucleotides (ASOs) represent one such gene-modulating tool. ASOs bind to specific RNA sequences and modulate their activity through various mechanisms, such as promoting RNA degradation, thereby altering the expression of target genes (Bennett et al., 2019). Tau protein is encoded by the microtubule-associated protein Tau (MAPT) gene, and its accumulation is associated with cognitive decline in AD. Researchers have developed modified oligonucleotides, known as MAPTRx, which target and degrade MAPT mRNA, significantly reducing Tau protein levels. While there are certain limitations, these findings highlight the potential for further development of MAPTRx as a clinical therapeutic for AD (Mummery et al., 2023). Similarly, the OL-1 AβPP antisense oligonucleotide tested in the Tg2576 mouse model demonstrated a reduction in amyloid-β (Aβ) protein production, accompanied by positive cognitive outcomes (Chauhan and Siegel, 2007).

Numerous studies have established that epigenetic modifications, such as DNA methylation and histone acetylation, play a critical role in AD. However, there are limited studies exploring the therapeutic potential of targeting DNA methylation for the treatment of AD (Cheng et al., 2019). Limited demethylation strategies, such as the dCas9-Ten-Eleven Translocation 1 (TET1) fusion, have shown potential as effective gene modulation approaches for the treatment of AD (Zhu et al., 2020). The demethylation of PSEN2 has been observed to exert an inhibitory effect on amyloid-β production (Qin et al., 2023). Well-established data suggests that epigenetic factors, such as histone deacetylases (HDACs), play a critical role in the pathogenesis of AD. Consequently, HDACs could serve as a promising therapeutic target for AD management. Studies conducted on both in vitro and in vivo models have demonstrated that HDAC inhibitors, such as sodium valproate and WT161, effectively reduce HDAC expression, modulate APP processing, and decrease amyloid-β accumulation. Furthermore, these inhibitors have shown to enhance cognitive function in in vivo AD mouse models (M. Zhang et al., 2024). CREB (cyclic-AMP response element binding protein) binding protein and its paralog E1A binding protein p300 (CBP/P300) are enzyme that catalyzes the acetylation of histone H3 at lysine 27 (H3K27ac), a modification that has been implicated in AD in previous studies. When the expression of CBP/P300 was reduced, researchers observed a subsequent increase in the accumulation of toxic amyloid-β (Aβ) peptides. Based on these findings, the researchers concluded that H3K27ac may play a protective role in modulating the pathogenesis of AD (M. Zhang et al., 2024).

Yao-Bo Li et al. have reviewed the role of dysregulated miRNAs in various pathological processes associated with AD, including Tau hyperphosphorylation, Aβ formation, oxidative stress, neuroinflammation, mitochondrial dysfunction, and synaptic depression, all of which contribute to the progression of the disease (Li et al., 2024). Thus, modulating specific miRNAs represents a promising therapeutic approach for managing AD. A study investigating the effects of intranasal insulin on miRNAs associated with AD found that intranasal insulin treatment alters the expression of miR-132, miR-181b, and miR-125b, leading to neuroprotective effects (Bazrgar et al., 2022). A recent study investigated the therapeutic potential of L-carnitine and found that it modulates the oxidative-anti-oxidative balance, leading to improved cognitive function and reduced anxiety in AD (Tork et al., 2024).

4.3. Stem Cell Therapy to Substitute Impaired Neurons

Stem cell therapy is considered a promising neuroregenerative treatment for neurodegenerative disorders such as AD. It exerts therapeutic efficacy through multiple mechanisms, including the reduction of Aβ aggregation, prevention of cell damage caused by toxic Tau proteins, repair of injured neurons, and promotion of synaptic regeneration. These processes collectively contribute to its potential effectiveness in managing AD (Cao et al., 2024; Duncan and Valenzuela, 2017). Intracerebral administration of bone marrow-derived mesenchymal stem cells (BM-MSCs) in AD mice has been shown to enhance the release of C-C motif chemokine ligand 5 (CCL5), thereby activating microglia with anti-Aβ properties (Lee et al., 2012). The neuroprotective roles of miRNAs have been discussed above; notably, BM-MSCs have been shown to induce the expression of miR-146a in astrocytes, leading to enhanced synaptic development and improved cognitive behavior (Nakano et al., 2020). Human amniotic mesenchymal stem cells (hAM-MSCs) have been shown to inhibit Aβ peptide accumulation by stimulating the release of Aβ-degrading enzymes. Additionally, hAM-MSCs promote neuronal proliferation and synaptic development (Zilka et al., 2011). In vitro studies on MSCs targeting Tau pathology demonstrate that stem cell therapy can prevent cell death induced by misfolded Tau proteins (Zilka et al., 2011). Brain-derived neurotrophic factor (BDNF)-modified human umbilical cord mesenchymal stem cells (hUC-MSCs) were shown to differentiate into cholinergic-like neurons, promoting neuronal

reconstruction and enhancing cognitive function in AD rats. These findings suggest the potential of hUC-MSCs as a therapeutic approach for AD (Yue et al., 2015). Embryonic stem cell (ESC)-derived basal forebrain cholinergic neurons (BFCNs) have been shown to improve memory function (Yue et al., 2015). The above observations underscore the potential of exogenous stem cells as a therapeutic approach for treating neurodegenerative disorders.

4.4. Possible Combination Therapies

Resistance to drugs, off-target side effects, low safety, and limited efficacy are common challenges associated with traditional monotherapies. As a result, combination therapies have emerged as a strategy to address complex disease mechanisms. The frequent failures of monotherapy have prompted a shift in the scientific community toward combination therapy. In line with these findings, the Alzheimer's Association Research Roundtable 2018 strongly emphasized the urgent need for combination therapies, highlighting their potential for advancing treatment options (Kabir et al., 2020). Among the various genetic modulators of Aβ, pyroglutamate-3Aβ (N3pE) is a particularly toxic form that plays a progressive role in the complex pathogenesis of AD. However, the combination of Varoglutamstat and Aducanumab has demonstrated effective inhibition of N3pE, highlighting the potential of this combination therapy for AD treatment (Hoffmann et al., 2021). Neurodegenerative diseases associated with cognitive decline often present with disruptions in social well-being, such as pseudobulbar affect, which can be alleviated by treatment with dextromethorphan in combination with ultra-low-dose quinidine (10.1002/ana.22093). While traditional therapies face challenges related to off-target effects and adverse reactions, recent findings suggest that combination therapies offer a promising approach to mitigate these issues, effectively masking the off-target effects observed with single-agent treatments (Breier et al., 2023). Similarly, a synergistic effect has been reported with the combination of NP106 and a TML-6-supplemented diet, a key outcome anticipated from such combination therapies (Su et al., 2022). The combination of radiotherapy with HDAC inhibition has also demonstrated a synergistic effect. Therefore, the use of low-dose radiotherapy could represent a versatile therapeutic strategy for the management of AD (Keshavan et al., 2018). In summary, various mechanisms and triggering factors contribute to the complex progression of disease, which could be effectively managed through combination therapies. The progression of the disease, along with its associated consequences, leads to a range of signs and symptoms that exacerbate its severity. In such cases, combination therapy offers the potential for synergistic management. This approach, with its diverse combinations, provides an important avenue for further research and underscores the urgent need for continued investigation.

4.5. Complementary and alternative medicine therapies (CAM)

CAM refers to approaches that fall outside of mainstream medicine. It includes a variety of traditional therapeutic options, such as the use of herbal medicines, acupuncture therapy, lifestyle modifications, nutritional supplementations, daily dietary practices, exercise, and yoga. These CAM options are believed to help cure or prevent AD. However, this concept of CAM remains biased, and further research is needed to fully understand its effectiveness (Ott and Owens, 1998).

Daily dietary practices: The Mediterranean diet is known to enhance cognitive function by reducing amyloidosis and tau pathology, (Ballarini et al., 2021) which are key factors in neurodegenerative diseases (Moustafa et al., 2022). Compared to a regular diet, the ketogenic diet, i.e, a diet rich in fats, low in carbohydrates, and sufficient in protein, has been shown to improve the quality of life in individuals with AD (Phillips et al., 2021). Moderate alcohol consumption has been associated with a reduced risk of Alzheimer's dementia; (Ballarini et al., 2021) however, in many developing countries and cultures with traditional beliefs, alcohol consumption is tabooed, and it also involves the risk of habit formation. A balanced diet rich in green leafy vegetables is reported as a CAM for AD.

Acupuncture therapy: A comparative study between subjects receiving acupuncture and those taking donepezil hydrochloride suggests that acupuncture is a safe and effective alternative for improving cognitive function in individuals with AD (Jia et al., 2017). In acupuncture therapy, synaptic plasticity serves as a key regulatory mechanism that positively influences various factors involved in cognitive decline. the enhancement of synaptic plasticity may represent a fundamental and integrative pathway underlying its cognitive benefits. acupuncture has been shown to improve memory by influencing a variety of biological pathways, including the regulation of synaptic proteins, Alzheimer's disease-associated proteins, gut microbiota composition (Jia et al., 2017).

Yoga techniques: Yoga, an ancient Vedic practice followed for over 4000 years, offers a therapeutic, that is devoid of any adverse effects associated with the consumption of active drug moieties, for the prevention and management of cognitive disorders, such as AD (Howes and Houghton, 2003). A daily 12-minute practice of Kirtan Kriya—a specific form of yoga—has been shown to improve cognitive function. Therefore, yoga may be integrated into treatment strategies to enhance outcomes. However, practicing yoga without proper guidance or using incorrect techniques can be potentially harmful (Ghaffari, 2019).

Herbal medicines: It is well established that various bioactive compounds found in specific herbal plants, such as *Ginkgo biloba*, *Bacopa monnieri*, *Salvia officinalis*, *Curcuma longa*, *Rosmarinus officinalis*, *Melissa officinalis*, and *Glycyrrhiza glabra*—as well as phenolic compounds from olive oil, omega-3 fatty acids, and fat-soluble bioactive molecules in vitamins, have potential in addressing the pathophysiological mechanisms of AD. These substances exert their effects by interfering with amyloid plaque formation and tau phosphorylation, and by reducing oxidative stress and inflammation. The safety of most herbal medicines is generally well documented (Bordoloi et al., 2024; Perry et al., 1999).

Lifestyle modifications: A physically inactive lifestyle is a root cause of various diseases and is also considered a significant risk factor for the development of AD. In contrast, regular physical exercise may play a protective role in aging. Studies have shown that consistent exercise enhances cerebral blood flow and helps prevent amyloid plaque formation and tau phosphorylation, both of which are associated with Alzheimer's pathology (De la Rosa et al., 2020). Aerobic exercises, such as swimming and similar activities, are commonly recommended for promoting cognitive stability and overall brain health (Pahlavani, 2023).

CAM therapies are often traditional, generally considered safe, easy to practice, and cost-effective, making them appealing to individuals with AD. However, some CAM approaches require further evaluation and validation through rigorous scientific research. Practices such as yoga and aerobic exercise, which have shown cognitive benefits, may also be effectively integrated with conventional treatments as part of an integrative medicine approach for the management of AD.

Future developments in therapeutic approaches for AD, such as the potential of gene therapy, nanotechnology, stem cell treatments, combination therapies, and complementary and alternative medicine (CAM) therapies, may help manage the intricate pathophysiology of AD and enhance treatment outcomes.

5. Clinical Wisdom and Future Insights

5.1. Investigations from Recent Clinical Trials

The conventional drug molecules used in managing AD are primarily classified into two subclasses: NMDA receptor antagonists and AChEIs (Mony and Paoletti, 2023). Despite advancements in developing drugs within these categories, ongoing research focuses on dose optimization, administration routes, dosage forms, and combination-based therapies

(W. Zhang et al., 2023). The literature revealed that there are 187 clinical trials in various phases (I, II, and III) for the treatment of AD and related conditions (clinicalTrials.gov). In brief, specifically, 31 drugs are under investigation in Phase I, 87 in Phase II, and 36 in Phase III (Cummings et al., 2023a, 2023b). Additionally, two phase II clinical trials (NCT05181475 and NCT05058040) are currently assessing the safety and efficacy of potential treatments. Moreover, in 2021, the FDA granted approval to aducanumab, followed by the traditional approval of Lecanemab in 2023. Recently, Phase III trials for donanemab have been completed, and the drug is currently under market authorization review (W. Zhang et al., 2023). Table 2 provides an overview of some clinical trials for managing AD and related conditions.

5.1.1. *Analyzing the Successes and Failures of Recent Aducanumab Trials*

In 2019, Knopman and his team reported that Biogen (the sponsor) conducted two large Phase III clinical trials of aducanumab. It involved 3285 participants from 20 countries. As well, these trials were 18-month, randomized, placebo-controlled, double-blind, parallel-group studies designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of aducanumab (Tampi et al., 2021). One showed positive trends in these trials, while the other demonstrated no significant benefits from aducanumab, leading Biogen to halt the trials. However, a post hoc analysis by the sponsor suggested that there was enough efficacy to justify submitting a new drug application (NDA) for AD treatment. A subset of participants who received a sufficiently high dose of aducanumab showed benefits in both studies. However, the post hoc analysis also identified subgroups showing apparent drug benefits unrelated to dose effects. Although the biomarker data consistently demonstrated target engagement, no clear evidence linked these biomarker changes to cognitive improvements (Knopman et al., 2021). According to published literature, on June 7, 2021, the U.S. FDA approved Biogen's application for aducanumab, a human IgG1 anti-Aβ monoclonal antibody that selectively targets Aβ aggregates. This approval marked the first disease-modifying treatment for AD, indicated for both mild cognitive impairment (MCI) and the early stages of dementia. Aducanumab, marketed as Aduhelm, was approved via the FDA's accelerated approval pathway. It has been reported that aducanumab presents a low risk of intracranial hemorrhage, with rates comparable to those in the placebo group (Tampi et al., 2021). Additionally, similar blood pressure and heart rate measurements were observed across both groups. Blood chemistry, urine analysis, and hematology studies also showed no significant differences between the treatment and placebo groups. However, abnormal electrocardiogram (ECG) findings were reported in both the aducanumab and placebo groups (Yiannopoulou and Papageorgiou, 2013). Despite the Food and Drug Administration's (FDA) approval of aducanumab, several issues have emerged questioning the validity of this decision. Concerns have been raised about the reliability of Aβ reduction as a surrogate marker for AD treatment and the unclear correlation between Aβ reduction and cognitive improvement. Additionally, the committee that reviewed the drug was not informed that the accelerated approval pathway was under consideration. Further controversy stems from the fact that a post-approval confirmatory trial is not expected to be completed until 2030, intensifying the debate surrounding aducanumab's approval (Alexander and Karlawish, 2021; Vaz et al., 2022).

5.1.2. *Understanding trial design defects and improving future investigations*

Placebo-controlled, parallel-group, double-blind, and randomized designs have been preferred in drug development for mild to moderate AD. In contrast, crossover designs have been deemed inadequate for this purpose (Knopman, 2008). Despite advancements in clinical trials, there remains a need for a well-planned approach to execution and analysis. Particular attention should be given to addressing methodological challenges and minimizing avoidable errors during the trial process (Schneider, 2022). The development of new drugs targeting the central nervous system (CNS) is generally a challenging process that requires a significant amount of time. Clinical trials often show a high rate of failure, particularly in the development of drugs for AD treatment. In many cases, although Phase II trials yield positive results, these outcomes do not translate into success in Phase III. This is primarily due to a lack of therapeutic efficacy and the occurrence of serious adverse effects (Godyń et al., 2016). Large Phase III clinical trials of disease-modifying molecules have failed to consistently demonstrate cognitive benefits, likely due to the complexity of AD and its various pathogenic mechanisms. Therefore, before pursuing advanced disease-modifying treatments, it is crucial to thoroughly investigate the mechanistic aspects of AD pathogenesis. Understanding the relationship between beta-amyloid, Tau proteins, and other contributing factors is essential for developing effective disease-modifying therapies for AD management. In some cases, available treatments target specific stages of the disease (Gulisano et al., 2018). For example, certain disease-modifying molecules have shown efficacy in treating mild AD but failed to address moderate AD and MCI. This highlights the importance of focusing on early-stage diagnosis based on biomarkers, as these biomarkers are closely linked to AD pathology. Consequently, future studies should prioritize biomarker-based approaches when designing therapeutic strategies. Despite the current use of aducanumab in clinics and the results from post-marketing studies, there remains a continuous need to develop and implement advanced care models for AD treatment. (Yiannopoulou and Papageorgiou, 2013) These models are crucial for improving the quality of life for patients and addressing the challenges faced by caregivers.

5.2. *Translational Barriers*

A gradual loss of mental abilities and memory is characteristic of AD, which continues to be one of the world's most significant health problems. Preclinical studies cannot be effectively translated into human therapeutics due to major translational obstacles despite tremendous progress in our knowledge of fundamental biology (Singh et al., 2024). This section covers two key issues: the need to bridge the gap between clinical insights and basic sciences and the challenges of translating preclinical discoveries into human applications (Gadhave et al., 2024b).

5.2.1. *Challenges in translating preclinical outcomes to human applications*

Animals are commonly used in preclinical investigations as a model for pathophysiologic conditions in humans with AD and for assessing treatment potential. Although these models contain informative material, inherent flaws make them inappropriate for application in real-life settings (Soufizadeh et al., 2024).

5.2.1.1. Species variabilities. Animal models, i.e., rodents, do not precisely mimic human AD pathophysiology. However, the modifications in the brain's anatomy, revolutions in immune response, and the complications of human mental functions may cause variations in drug metabolism and effectiveness. Such a variance frequently allows for productive results in animal experiments that are not clinically interpreted (Białoń and Wąsik, 2022).

5.2.1.2. End and outcome. The biochemical and molecular mechanisms, like Aβ plaque accumulation or Tau phosphorylation, are frequently underscored in preclinical experimentation. That does not reflect clinical findings such as enhancing cognition and life quality. That might impact researchers' incorrect insights into proper medication (Rajmohan and Reddy, 2017).

5.2.1.3. Complexity of disease mechanisms. Alzheimer's is a multifactorial disorder relating to genetic, environmental, and lifestyle factors. Preclinical research oversimplifies this complexity primarily because of the heterogeneity seen in human populations. Thus, findings from such

Table 2
Overview of some clinical trials for the management of AD and related conditions.

NCT Number	Study Title	Conditions	Interventions	Phases
NCT01245530	An Efficacy and Safety Study of INM−176 for the Treatment of Patients with Alzheimer's Type Dementia	Alzheimer Type Dementia	**Drug**: Aricept **Drug**: INM−176	Phase 3
NCT01266525	Effect of Different Doses of SAR110894 on Cognition in Patients with Mild to Moderate Alzheimer's Disease on Donepezil	Dementia Alzheimer's Type	**Drug**: SAR110894, **Drug**: Placebo (for SAR110894), **Drug**: Donepezil	Phase 2
NCT02434666	Long Term Extension Safety Study in Patients with Dementia of the Alzheimer's Type Who Completed Study CPC−001–07	Dementia of the Alzheimer's Type	**Drug**: CPC−201	Phase 2
NCT01585272	Tolerability of Rivastigmine Before and After Switching from Oral Formulation to Transdermal Patch in Alzheimer's Dementia	Alzheimer's Dementia	**Drug**: ENA713	Phase 4
NCT00322153	A Study of the Safety and Efficacy of Memantine in Moderate to Severe Alzheimer's Disease	Dementia of the Alzheimer's Type	**Drug**: Memantine ER, **Drug**: Placebo	Phase 3
NCT01297218	The Safety and Efficacy Evaluation of NEUROSTEMÂ®-AD in Patients with Alzheimer's Disease	Dementia of the Alzheimer's Type	**Biological**: Human Umbilical Cord Blood Derived-Mesenchymal Stem Cells	Phase 1
NCT01409564	Cilostazol Augmentation Study in Dementia	Alzheimer's Dementia	**Drug**: Cilostazol, **Drug**: Placebo	Phase 4
NCT04413344	Repurposing Bromocriptine for Abeta Metabolism in Alzheimer's Disease	Familial AD (FAD), PSEN1 Mutation	**Drug**: Bromocriptine. **Drug**: Placebos	Phase 1 Phase 2
NCT04462029	A Study to Compare the Pharmacokinetics of BR4002 and BR4002–1 in Healthy Volunteers	Dementia Alzheimer's	**Drug**: BR4002, **Drug**: BR4002–1	Early Phase 1
NCT00456417	Evaluation of [123I] MNI−187 and SPECT in Patients with Alzheimer's Disease in Comparison to Healthy Subjects	AD	**Drug**: 123-I MNI−187 Injection and Imaging Procedures	Phase 1
NCT04023994	A Single Ascending Dose Study to Investigate the Safety, Tolerability, Immunogenicity and Pharmacokinetics of Intravenously Administered RO7126209 in Healthy Participants	AD	**Drug**: RO7126209, **Drug**: Placebo	Phase 1
NCT02553928	Comparison of Once Daily and Twice Daily Dosing on Safety and Tolerability of Memantine in Patients with Alzheimer's	Alzheimer's Dementia (AD)	**Drug**: Memantine (once daily), **Drug**: Memantine (twice daily)	Phase 4
NCT03991988	Montelukast Therapy on Alzheimer's Disease	AD	**Drug**: Montelukast, **Drug**: Placebo oral tablet	Phase 2
NCT00982202	Pioglitazone in Alzheimer's Disease	AD	**Drug**: Pioglitazone, **Drug**: Placebo	Phase 2
NCT05686044	A Dose-ranging Study to Investigate Efficacy of Buntanetap in Mild to Moderate AD	AD	**Drug**: Buntanetap/Posiphen, **Drug**: Placebo	Phase 2, Phase 3
NCT05307692	A Study of Seltorexant in Participants with Probable Alzheimer's Disease	AD	**Drug**: Seltorexant, **Drug**: Placebo	Phase 2
NCT04971733	A Study to Assess Safety and Target Engagement of E2814 in Participants with Mild to Moderate Cognitive Impairment Due to Dominantly Inherited Alzheimer's Disease	AD	**Drug**: E2814	Phase 1, Phase 2
NCT03801642	Dapagliflozin In Alzheimer's Disease	AD	**Drug**: Dapagliflozin, **Other**: Placebo	Phase 1, Phase 2
NCT04669028	A Phase 3 Study of NE3107 in Probable Alzheimer's Disease	AD	**Drug**: NE3107, **Drug**: Placebo	Phase 3
NCT05318040	Safety, Tolerability and Pharmacokinetics of CMS121, a Drug Candidate for Alzheimer's Disease, in Healthy Subjects	AD	**Drug**: CMS121, **Drug**: Placebo	Phase 1
NCT00414622	GTS21–201 for Alzheimer Disease: GTS−21 Administered Daily for 28 Days to Participants with Probable Alzheimer's Disease	AD	**Drug**: DMXB-A	Phase 2
NCT00750529	Alzheimer and Sleep	AD	**Drug**: Galantamine and Donepezil	Phase1
NCT04538066	Bryostatin Treatment of Moderately Severe Alzheimer's Disease	AD	**Drug**: Bryostatin 1, **Other**: Placebo	Phase 2
NCT04735536	Pilot Clinical Study of CT1812 in Mild to Moderate Alzheimer's Disease Using EEG	AD	**Drug**: CT1812, **Other**: Placebo	Phase 2
NCT04381468	SEMA4D Blockade Safety and Brain Metabolic Activity in Alzheimer's Disease (AD)	AD	**Drug**: Pepinemab, **Drug**: Placebo	Phase 1, Phase 2
NCT04931459	A Study to Evaluate the Safety, Tolerability, and Blood Levels of ACU193 in Participants with MCI or Mild AD	AD	**Drug**: ACU193, **Drug**: Placebo	Phase 1
NCT05821153	Low Dose IL2 Immunotherapy in AD	AD	**Drug**: Aldesleukin	Phase 1
NCT04388254	Simufilam (PTI−125), 100 mg, for Mild-to-moderate Alzheimer's Disease Patients	AD	**Drug**: Simufilam 100 mg oral tablet, **Drug**: Placebo	Phase 2
NCT03605667	Study of BHV−4157 in Alzheimer's Disease	AD	**Drug**: troriluzole, **Drug**: Placebo oral capsule	Phase 2
NCT03744312	Imaging Inflammation in Alzheimer's Disease With 11C-ER176	AD	**Drug**: 11C-ER176, **Drug**: Florbetaben	Phase 1, Phase 2
NCT03790709	ANAVEX2–73 for Treatment of Early Alzheimer's Disease	AD	**Drug**: High dose ANAVEX2–73, **Drug**: Mid dose ANAVEX2–73, **Drug**: Placebo oral capsule	Phase 2, Phase 3
NCT04251182	Clinical Study Evaluating Efficacy and Safety of T3D−959 in Mild-to-moderate AD Subjects	AD	**Drug**: 15 mg T3D−959, **Drug**: 30 mg T3D−959, **Drug**: 45 mg T3D−959, **Drug**: Placebos	Phase 2
NCT04070378	Study of Daratumumab in Patients with Mild to Moderate Alzheimer's Disease	AD	**Drug**: Daratumumab Injection	Phase 2
NCT03757325	Study to Evaluate DNL747 in Subjects with Alzheimer's Disease	AD	**Drug**: DNL747, **Drug**: Placebo	Phase 1
NCT03748706	PTI−125 for Mild-to-moderate Alzheimer's Disease Patients	AD	**Drug**: PTI−125, 100 mg tablets	Phase 2
NCT03101085	S-Equol in Alzheimer's Disease 2 Trial	AD	**Drug**: S-equol and Placebo, **Drug**: Placebo and S-equol	Phase1, Phase 2

(*continued on next page*)

Table 2 (*continued*)

NCT Number	Study Title	Conditions	Interventions	Phases
NCT03417986	Clinical Trial to Explore the the Amyloid Beta Draining Effect of Thiethylperazine (TEP) in Subjects with Newly Diagnosed Early-to-mild Dementia Due to Alzheimer's Disease (AD) in Comparison to Healthy Volunteers	AD	**Drug**: TEP	Phase 2
NCT02353598	A Study of Crenezumab in Participants with Mild to Moderate Alzheimer Disease	AD	**Drug**: Crenezumab dose level 1, **Drug**: Crenezumab dose level 2, **Drug**: Crenezumb dose level 3, **Drug**: Placebo	Phase 1
NCT00013923	Effectiveness of A Nutritional Brain Metabolic Enhancer for Alzheimer Disease	AD	**Drug**: Nutritional Supplement	Phase 2
NCT06194552	A Multiple Dose Study of the Safety and Pharmacokinetics of NTRX−07	AD	**Drug**: NTRX−07, **Drug**: Placebo	Phase 1
NCT00018278	Electrophysiologic Measures of Treatment Response in Alzheimer Disease	AD	**Drug**: Aricept, **Drug**: Exelon, **Drug**: Nicoderm Patch	Phase 4
NCT03373604	Imaging Tau in Alzheimer's Disease and Normal Aging	AD	**Drug**: 18F-MK−6240, **Procedure**: Lumbar Puncture (optional)	Phase 2
NCT03823404	GAIN Trial: Phase 2/3 Study of COR388 in Subjects with Alzheimer's Disease	AD	**Drug**: COR388 capsule, **Drug**: Placebo capsule	Phase 2, Phase 3
NCT03901105	Evaluation of Flortaucipir PET Signal and Cognitive Change in Early Alzheimer's Disease	AD	**Drug**: Flortaucipir F18, **Procedure**: Brain PET Scan	Phase 3
NCT01872598	Masitinib in Patients with Mild to Moderate Alzheimer's Disease	AD	**Drug**: Masitinib, **Drug**: Placebo, **Drug**: Standard of care	Phase 3
NCT03367403	A Study of LY3002813 in Participants with Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ)	AD	**Drug**: Donanemab, **Drug**: Placebo, **Drug**: LY3202626	Phase 2
NCT03902548	Initial Investigation of [18 F] P16–129 in Alzheimer's Disease Patients and Healthy Volunteers	AD	**Drug**: [18 F] P16–129	Phase 1
NCT03522129	Study to Evaluate the Effect of CT1812 Treatment on Amyloid Beta Oligomer Displacement into CSF in Subjects with Mild to Moderate Alzheimer's Disease	AD	**Drug**: CT1812, **Drug**: Placebo	Phase 1
NCT03720548	A Study of LY3372993 in Healthy Participants and Participants with Alzheimer's Disease (AD)	AD	**Drug**: LY3372993, **Drug**: Placebo	Phase 1

Website: https://clinicaltrials.gov, Data Accessed on: 19/9/2024

investigations might be less relevant to the general patient population (Ringman et al., 2014).

5.2.1.4. Dosing and treatment regimens. Even the pharmacokinetics and pharmacodynamics of drugs can vary quite profoundly between species. Dosing regimens validated in animal models sometimes fail to translate entirely to humans. Such dosing regimens often require several adjustments, and more testing is usually necessary before being used for patients. These considerations emphasize the need to describe better preclinical models that more closely resemble the human condition and standardize methodologies to evaluate treatments more accurately (Toutain et al., 2010).

5.2.2. Bridging the gap between fundamental science and clinical implementation

However, bridging that gap between the day of conducting scientific research and its subsequent day of translation into clinical practices is the need of the hour. Some strategies for this purpose are listed here (Teachman et al., 2012).

5.2.2.1. Disciplinary interactions. More integral AD research may take place through interdisciplinary interaction among basic scientists, clinical researchers, and healthcare professionals rather than working in silos. Multidisciplinary teams may include diverse perspectives, aid in identifying relevant biomarkers, and build a better-designed clinical trial (Javaid et al., 2022).

5.2.2.2. Patient-centric research. Views and experiences of patients and caregivers would be taken as part of the research process to ensure that the studies address challenges and outcomes that matter most to those who have Alzheimer's. Meaningful engagement with patient advocacy groups would provide first-hand insights into what matters to patients and their families (Griffin et al., 2020).

5.2.2.3. Biomarkers. The selection and validation of promising biomarkers that suggest disease progression and response to treatment mark an essential improvement in designing clinical trials. Having reliable biomarkers makes it possible to diagnose early, stratify the patients better, and help in better clinical decisions (Umbricht et al., 2024).

5.2.2.4. Adaptive design of trials. Adaptive trial designs allow the parameters of a trial to be changed based on the interim results. That may provide ways of bringing more efficaciously conducted studies and identifying helpful treatment options to the investigator's doorstep sooner (Pallmann et al., 2018).

5.2.2.5. Regulatory support. Interactive dialogue with the regulatory body can strengthen, thereby helping to hasten the approval of a new therapy. This knowledge will help guide the studies that are carried out to meet the proper criteria for translation to the clinical setting. It is difficult to map a pathway from preclinical research through to clinical application in Alzheimer's disease. Overcoming these translational barriers will play a vital role in developing effective therapies. Collaborations, patient-centered outcomes, and innovative thoughtfulness in designing research may bring the scientific community closer to bridging this gap between fundamental research and meaningful clinical impact (Lottes et al., 2022).

5.3. Future clinical directions

5.3.1. Potential pathways for early intervention

In the case of AD, slowing its progression and effectively managing symptoms are crucial steps. This can be achieved through various potential pathways for early intervention (Kumar et al., 2015). To date, several pathways have been documented, focusing on early-stage detection and intervention. These range from lifestyle changes to advanced therapeutic options (Nangare and Patil, 2022). In brief, the use of biomarker-based recognition and monitoring of AD offers a

modern and key pathway for early intervention. This approach includes the detection of biomarkers such as β-amyloid and Tau proteins in blood, CSF, and other samples, helping to identify AD at its preclinical stages (Shah et al., 2023). Additionally, neurofilament light (NfL), which is associated with neurodegeneration, can also be considered for the early detection of AD. For more frequent monitoring, apolipoprotein E (ApoE) genotyping, which is linked to an increased risk of AD, plays a key role (Georgakas et al., 2023). Furthermore, other genes related to AD risk can be targeted for early-stage interventions. Lifestyle and environmental modifications, such as dietary interventions, exercise, cognitive training, and sleep management, assist in decreasing the risk of AD. Immunotherapies such as monoclonal antibodies that specifically target amyloid plaques can avoid or clear their accumulation in the brain. Likewise, Tau-targeted therapies, aimed at preventing Tau phosphorylation, can aid in slowing the progression of AD (Bittar et al., 2020). Other approaches include the modulation of neuroinflammation, metabolic and vascular interventions, cholinergic system support, targeting synaptic loss, and novel therapeutic strategies, all of which can contribute to slowing or preventing the progression of AD (Gadhave et al., 2023a).

5.3.2. Long-term therapeutic strategies for controlling AD

For effective treatment of AD, the research community is focusing on novel and potentially effective agents. These include antibodies targeting beta-amyloid, vaccines against Tau protein, as well as modulators or inhibitors of enzymes such as beta-secretase (Golde, 2022). Long-term therapeutic strategies for controlling AD primarily intend to slow disease progression, manage symptoms, and ultimately improve the quality of life for patients (Peng et al., 2023). These strategies can be broadly classified into two chief categories: pharmacological and non-pharmacological. Pharmacological strategies include the use of cholinesterase inhibitors (donepezil, rivastigmine, galantamine), NMDA receptor antagonists (memantine), disease-modifying therapies (such as monoclonal antibodies including aducanumab and lecanemab), and neuroprotective agents (Hansen et al., 2008). Non-pharmacological long-term strategies for AD management include cognitive training, rehabilitation, lifestyle modifications, mind-body interventions, and caregiver support and education. Despite these existing long-term therapeutic strategies, emerging and experimental approaches are also being explored (Kamatham et al., 2024b). These include gene therapy, stem cell therapy, vaccine development and neurostimulation devices (Gadhave et al., 2024b). In summary, a multifaceted approach is essential for effectively controlling AD, combining established treatments with innovative and experimental strategies.

Recent clinical research on AD highlights inconsistent results from medications like aducanumab, translational challenges from preclinical studies, and the need for early biomarker-based intervention, patient-centric and interdisciplinary research, as well as both pharmacological and non-pharmacological long-term treatment strategies.

6. Conclusion

AD's growth is increasingly prevalent, so a more advanced therapeutic approach is needed. While some research provides insight into the course of the illness, few effective neuro-regenerative and neuroprotective therapies are currently on the market. Improvements in understanding the various targets associated with AD, including intracellular and intercellular signal networks, have led to improved management of these disorders. Additional investigation on AD has to concentrate on developing better medication delivery strategies and gaining critical knowledge of the pathophysiology of disorders. At the same time, the work focused on the connections between different mechanisms, including neuroinflammation, Tau tangles, and Aβ plaques in AD. Furthermore, in the last ten years, there has been a significant advancement in the development of innovative diagnostic and imaging technologies for AD. The existing clinical data are presented in this paper. However, there is still an opportunity to advance clinical trial practice using novel therapeutic strategies. Finally, in the present review, we include available therapies for AD, developments in disease-modifying treatments, future trends in advanced therapeutic strategies, and clinical data. Novel therapeutic approaches that can target neurodegeneration caused by AD and deliver therapeutics more effectively demonstrate potential as a favorable therapeutic approach for the near future.

Authors' contributions

All authors participated in review editing and proof reading. All authors read and approved the final manuscript.

Consent for publication

All authors have approved to publish this manuscript.

Ethics approval and consent to participate

Not applicable.

Funding

None.

Availability of data and materials

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors would like to acknowledge the support from University of Technology Sydney, NSW, Australia and Centenary Institute, Camperdown, NSW, Australia.

Data Availability

Data will be made available on request.

References

Abd Elmonem, H.A., Morsi, R.M., Mansour, D.S., El-Sayed, E.-S.R., 2023. Mycofabricated ZnO nanoparticles ameliorate neurotoxicity in mice model of Alzheimer's disease via acetylcholinesterase inhibition and oxidative stress reduction. Biometals 36, 1391–1404. https://doi.org/10.1007/s10534-023-00525-6.

Abelein, A., 2023. Metal Binding of Alzheimer's Amyloid-β and Its Effect on Peptide Self-Assembly. Acc. Chem. Res. 56, 2653–2663. https://doi.org/10.1021/acs.accounts.3c00370.

Afsar, A., Chacon Castro, M. del C., Soladogun, A.S., Zhang, L., 2023. Recent Development in the Understanding of Molecular and Cellular Mechanisms Underlying the Etiopathogenesis of Alzheimer's Disease. Int. J. Mol. Sci. 24, 7258. https://doi.org/10.3390/ijms24087258.

Aggarwal, N.T., Mielke, M.M., 2023. Sex Differences in Alzheimer's Disease. Neurol. Clin. 41, 343. https://doi.org/10.1016/j.ncl.2023.01.001.

Agraharam, G., Saravanan, N., Girigoswami, A., Girigoswami, K., 2022. Future of Alzheimer's Disease: Nanotechnology-Based Diagnostics and Therapeutic Approach. BioNanoSci 12, 1002–1017. https://doi.org/10.1007/s12668-022-00998-8.

Agrawal, M., Ajazuddin, null, Tripathi, Saraf, D.K., Swarnlata, Saraf, Shailendra, Antimisiaris, Mourtas, S.G., Hammarlund-Udenaes, S., Alexander, A, M., 2017. Recent advancements in liposomes targeting strategies to cross blood-brain barrier (BBB) for the treatment of Alzheimer's disease. J. Control Release 260, 61–77. https://doi.org/10.1016/j.jconrel.2017.05.019.

Agrawal, M., Prathyusha, E., Ahmed, H., Dubey, S.K., Kesharwani, P., Singhvi, G., Naidu, V.G.M., Alexander, A., 2021b. Biomaterials in treatment of Alzheimer's

disease. Neurochem. Int. 145, 105008. https://doi.org/10.1016/j.neuint.2021.105008.
Agrawal, M., Prathyusha, E., Ahmed, H., Dubey, S.K., Kesharwani, P., Singhvi, G., Naidu, V.G.M., Alexander, A., 2021a. Biomaterials in treatment of Alzheimer's disease. Neurochem. Int. 145, 105008. https://doi.org/10.1016/j.neuint.2021.105008.
Aili, M., Zhou, K., Zhan, J., Zheng, H., Luo, F., 2023. Anti-inflammatory role of gold nanoparticles in the prevention and treatment of Alzheimer's disease. J. Mater. Chem. B 11, 8605–8621. https://doi.org/10.1039/d3tb01023f.
Alavi Naini, S.M., Soussi-Yanicostas, N., 2015. Tau Hyperphosphorylation and Oxidative Stress, a Critical Vicious Circle in Neurodegenerative Tauopathies? Oxid. Med Cell Longev. 2015, 151979. https://doi.org/10.1155/2015/151979.
Alexander, G.C., Karlawish, J., 2021. The Problem of Aducanumab for the Treatment of Alzheimer Disease. Ann. Intern Med 174, 1303–1304. https://doi.org/10.7326/M21-2603.
Amin, F.U., Hoshiar, A.K., Do, T.D., Noh, Y., Shah, S.A., Khan, M.S., Yoon, J., Kim, M.O., 2017. Osmotin-loaded magnetic nanoparticles with electromagnetic guidance for the treatment of Alzheimer's disease. Nanoscale 9, 10619–10632. https://doi.org/10.1039/c7nr00772h.
Amiri, H., Saeidi, K., Borhani, P., Manafirad, A., Ghavami, M., Zerbi, V., 2013. Alzheimer's disease: pathophysiology and applications of magnetic nanoparticles as MRI theranostic agents. ACS Chem. Neurosci. 4, 1417–1429. https://doi.org/10.1021/cn4001582.
Arafah, A., Khatoon, S., Rasool, I., Khan, A., Rather, M.A., Abujabal, K.A., Faqih, Y.A.H., Rashid, H., Rashid, S.M., Bilal Ahmad, S., Alexiou, A., Rehman, M.U., 2023. The Future of Precision Medicine in the Cure of Alzheimer's Disease. Biomedicines 11, 335. https://doi.org/10.3390/biomedicines11020335.
Athanasopoulos, D., Karagiannis, G., Tsolaki, M., 2016. Recent Findings in Alzheimer Disease and Nutrition Focusing on Epigenetics. Adv. Nutr. 7, 917–927. https://doi.org/10.3945/an.116.012229.
Azargoonjahromi, A., 2024. The duality of amyloid-β: its role in normal and Alzheimer's disease states. Mol. Brain 17, 44. https://doi.org/10.1186/s13041-024-01118-1.
Ballarini, T., Melo van Lent, D., Brunner, J., Schröder, A., Wolfsgruber, S., Altenstein, S., Brosseron, F., Buerger, K., Dechent, P., Dobisch, L., Düzel, E., Ertl-Wagner, B., Fliessbach, K., Freiesleben, S.D., Frommann, I., Glanz, W., Hauser, D., Haynes, J.D., Heneka, M.T., Janowitz, D., Kilimann, I., Laske, C., Maier, F., Metzger, C.D., Munk, M.H., Perneczky, R., Peters, O., Priller, J., Ramirez, A., Rauchmann, B.-S., Roy, N., Scheffler, K., Schneider, A., Spottke, A., Spruth, E.J., Teipel, S.J., Vukovich, R., Wiltfang, J., Jessen, F., Wagner, M., on behalf of the DELCODE Study Group, 2021. Mediterranean Diet, Alzheimer Disease Biomarkers, and Brain Atrophy in Old Age. Neurology 96, e2920–e2932. https://doi.org/10.1212/WNL.0000000000012067.
Barman, N.C., Khan, N.M., Islam, M., Nain, Z., Roy, R.K., Haque, A., Barman, S.K., 2020. CRISPR-Cas9: A Promising Genome Editing Therapeutic Tool for Alzheimer's Disease-A Narrative Review. Neurol. Ther. 9, 419–434. https://doi.org/10.1007/s40120-020-00218-z.
Baryakova, T.H., Pogostin, B.H., Langer, R., McHugh, K.J., 2023. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat. Rev. Drug Discov. 22, 387–409. https://doi.org/10.1038/s41573-023-00670-0.
Bashir, B., Vishwas, S., Gupta, G., Paudel, K.R., Dureja, H., Kumar, P., Cho, H., Sugandhi, V.V., Kumbhar, P.S., Disouza, J., Dhanasekaran, M., Goh, B.H., Gulati, M., Dua, K., Singh, S.K., 2025. Does drug repurposing bridge the gaps in management of Parkinson's disease? Unravelling the facts and fallacies. Ageing Res. Rev. 105, 102693. https://doi.org/10.1016/j.arr.2025.102693.
Bazrgar, M., Khodabakhsh, P., Dargahi, L., Mohagheghi, F., Ahmadiani, A., 2022. MicroRNA modulation is a potential molecular mechanism for neuroprotective effects of intranasal insulin administration in amyloid βeta oligomer induced Alzheimer's like rat model. Exp. Gerontol. 164, 111812. https://doi.org/10.1016/j.exger.2022.111812.
Behera, A., Sa, N., Pradhan, S.P., Swain, S., Sahu, P.K., 2023a. Metal Nanoparticles in Alzheimer's Disease. J. Alzheimers Dis. Rep. 7, 791–810. https://doi.org/10.3233/ADR-220112.
Behera, A., Sa, N., Pradhan, S.P., Swain, S., Sahu, P.K., 2023b. Metal Nanoparticles in Alzheimer's Disease. J. Alzheimers Dis. Rep. 7, 791–810. https://doi.org/10.3233/ADR-220112.
Behera, A., Sa, N., Pradhan, S.P., Swain, S., Sahu, P.K., 2023c. Metal Nanoparticles in Alzheimer's Disease. J. Alzheimers Dis. Rep. 7, 791–810. https://doi.org/10.3233/ADR-220112.
Bekris, L.M., Yu, C.-E., Bird, T.D., Tsuang, D.W., 2010. Genetics of Alzheimer Disease. J. Geriatr. Psychiatry Neurol. 23, 213–227. https://doi.org/10.1177/0891988710383571.
Bennett, C.F., Krainer, A.R., Cleveland, D.W., 2019. Antisense Oligonucleotide Therapies for Neurodegenerative Diseases. Annu Rev. Neurosci. 42, 385–406. https://doi.org/10.1146/annurev-neuro-070918-050501.
Bhardwaj, S., Kesari, K.K., Rachamalla, M., Mani, S., Ashraf, G.Md, Jha, S.K., Kumar, P., Ambasta, R.K., Dureja, H., Devkota, H.P., Gupta, G., Chellappan, D.K., Singh, S.K., Dua, K., Ruokolainen, J., Kamal, M.A., Ojha, S., Jha, N.K., 2022b. CRISPR/Cas9 gene editing: New hope for Alzheimer's disease therapeutics. J. Adv. Res. 40, 207–221. https://doi.org/10.1016/j.jare.2021.07.001.
Bhardwaj, S., Kesari, K.K., Rachamalla, M., Mani, S., Ashraf, G.Md, Jha, S.K., Kumar, P., Ambasta, R.K., Dureja, H., Devkota, H.P., Gupta, G., Chellappan, D.K., Singh, S.K., Dua, K., Ruokolainen, J., Kamal, M.A., Ojha, S., Jha, N.K., 2022a. CRISPR/Cas9 gene editing: New hope for Alzheimer's disease therapeutics. J. Adv. Res. 40, 207–221. https://doi.org/10.1016/j.jare.2021.07.001.
Bhatt, M., Sharma, M., Das, B., 2024. The Role of Inflammatory Cascade and Reactive Astrogliosis in Glial Scar Formation Post-spinal Cord Injury. Cell Mol. Neurobiol. 44, 78. https://doi.org/10.1007/s10571-024-01519-9.
Bhattacharjee, N., Paul, R., Giri, A., Borah, A., 2016. Chronic exposure of homocysteine in mice contributes to dopamine loss by enhancing oxidative stress in nigrostriatum and produces behavioral phenotypes of Parkinson's disease. Biochem. Biophys. Rep. 6, 47–53. https://doi.org/10.1016/j.bbrep.2016.02.013.
Białoń, M., Wąsik, A., 2022. Advantages and Limitations of Animal Schizophrenia Models. Int J. Mol. Sci. 23, 5968. https://doi.org/10.3390/ijms23115968.
Bittar, A., Bhatt, N., Kayed, R., 2020. Advances and considerations in AD tau-targeted immunotherapy. Neurobiol. Dis. 134, 104707. https://doi.org/10.1016/j.nbd.2019.104707.
Bonnycastle, K., Davenport, E.C., Cousin, M.A., 2021. Presynaptic dysfunction in neurodevelopmental disorders: Insights from the synaptic vesicle life cycle. J. Neurochem. 157, 179–207. https://doi.org/10.1111/jnc.15035.
Bonvicini, C., Scassellati, C., Benussi, L., Di Maria, E., Maj, C., Ciani, M., Fostinelli, S., Mega, A., Bocchetta, M., Lanzi, G., Giacopuzzi, E., Ferraboli, S., Pievani, M., Fedi, V., Defanti, C.A., Giliani, S., Alzheimer's Disease Neuroimaging Initiative, Frisoni, G.B., Ghidoni, R., Gennarelli, M., 2019. Next Generation Sequencing Analysis in Early Onset Dementia Patients. J. Alzheimers Dis. 67, 243–256. https://doi.org/10.3233/JAD-180482.
Bordoloi, S., Pathak, K., Devi, M., Saikia, R., Das, J., Kashyap, V.H., Das, D., Ahmad, M. Z., Abdel-Wahab, B.A., 2024. Some promising medicinal plants used in Alzheimer's disease: an ethnopharmacological perspective. Discov. Appl. Sci. 6, 215. https://doi.org/10.1007/s42452-024-05811-7.
Botto, R., Callai, N., Cermelli, A., Causarano, L., Rainero, I., 2022. Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. Neurol. Sci. 43, 4107. https://doi.org/10.1007/s10072-022-06068-x.
Boutajangout, A., Sigurdsson, E.M., Krishnamurthy, P.K., 2011. Tau as a Therapeutic Target for Alzheimer's Disease. Curr. Alzheimer Res 8, 666–677.
Boxer, A.L., Sperling, R., 2023. Accelerating Alzheimer's therapeutic development: The past and future of clinical trials. Cell 186, 4757–4772. https://doi.org/10.1016/j.cell.2023.09.023.
Breier, A., Brannan, S.K., Paul, S.M., Miller, A.C., 2023. Evidence of trospium's ability to mitigate cholinergic adverse events related to xanomeline: phase 1 study results. Psychopharmacol. (Berl.) 240, 1191–1198. https://doi.org/10.1007/s00213-023-06362-2.
Breijyeh, Z., Karaman, R., 2020. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules 25, 5789. https://doi.org/10.3390/molecules25245789.
Bullock, R., Touchon, J., Bergman, H., Gambina, G., He, Y., Rapatz, G., Nagel, J., Lane, R., 2005. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr. Med Res Opin. 21, 1317–1327. https://doi.org/10.1185/030079905X56565.
Cai, Y., An, S.S.A., Kim, S., 2015. Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. Clin. Interv. Aging 10 1163. https://doi.org/10.2147/CIA.S85808.
Cao, Z., Kong, F., Ding, J., Chen, C., He, F., Deng, W., 2024. Promoting Alzheimer's disease research and therapy with stem cell technology. Stem Cell Res Ther. 15, 136. https://doi.org/10.1186/s13287-024-03737-w.
Cerejeira, J., Lagarto, L., Mukaetova-Ladinska, E.B., 2012. Behavioral and Psychological Symptoms of Dementia. Front. Neurol. 3, 73. https://doi.org/10.3389/fneur.2012.00073.
Cetin, S., Knez, D., Gobec, S., Kos, J., Pišlar, A., 2022. Cell models for Alzheimer's and Parkinson's disease: At the interface of biology and drug discovery. Biomed. Pharmacother. 149, 112924. https://doi.org/10.1016/j.biopha.2022.112924.
Chauhan, N.B., Siegel, G.J., 2007. Antisense Inhibition at the β-Secretase-Site of APP Reduces Cerebral Amyloid and AChE Activity in Tg2576. Neuroscience 146, 143–151. https://doi.org/10.1016/j.neuroscience.2007.01.008.
Chavda, V.P., Sugandhi, V.V., Pardeshi, C.V., Patil, R.J., Joshi, M., Patel, B., Khadela, A., Bezbaruah, R., Bhattacharjee, B., Balar, P.C., Vora, L.K., 2023. Engineered exosomes for cancer theranostics: Next-generation tumor targeting. J. Drug Deliv. Sci. Technol. 85, 104579. https://doi.org/10.1016/j.jddst.2023.104579.
Chen, G.-F., Xu, T.-H., Yan, Y., Zhou, Y.-R., Jiang, Y., Melcher, K., Xu, H.E., 2017. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharm. Sin. 38, 1205–1235. https://doi.org/10.1038/aps.2017.28.
Chen, K.-L., Yu, R.-J., Zhong, C.-B., Wang, Z., Xie, B.-K., Ma, H., Ao, M., Zheng, P., Ewing, A.G., Long, Y.-T., 2024. Electrochemical Monitoring of Real-Time Vesicle Dynamics Induced by Tau in a Confined Nanopipette. Angew. Chem. Int. Ed. 63, e202406677. https://doi.org/10.1002/anie.202406677.
Chen, Y., He, Y., Han, J., Wei, W., Chen, F., 2023. Blood-brain barrier dysfunction and Alzheimer's disease: associations, pathogenic mechanisms, and therapeutic potential. Front Aging Neurosci. 15, 1258640. https://doi.org/10.3389/fnagi.2023.1258640.
Chen, Z., Zhong, C., 2013. Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: Implications for diagnostic and therapeutic strategies. Prog. Neurobiol. 108, 21–43. https://doi.org/10.1016/j.pneurobio.2013.06.004.
Chen, Z.-R., Huang, J.-B., Yang, S.-L., Hong, F.-F., 2022. Role of Cholinergic Signaling in Alzheimer's Disease. Molecules 27, 1816. https://doi.org/10.3390/molecules27061816.
Cheng, Y., Bai, F., 2018. The Association of Tau With Mitochondrial Dysfunction in Alzheimer's Disease. Front Neurosci. 12, 163. https://doi.org/10.3389/fnins.2018.00163.
Cheng, Y., He, C., Wang, M., Ma, X., Mo, F., Yang, S., Han, J., Wei, X., 2019. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduct. Target Ther. 4, 62. https://doi.org/10.1038/s41392-019-0095-0.

Chowen, J.A., Garcia-Segura, L.M., 2020. Microglia, neurodegeneration and loss of neuroendocrine control. Prog. Neurobiol. 184, 101720. https://doi.org/10.1016/j.pneurobio.2019.101720.
Chvojkova, M., Kolar, D., Kovacova, K., Cejkova, L., Misiachna, A., Hakenova, K., Gorecki, L., Horak, M., Korabecny, J., Soukup, O., Vales, K., 2024. Pro-cognitive effects of dual tacrine derivatives acting as cholinesterase inhibitors and NMDA receptor antagonists. Biomed. Pharmacother. 176, 116821. https://doi.org/10.1016/j.biopha.2024.116821.
Cipriani, G., Danti, S., Picchi, L., Nuti, A., Fiorino, M.D., 2020. Daily functioning and dementia. Dement Neuropsychol. 14, 93–102. https://doi.org/10.1590/1980-57642020dn14-020001.
Collaborators, G., 2022. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019, 2019 D.F Lancet Public Health 7, e105. https://doi.org/10.1016/S2468-2667(21)00249-8.
Čolović, M.B., Krstić, D.Z., Lazarević-Pašti, T.D., Bondžić, A.M., Vasić, V.M., 2013. Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. Curr. Neuropharmacol. 11, 315–335. https://doi.org/10.2174/1570159X11311030006.
Constantinescu, R., Romer, M., Zetterberg, H., Rosengren, L., Kieburtz, K., 2011. Increased levels of total tau protein in the cerebrospinal fluid in Huntington's disease. Park. Relat. Disord. 17, 714–715. https://doi.org/10.1016/j.parkreldis.2011.06.010.
Cornell, J., Salinas, S., Huang, H.-Y., Zhou, M., 2021. Microglia regulation of synaptic plasticity and learning and memory. Neural Regen. Res 17, 705–716. https://doi.org/10.4103/1673-5374.322423.
Correll, C.U., Kim, E., Sliwa, J.K., Hamm, W., Gopal, S., Mathews, M., Venkatasubramanian, R., Saklad, S.R., 2021. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. CNS Drugs 35, 39–59. https://doi.org/10.1007/s40263-020-00779-5.
Cui, L., Li, H., Xi, Y., Hu, Q., Liu, H., Fan, J., Xiang, Y., Zhang, X., Shui, W., Lai, Y., 2022. Vesicle trafficking and vesicle fusion: mechanisms, biological functions, and their implications for potential disease therapy. Mol. Biomed. 3, 29. https://doi.org/10.1186/s43556-022-00090-3.
Cummings, J., 2019. The Role of Biomarkers in Alzheimer's Disease Drug Development. Adv. Exp. Med Biol. 1118, 29–61. https://doi.org/10.1007/978-3-030-05542-4_2.
Cummings, J., Zhou, Y., Lee, G., Zhong, K., Fonseca, J., Cheng, F., 2023b. Alzheimer's disease drug development pipeline: 2023. Alzheimers Dement (N. Y 9, e12385. https://doi.org/10.1002/trc2.12385.
Cummings, J., Zhou, Y., Lee, G., Zhong, K., Fonseca, J., Cheng, F., 2023a. Alzheimer's disease drug development pipeline: 2023. Alzheimer'S. Dement.: Transl. Res. Clin. Interv. 9, e12385. https://doi.org/10.1002/trc2.12385.
Cummings, J., Osse, A.M.L., Cammann, D., Powell, J., Chen, J., 2024. Anti-Amyloid Monoclonal Antibodies for the Treatment of Alzheimer's Disease. BioDrugs 38, 5–22. https://doi.org/10.1007/s40259-023-00633-2.
D'Egidio, F., Castelli, V., d'Angelo, M., Ammannito, F., Quintiliani, M., Cimini, A., 2024. Brain incoming call from glia during neuroinflammation: Roles of extracellular vesicles. Neurobiol. Dis. 201, 106663. https://doi.org/10.1016/j.nbd.2024.106663.
Dash, U.C., Bhol, N.K., Swain, S.K., Samal, R.R., Nayak, P.K., Raina, V., Panda, S.K., Kerry, R.G., Duttaroy, A.K., Jena, A.B., 2024. Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. Acta Pharm. Sin. B. https://doi.org/10.1016/j.apsb.2024.10.004.
De la Rosa, A., Olaso-Gonzalez, G., Arc-Chagnaud, C., Millan, F., Salvador-Pascual, A., García-Lucerga, C., Blasco-Lafarga, C., Garcia-Dominguez, E., Carretero, A., Correas, A.G., Viña, J., Gomez-Cabrera, M.C., 2020. Physical exercise in the prevention and treatment of Alzheimer's disease. J. Sport Health Sci. 9, 394–404. https://doi.org/10.1016/j.jshs.2020.01.004.
Deng, Q., Wu, C., Parker, E., Liu, T.C.-Y., Duan, R., Yang, L., 2024. Microglia and Astrocytes in Alzheimer's Disease: Significance and Summary of Recent Advances. Aging Dis. 15, 1537–1564. https://doi.org/10.14336/AD.2023.0907.
DeTure, M.A., Dickson, D.W., 2019. The neuropathological diagnosis of Alzheimer's disease. Mol. Neurodegener. 14, 32. https://doi.org/10.1186/s13024-019-0333-5.
DiBattista, A.M., Heinsinger, N.M., Rebeck, G.W., 2016. Alzheimer's Disease Genetic Risk Factor APOE-ε4 Also Affects Normal Brain Function. Curr. Alzheimer Res. 13, 1200. https://doi.org/10.2174/1567205013666160401115127.
Ding, N., Lei, Y., Hu, Y., Wei, J., Wang, W., Zhang, R., Cai, F., 2024. Research Progress of Novel Inorganic Nanomaterials in the Diagnosis and Treatment of Alzheimer's Disease. Neurol. India 72, 943–950. https://doi.org/10.4103/neurol-india.Neurol-India-D-23-00592.
Dou, K.-X., Tan, M.-S., Tan, C.-C., Cao, X.-P., Hou, X.-H., Guo, Q.-H., Tan, L., Mok, V., Yu, J.-T., 2018. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimer'S. Res. Ther. 10, 126. https://doi.org/10.1186/s13195-018-0457-9.
Drummond, E., Wisniewski, T., 2017. Alzheimer's Disease: Experimental Models and Reality. Acta Neuropathol. 133, 155–175. https://doi.org/10.1007/s00401-016-1662-x.
Dubey, S.K., Salunkhe, S., Agrawal, M., Kali, M., Singhvi, G., Tiwari, S., Saraf, Swarnlata, Saraf, Shailendra, Alexander, A., 2020. Understanding the Pharmaceutical Aspects of Dendrimers for the Delivery of Anticancer Drugs. Curr. Drug Targets 21, 528–540. https://doi.org/10.2174/1389450120666191031092259.
Duman, J.G., Blanco, F.A., Cronkite, C.A., Ru, Q., Erikson, K.C., Mulherkar, S., Saifullah, A.B., Firozi, K., Tolias, K.F., 2022. Rac-maninoff and Rho-vel: The symphony of Rho-GTPase signaling at excitatory synapses. Small GTPases 13, 14–47. https://doi.org/10.1080/21541248.2021.1885264.
Duncan, T., Valenzuela, M., 2017. Alzheimer's disease, dementia, and stem cell therapy. Stem Cell Res Ther. 8, 111. https://doi.org/10.1186/s13287-017-0567-5.
Eskander, M.F., Nagykery, N.G., Leung, E.Y., Khelghati, B., Geula, C., 2005. Rivastigmine is a potent inhibitor of acetyl- and butyrylcholinesterase in Alzheimer's plaques and tangles. Brain Res 1060, 144–152. https://doi.org/10.1016/j.brainres.2005.08.039.
Fakhoury, M., 2018. Microglia and Astrocytes in Alzheimer's Disease: Implications for Therapy. Curr. Neuropharmacol. 16, 508–518. https://doi.org/10.2174/1570159X15666170720095240.
Feng, Y.-S., Tan, Z.-X., Wu, L.-Y., Dong, F., Zhang, F., 2021. The involvement of NLRP3 inflammasome in the treatment of neurodegenerative diseases. Biomed. Pharmacother. 138, 111428. https://doi.org/10.1016/j.biopha.2021.111428.
Foust, K.D., Nurre, E., Montgomery, C.L., Hernandez, A., Chan, C.M., Kaspar, B.K., 2009. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. Nat. Biotechnol. 27, 59–65. https://doi.org/10.1038/nbt.1515.
Gadhave, D., Choudhury, H., Kokare, C., 2019. Neutropenia and leukopenia protective intranasal olanzapine-loaded lipid-based nanocarriers engineered for brain delivery. Appl. Nanosci. 9, 151–168. https://doi.org/10.1007/s13204-018-0909-3.
Gadhave, D., Tupe, S., Tagalpallewar, A., Gorain, B., Choudhury, H., Kokare, C., 2021. Nose-to-brain delivery of amisulpride-loaded lipid-based poloxamer-gellan gum nanoemulgel: *In vitro* and *in vivo* pharmacological studies. Int. J. Pharm. 607, 121050. https://doi.org/10.1016/j.ijpharm.2021.121050.
Gadhave, D., Khot, S., Tupe, S., Shinde, M., Tagalpallewar, A., Gorain, B., Kokare, C., 2022. Nose-to-brain delivery of octreotide acetate in situ gel for pituitary adenoma: Pharmacological and *in vitro* cytotoxicity studies. Int. J. Pharm. 629, 122372. https://doi.org/10.1016/j.ijpharm.2022.122372.
Gadhave, D., Gupta, A., Khot, S., Tagalpallewar, A., Kokare, C., 2023. Nose-to-brain delivery of paliperidone palmitate poloxamer-guar gum nanogel: Formulation, optimization and pharmacological studies in rats. Ann. Pharm. Françaises 81, 315–333. https://doi.org/10.1016/j.pharma.2022.08.010.
Gadhave, D.G., Kokare, C.R., 2019. Nanostructured lipid carriers engineered for intranasal delivery of teriflunomide in multiple sclerosis: optimization and in vivo studies. Drug Dev. Ind. Pharm. 45, 839–851. https://doi.org/10.1080/03639045.2019.1576724.
Gadhave, D.G., Quadros, M., Ugale, A.R., Goyal, M., Ayehunie, S., Gupta, V., 2024a. Mucoadhesive chitosan-poly (lactic-*co*-glycolic acid) nanoparticles for intranasal delivery of quetiapine – Development & characterization in physiologically relevant 3D tissue models. Int. J. Biol. Macromol. 267, 131491. https://doi.org/10.1016/j.ijbiomac.2024.131491.
Gadhave, D.G., Sugandhi, V.V., Jha, S.K., Nangare, S.N., Gupta, G., Singh, S.K., Dua, K., Cho, H., Hansbro, P.M., Paudel, K.R., 2024b. Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance. Ageing Res. Rev. 99, 102357. https://doi.org/10.1016/j.arr.2024.102357.
Gadhave, D.G., Sugandhi, V.V., Kokare, C.R., 2024c. Potential biomaterials and experimental animal models for inventing new drug delivery approaches in the neurodegenerative disorder: Multiple sclerosis. Brain Res 1822, 148674. https://doi.org/10.1016/j.brainres.2023.148674.
Gadhave, D.G., Sugandhi, V.V., Sarvepalli, S., Kokare, C.R., 2024d. Corrigendum to "Potential biomaterials and experimental animal models for inventing new drug delivery approaches in the neurodegenerative disorder: Multiple sclerosis" [Brain Res. 1822 (2023) 148674. Brain Res. 1832. https://doi.org/10.1016/j.brainres.2024.148808.
Gadhave, Dnyandev, Quadros, M., Ugale, A.R., Goyal, M., Gupta, V., 2023. A Nanoemulgel for Nose-to-Brain delivery of Quetiapine – QbD-Enabled formulation development & *in-vitro* characterization. Int. J. Pharm. 648, 123566. https://doi.org/10.1016/j.ijpharm.2023.123566.
Galindo, A.N., Rubio, D.A.F., Hettiaratchi, M.H., 2024. Biomaterial strategies for regulating the neuroinflammatory response. Mater. Adv. 5, 4025–4054. https://doi.org/10.1039/D3MA00736G.
Gao, C., Jiang, J., Tan, Y., Chen, S., 2023. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct. Target Ther. 8, 359. https://doi.org/10.1038/s41392-023-01588-0.
Gendron, T.F., Petrucelli, L., 2009. The role of tau in neurodegeneration. Mol. Neurodegener. 4, 13. https://doi.org/10.1186/1750-1326-4-13.
Georgakas, J.E., Howe, M.D., Thompson, L.I., Riera, N.M., Riddle, M.C., 2023. Biomarkers of Alzheimer's disease: Past, present and future clinical use. Biomark. Neuropsychiatry 8, 100063. https://doi.org/10.1016/j.bionps.2023.100063.
Ghaffari, M., 2019. Yoga as A Complementary Therapeutic Modality for People with Alzheimer's Disease: A Review. JYP 8, 5–6. https://doi.org/10.19080/JYP.2019.08.555740.
Gholami, A., 2023. Alzheimer's disease: The role of proteins in formation, mechanisms, and new therapeutic approaches. Neurosci. Lett. 817, 137532. https://doi.org/10.1016/j.neulet.2023.137532.
Gibbons, G.S., Lee, V.M.Y., Trojanowski, J.Q., 2019. Mechanisms of Cell-to-Cell Transmission of Pathological Tau. JAMA Neurol. 76, 101–108. https://doi.org/10.1001/jamaneurol.2018.2505.
Godyń, J., Jończyk, J., Panek, D., Malawska, B., 2016. Therapeutic strategies for Alzheimer's disease in clinical trials. Pharm. Rep. 68, 127–138. https://doi.org/10.1016/j.pharep.2015.07.006.
Golde, T.E., 2022. Disease-Modifying Therapies for Alzheimer's Disease: More Questions than Answers. Neurotherapeutics 19, 209–227. https://doi.org/10.1007/s13311-022-01201-2.
Gomez-Arboledas, A., Acharya, M.M., Tenner, A.J., 2021. The Role of Complement in Synaptic Pruning and Neurodegeneration. Immunotargets Ther. 10, 373–386. https://doi.org/10.2147/ITT.S305420.
Gothwal, A., Kumar, H., Nakhate, K.T., Ajazuddin, null, Dutta, Borah, A., Gupta, U, A., 2019. Lactoferrin Coupled Lower Generation PAMAM Dendrimers for Brain Targeted Delivery of Memantine in Aluminum-Chloride-Induced Alzheimer's Disease in Mice.

Bioconjug Chem. 30, 2573–2583. https://doi.org/10.1021/acs.bioconjchem.9b00505.
Grabowska-Pyrzewicz, W., Want, A., Leszek, J., Wojda, U., 2021. Antisense oligonucleotides for Alzheimer's disease therapy: from the mRNA to miRNA paradigm. eBioMedicine 74. https://doi.org/10.1016/j.ebiom.2021.103691.
Gradisnik, L., Velnar, T., 2023. Astrocytes in the central nervous system and their functions in health and disease: A review. World J. Clin. Cases 11, 3385–3394. https://doi.org/10.12998/wjcc.v11.i15.3385.
Griffin, J.M., Riffin, C., Havyer, R.D., Biggar, V.S., Comer, M., Frangiosa, T.L., Bangerter, L.R., 2020. Integrating Family Caregivers of People With Alzheimer's Disease and Dementias into Clinical Appointments: Identifying Potential Best Practices. J. Appl. Gerontol. 39, 1184–1194. https://doi.org/10.1177/0733464819880449.
Griffiths, J., Grant, S.G.N., 2023. Synapse pathology in Alzheimer's disease. Semin. Cell Dev. Biol., Spec. Issue.: Alzheimer'S. Dis.: Eff. Brain Circuits Synap. 139, 13–23. https://doi.org/10.1016/j.semcdb.2022.05.028.
Guedj, E., Varrone, A., Boellaard, R., Albert, N.L., Barthel, H., Berckel, B. van, Brendel, M., Cecchin, D., Ekmekcioglu, O., Garibotto, V., Lammertsma, A.A., Law, I., Peñuelas, I., Semah, F., Traub-Weidinger, T., Giessen, E., van de, Weehaeghe, D.V., Morbelli, S., 2021. EANM procedure guidelines for brain PET imaging using [18F] FDG, version 3. Eur. J. Nucl. Med. Mol. Imaging 49, 632. https://doi.org/10.1007/s00259-021-05603-w.
Gulisano, W., Maugeri, D., Baltrons, M.A., Fà, M., Amato, A., Palmeri, A., D'Adamio, L., Grassi, C., Devanand, D.P., Honig, L.S., Puzzo, D., Arancio, O., 2018. Role of Amyloid-β and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. J. Alzheimers Dis. 64, S611–S631. https://doi.org/10.3233/JAD-179935.
Halliday, G., 2017. Pathology and hippocampal atrophy in Alzheimer's disease. Lancet Neurol. 16, 862–864. https://doi.org/10.1016/S1474-4422(17)30343-5.
Hampel, H., Hardy, J., Blennow, K., Chen, C., Perry, G., Kim, S.H., Villemagne, V.L., Aisen, P., Vendruscolo, M., Iwatsubo, T., Masters, C.L., Cho, M., Lannfelt, L., Cummings, J.L., Vergallo, A., 2021. The Amyloid-β Pathway in Alzheimer's Disease. Mol. Psychiatry 26, 5481–5503. https://doi.org/10.1038/s41380-021-01249-0.
Hampel, H., Elhage, A., Cho, M., Apostolova, L.G., Nicoll, J.A.R., Atri, A., 2023. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain 146, 4414–4424. https://doi.org/10.1093/brain/awad188.
Hansen, R.A., Gartlehner, G., Webb, A.P., Morgan, L.C., Moore, C.G., Jonas, D.E., 2008. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: A systematic review and meta-analysis. Clin. Inter. Aging 3, 211–225.
Harper, A., 2010. Mouse models of neurological disorders—A comparison of heritable and acquired traits. Biochim. Et. Biophys. Acta (BBA) - Mol. Basis Dis., Mouse Models Hum. Neurol. Disord. 1802, 785–795. https://doi.org/10.1016/j.bbadis.2010.05.009.
Hassan, N.A., Alshamari, A.K., Hassan, A.A., Elharrif, M.G., Alhajri, A.M., Sattam, M., Khattab, R.R., 2022. Advances on Therapeutic Strategies for Alzheimer's Disease: From Medicinal Plant to Nanotechnology. Molecules 27, 4839. https://doi.org/10.3390/molecules27154839.
Hoffmann, T., Rahfeld, J.-U., Schenk, M., Ponath, F., Makioka, K., Hutter-Paier, B., Lues, I., Lemere, C.A., Schilling, S., 2021. Combination of the Glutaminyl Cyclase Inhibitor PQ912 (Varoglutamstat) and the Murine Monoclonal Antibody PBD-C06 (m6) Shows Additive Effects on Brain Aβ Pathology in Transgenic Mice. Int J. Mol. Sci. 22, 11791. https://doi.org/10.3390/ijms222111791.
Hoogmartens, J., Cacace, R., Van Broeckhoven, C., 2021. Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants. Alzheimers Dement (Amst. 13, e12155. https://doi.org/10.1002/dad2.12155.
Hossain, M., Jhee, S.S., Shiovitz, T., McDonald, C., Sedek, G., Pommier, F., Cutler, N.R., 2002. Estimation of the absolute bioavailability of rivastigmine in patients with mild to moderate dementia of the Alzheimer's type. Clin. Pharm. 41, 225–234. https://doi.org/10.2165/00003088-200241030-00006.
Howes, M.-J.R., Houghton, P.J., 2003. Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. Pharmacol. Biochem. Behav., Plants Cent. Nerv. Syst. 75, 513–527. https://doi.org/10.1016/S0091-3057(03)00128-X.
Hurley, E.M., Mozolewski, P., Dobrowolski, R., Hsieh, J., 2023. Familial Alzheimer's disease-associated PSEN1 mutations affect neurodevelopment through increased Notch signaling. Stem Cell Rep. 18, 1516–1533. https://doi.org/10.1016/j.stemcr.2023.05.018.
Iacobucci, G.J., Popescu, G.K., 2024. Calcium- and calmodulin-dependent inhibition of NMDA receptor currents. Biophys. J. 123, 277–293. https://doi.org/10.1016/j.bpj.2023.12.018.
Igartúa, D.E., Martinez, C.S., Del, V., Alonso, S., Prieto, M.J., 2020. Combined Therapy for Alzheimer's Disease: Tacrine and PAMAM Dendrimers Co-Administration Reduces the Side Effects of the Drug without Modifying its Activity. AAPS PharmSciTech 21, 110. https://doi.org/10.1208/s12249-020-01652-w.
Iqbal, K., Liu, F., Gong, C.-X., Grundke-Iqbal, I., 2010. Tau in Alzheimer Disease and Related Tauopathies. Curr. Alzheimer Res 7, 656–664.
Ittner, A., Ittner, L.M., 2018. Dendritic Tau in Alzheimer's Disease. Neuron 99, 13–27. https://doi.org/10.1016/j.neuron.2018.06.003.
Iyaswamy, A., Thakur, A., Guan, X.-J., Krishnamoorthi, S., Fung, T.Y., Lu, K., Gaurav, I., Yang, Z., Su, C.-F., Lau, K.-F., Zhang, K., Ng, R.C.-L., Lian, Q., Cheung, K.-H., Ye, K., Chen, H.J., Li, M., 2023. Fe65-engineered neuronal exosomes encapsulating corynoxine-B ameliorate cognition and pathology of Alzheimer's disease. Signal Transduct. Target Ther. 8, 404. https://doi.org/10.1038/s41392-023-01657-4.
Jack, Jr, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Contributors, Elliott, C., Masliah, E., Ryan, L., Silverberg, N., 2018. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer'S. Dement. 14, 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.
Jalili, C., Kiani, A., Gholami, M., Bahrehmand, F., Fakhri, S., Kakehbaraei, S., Kakebaraei, S., 2023. Brain targeting based nanocarriers loaded with resveratrol in Alzheimer's disease: A review. IET Nanobiotechnol 17, 154–170. https://doi.org/10.1049/nbt2.12127.
Jankovic, A., Chaudhary, G., Goia, F., 2021. Designing the design of experiments (DOE) – An investigation on the influence of different factorial designs on the characterization of complex systems. Energy Build. 250, 111298. https://doi.org/10.1016/j.enbuild.2021.111298.
Jann, M.W., 2000. Rivastigmine, a new-generation cholinesterase inhibitor for the treatment of Alzheimer's disease. Pharmacotherapy 20, 1–12. https://doi.org/10.1592/phco.20.1.1.34664.
Javaid, M., Haleem, A., Pratap Singh, R., Suman, R., Rab, S., 2022. Significance of machine learning in healthcare: Features, pillars and applications. Int. J. Intell. Netw. 3, 58–73. https://doi.org/10.1016/j.ijin.2022.05.002.
Jha, S.K., Jha, N.K., Kumar, D., Ambasta, R.K., Kumar, P., 2017. Linking mitochondrial dysfunction, metabolic syndrome and stress signaling in Neurodegeneration. Biochim. Et. Biophys. Acta (BBA) - Mol. Basis Dis., Oxid. Stress Mitochondrial Qual. Diabetes/Obes. Crit. Illn. Spectr. Dis. 1863, 1132–1146. https://doi.org/10.1016/j.bbadis.2016.06.015.
Jia, Y., Zhang, X., Yu, J., Han, J., Yu, T., Shi, J., Zhao, L., Nie, K., 2017. Acupuncture for patients with mild to moderate Alzheimer's disease: a randomized controlled trial. BMC Complement. Altern. Med. 17, 556. https://doi.org/10.1186/s12906-017-2064-x.
Jiang, C., Meng, L., Yang, B., Luo, X., 2020. Application of CRISPR/Cas9 gene editing technique in the study of cancer treatment. Clin. Genet 97, 73–88. https://doi.org/10.1111/cge.13589.
Jiang, D., Yang, X., Li, M., Wang, Yan, Wang, Yong, 2015. Efficacy and safety of galantamine treatment for patients with Alzheimer's disease: a meta-analysis of randomized controlled trials. J. Neural Transm. (Vienna) 122, 1157–1166. https://doi.org/10.1007/s00702-014-1358-0.
Kabir, Md.T., Uddin, Md.S., Mamun, A.A., Jeandet, P., Aleya, L., Mansouri, R.A., Ashraf, G.M., Mathew, B., Bin-Jumah, M.N., Abdel-Daim, M.M., 2020. Combination Drug Therapy for the Management of Alzheimer's Disease. Int J. Mol. Sci. 21, 3272. https://doi.org/10.3390/ijms21093272.
Kadavath, H., Hofele, R.V., Biernat, J., Kumar, S., Tepper, K., Urlaub, H., Mandelkow, E., Zweckstetter, M., 2015. Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. Proc. Natl. Acad. Sci. USA 112, 7501–7506. https://doi.org/10.1073/pnas.1504081112.
Kakuda, N., Takami, M., Okochi, M., Kasuga, K., Ihara, Y., Ikeuchi, T., 2021. Switched Aβ43 generation in familial Alzheimer's disease with presenilin 1 mutation. Transl. Psychiatry 11, 558. https://doi.org/10.1038/s41398-021-01684-1.
Kamatham, P.T., Shukla, R., Khatri, D.K., Vora, L.K., 2024b. Pathogenesis, diagnostics, and therapeutics for Alzheimer's disease: Breaking the memory barrier. Ageing Res. Rev. 101, 102481. https://doi.org/10.1016/j.arr.2024.102481.
Kamatham, P.T., Shukla, R., Khatri, D.K., Vora, L.K., 2024a. Pathogenesis, diagnostics, and therapeutics for Alzheimer's disease: Breaking the memory barrier. Ageing Res. Rev. 101, 102481. https://doi.org/10.1016/j.arr.2024.102481.
Kandiah, N., Pai, M.-C., Senanarong, V., Looi, I., Ampil, E., Park, K.W., Karanam, A.K., Christopher, S., 2017. Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. Clin. Inter. Aging 12, 697–707. https://doi.org/10.2147/CIA.S129145.
Kandimalla, R., Saeed, M., Tyagi, N., Gupta, R.C., Aqil, F., 2023. Exosome-based approaches in the management of Alzheimer's disease. Neurosci. Biobehav. Rev. 144, 104974. https://doi.org/10.1016/j.neubiorev.2022.104974.
Keshavan, A., Heslegrave, A., Zetterberg, H., Schott, J.M., 2018. Stability of blood-based biomarkers of Alzheimer's disease over multiple freeze-thaw cycles. Alzheimers Dement (Amst. 10, 448–451. https://doi.org/10.1016/j.dadm.2018.06.001.
Kim, S., Nam, Y., Kim, H. soo, Jung, H., Jeon, S.G., Hong, S.B., Moon, M., 2022. Alteration of Neural Pathways and Its Implications in Alzheimer's Disease. Biomedicines 10, 845. https://doi.org/10.3390/biomedicines10040845.
Knight, R., Khondoker, M., Magill, N., Stewart, R., Landau, S., 2018. A Systematic Review and Meta-Analysis of the Effectiveness of Acetylcholinesterase Inhibitors and Memantine in Treating the Cognitive Symptoms of Dementia. Dement Geriatr. Cogn. Disord. 45, 131–151. https://doi.org/10.1159/000486546.
Knopman, D.S., 2008. Clinical trial design issues in mild to moderate Alzheimer disease. Cogn. Behav. Neurol. 21, 197–201. https://doi.org/10.1097/WNN.0b013e318190cf75.
Knopman, D.S., Jones, D.T., Greicius, M.D., 2021. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimers Dement 17, 696–701. https://doi.org/10.1002/alz.12213.
Kokare, C., Koli, D., Gadhave, D., Mote, C., Khandekar, G., 2020. Efavirenz-loaded intranasal microemulsion for crossing blood-CNS interfaces in neuronal-AIDS: pharmacokinetic and *in vivo* safety evaluation. Pharm. Dev. Technol. 25, 28–39. https://doi.org/10.1080/10837450.2019.1659818.
Kumar, A., Singh, A., Ekavali, 2015. A review on Alzheimer's disease pathophysiology and its management: an update (null). Pharm. Rep. 67, 195–203. https://doi.org/10.1016/j.pharep.2014.09.004.
La Joie, R., Perrotin, A., de La Sayette, V., Egret, S., Doeuvre, L., Belliard, S., Eustache, F., Desgranges, B., Chételat, G., 2013. Hippocampal subfield volumetry in mild

cognitive impairment, Alzheimer's disease and semantic dementia. NeuroImage: Clin. 3, 155–162. https://doi.org/10.1016/j.nicl.2013.08.007.
Lally, C., Joyce, K., Pandit, A., 2022. Biomaterials enhancing performance of cell and nucleic-acid therapies: An opportunity in the brain. Biomater. Biosyst. 5, 100036. https://doi.org/10.1016/j.bbiosy.2021.100036.
Lanoiselée, H.-M., Nicolas, G., Wallon, D., Rovelet-Lecrux, A., Lacour, M., Rousseau, S., Richard, A.-C., Pasquier, F., Rollin-Sillaire, A., Martinaud, O., Quillard-Muraine, M., de la Sayette, V., Boutoleau-Bretonniere, C., Etcharry-Bouyx, F., Chauviré, V., Sarazin, M., le Ber, I., Epelbaum, S., Jonveaux, T., Rouaud, O., Ceccaldi, M., Félician, O., Godefroy, O., Formaglio, M., Croisile, B., Auriacombe, S., Chamard, L., Vincent, J.-L., Sauvée, M., Marelli-Tosi, C., Gabelle, A., Ozsancak, C., Pariente, J., Paquet, C., Hannequin, D., Campion, D., 2017. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med 14, e1002270. https://doi.org/10.1371/journal.pmed.1002270.
Lee, J.K., Schuchman, E.H., Jin, H.K., Bae, J., 2012. Soluble CCL5 derived from bone marrow-derived mesenchymal stem cells and activated by amyloid β ameliorates Alzheimer's disease in mice by recruiting bone marrow-induced microglia immune responses. Stem Cells 30, 1544–1555. https://doi.org/10.1002/stem.1125.
Lee, M.J., Lee, J.H., Rubinsztein, D.C., 2013. Tau degradation: the ubiquitin-proteasome system versus the autophagy-lysosome system. Prog. Neurobiol. 105, 49–59. https://doi.org/10.1016/j.pneurobio.2013.03.001.
Lenina, O.A., Zueva, I.V., Zobov, V.V., Semenov, V.E., Masson, P., Petrov, K.A., 2020. Slow-binding reversible inhibitor of acetylcholinesterase with long-lasting action for prophylaxis of organophosphate poisoning. Sci. Rep. 10, 16611. https://doi.org/10.1038/s41598-020-73822-6.
Levine, S.Z., Yoshida, K., Goldberg, Y., Samara, M., Cipriani, A., Efthimiou, O., Iwatsubo, T., Leucht, S., Furukawa, T.A., 2021. Linking the Mini-Mental State Examination, the Alzheimer's Disease Assessment Scale–Cognitive Subscale and the Severe Impairment Battery: evidence from individual participant data from five randomised clinical trials of donepezil. Evid. Based Ment. Health 24, 56–61. https://doi.org/10.1136/ebmental-2020-300184.
Li, D.-D., Zhang, Y.-H., Zhang, W., Zhao, P., 2019. Meta-Analysis of Randomized Controlled Trials on the Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease. Front Neurosci. 13, 472. https://doi.org/10.3389/fnins.2019.00472.
Li, X., Feng, X., Sun, X., Hou, N., Han, F., Liu, Y., 2022. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. Front. Aging Neurosci. 14. https://doi.org/10.3389/fnagi.2022.937486.
Li, Y.-B., Fu, Q., Guo, M., Du, Y., Chen, Y., Cheng, Y., 2024. MicroRNAs: pioneering regulators in Alzheimer's disease pathogenesis, diagnosis, and therapy. Transl. Psychiatry 14, 367. https://doi.org/10.1038/s41398-024-03075-8.
Liss, J.L., Assunção, S.S., Cummings, J., Atri, A., Geldmacher, D.S., Candela, S.F., Devanand, D.P., Fillit, H.M., Susman, J., Mintzer, J., Bittner, T., Brunton, S.A., Kerwin, D.R., Jackson, W.C., Small, G.W., Grossberg, G.T., Clevenger, C.K., Cotter, V., Stefanacci, R., Wise-Brown, A., Sabbagh, M.N., 2021. Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis. J. Intern. Med. 290, 310. https://doi.org/10.1111/joim.13244.
Liston, D.R., Nielsen, J.A., Villalobos, A., Chapin, D., Jones, S.B., Hubbard, S.T., Shalaby, I.A., Ramirez, A., Nason, D., White, W.F., 2004. Pharmacology of selective acetylcholinesterase inhibitors: implications for use in Alzheimer's disease. Eur. J. Pharm. 486, 9–17. https://doi.org/10.1016/j.ejphar.2003.11.080.
Liu, C.-C., Kanekiyo, T., Xu, H., Bu, G., 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. Nat. Rev. Neurol. 9, 106–118. https://doi.org/10.1038/nrneurol.2012.263.
Liu, J., Chang, L., Song, Y., Li, H., Wu, Y., 2019. The Role of NMDA Receptors in Alzheimer's Disease. Front Neurosci. 13, 43. https://doi.org/10.3389/fnins.2019.00043.
Liu, Y.-N., Qin, Y., Wu, B., Peng, H., Li, M., Luo, H., Liu, L.-L., 2022. DNA methylation in polycystic ovary syndrome: Emerging evidence and challenges. Reprod. Toxicol. 111, 11–19. https://doi.org/10.1016/j.reprotox.2022.04.010.
Liu, Z., Cheng, L., Cao, W., Shen, C., Qiu, Y., Li, C., Xiong, Y., Yang, S.B., Chen, Z., Yin, X., Zhang, X., 2024. Present and future use of exosomes containing proteins and RNAs in neurodegenerative diseases for synaptic function regulation: A comprehensive review. Int J. Biol. Macromol. 280, 135826. https://doi.org/10.1016/j.ijbiomac.2024.135826.
Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Ogunniyi, A., Orgeta, V., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L.S., Selbæk, G., Teri, L., Mukadam, N., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet (Lond., Engl.) 396, 413. https://doi.org/10.1016/S0140-6736(20)30367-6.
Livingston, G., Huntley, J., Liu, K.Y., Costafreda, S.G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., Brayne, C., Fox, N.C., Ferri, C.P., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Nakasujja, N., Rockwood, K., Samus, Q., Shirai, K., Singh-Manoux, A., Schneider, L.S., Walsh, S., Yao, Y., Sommerlad, A., Mukadam, N., 2024. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet 404, 572–628. https://doi.org/10.1016/S0140-6736(24)01296-0.
Loewa, A., Feng, J.J., Hedtrich, S., 2023. Human disease models in drug development. Nat. Rev. Bioeng. 1, 15. https://doi.org/10.1038/s44222-023-00063-3.
Longfield, S.F., Gormal, R.S., Feller, M., Parutto, P., Reingruber, J., Wallis, T.P., Joensuu, M., Augustine, G.J., Martínez-Mármol, R., Holcman, D., Meunier, F.A., 2024. Synapsin 2a tetramerisation selectively controls the presynaptic nanoscale organisation of reserve synaptic vesicles. Nat. Commun. 15, 2217. https://doi.org/10.1038/s41467-024-46256-1.
Lopez-Barbosa, N., Garcia, J.G., Cifuentes, J., Castro, L.M., Vargas, F., Ostos, C., Cardona-Gomez, G.P., Hernandez, A.M., Cruz, J.C., 2020. Multifunctional magnetite nanoparticles to enable delivery of siRNA for the potential treatment of Alzheimer's. Drug Deliv. 27, 864–875. https://doi.org/10.1080/10717544.2020.1775724.
Lottes, A.E., Cavanaugh, K.J., Chan, Y.Y.-F., Devlin, V.J., Goergen, C.J., Jean, R., Linnes, J.C., Malone, M., Peat, R., Reuter, D.G., Taylor, K., Wodicka, G.R., 2022. Navigating the Regulatory Pathway for Medical Devices—a Conversation with the FDA, Clinicians, Researchers, and Industry Experts. J. Cardiovasc Transl. Res 15, 927–943. https://doi.org/10.1007/s12265-022-10232-1.
Maggiore, A., Latina, V., D'Erme, M., Amadoro, G., Coccurello, R., 2024. Non-canonical pathways associated to Amyloid beta and tau protein dyshomeostasis in Alzheimer's disease: A narrative review. Ageing Res. Rev. 102, 102578. https://doi.org/10.1016/j.arr.2024.102578.
Maguire, C.A., Ramirez, S.H., Merkel, S.F., Sena-Esteves, M., Breakefield, X.O., 2014. Gene therapy for the nervous system: challenges and new strategies. Neurotherapeutics 11, 817–839. https://doi.org/10.1007/s13311-014-0299-5.
Manczak, M., Kandimalla, R., Fry, D., Sesaki, H., Reddy, P.H., 2016. Protective effects of reduced dynamin-related protein 1 against amyloid beta-induced mitochondrial dysfunction and synaptic damage in Alzheimer's disease. Hum. Mol. Genet 25, 5148–5166. https://doi.org/10.1093/hmg/ddw330.
Mandelkow, E.-M., Mandelkow, E., 2012. Biochemistry and Cell Biology of Tau Protein in Neurofibrillary Degeneration. Cold Spring Harb. Perspect. Med 2, a006247. https://doi.org/10.1101/cshperspect.a006247.
Marucci, G., Buccioni, M., Ben, D.D., Lambertucci, C., Volpini, R., Amenta, F., 2021. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. Neuropharmacology 190, 108352. https://doi.org/10.1016/j.neuropharm.2020.108352.
Matuz-Mares, D., González-Andrade, M., Araiza-Villanueva, M.G., Vilchis-Landeros, M. M., Vázquez-Meza, H., 2022. Mitochondrial Calcium: Effects of Its Imbalance in Disease. Antioxid. (Basel) 11, 801. https://doi.org/10.3390/antiox11050801.
Medeiros, R., Baglietto-Vargas, D., LaFerla, F.M., 2010. The Role of Tau in Alzheimer's Disease and Related Disorders. CNS Neurosci. Ther. 17, 514–524. https://doi.org/10.1111/j.1755-5949.2010.00177.x.
Mendez, M.F., 2019. Early-onset Alzheimer Disease and Its Variants. Contin. (Minne Minn. 25, 34–51. https://doi.org/10.1212/CON.0000000000000687.
Miao, J., Ma, H., Yang, Y., Liao, Y., Lin, C., Zheng, J., Yu, M., Lan, J., 2023. Microglia in Alzheimer's disease: pathogenesis, mechanisms, and therapeutic potentials. Front Aging Neurosci. 15, 1201982. https://doi.org/10.3389/fnagi.2023.1201982.
Mick, P., Kabir, R., Karunatilake, M., Kathleen Pichora-Fuller, M., Young, T.-L., Sosero, Y., Gan-or, Z., Wittich, W., Phillips, N.A., 2024. *APOE*-ε4 is not associated with pure-tone hearing thresholds, visual acuity or cognition, cross-sectionally or over 3 years of follow up in the Canadian Longitudinal Study on Aging. Neurobiol. Aging 138, 72–82. https://doi.org/10.1016/j.neurobiolaging.2024.01.006.
Mietelska-Porowska, A., Wasik, U., Goras, M., Filipek, A., Niewiadomska, G., 2014. Tau Protein Modifications and Interactions: Their Role in Function and Dysfunction. Int J. Mol. Sci. 15, 4671–4713. https://doi.org/10.3390/ijms15034671.
Moloney, C.M., Lowe, V.J., Murray, M.E., 2021. Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. Alzheimers Dement 17, 1554–1574. https://doi.org/10.1002/alz.12321.
Mony, L., Paoletti, P., 2023. Mechanisms of NMDA receptor regulation. Curr. Opin. Neurobiol. 83, 102815. https://doi.org/10.1016/j.conb.2023.102815.
Morris, G.P., Clark, I.A., Vissel, B., 2018. Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease. Acta Neuropathol. 136, 663–689. https://doi.org/10.1007/s00401-018-1918-8.
Motebennur, S.L., Nandeshwarappa, B.P., Katagi, M.S., 2023. Drug Candidates for the Treatment of Alzheimer's Disease: New Findings from 2021 and 2022. Drugs Drug Candidates 2, 571–590. https://doi.org/10.3390/ddc2030030.
Moustafa, B., Trifan, G., Isasi, C.R., Lipton, R.B., Sotres-Alvarez, D., Cai, J., Tarraf, W., Stickel, A., Mattei, J., Talavera, G.A., Daviglus, M.L., González, H.M., Testai, F.D., 2022. Association of Mediterranean Diet With Cognitive Decline Among Diverse Hispanic or Latino Adults From the Hispanic Community Health Study/Study of Latinos. JAMA Netw. Open 5, e2221982. https://doi.org/10.1001/jamanetworkopen.2022.21982.
Mummery, C.J., Börjesson-Hanson, A., Blackburn, D.J., Vijverberg, E.G.B., De Deyn, P.P., Ducharme, S., Jonsson, M., Schneider, A., Rinne, J.O., Ludolph, A.C., Bodenschatz, R., Kordasiewicz, H., Swayze, E.E., Fitzsimmons, B., Mignon, L., Moore, K.M., Yun, C., Baumann, T., Li, D., Norris, D.A., Crean, R., Graham, D.L., Huang, E., Ratti, E., Bennett, C.F., Junge, C., Lane, R.M., 2023. Tau-targeting antisense oligonucleotide MAPTRx in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. Nat. Med 29, 1437–1447. https://doi.org/10.1038/s41591-023-02326-3.
Nakano, M., Kubota, K., Kobayashi, E., Chikenji, T.S., Saito, Y., Konari, N., Fujimiya, M., 2020. Bone marrow-derived mesenchymal stem cells improve cognitive impairment in an Alzheimer's disease model by increasing the expression of microRNA-146a in hippocampus. Sci. Rep. 10, 10772. https://doi.org/10.1038/s41598-020-67460-1.
Nandi, A., Counts, N., Bröker, J., Malik, S., Chen, S., Han, R., Klusty, J., Seligman, B., Tortorice, D., Vigo, D., Bloom, D.E., 2024. Cost of care for Alzheimer's disease and related dementias in the United States: 2016 to 2060. NPJ Aging 10, 13. https://doi.org/10.1038/s41514-024-00136-6.
Nangare, S., Patil, P., 2022. Nanoarchitectured Bioconjugates and Bioreceptors Mediated Surface Plasmon Resonance Biosensor for In Vitro Diagnosis of Alzheimer's Disease: Development and Future Prospects. Crit. Rev. Anal. Chem. 52, 1139–1169. https://doi.org/10.1080/10408347.2020.1864716.

Nasb, M., Tao, W., Chen, N., 2024. Alzheimer's Disease Puzzle: Delving into Pathogenesis Hypotheses. Aging Dis. 15, 43–73. https://doi.org/10.14336/AD.2023.0608.
Naziris, N., Demetzos, C., 2021. Liposomes: Production Methods and Application in Alzheimer's Disease. Adv. Exp. Med Biol. 1339, 385–394. https://doi.org/10.1007/978-3-030-78787-5_48.
Newman, M., Musgrave, F.I., Lardelli, M., 2007. Alzheimer disease: Amyloidogenesis, the presenilins and animal models. Biochim. Et. Biophys. Acta (BBA) - Mol. Basis Dis. 1772, 285–297. https://doi.org/10.1016/j.bbadis.2006.12.001.
Nimmo, J., Byrne, R.A.J., Daskoulidou, N., Watkins, L.M., Carpanini, S.M., Zelek, W.M., Morgan, B.P., 2024. The complement system in neurodegenerative diseases. Clin. Sci. (Lond.) 138, 387–412. https://doi.org/10.1042/CS20230513.
Olaso-Gonzalez, G., Inzitari, M., Bellelli, G., Morandi, A., Barcons, N., Viña, J., 2022. Impact of supplementation with vitamins B6, B12, and/or folic acid on the reduction of homocysteine levels in patients with mild cognitive impairment: A systematic review. IUBMB Life 74, 74–84. https://doi.org/10.1002/iub.2507.
Olivares, D., Deshpande, V.K., Shi, Y., Lahiri, D.K., Greig, N.H., Rogers, J.T., Huang, X., 2012. N-Methyl D-Aspartate (NMDA) Receptor Antagonists and Memantine Treatment for Alzheimer's Disease, Vascular Dementia and Parkinson's Disease. Curr. Alzheimer Res 9, 746–758.
Ongnok, B., Khuanjing, T., Chunchai, T., Kerdphoo, S., Jaiwongkam, T., Chattipakorn, N., Chattipakorn, S.C., 2021. Donepezil provides neuroprotective effects against brain injury and Alzheimer's pathology under conditions of cardiac ischemia/reperfusion injury. Biochim Biophys. Acta Mol. Basis Dis. 1867, 165975. https://doi.org/10.1016/j.bbadis.2020.165975.
Onor, M.L., Trevisiol, M., Aguglia, E., 2007. Rivastigmine in the treatment of Alzheimer's disease: an update. Clin. Inter. Aging 2, 17–32.
Ordóñez-Gutiérrez, L., Wandosell, F., 2020. Nanoliposomes as a Therapeutic Tool for Alzheimer's Disease. Front Synaptic Neurosci. 12, 20. https://doi.org/10.3389/fnsyn.2020.00020.
Ott, B.R., Owens, N.J., 1998. Complementary and Alternative Medicines for Alzheimer's Disease. J. Geriatr. Psychiatry Neurol. 11, 163–173. https://doi.org/10.1177/089198879901100401.
Pahlavani, H.A., 2023. Exercise therapy to prevent and treat Alzheimer's disease. Front. Aging Neurosci. 15. https://doi.org/10.3389/fnagi.2023.1243869.
Pallmann, P., Bedding, A.W., Choodari-Oskooei, B., Dimairo, M., Flight, L., Hampson, L. V., Holmes, J., Mander, A.P., Odondi, L., Sydes, M.R., Villar, S.S., Wason, J.M.S., Weir, C.J., Wheeler, G.M., Yap, C., Jaki, T., 2018. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med. 16, 29. https://doi.org/10.1186/s12916-018-1017-7.
Pantwalawalkar, J., Chandankar, S., Tade, R., Khan, Z., Shaikh, M., Powar, T., Patil, P., Sugandhi, V., Nangare, S., 2022. Graphene quantum dot based ultrasensitive probe for biosensing of prostate cancer biomarkers: current updates and future challenges. Adv. Nat. Sci: Nanosci. Nanotechnol. 13, 013001. https://doi.org/10.1088/2043-6262/ac5e35.
Pardridge, W.M., 2009. Alzheimer's disease drug development and the problem of the blood-brain barrier. Alzheimer'S. Dement.: J. Alzheimer'S. Assoc. 5, 427. https://doi.org/10.1016/j.jalz.2009.06.003.
Parsons, C.G., Stöffler, A., Danysz, W., 2007. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system–too little activation is bad, too much is even worse. Neuropharmacology 53, 699–723. https://doi.org/10.1016/j.neuropharm.2007.07.013.
Passeri, E., Elkhoury, K., Morsink, M., Broersen, K., Linder, M., Tamayol, A., Malaplate, C., Yen, F.T., Arab-Tehrany, E., 2022. Alzheimer's Disease: Treatment Strategies and Their Limitations. Int J. Mol. Sci. 23, 13954. https://doi.org/10.3390/ijms232213954.
Peng, Y., Jin, H., Xue, Y., Chen, Q., Yao, S., Du, M., Liu, S., 2023. Current and future therapeutic strategies for Alzheimer's disease: an overview of drug development bottlenecks. Front Aging Neurosci. 15, 1206572. https://doi.org/10.3389/fnagi.2023.1206572.
Perry, E.K., Pickering, A.T., Wang, W.W., Houghton, P.J., Perry, N.S.L., 1999. Medicinal Plants and Alzheimer's Disease: from Ethnobotany to Phytotherapy. J. Pharm. Pharmacol. 51, 527–534. https://doi.org/10.1211/0022357991772808.
Peruzzo, R., Costa, R., Bachmann, M., Leanza, L., Szabò, I., 2020. Mitochondrial Metabolism, Contact Sites and Cellular Calcium Signaling: Implications for Tumorigenesis. Cancers (Basel) 12, 2574. https://doi.org/10.3390/cancers12092574.
Phillips, M.C.L., Deprez, L.M., Mortimer, G.M.N., Murtagh, D.K.J., McCoy, S., Mylchreest, R., Gilbertson, L.J., Clark, K.M., Simpson, P.V., McManus, E.J., Oh, J.-E., Yadavaraj, S., King, V.M., Pillai, A., Romero-Ferrando, B., Brinkhuis, M., Copeland, B.M., Samad, S., Liao, S., Schepel, J.A.C., 2021. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. Alzheimer'S. Res. Ther. 13, 51. https://doi.org/10.1186/s13195-021-00783-x.
Pichardo-Rojas, D., Pichardo-Rojas, P.S., Cornejo-Bravo, J.M., Serrano-Medina, A., 2023. Memantine as a neuroprotective agent in ischemic stroke: Preclinical and clinical analysis. Front. Neurosci. 17. https://doi.org/10.3389/fnins.2023.1096372.
Pires, M., Rego, A.C., 2023. Apoe4 and Alzheimer's Disease Pathogenesis—Mitochondrial Deregulation and Targeted Therapeutic Strategies. Int J. Mol. Sci. 24, 778. https://doi.org/10.3390/ijms24010778.
Prabha, S., Sajad, M., Hasan, G.M., Islam, A., Imtaiyaz Hassan, M., Thakur, S.C., 2024. Recent advancement in understanding of Alzheimer's disease: Risk factors, subtypes, and drug targets and potential therapeutics. Ageing Res. Rev. 101, 102476. https://doi.org/10.1016/j.arr.2024.102476.
Prajapati, V., Shinde, S., Shrivastav, P., Prajapati, B.G., 2024. Chapter 7 - New biologicals and biomaterials in the therapy of Alzheimer's disease, in. In: Prajapati, B.G., Chellappan, D.K., Kendre, P.N. (Eds.), Alzheimer's Disease and Advanced Drug Delivery Strategies. Academic Press, pp. 93–114. ⟨https://doi.org/10.1016/B978-0-443-13205-6.00016-9⟩.
Preethy H, A., Rajendran, K., Sukumar, A.J., Krishnan, U.M., 2024. Emerging paradigms in Alzheimer's therapy. Eur. J. Pharmacol. 981, 176872. https://doi.org/10.1016/j.ejphar.2024.176872.
Puzzo, D., Lee, L., Palmeri, A., Calabrese, G., Arancio, O., 2014. Behavioral assays with mouse models of Alzheimer's disease: practical considerations and guidelines. Biochem Pharm. 88, 450–467. https://doi.org/10.1016/j.bcp.2014.01.011.
Qi, Y., Guo, L., Jiang, Y., Shi, Y., Sui, H., Zhao, L., 2020. Brain delivery of quercetin-loaded exosomes improved cognitive function in AD mice by inhibiting phosphorylated tau-mediated neurofibrillary tangles. Drug Deliv. 27, 745–755. https://doi.org/10.1080/10717544.2020.1762262.
Qin, H.-Y., Liu, J.-Y., Fang, C.-L., Deng, Y.-P., Zhang, Y., 2023. DNA methylation: The epigenetic mechanism of Alzheimer's disease. Ibrain 9, 463–472. https://doi.org/10.1002/ibra.12121.
Quan, M., Cao, S., Wang, Q., Wang, S., Jia, J., 2023. Genetic Phenotypes of Alzheimer's Disease: Mechanisms and Potential Therapy. Phenomics 3, 333–349. https://doi.org/10.1007/s43657-023-00098-x.
Rahman, S., Haque, T.N., Sugandhi, V.V., Saraswat, A.L., Xin, X., Cho, H., 2023. Topical Cream Carrying Drug-Loaded Nanogels for Melanoma Treatment. Pharm. Res 40, 2291–2301. https://doi.org/10.1007/s11095-023-03506-z.
Rajmohan, R., Reddy, P.H., 2017. Amyloid Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons. J. Alzheimers Dis. 57, 975–999. https://doi.org/10.3233/JAD-160612.
Ranjan, S., Choudhary, P., Shivalkar, S., Dwivedi, S., Singh, S., 2025. Potential of hyaluronic acid and collagen-based scaffolds in promoting stem cell neuronal differentiation for neuroregenerative therapies: A review. Int. J. Biol. Macromol. 309, 142981. https://doi.org/10.1016/j.ijbiomac.2025.142981.
Rao, Y.L., Ganaraja, B., Murlimanju, B.V., Joy, T., Krishnamurthy, A., Agrawal, A., 2022. Hippocampus and its involvement in Alzheimer's disease: a review. 3 Biotech 12, 55. https://doi.org/10.1007/s13205-022-03123-4.
Raulin, A.-C., Doss, S.V., Trottier, Z.A., Ikezu, T.C., Bu, G., Liu, C.-C., 2022. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol. Neurodegener. 17, 72. https://doi.org/10.1186/s13024-022-00574-4.
Rawat, P., Sehar, U., Bisht, J., Selman, A., Culberson, J., Reddy, P.H., 2022. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. Int J. Mol. Sci. 23, 12841. https://doi.org/10.3390/ijms232112841.
Reed, M.S., Ferré, M., Martin-Ortega, J., Blanche, R., Lawford-Rolfe, R., Dallimer, M., Holden, J., 2021. Evaluating impact from research: A methodological framework. Res. Policy 50, 104147. https://doi.org/10.1016/j.respol.2020.104147.
Reitz, C., Rogaeva, E., Beecham, G.W., 2020. Late-onset vs nonmendelian early-onset Alzheimer disease. Neurol. Genet. 6, e512. https://doi.org/10.1212/NXG.0000000000000512.
Revdekar, A., Shende, P., 2021. Block copolymers in Alzheimer's disease therapy: A perceptive to revolutionize biomaterials. J. Control. Release 340, 271–281. https://doi.org/10.1016/j.jconrel.2021.11.007.
Ringman, J.M., Goate, A., Masters, C.L., Cairns, N.J., Danek, A., Graff-Radford, N., Ghetti, B., Morris, J.C., 2014. Genetic Heterogeneity in Alzheimer Disease and Implications for Treatment Strategies. Curr. Neurol. Neurosci. Rep. 14, 499. https://doi.org/10.1007/s11910-014-0499-8.
Robbins, M., Clayton, E., Kaminski Schierle, G.S., 2021. Synaptic tau: A pathological or physiological phenomenon? Acta Neuropathol. Commun. 9, 1–30. https://doi.org/10.1186/s40478-021-01246-y.
Rogers, S.L., Doody, R.S., Mohs, R.C., Friedhoff, L.T., 1998. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch. Intern Med 158, 1021–1031. https://doi.org/10.1001/archinte.158.9.1021.
Roy, R.G., Mandal, P.K., Maroon, J.C., 2023. Oxidative Stress Occurs Prior to Amyloid Aβ Plaque Formation and Tau Phosphorylation in Alzheimer's Disease: Role of Glutathione and Metal Ions. ACS Chem. Neurosci. 14, 2944–2954. https://doi.org/10.1021/acschemneuro.3c00486.
Rujeedawa, T., Félez, E.C., Clare, I.C.H., Fortea, J., Strydom, A., Rebillat, A.-S., Coppus, A., Levin, J., Zaman, S.H., 2021. The Clinical and Neuropathological Features of Sporadic (Late-Onset) and Genetic Forms of Alzheimer's Disease. J. Clin. Med. 10, 4582. https://doi.org/10.3390/jcm10194582.
Santos, C.Y., Snyder, P.J., Wu, W.-C., Zhang, M., Echeverria, A., Alber, J., 2017. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement (Amst. 7, 69–87. https://doi.org/10.1016/j.dadm.2017.01.005.
Schneider, L.S., 2022. Editorial: Aducanumab Trials EMERGE But Don't ENGAGE. J. Prev. Alzheimers Dis. 9, 193–196. https://doi.org/10.14283/jpad.2022.37.
Se Thoe, E., Fauzi, A., Tang, Y.Q., Chamyuang, S., Chia, A.Y.Y., 2021. A review on advances of treatment modalities for Alzheimer's disease. Life Sci. 276, 119129. https://doi.org/10.1016/j.lfs.2021.119129.
Segovia-Zafra, A., Di Zeo-Sánchez, D.E., López-Gómez, C., Pérez-Valdés, Z., García-Fuentes, E., Andrade, R.J., Lucena, M.I., Villanueva-Paz, M., 2021. Preclinical models of idiosyncratic drug-induced liver injury (iDILI): Moving towards prediction. Acta Pharm. Sin. B 11, 3685–3726. https://doi.org/10.1016/j.apsb.2021.11.013.
Sehar, U., Rawat, P., Reddy, A.P., Kopel, J., Reddy, P.H., 2022. Amyloid Beta in Aging and Alzheimer's Disease. Int. J. Mol. Sci. 23, 12924. https://doi.org/10.3390/ijms232112924.
Sengupta, U., Kayed, R., 2022. Amyloid β, Tau, and α-Synuclein aggregates in the pathogenesis, prognosis, and therapeutics for neurodegenerative diseases. Prog. Neurobiol. 214, 102270. https://doi.org/10.1016/j.pneurobio.2022.102270.

Seyhan, A.A., 2019. Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles. Transl. Med. Commun. 4, 18. https://doi.org/10.1186/s41231-019-0050-7.

Shah, D., Mahurkar, N., Gadhave, D., Nikhate, R., Kakad, K., 2023. Hepatoprotective activity of *Balsamodendron mukul* extract against Paracetamol-induced liver toxicity in rats: In vivo pharmacological and toxicological evaluation. Ann. Pharm. Françaises 81, 814–825. https://doi.org/10.1016/j.pharma.2023.04.003.

Sharma, V.K., Mehta, V., Singh, T.G., 2020. Alzheimer's Disorder: Epigenetic Connection and Associated Risk Factors. Curr. Neuropharmacol. 18, 740–753. https://doi.org/10.2174/1570159X18666200128125641.

Shin, J.-H., 2022. Dementia Epidemiology Fact Sheet 2022. Ann. Rehabil. Med. 46, 53. https://doi.org/10.5535/arm.22027.

Sin, M.-K., Zamrini, E., Ahmed, A., Nho, K., Hajjar, I., 2023. Anti-Amyloid Therapy, AD, and ARIA: Untangling the Role of CAA. J. Clin. Med 12, 6792. https://doi.org/10.3390/jcm12216792.

Singh, B., Day, C.M., Abdella, S., Garg, S., 2024. Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. J. Control. Release 367, 402–424. https://doi.org/10.1016/j.jconrel.2024.01.047.

Sinsky, J., Pichlerova, K., Hanes, J., 2021. Tau Protein Interaction Partners and Their Roles in Alzheimer's Disease and Other Tauopathies. Int J. Mol. Sci. 22, 9207. https://doi.org/10.3390/ijms22179207.

Slika, H., Shahani, A., Gattu, K., Mundrathi, V., Solan, A.A., Gonzalez, B., Haque, T.N., Rahman, S., Sugandhi, V.V., Lee, J., Velarde, E., Alomari, S., Pacis, V.L., Brem, H., Tyler, B., Xin, X., Cho, H., 2025. Intracranial Nanogel Pellets Carrying Temozolomide and Paclitaxel for Adjuvant Brain Cancer Therapy. Mol. Pharm. 22, 131–141. https://doi.org/10.1021/acs.molpharmaceut.4c00708.

Soufizadeh, P., Mansouri, V., Ahmadbeigi, N., 2024. A review of animal models utilized in preclinical studies of approved gene therapy products: trends and insights. Lab Anim. Res 40, 17. https://doi.org/10.1186/s42826-024-00195-6.

Sperling, R., Mormino, E., Johnson, K., 2014. The evolution of preclinical Alzheimer's disease: Implications for prevention trials. Neuron 84, 608. https://doi.org/10.1016/j.neuron.2014.10.038.

Sperling, R.A., Jack, C.R., Black, S.E., Frosch, M.P., Greenberg, S.M., Hyman, B.T., Scheltens, P., Carrillo, M.C., Thies, W., Bednar, M.M., Black, R.S., Brashear, H.R., Grundman, M., Siemers, E.R., Feldman, H.H., Schindler, R.J., 2011. Amyloid Related Imaging Abnormalities (ARIA) in Amyloid Modifying Therapeutic Trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement 7, 367–385. https://doi.org/10.1016/j.jalz.2011.05.2351.

Srikanth, M., Kessler, J.A., 2012. Nanotechnology—novel therapeutics for CNS disorders. Nat. Rev. Neurol. 8, 307–318. https://doi.org/10.1038/nrneurol.2012.76.

Su, D., Chen, Z., An, X., Yang, Junkai, Yang, Jinan, Wang, X., Qu, Y., Gong, C., Chai, Y., Liu, X., Cheng, W., Wang, D., Wu, Y., Ma, J., Zhao, X., Wang, Q., Xu, Y., Peng, H., Ai, J., 2024. MicroRNA-195 liposomes for therapy of Alzheimer's disease. J. Control Release 365, 583–601. https://doi.org/10.1016/j.jconrel.2023.12.003.

Su, I.-J., Hsu, C.-Y., Shen, S., Chao, P.-K., Hsu, J.T.-A., Hsueh, J.-T., Liang, J.-J., Hsu, Y.-T., Shie, F.-S., 2022. The Beneficial Effects of Combining Anti-Aβ Antibody NP106 and Curcumin Analog TML-6 on the Treatment of Alzheimer's Disease in APP/PS1 Mice. Int J. Mol. Sci. 23, 556. https://doi.org/10.3390/ijms23010556.

Sugandhi, V.V., Mahajan, H.S., 2022. Development of vitamin B12 containing pullulan-bovine serum albumin microparticles designed dry powder inhaler: *In-vitro* and *in-vivo* study. J. Drug Deliv. Sci. Technol. 70, 103212. https://doi.org/10.1016/j.jddst.2022.103212.

Tahami Monfared, A.A., Byrnes, M.J., White, L.A., Zhang, Q., 2022. Alzheimer's Disease: Epidemiology and Clinical Progression. Neurol. Ther. 11, 553–569. https://doi.org/10.1007/s40120-022-00338-8.

Takallu, S., Aiyelabegan, H.T., Zomorodi, A.R., Alexandrovna, K.V., Aflakian, F., Asvar, Z., Moradi, F., Behbahani, M.R., Mirzaei, E., Sarhadi, F., Vakili-Ghartavol, R., 2024. Nanotechnology improves the detection of bacteria: Recent advances and future perspectives. Heliyon 10, e32020. https://doi.org/10.1016/j.heliyon.2024.e32020.

Tamargo, J., Le Heuzey, J.-Y., Mabo, P., 2015. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. Eur. J. Clin. Pharm. 71, 549–567. https://doi.org/10.1007/s00228-015-1832-0.

Tampi, R.R., Forester, B.P., Agronin, M., 2021. Aducanumab: evidence from clinical trial data and controversies, 7–3 Drugs Context 10, 2021. https://doi.org/10.7573/dic.2021-7-3.

Tang, B., Wang, Y., Ren, J., 2023. Basic information about memantine and its treatment of Alzheimer's disease and other clinical applications. Ibrain 9, 340–348. https://doi.org/10.1002/ibra.12098.

Tarawneh, R., Holtzman, D.M., 2012. The Clinical Problem of Symptomatic Alzheimer Disease and Mild Cognitive Impairment. Cold Spring Harb. Perspect. Med. 2, a006148. https://doi.org/10.1101/cshperspect.a006148.

Teachman, B.A., Drabick, D.A.G., Hershenberg, R., Vivian, D., Wolfe, B.E., Goldfried, M. R., 2012. Bridging the Gap Between Clinical Research and Clinical Practice: Introduction to the Special Section. Psychother. (Chic.) 49, 97–100. https://doi.org/10.1037/a0027346.

Teralı, K., Ozbeyli, D., Yiğit-Hanoğlu, D., Başer, K.H.C., Şener, G., Aykac, A., 2024. A comprehensive assessment of the cholinergic-supporting and cognitive-enhancing effects of Rosa damascena Mill. (Damask rose) essential oil on scopolamine-induced amnestic rats. Brain Behav. 14, e3507. https://doi.org/10.1002/brb3.3507.

Thapa, R., Magar, A.T., Shrestha, J., Panth, N., Idrees, S., Sadaf, T., Bashyal, S., Elwakil, B.H., Sugandhi, V.V., Rojekar, S., Nikhate, R., Gupta, G., Singh, S.K., Dua, K., Hansbro, P.M., Paudel, K.R., 2024. Influence of gut and lung dysbiosis on lung cancer progression and their modulation as promising therapeutic targets: a comprehensive review. MedComm 5, e70018. https://doi.org/10.1002/mco2.70018.

Theofilas, P., Ehrenberg, A.J., Nguy, A., Thackrey, J.M., Dunlop, S., Mejia, M.B., Alho, A. T., Leite, R.E.P., Rodriguez, R.D., Suemoto, C.K., Nascimento, C.F., Chin, M., Medina-Cleghorn, D., Cuervo, A.M., Arkin, M., Seeley, W.W., Miller, B.L., Nitrini, R., Pasqualucci, C.A., Filho, W.J., Rueb, U., Neuhaus, J., Heinsen, H., Grinberg, L.T., 2018. Probing the correlation of neuronal loss, neurofibrillary tangles and cell death markers across the Alzheimer's disease's Braak stages: a quantitative study in humans. Neurobiol. Aging 61, 1–12. https://doi.org/10.1016/j.neurobiolaging.2017.09.007.

Tian, L., Lin, B., Wu, L., Li, K., Liu, H., Yan, J., Liu, X., Xi, Z., 2015. Neurotoxicity induced by zinc oxide nanoparticles: age-related differences and interaction. Sci. Rep. 5, 16117. https://doi.org/10.1038/srep16117.

Tiwari, V., Tiwari, A., Sharma, A., Kumar, M., Kaushik, D., Sagadevan, S., 2023. An optimistic approach to nanotechnology in Alzheimer's disease management: An overview. J. Drug Deliv. Sci. Technol. 86, 104722. https://doi.org/10.1016/j.jddst.2023.104722.

Tolar, M., Hey, J., Power, A., Abushakra, S., 2021. Neurotoxic Soluble Amyloid Oligomers Drive Alzheimer's Pathogenesis and Represent a Clinically Validated Target for Slowing Disease Progression. Int J. Mol. Sci. 22, 6355. https://doi.org/10.3390/ijms22126355.

Tork, Y.J., Naseri, E., Basir, H.S., Komaki, A., 2024. Protective effects of L-carnitine against beta-amyloid-induced memory impairment and anxiety-like behavior in a rat model of Alzheimer's disease. Eur. J. Pharmacol. 982, 176879. https://doi.org/10.1016/j.ejphar.2024.176879.

Toutain, P.-L., Ferran, A., Bousquet-Mélou, A., 2010. Species differences in pharmacokinetics and pharmacodynamics. Handb. Exp. Pharm. 19–48. https://doi.org/10.1007/978-3-642-10324-7_2.

Tsalenchuk, M., Gentleman, S.M., Marzi, S.J., 2023. Linking environmental risk factors with epigenetic mechanisms in Parkinson's disease. npj Park. Dis. 9, 1–12. https://doi.org/10.1038/s41531-023-00568-z.

Umbricht, D., Kas, M.J.H., Dawson, G.R., 2024. The role of biomarkers in clinical development of drugs for neuropsychiatric disorders - A pragmatic guide. Eur. Neuropsychopharmacol. 88, 66–77. https://doi.org/10.1016/j.euroneuro.2024.08.511.

Usai, C., Mateu, L., Brander, C., Vergara-Alert, J., Segalés, J., 2023. Animal models to study the neurological manifestations of the post-COVID-19 condition. Lab Anim. (NY) 52, 202–210. https://doi.org/10.1038/s41684-023-01231-z.

Van Cauwenberghe, C., Van Broeckhoven, C., Sleegers, K., 2016. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet. Med. 18, 421–430. https://doi.org/10.1038/gim.2015.117.

Vaz, M., Silva, V., Monteiro, C., Silvestre, S., 2022. Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities. Clin. Inter. Aging 17, 797–810. https://doi.org/10.2147/CIA.S325026.

Veldsman, M., 2017. Brain Atrophy Estimated from Structural Magnetic Resonance Imaging as a Marker of Large-Scale Network-Based Neurodegeneration in Aging and Stroke. Geriatrics 2, 34. https://doi.org/10.3390/geriatrics2040034.

Vitek, M.P., Araujo, J.A., Fossel, M., Greenberg, B.D., Howell, G.R., Rizzo, S.J.S., Seyfried, N.T., Tenner, A.J., Territo, P.R., Windisch, M., Bain, L.J., Ross, A., Carrillo, M.C., Lamb, B.T., Edelmayer, R.M., 2021. Translational animal models for Alzheimer's disease: An Alzheimer's Association Business Consortium Think Tank. Alzheimers Dement (N. Y 6, e12114. https://doi.org/10.1002/trc2.12114.

Vogels, T., Leuzy, A., Cicognola, C., Ashton, N.J., Smolek, T., Novak, M., Blennow, K., Zetterberg, H., Hromadka, T., Zilka, N., Schöll, M., 2020. Propagation of Tau Pathology: Integrating Insights From Postmortem and In Vivo Studies. Biol. Psychiatry 87, 808–818. https://doi.org/10.1016/j.biopsych.2019.09.019.

Wang, X., Gadhave, D., Chauhan, G., Gupta, V., 2024. Development and characterization of inhaled nintedanib-loaded PLGA nanoparticles using scalable high-pressure homogenization technique. J. Drug Deliv. Sci. Technol. 91, 105233. https://doi.org/10.1016/j.jddst.2023.105233.

Wechsler, M.E., Ramirez, J.E.V., Peppas, N.A., 2019. 110th Anniversary: Nanoparticle mediated drug delivery for the treatment of Alzheimer's disease: Crossing the blood-brain barrier. Ind. Eng. Chem. Res 58, 15079–15087. https://doi.org/10.1021/acs.iecr.9b02196.

Wells, C., Brennan, S., Keon, M., Ooi, L., 2021. The role of amyloid oligomers in neurodegenerative pathologies. Int. J. Biol. Macromol. 181, 582–604. https://doi.org/10.1016/j.ijbiomac.2021.03.113.

Wu, D., Chen, Q., Chen, X., Han, F., Chen, Z., Wang, Y., 2023. The blood–brain barrier: Structure, regulation and drug delivery. Signal Transduct. Target Ther. 8, 217. https://doi.org/10.1038/s41392-023-01481-w.

Wu, M., Zhang, M., Yin, X., Chen, K., Hu, Z., Zhou, Q., Cao, X., Chen, Z., Liu, D., 2021. The role of pathological tau in synaptic dysfunction in Alzheimer's diseases. Transl. Neurodegener. 10, 45. https://doi.org/10.1186/s40035-021-00270-1.

Xiao, X., Liu, H., Liu, X., Zhang, W., Zhang, S., Jiao, B., 2021. APP, PSEN1, and PSEN2 Variants in Alzheimer's Disease: Systematic Re-evaluation According to ACMG Guidelines. Front. Aging Neurosci. 13. https://doi.org/10.3389/fnagi.2021.695808.

Xu, Y., Li, Z., 2020. CRISPR-Cas systems: Overview, innovations and applications in human disease research and gene therapy. Comput. Struct. Biotechnol. J. 18, 2401–2415. https://doi.org/10.1016/j.csbj.2020.08.031.

Yaghmaei, E., Lu, H., Ehwerhemuepha, L., Zheng, J., Danioko, S., Rezaie, A., Sajjadi, S. A., Rakovski, C., 2024. Combined use of Donepezil and Memantine increases the probability of five-year survival of Alzheimer's disease patients. Commun. Med (Lond.) 4, 99. https://doi.org/10.1038/s43856-024-00527-6.

Yamazaki, Y., Painter, M.M., Bu, G., Kanekiyo, T., 2016. Apolipoprotein E as a Therapeutic Target in Alzheimer's disease: A Review of Basic Research and Clinical Evidence. CNS Drugs 30, 773–789. https://doi.org/10.1007/s40263-016-0361-4.

Yamazaki, Y., Zhao, N., Caulfield, T.R., Liu, C.-C., Bu, G., 2019. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat. Rev. Neurol. 15, 501. https://doi.org/10.1038/s41582-019-0228-7.

Yang, C.-C., Yang, S.-Y., Chieh, J.-J., Horng, H.-E., Hong, C.-Y., Yang, H.-C., Chen, K.H., Shih, B.Y., Chen, T.-F., Chiu, M.-J., 2011. Biofunctionalized magnetic nanoparticles for specifically detecting biomarkers of Alzheimer's disease in vitro. ACS Chem. Neurosci. 2, 500–505. https://doi.org/10.1021/cn200028j.

Yang, Z., Zou, Y., Wang, L., 2023. Neurotransmitters in Prevention and Treatment of Alzheimer's Disease. Int J. Mol. Sci. 24, 3841. https://doi.org/10.3390/ijms24043841.

Yiannopoulou, K.G., Papageorgiou, S.G., 2013. Current and future treatments for Alzheimer's disease. Ther. Adv. Neurol. Disord. 6, 19. https://doi.org/10.1177/1756285612461679.

Yin, H., Kanasty, R.L., Eltoukhy, A.A., Vegas, A.J., Dorkin, J.R., Anderson, D.G., 2014. Non-viral vectors for gene-based therapy. Nat. Rev. Genet 15, 541–555. https://doi.org/10.1038/nrg3763.

Yu, T.-W., Lane, H.-Y., Lin, C.-H., 2021. Novel Therapeutic Approaches for Alzheimer's Disease: An Updated Review. Int. J. Mol. Sci. 22, 8208. https://doi.org/10.3390/ijms22158208.

Yue, W., Li, Y., Zhang, T., Jiang, M., Qian, Y., Zhang, M., Sheng, N., Feng, S., Tang, K., Yu, X., Shu, Y., Yue, C., Jing, N., 2015. ESC-Derived Basal Forebrain Cholinergic Neurons Ameliorate the Cognitive Symptoms Associated with Alzheimer's Disease in Mouse Models. Stem Cell Rep. 5, 776–790. https://doi.org/10.1016/j.stemcr.2015.09.010.

Zenaro, E., Piacentino, G., Constantin, G., 2017. The blood-brain barrier in Alzheimer's disease. Neurobiol. Dis. 107, 41–56. https://doi.org/10.1016/j.nbd.2016.07.007.

Zhang, H., Wei, W., Zhao, M., Ma, L., Jiang, X., Pei, H., Cao, Y., Li, H., 2021. Interaction between Aβ and Tau in the Pathogenesis of Alzheimer's Disease. Int J. Biol. Sci. 17, 2181–2192. https://doi.org/10.7150/ijbs.57078.

Zhang, H., Jiang, X., Ma, L., Wei, W., Li, Z., Chang, S., Wen, J., Sun, J., Li, H., 2022. Role of Aβ in Alzheimer's-related synaptic dysfunction. Front Cell Dev. Biol. 10, 964075. https://doi.org/10.3389/fcell.2022.964075.

Zhang, M., Wang, W., Ye, Q., Fu, Y., Li, X., Yang, K., Gao, F., Zhou, A., Wei, Y., Tian, S., Li, S., Wei, F., Shi, W., Li, W.-D., 2024. Histone deacetylase inhibitors VPA and WT161 ameliorate the pathological features and cognitive impairments of the APP/PS1 Alzheimer's disease mouse model by regulating the expression of APP secretases. Alzheimers Res Ther. 16, 15. https://doi.org/10.1186/s13195-024-01384-0.

Zhang, X., Liu, H., Huang, Y., Wang, R., 2023. A meta-analysis of neurogenic exosomes in the diagnosis of Alzheimer's disease. Heliyon 9, e20604. https://doi.org/10.1016/j.heliyon.2023.e20604.

Zhang, Y., Li, P., Feng, J., Wu, M., 2016. Dysfunction of NMDA receptors in Alzheimer's disease. Neurol. Sci. 37, 1039–1047. https://doi.org/10.1007/s10072-016-2546-5.

Zhong, G., Long, H., Zhou, T., Liu, Y., Zhao, J., Han, J., Yang, X., Yu, Y., Chen, F., Shi, S., 2022. Blood-brain barrier Permeable nanoparticles for Alzheimer's disease treatment by selective mitophagy of microglia. Biomaterials 288, 121690. https://doi.org/10.1016/j.biomaterials.2022.121690.

Zhou, Y., Danbolt, N.C., 2014. Glutamate as a neurotransmitter in the healthy brain. J. Neural Transm. (Vienna) 121, 799–817. https://doi.org/10.1007/s00702-014-1180-8.

Zhu, T., Brown, A.P., Ji, H., 2020. The Emerging Role of Ten-Eleven Translocation 1 in Epigenetic Responses to Environmental Exposures. Epigenet Insights 13, 2516865720910155. https://doi.org/10.1177/2516865720910155.

Zilka, N., Zilkova, M., Kazmerova, Z., Sarissky, M., Cigankova, V., Novak, M., 2011. Mesenchymal stem cells rescue the Alzheimer's disease cell model from cell death induced by misfolded truncated tau. Neuroscience 193, 330–337. https://doi.org/10.1016/j.neuroscience.2011.06.088.