International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 17, Issue 1, 2025

Review Article

ALZHEIMER'S DISEASE: COMPREHENSIVE INSIGHTS INTO RISK FACTORS, BIOMARKERS, AND ADVANCED TREATMENT APPROACHES

SURESH JANADRI*, SHREELAXMI DADMI, MANJUNATHA P. MUDAGAL, UDAY RAJ SHARMA, SURENDRA VADA, THIRIVEEDI HARIBABU

Department of Pharmacology, Acharya and BM Reddy College of Pharmacy, Acharya Dr. Sarvepalli Radhakrishna Road, Achit Nagar (Post), Soladevanahalli, Bengaluru, India

***Corresponding author: Suresh Janadri; *Email: sureshjanadri@gmail.com**

Received: 25 Oct 2024, Revised and Accepted: 09 Dec 2024

ABSTRACT

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder primarily affecting individuals over 60. It is a multifactorial disease driven by both modifiable factors, such as lifestyle, diet, and prior health conditions, as well as non-modifiable factors, like age, genetics, and family history. The key pathological features of AD include the buildup of amyloid β plaques and neurofibrillary tangles resulting from hyperphosphorylated tau proteins in the brain. Biomarkers like amyloid β and tau protein levels in cerebrospinal fluid (CSF) and blood are essential for diagnosing and tracking AD progression. Current research focuses on developing drugs targeting multiple aspects of AD pathology, including inflammation, oxidative stress, synaptic dysfunction, and protein accumulation. These treatments aim to slow cognitive decline and neuronal damage. Given the complexity of AD, multi-targeted therapeutic approaches are being explored to enhance treatment efficacy. This review provides an overview of AD risk factors, key biomarkers used for diagnosis, and the latest advances in clinical drug development.

Keywords: Alzheimer's disease, Diabetes, Amyloid beta, Tau therapy, Anti-amyloid therapy, Apolipoprotein E

DOI: https://dx.doi.org/10.22159/ijcpr.2025v17i1.6039 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD) an irreversible conditions and cause atrophies in the cerebral cortex of the brain [1]. Alzheimer's disease is a complex disorder characterized by central nervous system neurodegeneration with significant involvement of the cholinergic system, resulting in gradual cognitive decline and dementia [2]. Recent discoveries, such as the detection of amyloid-beta (Aβ), tumor necrosis factors (TNFs), and neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein are potential causes of Alzheimer's disease development. Multi-targeted compounds that inhibit cholinesterases while also interfering with Aβ-aggregation and/or tau protein neuroinflammation may be useful in the treatment of Alzheimer's disease [3, 4]. Alzheimer's disease (AD) is marked by intracellular neurofibrillary tangles containing tau and extracellular plaques containing amyloid β (Aβ) [5], which results in a gradual decline in mental behavioral, functional, as well as cognitive capabilities [6, 7].

According to the World Alzheimer Report 2022, more than 55 million people worldwide have AD or associated disorders, with that fig. expected to rise to 82 million by 2030 and 138 million by 2050 [8]. AD ranks as the fourth most common cause of death for older adults [9]. The number of Alzheimer's deaths in the US increased by 54.5% in 2014 to 25.4 deaths per 100,000 people, up from 16.5 in 1999. The percentage of Alzheimer's victims who passed away in hospitals dropped from 14.7% to 6.6%, whereas the percentage of victims who passed away at home rose from 13.9% to 24.9% [10]. According to recent studies conducted in 2022, the incidence cases of AD has increased to 7.24 million globally [11].

Various modifiable and non-modifiable factors are responsible for causing sporadic forms of AD [12]. Modifiable factors like Environmental influences, which can include lifestyle, diet, education, and exposure to various health factors, are also thought to play a role in the development of Alzheimer's disease. Non-modifiable factors like genetic influences i. e., mutations in specific genes (e. g., APP, PSEN1, PSEN2), gender, entity, and family histories may impact the risk of developing AD [13].

Biomarkers are measurable indicators of a biological state or condition. They can be molecules, genes, proteins, or other substances that are present in the body and can be detected and measured. Since there are no distinct symptoms or indicators for AD, biomarkers may help with early diagnosis, which is especially challenging. More importantly, they may help to identify people with preclinical Alzheimer's disease (those with AD neuropathology but no clinical symptoms) [14]. In addition to helping with disease diagnosis, biomarkers may also be useful for tracking the course of a disease and its reaction to therapy. Biomarkers for Alzheimer's disease also can be evaluated from cerebrospinal fluid and blood serum [15].

The increasing prevalence of these diseases suggests that current treatment strategies are insufficient to effectively manage and prevent them [16]. As a result, novel treatment strategies are being investigated to cure these diseases by targeting the underlying mechanisms at the molecular level [17]. Novel therapies like gene therapy, stem cell therapy and targeting various mechanisms like inflammation, cell death, oxidative stress, amyloid beta (Aβ) peptide, tau protein, apolipoprotein E 4 (APOE4) effects, lipids and lipoprotein receptors, neurotransmitter receptors, neurogenesis, proteostasis, bioenergetics and metabolism, vascular factors and/or treating the diseases induce the Alzheimer's disease [18].

Causative factors

Age

Alzheimer's disease (AD) is the most common cause of dementia, affecting up to 20% of individuals>80 years of age [19]. A major meta-analysis discovered that brain amyloidosis is substantially linked with age; aging causes alterations in the transcriptome, resulting in two kinds of activated microglia (ARMs and IRMs) as well as AB deposition and that the curve showing the increase in amyloid with age corresponds to the increase in dementia prevalence with age [20, 21]. Both the entorhinal cortex (EC) and the hippocampus are sensitive to both normal aging and early Alzheimer's disease pathology. There is evidence that the anterolateral entorhinal cortex (AlEC) malfunctions in both healthy aging and preclinical Alzheimer's disease Tauopathy is associated with cognitive impairment in AD [22]. As a result, tauopathy affects the entire EC and spreads to the medial temporal lobe, including the

hippocampus. The development of tauopathy across the EC, including the pmEC, could compromise grid-cell activity and contribute to pure path integration (PPI) impairments in the early stages of Alzheimer's disease [23].

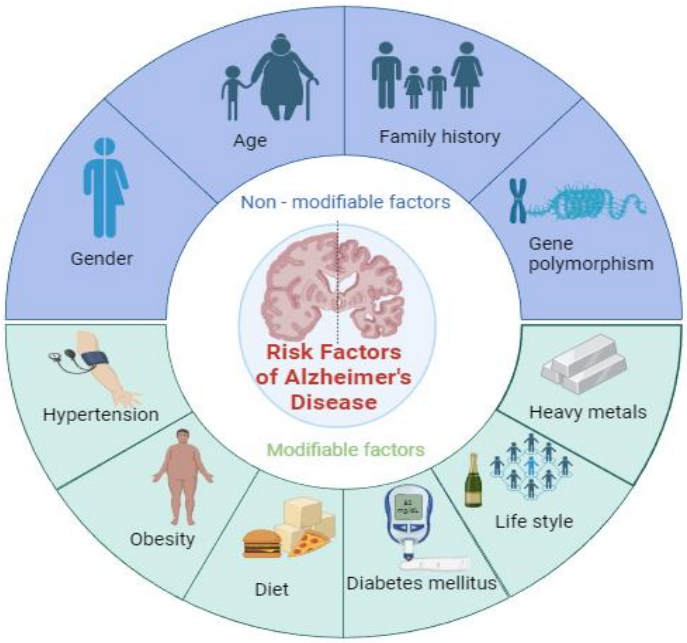

Fig. 1: Classification of risk factors related to alzheimer's diseases

Alzheimer's disease risk is influenced by both non-modifiable and modifiable factors. Non-modifiable factors include age, family history, specific genetic variations such as those in the APOE gene, and gender, with women being more susceptible. Modifiable factors that can be managed to reduce the risk include hypertension, obesity, poor dietary habits, and diabetes mellitus. Lifestyle choices, such as physical inactivity, smoking, and excessive alcohol consumption, also play a significant role. Additionally, exposure to heavy metals like lead and mercury has been linked to an increased risk of Alzheimer's disease.

Social isolation

Loneliness affects 12% to 40% of persons with age 65 and more, making them especially vulnerable to social isolation. Seniors who express feelings of loneliness are more likely to experience cognitive decline, memory impairment, and/or dementia [24]. Social Isolation and living alone may develop the possibility of getting Alzheimer's disease and dementia twice the risk [25]. Loneliness was one of the psychopathological aspects attributed to MCI [26]. Different cognitive domains are affected by social engagement at different times. Increased social interaction enhances speed, perceptual organization, and episodic memory but not working memory. While a larger social network may not always result in better mental efficiency, it may decrease specific cognitive domains, such as perceptual speed [27]. The categorization of risk factors associated with Alzheimer's disease as depicted in fig. 1.

Disease factors

Diabetes

According to a recent meta-analysis, the risk of developing AD is 50% higher in T2D (Type 2 diabetes) patients over age-matched non-diabetic individuals [28]. T2D and Alzheimer's disease are metabolic diseases having similar characteristics in mitochondrial dysfunction and oxidative stress, impaired brain glucose metabolism, inflammation, insulin resistance (IR), advanced glycation end products formation, overproduction and aggregation of amyloid beta (Aβ), and tau protein hyper phosphorylation and deposition. This has led to the concept of "Type 3 diabetes" or "diabetes of the brain" [29, 30]. Glucose concentration will be higher in the brain tissue of Alzheimer's patients in comparison to the age-matched non-diabetic patients [31]. This complication can lead to the condition called Diabetic encephalopathy [32].

Hypertension

A person who had hypertension in midlife had a higher risk of Alzheimer's disease than a person who was normotensive in midlife. Stroke is thought to act as a mediator in the relationship between high blood pressure (BP), cognitive decline and vascular dementia [33]. Angiotensin II directly causes brain oxidative stress and BBB disruption in hypertensive patient [34]. Hypertension is linked with Alzheimer's disease from mainly intracranial and extracranial mechanisms. Intracranial mechanisms-cerebral ischemia (41.3%), cerebral hemorrhage (19-63%), brain atrophy. Extracranial mechanisms-chronic kidney disease (40%), Extra-large vessels, cardiac disease (28%).

A meta-analysis of population-based studies reported that prevalence of 41.3% (95%CI 29.6–53.1%) in hospital-based studies of stroke-induced dementia [35]. the higher blood pressure in the brain causes acute ischemic stroke and transient ischemic attack, which is characterized by the blockage of the blood vessels in the brain, thereby the insufficient blood supply to the brain cells that further leads to vascular dementia i. e. Post-stroke cognitive impairment (PSCI) [36]. Hypertension is a preventable risk factor for brain atrophy, which is one of the leading causes of neurodegenerative diseases. And elevated levels of neurofibrillary tangles and neuritic plaques in the hippocampus and neocortex [37, 33]. Oxidative stress-induced inflammation leads to the damage of the blood-brain barrier along with the microglia activation. Thereby impairment of glymphatic clearance pathway for amyloid clearance [38]. There is a 19-63% risk of having cognitive impairment in patients with intracerebral hemorrhage [39]. Patients with chronic kidney disease (CKD) are more likely to develop neurological decline or dementia. The angiotensin AT1 receptor contributes to the higher exposure of AD mice to CKD-induced cognitive impairment by blood-brain barrier (BBB) disruption or oxidative stress [40]. RAS-activated M1 microglia release proinflammatory signals that exacerbate cognitive dysfunction in the cortex, hippocampus, basal ganglia, and neuronal death [41]. There is a correlation between large vessel atherosclerosis and a higher risk of both ischemic stroke

and Alzheimer's [42]. There is 28% relative odds increase in dementia risk in those with heart failure. Hypertension is a major risk factor for atrial fibrillation, which is linked to an increased risk of cognitive impairment. Atrial fibrillation was linked to a 50% increase in the relative odds of dementia or cognitive impairment in a meta-analysis of 43 cohort studies [43].

Obesity

Numerous factors, including oxidative stress, inflammation, dyslipidemia, insulin resistance, and metabolic syndrome, have been linked between neurodegenerative diseases and obesity [44]. Having a high-fat diet AD [45], and disruption in the mitogen-activated protein (p38 MAPK) leads to Aβ aggregation and tau phosphorylation [46] Higher BMI at middle age and late ages 70, 75, and 79 years have a higher risk of occurrence of dementia [47]. Cognitive function impairment in obesity-induced AD rats was triggered by disruptions in the antioxidant defense system, specifically high malondialdehyde (MDA) and low total antioxidant capacity (TAC) levels in the brain [48]. Improper adipokine regulation and long-chain fatty acid (C16, C18) deposition in brain tissue alters the vascular functions in the brain, making insulin resistance and also triggering astrocyte pro-inflammatory cascade that makes Aβ accumulation and tau phosphorylation [49, 50].

AIDS

The human immunodeficiency virus (HIV) can pass through the blood-brain barrier, causing neuronal dysfunction and cognitive decline. HIV patients may develop Aβ plaques or neurofibrillary tangles, suggesting a link between the two diseases. The virus may modulate Aβ and tau pathways, leading to neuroinflammation in both conditions [51]. The steps involved in causing Alzheimer's disease by various disease conditions have been mentioned in fig. 2.

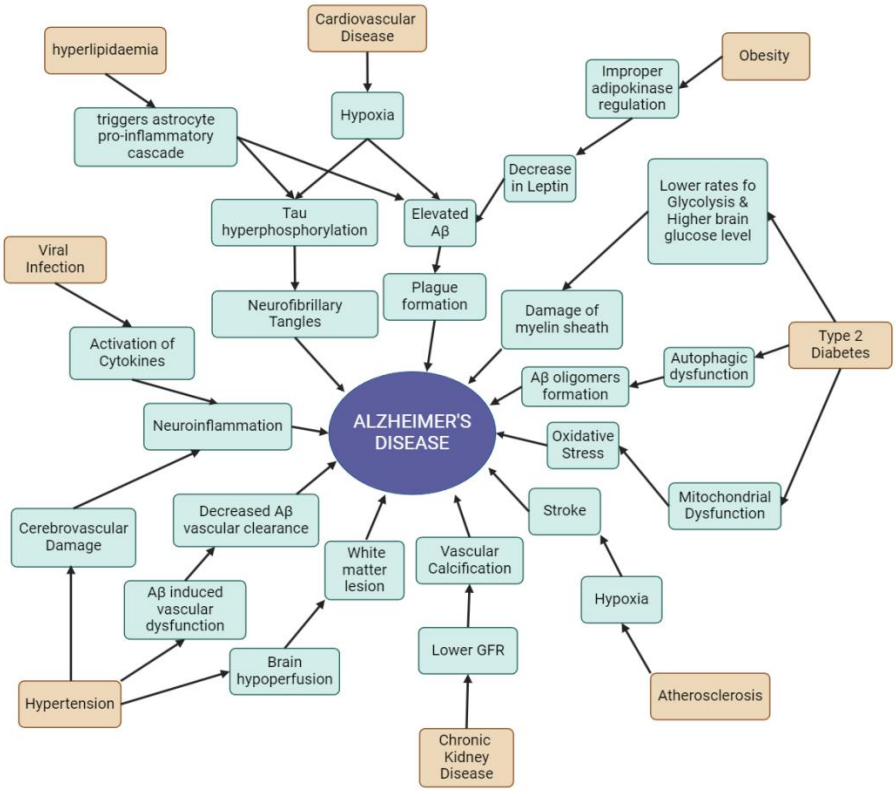

Fig. 2: Steps involved in causing Alzheimer's diseases by various disease conditions

The fig. illustrates how various factors contribute to Alzheimer's disease. Cardiovascular disease and lead to hypoxia and neuroinflammation, increasing amyloid-beta (Aβ) levels and tau hyperphosphorylation, resulting in plaque formation and neurofibrillary tangles. Hypertension causes cerebrovascular damage and brain hypo perfusion, while obesity and type 2 diabetes impair brain metabolism, increasing Aβ and oxidative stress. Chronic kidney disease and atherosclerosis exacerbate hypoxia and vascular issues. These interconnected factors collectively contribute to the pathological features of Alzheimer's disease, including plaque formation, neuroinflammation, and neuronal damage.

Heavy metals

Aluminum exposure is believed to cause neurotoxicity in the central nervous system by damaging mitochondria, leading to excessive production of reactive oxygen species (ROS), DNA damage, and ultimately apoptotic cell death. This process is associated with a decrease in enzymatic activities, increased misfolded proteins, and oxidative stress [52]. Aluminum has been shown to bind negatively charged brain phospholipids with great affinity. These phospholipids contain polyunsaturated fatty acids that are readily attacked by reactive oxygen species (ROS) [53].

Lead acts as a neurotoxicant, causing non-specific brain disruption through oxidative stress and subsequent mitochondrial damage. In addition, it interferes with the essential metals' homeostatic levels and the metal signaling pathways that lead to neuroinflammation. It has been demonstrated that lead treatment causes deficits in learning and memory in addition to increasing levels of tau protein, amyloid β protein precursor, and amyloid β in the brain [54].

Cadmium, a redox-inactive metal, causes oxidative stress, which triggers neurodegeneration signaling pathways like mitogen-activated protein kinase (MAPK), protein kinase B (Akt), mammalian target of rapamycin (mTOR) and FasL-mediated mitochondrial apoptosis, ultimately leading to neuronal degeneration. Extracellular calcium influx increases due to disruptions in intracellular calcium homeostasis, and neuronal apoptosis is triggered by activating the MAPK and mTOR signaling pathways. Furthermore, affecting brain ion balance and nutrient uptake, cadmium damages the cerebral microvascular endothelium and raises BBB permeability [54].

Manganese is trace metal is essential for bone growth, blood clotting, immunity, carbohydrate metabolism, and brain function. High manganese exposure can accumulate in the brain and be neurotoxic. High manganese levels can impair cognitive function and contribute to Alzheimer's disease (AD). Oxidative stress, mitochondrial dysfunction, dysregulation of autophagy, build-up of intracellular toxic metabolites, and apoptosis are some of the underlying processes [54].

Elevated brain iron in AD has been linked to an accelerated clinical decline. High brain iron content produces ROS, which ultimately causes cell death. Iron chelation is thought to have neuroprotective effects by lowering brain iron levels, blocking the development of tau and Aβ pathology, and reducing harmful ROS [55].

Diet

The Western diet (WD) consists of ultra-processed, refined foods high in simple carbohydrates, salt, saturated fat, and cholesterol, which will increase the amyloid β and tau protein levels in the brain. Inadequate intake of vegetables, fruits which makes low intake of nicotinic acid (B3), folic acid flavonoids, vitamin B9, and betulinic acid following brain atrophy, age-related cognition decline, affects BBB permeability and, thereby the risk of Alzheimer's disease more [56, 57].

Genetic polymorphism

TREM2, or trigger-expressing receptor expressed on myeloid cells 2, is a transmembrane receptor that is highly expressed in microglia cells and is involved in phagocytosis, inflammation, and glial cell activation. A genetic mutation in TREM2 enhances the risk of late-ons*et al.* zheimer's disease [58].

β-site APP Cleaving Enzyme 1 (BACE1) is a β-secretase enzyme essential for the generation of Amyloid β monomeric forms like $A\beta_{42}$. It is widely expressed in brain neurons. Mutations in the BACE1 gene can affect Beta-Secretase 1, resulting in increased production of amyloid-beta peptides, particularly longer, toxic forms. This leads to the build-up of amyloid plaques in the brain, which is a characteristic feature of Alzheimer's disease. These plaques disrupt neuronal communication, cause neuroinflammation, and eventually result in neuronal death and cognitive decline, exacerbating Alzheimer's disease progression [59].

Alzheimer's disease is associated with the gamma-secretase complex gene Presenilin 1 (PS1). The dysregulation of gamma-secretase activity resulting from mutations in the PS1 gene can lead to an increase in the production of amyloid-beta peptides, especially the plaque-forming amyloid-beta 42 peptides. These plaques cause inflammation, impair neuronal function and ultimately result in neuronal death, all of which contribute to the neurodegenerative process. These mutations are associated with early-onset familial Alzheimer's disease, which makes up a tiny portion of cases and usually appears before the age of 65. The precise processes by which PS1 mutations contribute to the pathology of Alzheimer's disease, however, are still being studied [60].

Biomarkers

Oxidative biomarkers

Anti-Oxidants like Superoxide Dismutase (SOD), Catalase (CAT), And Glutathione Peroxidase antioxidants will neutralize the reactive oxygen species (ROS) produced excessively in the body due to various causes. Antioxidant enzymes like superoxide dismutase (SOD), Catalase (CAT), and glutathione peroxidase activity towards breaking down of superoxide and hydrogen peroxide will be compromised in the Alzheimer's CSF and Plasma [61]. Oxidative Stress Markers like F_2-Isops are prostaglandin-like compounds. The esterified F_2-Isops increases the free F_2-Isops in the tissue undergone oxidative stress, 3-Nitrotyrosine, Nitric Oxide, and Malondialdehyde are the compounds synthesized by lipid peroxidation in the brain upon accumulation of the Aβ [62, 63].

CSF biomarkers

APoD (Apolipoprotein D) is highly expressed in the brain, particularly in areas affected by AD, and its levels are often elevated in response to oxidative stress and inflammation, both of which are central to Alzheimer's pathology. APoD is thought to have neuroprotective functions by mitigating oxidative damage and promoting the clearance of harmful lipids. In AD, increased APoD expression has been observed in regions with amyloid-beta plaques and tau tangles, suggesting it may be part of the brain's response to ongoing neurodegeneration [64].

Aβ42 is considered to be at a higher level in the plasma in patients with AD. Usually, the Aβ42 binds with low-density lipoprotein receptor-related protein-1 (LRP1) in the brain but in the AD patient, the binding of Aβ42 with low-density lipoprotein receptor-related protein-1 (LRP1) is compromised, the biomarker efflux from the brain through the blood-brain barrier (BBB) and reaches plasma. A deposition can activate astrocytes and microglia through ROS generation, resulting in activation of the brain inflammatory pathway [64].

Tau proteins in neuronal axons help stabilize microtubules in the central nervous system (CNS). They consist of six soluble isoforms and numerous phosphorylation sites [65]. In neurons, hyperphosphorylated tau proteins detach from microtubules and form insoluble aggregates known as neurofibrillary tangles. There are two tau markers namely, total tau (t-tau) and phosphorylated tau (p-tau). The t-tau level in CSF represents the neuronal injury and p-tau represents the hyperphosphorylation of tau and formed neurofibrillary tangles [66, 67].

GFAP (Glial fibrillary acidic protein) is an astrocytic marker that mainly measures astrocytosis. CSF GFAP and plasma GFAP both are positively related to both age and gender. Plasma GFAP is associated with the accumulation of amyloid-β-PET in the neocortical regions and also its higher concentration is associated with Tau-PET. The accurate status of Amyloid – β deposition can be measured through the plasma GFAP marker [68].

YKL-40 is a secreted glycoprotein and it has a part in the activation of the innate immune system. Its elevated level in reactive astrocytes and microglial cells are directly associated with the neuroinflammatory processes. Dementia patients will have higher levels of YKL-40 in the CSF [69]. YKL-40 levels are elevated in autosomal dominant Alzheimer's disease mutation carriers 15 to 19 years before symptom onset, shortly after the start of brain amyloid accumulation. So, this biomarker can be used for the early detection of Alzheimer's disease [70].

Aquaporin 4 (AQP4) is the primary water channel found in the central nervous system (CNS), specifically in astrocytes. AQP4 plays a role in neurological diseases by regulating brain fluid and ion homeostasis, potassium uptake and release by astrocytes, migration and glial scarring, neural signal transduction, proinflammatory factor secretion, astrocyte-to-astrocyte cell communication, and synaptic plasticity. Reducing AQP4 will impair learning and memory, it also affects synaptic plasticity. Maintaining the level of AQP4 in astrocytes is one of the molecular-level therapies for AD [71, 72].

α-Synuclein is the precursor protein of a non-amyloid β component of senile plaques (NACP) and positive aggregates are found in limbic regions in Alzheimer's disease. It plays a part in synaptic adaptations, such as synaptic plasticity during development, learning, and the regulation of synaptic vesicle mobilization at nerve terminals. Polymorphism of the α-syn gene and higher levels in CFS will be diagnosed as Alzheimer's Disease [73].

Apolipoprotein E (APOE) is a protein involved in lipid metabolism and transporting lipids, in the central nervous system. It plays a crucial role in the clearance of the Aβ and is associated with the Tau protein aggregation. It also maintains the BBB integrity and the synaptic plasticity. Damage in the BBB integrity leads to neuroinflammation [74].

Elevated levels of YWHAG in cerebrospinal fluid (CSF) may indicate ongoing neurodegenerative processes. This protein is released into the CSF when neurons are stressed or damaged, making its concentration a reflection of the extent of neurodegeneration. Increased YWHAG levels have been observed in AD patients and correlate with the severity of cognitive impairment and brain damage. Consequently, measuring YWHAG in CSF can help monitor disease progression and evaluate the effectiveness of therapeutic

interventions, providing valuable insights into the state of neurodegeneration in Alzheimer's disease [75].

The degradation of MBP (Myelin Basic Protein) contributes to demyelination, leading to impaired neuronal communication and cognitive decline. Elevated levels of MBP in cerebrospinal fluid (CSF) are often observed in AD, indicating ongoing neurodegeneration and white matter damage. MBP also interacts with amyloid-beta (Aβ) peptides, promoting plaque formation, a key feature of AD pathology [76].

Clusterin involves the clearance of amyloid-beta (Aβ) plaques. Clusterin binds to Aβ peptides, facilitating their transport and clearance from the brain, which may help mitigate plaque formation. However, elevated levels of clusterin have also been associated with increased amyloid burden and cognitive decline, suggesting a complex role in AD [77].

MMPs (Matrix Metalloproteinases) are enzymes that degrade extracellular matrix components and are involved in Alzheimer's disease (AD) through their effects on amyloid-beta (Aβ) plaques. While MMPs can aid in clearing Aβ, excessive activity may disrupt the blood-brain barrier and exacerbate neuroinflammation. Elevated levels of certain MMPs, like MMP-9, are linked to AD progression, highlighting their potential as both therapeutic targets and biomarkers [78].

SNAP-25 (Synaptosomal-Associated Protein 25) is a critical protein involved in the regulation of neurotransmitter release by facilitating the fusion of synaptic vesicles with the presynaptic membrane. In Alzheimer's disease (AD), SNAP-25 levels and function are often disrupted, leading to impaired synaptic transmission and communication between neurons. This disruption is particularly significant as synaptic dysfunction is one of the earliest pathological features of AD and closely correlates with cognitive decline [79].

Plasma metabolites

Leptin is a 16 kDa adipokine that is mainly secreted by adipocytes and plays a crucial role in controlling body weight and fat reserves. Leptin influences hippocampal neuron excitability through both synaptic and nonsynaptic pathways, mainly acting on arcuate nuclei in the hypothalamus. It also affects hippocampal-dependent learning and memory [79]. Leptin activates AMPK signaling pathways, which reduces Aβ deposition in neuronal cultures. A negative correlation was observed between plasma leptin and presenilin 1 protein expression, indicating that leptin controls γ-secretase activity *in vivo*. The Aβ-cleaving enzyme aspartyl protease β-site is decreased by leptin, reducing Aβ deposition [80-82].

BGLAP (Bone Gamma-Carboxyglutamate Protein), also known as osteocalcin, is a protein primarily involved in bone metabolism; osteocalcin can cross the blood-brain barrier and influence brain regions involved in memory and cognition. In the context of Alzheimer's disease (AD), lower levels of osteocalcin have been associated with an increased risk of cognitive decline. This protein is believed to enhance the production of neurotransmitters and support neurogenesis, potentially offering protective effects against neurodegenerative processes [83].

Flotillin is connected to amyloid-beta plaques due to its role in organizing lipid rafts and processing amyloid precursor protein (APP). It may also affect tau protein pathology through its influence on cellular signaling and membrane dynamics. Variations in flotillin levels or function could, therefore impact both the formation of amyloid-beta plaques and tau protein abnormalities in Alzheimer's disease. Elevated or reduced flotillin in cerebrospinal fluid or blood could reflect disease presence or progression [84].

Inflammatory biomarkers

α1-anti-chymotrypsin (a1-ACT), which are produced by astrocytes. The compounds released from the astrocytes, microglia and neurons act as the inflammatory mediators; cytokines such as TNF-α, IL-1b and IL-6; and chemokines such as macrophage colony-stimulating factor and macrophage inflammatory proteins [85].

APoD (Apolipoprotein D): APoD is widely expressed in the brain, especially in AD-affected regions, and its levels are frequently raised in response to oxidative stress and inflammation, two factors that are essential to the pathophysiology of Alzheimer's disease. APoD is hypothesized to have neuroprotective properties via reducing oxidative damage and increasing the clearance of toxic lipids. Greater expression of APoD has been seen in areas of AD where tau tangles and amyloid-beta plaques are present, indicating that this may be the brain's response to the ongoing neurodegeneration [86].

Since neuroinflammation plays a major role in AD pathophysiology, CRISPLD2's (Cysteine-Rich Secretory Protein LCCL Domain Containing 2) involvement in controlling inflammation and its anti-inflammatory capabilities are especially pertinent. Chronic inflammation contributes to the advancement of neurodegeneration in Alzheimer's disease, and proteins such as CRISPLD2 may assist to mitigate these effects. Recent research suggests that CRISPLD2 may be activated in the brain in response to inflammatory signals, possibly serving as a defence mechanism against the deleterious consequences of protracted inflammation [87].

Advancements in treatment

Alzheimer's is a multifactorial disease, though we need multi-therapeutic approaches to cure the Alzheimer's disease. Memory, thinking, behavioral, and learning impairments are the main characteristics of AD [88]. Reducing extracellular deposition of Amyloid β and intracellular deposition of tau proteins are the major objectives of the therapies for Alzheimer's disease [89]. As AD is an irreversible chronic condition, we can control the disease but cannot cure it completely [90].

Table 1: Ongoing therapeutic agents targeting tau pathology in alzheimer's disease

Name	Type	Phase	Site of action	Mechanism of action	Reference
ABBV-181	Monoclonal Antibody	Phase 2/3	Tau protein	Targets specific epitopes of tau protein to inhibit aggregation and reduce neurofibrillary tangles.	[91]
TauVID (Flortaucipir)	PET Imaging Agent	Phase 2	Tau protein aggregates	Binds to tau aggregates for imaging purposes to assess tau pathology and treatment efficacy.	[92]
LMTX (TRx0237)	Tau Aggregation Inhibitor	Phase 3	Tau protein	Inhibits tau aggregation, preventing the formation of neurofibrillary tangles.	[93]
AADvac1	Vaccine	Phase 2	Tau protein	Stimulates an immune response against tau protein to reduce tangles and neurodegeneration.	[95]
PTI-125	Small Molecule	Phase 2	Tau protein	Binds to tau protein to inhibit its aggregation and mitigate tau-related neurodegeneration.	[91]
TPI-287	Small Molecule	Phase 2	Tau protein and microtubules	Stabilizes microtubules and inhibits tau aggregation.	[94]
GV-971 (Oligomannate)	Marine-derived Polysaccharide	Phase 3	Tau protein and amyloid-beta	Modulates neuroinflammation and targets both tau and amyloid-beta to reduce associated pathology.	[96]

Tau therapy

Tau therapies for Alzheimer's disease mentioned in table 1 focus on targeting the tau protein, which forms harmful tangles in the brain. ABBV-181 is a monoclonal antibody that inhibits tau aggregation by targeting specific tau epitopes [91], while TauVID (Flortaucipir) is used as a PET imaging agent to visualize tau pathology [92]. LMTX (TRx0237) and PTI-125 are designed to prevent the formation of neurofibrillary tangles by inhibiting tau aggregation [93]. TPI-287 not only inhibits tau aggregation but also stabilizes microtubules [94].

AADvac1 is a vaccine that stimulates an immune response against tau [95] and GV-971 (Oligomannate) targets both tau and amyloid-beta to reduce neuroinflammation and associated pathology [96].

Anti-amyloid therapy

Anti-amyloid drugs for Alzheimer's target amyloid-beta plaques to reduce their buildup and associated damage mentioned in table 2. Lecanemab (Leqembi) [97], an approved drug, and other monoclonal antibodies like Donanemab and Gantenerumab promote plaque clearance. Crenezumab targets both plaques and soluble forms [98], while ALZ-801 prevents oligomer aggregation [99]. Vaccines like ACC-001 [100] and UB-311 stimulate the immune system to clear amyloid-beta, aiming to halt plaque formation and progression [101-103].

Table 2: Ongoing therapeutic agents targeting amyloid-beta in alzheimer's disease

Name	Type	Phase	Site of action	Mechanism of action	Reference
Lecanemab (Leqembi)	Monoclonal Antibody	Approved	Amyloid-beta plaques and soluble amyloid-beta	Binds to amyloid-beta plaques and soluble forms, promoting clearance through microglial phagocytosis.	97
Donanemab	Monoclonal Antibody	Phase 3	N3pE-modified amyloid-beta plaques	Targets N3pE-modified amyloid-beta, promoting plaque removal by the immune system.	98
Gantenerumab	Monoclonal Antibody	Phase 3	Amyloid-beta plaques	Binds to amyloid-beta plaques, inducing microglial activation to enhance plaque clearance.	98
Crenezumab	Monoclonal Antibody	Phase 3	Amyloid-beta plaques and soluble amyloid-beta	Binds to amyloid-beta plaques and soluble forms, promoting removal and reducing plaque formation.	98
ALZ-801	Modified Drug	Phase 3	Amyloid-beta oligomers and plaques	Binds to amyloid-beta oligomers, preventing aggregation and promoting plaque clearance.	99
IV Immunoglobulin (IVIG)	Immunotherapy	Phase 3	Amyloid-beta plaques and neuroinflammation	Contains diverse antibodies that modulate immune response, reduce inflammation, and aid in plaque clearance.	102
ACC-001	Vaccine	Phase 1/2	Amyloid-beta peptides and plaques	Induces immune response against amyloid-beta, promoting plaque removal via antibody binding.	100
Eli Lilly's Amyloid-beta Vaccine (LY3303560)	Vaccine	Phase 1	Amyloid-beta plaques	Stimulates immune system to produce antibodies against amyloid-beta plaques, facilitating their clearance.	103
Protofibril Vaccine	Vaccine	Phase 1/2	Protofibril forms of amyloid-beta	Targets protofibrils to induce immune response and prevent their aggregation into plaques.	103
UB-311	Vaccine	Phase 2	Amyloid-beta plaques and soluble amyloid-beta	Stimulates immune response to produce antibodies against amyloid-beta, aiding in plaque removal.	101

Gene and cell therapies

Gene and cell therapies are innovative approaches being explored for Alzheimer's disease, targeting the root causes of neurodegeneration. AAV2-CRISPR uses viral vectors to deliver gene-editing tools [104], while Cerebrolysin and NeuroStem-1 focus on neuroprotection and repair using peptides and stem cells, respectively [105, 106]. Stem Cell-Derived Neurons aim to replace damaged neurons [106], and GDNF Therapy delivers neurotrophic factors to support neuron survival [108]. In preclinical stages, Ad5-CMV-PSEN1 and AAV-GFAP are designed to modify gene expression and enhance astrocyte function, offering hope for slowing disease progression [109, 106, 110].

Table 3: Current and emerging gene and cell therapies for Alzheimer's disease

Name	Type	Phase	Site of action	Mechanism of action	Reference
AAV2-CRISPR	Gene therapy	Early clinical trials	Target genes associated with Alzheimer's	Uses adeno-associated virus (AAV) vectors to deliver CRISPR/Cas9 gene-editing tools to modify genes related to Alzheimer's pathology.	[104]
Cerebrolysin	Cell therapy	Phase 3	Brain neuroprotection	A peptide mixture derived from pig brain tissue that is believed to enhance neuroprotection and support neuronal survival.	[105]
NeuroStem-1	Stem cell therapy	Phase 1	Brain regions affected by Alzheimer's	Uses human neural stem cells to replace damaged neurons and promote repair in the brain.	[106]
Stem Cell-Derived Neurons	Cell therapy	Preclinical to phase 1	Brain regions affected by Alzheimer's	Transplants neurons derived from human stem cells into the brain to replace damaged neurons and restore function.	[107]
GDNF (Glial cell line-derived neurotrophic factor) therapy	Gene therapy	Preclinical	Neurons in the brain	Delivers GDNF to support neuron survival and function, aiming to slow the progression of neurodegeneration.	[108]
Ad5-CMV-PSEN1	Gene therapy	Preclinical	Neurons in the brain	Uses adenoviral vectors to deliver PSEN1 (Presenilin 1) to modify gene expression and influence Alzheimer's disease progression.	[109]
AAV-GFAP	Gene therapy	Preclinical	Astrocytes in the brain	Delivers genes that encode for growth factors to support astrocyte function and protect against neurodegeneration	[107]

CONCLUSION

Alzheimer's disease (AD) is a multifaceted neurodegenerative condition primarily affecting older individuals, characterized by the accumulation of amyloid-beta plaques and tau protein tangles in the brain. Age-related changes in the transcriptome, social isolation, and various health factors, including diabetes, hypertension, and obesity, contribute to its development. Genetic predispositions also play a significant role, with polymorphisms in genes like TREM2 and BACE1 influencing susceptibility. Biomarkers such as oxidative stress indicators, CNS metabolites, plasma metabolites, and inflammatory markers provide insights into AD pathology and serve

as potential targets for therapeutic interventions. Oxidative stress, reflected in compromised antioxidant enzymes and increased oxidative stress markers, contributes to neuronal damage and Aβ accumulation. CNS metabolites like APP, Aβ42, tau proteins, and inflammatory markers like α1-anti-chymotrypsin exacerbate neuroinflammation, furthering disease progression. In therapeutic endeavors, targeting amyloid β deposition and tau protein accumulation remains pivotal. Novel compounds like salicylic acid–donepezil–rivastigmine hybrids offer multifunctional effects including inflammation inhibition and neuroprotection. Therapeutic strategies encompass diverse approaches such as anti-amyloid and tau therapies, inflammation modulation, neurogenesis promotion, and metabolic optimization. However, AD remains irreversible, necessitating a shift towards disease management rather than a complete cure. While there is ongoing research and innovation in therapeutic developments, the complexity of AD demands a comprehensive approach involving early detection, lifestyle interventions, and personalized treatment plans to improve the quality of life for affected individuals and their caregivers.

In the future, Alzheimer's disease research and treatment will focus on early detection methods, personalized medicine, and disease-modifying therapies. Non-pharmacological interventions, digital health technologies, and combination therapies will also play important roles. Immunotherapy and brain stimulation techniques show promise, while multidisciplinary care models will cater to the complex needs of patients and caregivers. Global collaboration and advocacy efforts will be crucial in advancing Alzheimer's care and reducing its impact worldwide.

ACKNOWLEDGMENT

All authors contributed to the conceptualization, design, research, writing, and review of the manuscript. They all approved the final version for publication. The authors express gratitude to the chairman, management, principal, teaching, and non-teaching staff of Acharya and BM Reddy College of Pharmacy, Bengaluru, for their support during the review submission process.

FUNDING

No funding was provided for this study.

AUTHORS CONTRIBUTIONS

Suresh Janadri: Conceptualization, Supervision, Shreelaxmi Dadmi: Writing Original draft preparation and Visualization, Manjunatha P Mudagal: Conceptualization and Supervision, Uday Raj Sharma: Reviewing and Editing, Surendra Vada: Reviewing and Editing, Thiriveedi Haribabu: Visualization.

CONFLICTS OF INTERESTS

The authors have no conflicts of interest to declare.

REFERENCES

1. Ganaie MA, Kumari A, Girard A, Kasa Vubu J, Tanveer M, Alzheimers Disease Neuroimaging Initiative. Diagnosis of alzheimers disease via intuitionistic fuzzy least squares twin SVM. Appl Soft Comput. 2023 Dec 1;149:110899. doi: 10.1016/j.asoc.2023.110899.
2. Vrabec R, Blunden G, Cahlikova L. Natural alkaloids as multi-target compounds towards factors implicated in alzheimers disease. Int J Mol Sci. 2023 Feb 23;24(5):4399. doi: 10.3390/ijms24054399, PMID 36901826.
3. Zhang S, Butt MJ, Iqatish AM, Zulfiqar K. Chinas belt and road initiative (BRI) under the vision of maritime community with a shared future and its impacts on global fisheries governance. Heliyon. 2023;9(4):e15398. doi: 10.1016/j.heliyon.2023.e15398, PMID 37151664.
4. Goedert M, Spillantini MG, Crowther RA. Tau proteins and neurofibrillary degeneration. Brain Pathol. 1991 Jul;1(4):279-86. doi: 10.1111/j.1750-3639.1991.tb00671.x, PMID 1669718.
5. Knopman DS, Amieva H, Petersen RC, Chetelat G, Holtzman DM, Hyman BT. Alzheimer disease. Nat Rev Dis Primers. 2021 May 13;7(1):33. doi: 10.1038/s41572-021-00269-y, PMID 33986301.
6. Anand R, Gill KD, Mahdi AA. Therapeutics of alzheimers disease: past present and future. Neuropharmacology. 2014 Jan 1;76(A):27-50. doi: 10.1016/j.neuropharm.2013.07.004, PMID 23891641.
7. Sagare AP, Deane R, Zetterberg H, Wallin A, Blennow K, Zlokovic BV. Impaired lipoprotein receptor-mediated peripheral binding of plasma amyloid-β is an early biomarker for mild cognitive impairment preceding alzheimers disease. J Alzheimers Dis. 2011 Jan 1;24(1):25-34. doi: 10.3233/JAD-2010-101248, PMID 21157031.
8. Huang LK, Chao SP, HU CJ. Clinical trials of new drugs for alzheimer disease. J Biomed Sci. 2020;27(1):18. doi: 10.1186/s12929-019-0609-7, PMID 31906949.
9. Wolters FJ, Ikram MA. Epidemiology of vascular dementia. Arterioscler Thromb Vasc Biol. 2019 Aug;39(8):1542-9. doi: 10.1161/ATVBAHA.119.311908, PMID 31294622.
10. Kakara RS, Lee R, Eckstrom EN. Cause-specific mortality among adults aged ≥65 y in the United States, 1999 through 2020. Public Health Rep. 2024 Jan;139(1):54-8. doi: 10.1177/00333549231155869, PMID 36905313.
11. LI X, Feng X, Sun X, Hou N, Han F, Liu Y. Global regional and national burden of alzheimers disease and other dementias, 1990-2019. Front Aging Neurosci. 2022 Oct 10;14:937486. doi: 10.3389/fnagi.2022.937486, PMID 36299608.
12. Sutherland GT, Lim J, Srikanth V, Bruce DG. Epidemiological approaches to understanding the link between type 2 diabetes and dementia. J Alzheimers Dis. 2017 Jan 1;59(2):393-403. doi: 10.3233/JAD-161194, PMID 28372332.
13. Allwright M, Mundell HD, Mc Corkindale AN, Lindley RI, Austin PJ, Guennewig B. Ranking the risk factors for alzheimers disease; findings from the UK biobank study. Aging Brain. 2023 Jan 1;3:100081. doi: 10.1016/j.nbas.2023.100081, PMID 37384134.
14. Timsina J, Ali M, DO A, Wang L, Western D, Sung YJ. Harmonization of CSF and imaging biomarkers in alzheimers disease: need and practical applications for genetics studies and preclinical classification. Neurobiol Dis. 2024 Jan 1;190:106373. doi: 10.1016/j.nbd.2023.106373, PMID 38072165.
15. Allison SL, Jonaitis EM, Koscik RL, Hermann BP, Mueller KD, Cary RP. Neurodegeneration alzheimers disease biomarkers and longitudinal verbal learning and memory performance in late middle age. Neurobiol Aging. 2021 Jun 1;102:151-60. doi: 10.1016/j.neurobiolaging.2021.01.030, PMID 33765428.
16. Wang T, Liu XH, Guan J, GE S, WU MB, Lin JP. Advancement of multi-target drug discoveries and promising applications in the field of alzheimers disease. Eur J Med Chem. 2019 May 1;169:200-23. doi: 10.1016/j.ejmech.2019.02.076, PMID 30884327.
17. Zheng L, WU S, Jin H, WU J, Wang X, Cao Y. Molecular mechanisms and therapeutic potential of icariin in the treatment of alzheimers disease. Phytomedicine. 2023 Jul 25;116:154890. doi: 10.1016/j.phymed.2023.154890, PMID 37229892.
18. Liggins C, Snyder HM, Silverberg N, Petanceska S, Refolo LM, Ryan L. International alzheimers disease research portfolio (IADRP) aims to capture global alzheimers disease research funding. Alzheimers Dement. 2014 May;10(3):405-8. doi: 10.1016/j.jalz.2013.12.013, PMID 24780512.
19. Litke R, Garcharna LC, Jiwani S, Neugroschl J. Modifiable risk factors in alzheimer disease and related dementias: a review. Clin Ther. 2021 Jun 1;43(6):953-65. doi: 10.1016/j.clinthera.2021.05.006, PMID 34108080.
20. Scheltens P, Blennow K, Breteler MM, DE Strooper B, Frisoni GB, Salloway S. Alzheimers disease. Lancet. 2016 Jul 30;388(10043):505-17. doi: 10.1016/S0140-6736(15)01124-1, PMID 26921134.
21. Sala Frigerio CS, Wolfs L, Fattorelli N, Thrupp N, Voytyuk I, Schmidt I. The major risk factors for alzheimers disease: age sex and genes modulate the microglia response to Aβ plaques. Cell Rep. 2019 Apr 23;27(4):1293-1306.e6. doi: 10.1016/j.celrep.2019.03.099, PMID 31018141.
22. Reagh ZM, Noche JA, Tustison NJ, Delisle D, Murray EA, Yassa MA. Functional imbalance of anterolateral entorhinal cortex and hippocampal dentate/CA3 underlies age-related object pattern separation deficits. Neuron. 2018 Mar 7;97(5):1187-1198.e4. doi: 10.1016/j.neuron.2018.01.039, PMID 29518359.
23. Colmant L, Bierbrauer A, Bellaali Y, Kunz L, Van Dongen J, Sleegers K. Dissociating effects of aging and genetic risk of

sporadic alzheimers disease on path integration. Neurobiol Aging. 2023 Nov 1;131:170-81. doi: 10.1016/j.neurobiolaging.2023.07.025, PMID 37672944.

24. D OLEIRE Uquillas F, Jacobs HI, Biddle KD, Properzi M, Hanseeuw B, Schultz AP. Regional tau pathology and loneliness in cognitively normal older adults. Transl Psychiatry Translator. 2018 Dec 18;8(1):282. doi: 10.1038/s41398-018-0345-x, PMID 30563962.
25. Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL. Loneliness and risk of alzheimer disease. Arch Gen Psychiatry. 2007 Feb 1;64(2):234-40. doi: 10.1001/archpsyc.64.2.234, PMID 17283291.
26. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community based longitudinal study. Lancet. 2000 Apr 15;355(9212):1315-9. doi: 10.1016/S0140-6736(00)02113-9, PMID 10776744.
27. Pugh E, DE Vito A, Divers R, Robinson A, Weitzner DS, Calamia M. Social factors that predict cognitive decline in older African American adults. Int J Geriatr Psychiatry. 2021 Mar;36(3):403-10. doi: 10.1002/gps.5435, PMID 32946627.
28. Zhang J, Chen C, Hua S, Liao H, Wang M, Xiong Y. An updated meta-analysis of cohort studies: diabetes and risk of alzheimers disease. Diabetes Res Clin Pract. 2017 Feb 1;124:41-7. doi: 10.1016/j.diabres.2016.10.024, PMID 28088029.
29. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R. Impaired insulin and insulin like growth factor expression and signaling mechanisms in alzheimers disease is this type 3 diabetes? J Alzheimers Dis. 2005 Mar 3;7(1):63-80. doi: 10.3233/JAD-2005-7107, PMID 15750215.
30. Lynn J, Park M, Ogunwale C, Acquaah Mensah GK. A tale of two diseases: exploring mechanisms linking diabetes mellitus with alzheimers disease. J Alzheimers Dis. 2022 Jan 1;85(2):485-501. doi: 10.3233/JAD-210612, PMID 34842187.
31. AN Y, Varma VR, Varma S, Casanova R, Dammer E, Pletnikova O. Evidence for brain glucose dysregulation in alzheimers disease. Alzheimers Dement. 2018 Mar 1;14(3):318-29. doi: 10.1016/j.jalz.2017.09.011, PMID 29055815.
32. Zhou Y, Luo Y, Dai J. Axonal and dendritic changes are associated with diabetic encephalopathy in rats: an important risk factor for alzheimers disease. J Alzheimers Dis. 2013 Jan 1;34(4):937-47. doi: 10.3233/JAD-121762, PMID 23302655.
33. Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W. Midlife blood pressure and neuritic plaques neurofibrillary tangles and brain weight at death: the has Honolulu Asia aging study. Neurobiol Aging. 2000;21(1):57-62. doi: 10.1016/s0197-4580(00)00106-8, PMID 10794849.
34. Kim Mitsuyama S, Yamamoto E, Tanaka T, Zhan Y, Izumi Y, Izumiya Y. Critical role of angiotensin II in excess salt induced brain oxidative stress of stroke prone spontaneously hypertensive rats. Stroke. 2005;36(5):1083-8. doi: 10.1161/01.STR.0000163084.16505.e3, PMID 15817892.
35. Pendlebury ST, Rothwell PM. Prevalence incidence and factors associated with pre stroke and post stroke dementia: a systematic review and meta-analysis. Lancet Neurol. 2009 Nov 1;8(11):1006-18. doi: 10.1016/S1474-4422(09)70236-4, PMID 19782001.
36. Wang F, Hua S, Zhang Y, YU H, Zhang Z, Zhu J. Association between small vessel disease markers medial temporal lobe atrophy and cognitive impairment after stroke: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2021 Jan 1;30(1):105460. doi: 10.1016/j.jstrokecerebrovasdis.2020.105460, PMID 33227579.
37. Shah NS, Vidal JS, Masaki K, Petrovitch H, Ross GW, Tilley C. Midlife blood pressure plasma β-amyloid and the risk for alzheimer disease: the Honolulu Asia aging study. Hypertension. 2012 Apr;59(4):780-6. doi: 10.1161/HYPERTENSIONAHA.111.178962, PMID 22392902.
38. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Diaz Arrastia R, Park DC. Risk factors for β-amyloid deposition in healthy aging: vascular and genetic effects. JAMA Neurol. 2013 May 1;70(5):600-6. doi: 10.1001/jamaneurol.2013.1342, PMID 23553344.
39. Potter T, Lioutas VA, Tano M, Pan A, Meeks J, Woo D. Cognitive impairment after intracerebral hemorrhage: a systematic review of current evidence and knowledge gaps. Front Neurol. 2021 Aug 27;12:716632. doi: 10.3389/fneur.2021.716632, PMID 34512528.
40. Nakagawa T, Hasegawa Y, Uekawa K, Kim Mitsuyama S. Chronic kidney disease accelerates cognitive impairment in a mouse model of alzheimers disease through angiotensin II. Exp Gerontol. 2017 Jan 1;87(A):108-12. doi: 10.1016/j.exger.2016.11.012, PMID 27916702.
41. Jackson L, Eldahshan W, Fagan SC, Ergul A. Within the brain: the renin angiotensin system. Int J Mol Sci. 2018 Mar 15;19(3):876. doi: 10.3390/ijms19030876, PMID 29543776.
42. Bos D, Vernooij MW, DE Bruijn RF, Koudstaal PJ, Hofman A, Franco OH. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. Alzheimers Dement. 2015 Jun 1;11(6):639-47.e1. doi: 10.1016/j.jalz.2014.05.1758, PMID 25150731.
43. Papanastasiou CA, Theochari CA, Zareifopoulos N, Arfaras Melainis A, Giannakoulas G, Karamitsos TD. Atrial fibrillation is associated with cognitive impairment all cause dementia vascular dementia and alzheimers disease: a systematic review and meta-analysis. J Gen Intern Med. 2021 Oct;36(10):3122-35. doi: 10.1007/s11606-021-06954-8, PMID 34244959.
44. Maeda S, Kagami Y, Ogura M, Taji H, Suzuki R, Kondo E. CD34+-selected autologous peripheral blood stem cell transplantation conditioned with total body irradiation for malignant lymphoma: increased risk of infectious complications. Int J Hematol. 2001;74(2):214-21. doi: 10.1007/BF02982008, PMID 11594525.
45. Julien C, Tremblay C, Phivilay A, Berthiaume L, Emond V, Julien P. High fat diet aggravates amyloid beta and tau pathologies in the 3xTg-AD mouse model. Neurobiol Aging. 2010 Sep 1;31(9):1516-31. doi: 10.1016/j.neurobiolaging.2008.08.022, PMID 18926603.
46. Gomez Lazaro M, Galindo MF, Melero Fernandez DE Mera RM, Fernandez Gomez FJ, Concannon CG, Segura MF. Reactive oxygen species and p38 mitogen-activated protein kinase activate bax to induce mitochondrial cytochrome c release and apoptosis in response to malonate. Mol Pharmacol. 2007 Mar 1;71(3):736-43. doi: 10.1124/mol.106.030718, PMID 17172466.
47. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18 y follow-up of overweight and risk of alzheimer disease. Arch Intern Med. 2003 Jul 14;163(13):1524-8. doi: 10.1001/archinte.163.13.1524, PMID 12860573.
48. Wahid RM, Samy W, El Sayed SF. Cognitive impairment in obese rat model: role of glial cells. Int J Obes (Lond). 2021 Oct;45(10):2191-6. doi: 10.1038/s41366-021-00880-9, PMID 34140627.
49. Fan L, Borenstein AR, Wang S, Nho K, Zhu X, Wen W. Associations of circulating saturated long chain fatty acids with risk of mild cognitive impairment and alzheimers disease in the alzheimers disease neuroimaging initiative (ADNI) cohort. E Biomedicine. 2023 Nov 1;97:104818. doi: 10.1016/j.ebiom.2023.104818.
50. Harilal S, Jose J, Parambi DG, Kumar R, Mathew GE, Uddin MS. Advancements in nanotherapeutics for alzheimers disease: current perspectives. J Pharm Pharmacol. 2019 Sep;71(9):1370-83. doi: 10.1111/jphp.13132, PMID 31304982.
51. Canet G, Dias C, Gabelle A, Simonin Y, Gosselet F, Marchi N. HIV neuroinfection and alzheimers disease: similarities and potential links? Front Cell Neurosci. 2018 Sep 11;12:307. doi: 10.3389/fncel.2018.00307, PMID 30254568.
52. Dibacto RE, Ambamba BD, Ella FA, Nyangono CF, Nanhah JV, Fonkoua M. The neuroprotective effect of Xylopia parviflora against aluminum chloride induced neurotoxicity in rats. Heliyon. 2022 Jul 1;8(7):e09918. doi: 10.1016/j.heliyon.2022.e09896.
53. Ogunlade B, Adelakun SA, Agie JA. Nutritional supplementation of gallic acid ameliorates alzheimer type hippocampal neurodegeneration and cognitive impairment induced by aluminum chloride exposure in adult wistar rats. Drug Chem Toxicol. 2022 Mar 4;45(2):651-62. doi: 10.1080/01480545.2020.1754849, PMID 32329360.
54. Bakulski KM, Seo YA, Hickman RC, Brandt D, Vadari HS, HU H. Heavy metals exposure and alzheimers disease and related

dementias. J Alzheimers Dis. 2020 Jan 1;76(4):1215-42. doi: 10.3233/JAD-200282, PMID 32651318.
55. Sperling RA, Jack JR CR, Black SE, Frosch MP, Greenberg SM, Hyman BT. Amyloid related imaging abnormalities in amyloid modifying therapeutic trials: recommendations from the alzheimers association research roundtable workgroup. Alzheimers Dement. 2011 Jul 1;7(4):367-85. doi: 10.1016/j.jalz.2011.05.2351, PMID 21784348.
56. Adams JD. Probable causes of alzheimers disease. Sci. 2021 Mar 2;3(1):16. doi: 10.3390/sci3010016.
57. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA. Mind diet slows cognitive decline with aging. Alzheimers Dement. 2015 Sep 1;11(9):1015-22. doi: 10.1016/j.jalz.2015.04.011, PMID 26086182.
58. Ulland TK, Colonna M. TREM2 a key player in microglial biology and alzheimer disease. Nat Rev Neurol. 2018 Nov;14(11):667-75. doi: 10.1038/s41582-018-0072-1, PMID 30266932.
59. Ohno M, Cole SL, Yasvoina M, Zhao J, Citron M, Berry R. BACE1 gene deletion prevents neuron loss and memory deficits in 5XFAD APP/PS1 transgenic mice. Neurobiol Dis. 2007 Apr 1;26(1):134-45. doi: 10.1016/j.nbd.2006.12.008, PMID 17258906.
60. Giliberto L, Borghi R, Piccini A, Mangerini R, Sorbi S, Cirmena G. Mutant presenilin 1 increases the expression and activity of BACE1. J Biol Chem. 2009 Apr 3;284(14):9027-38. doi: 10.1074/jbc.M805685200, PMID 19196715.
61. Nuzzo D, Galizzi G, Amato A, Terzo S, Picone P, Cristaldi L. Regular intake of pistachio mitigates the deleterious effects of a high fat diet in the brain of obese mice. Antioxidants (Basel). 2020 Apr 15;9(4):317. doi: 10.3390/antiox9040317, PMID 32326575.
62. Montine TJ, Quinn J, Kaye J, Morrow JD. F2-isoprostanes as biomarkers of late onset alzheimers disease. J Mol Neurosci. 2007 Sep;33(1):114-9. doi: 10.1007/s12031-007-0044-1, PMID 17901555.
63. Nie Y, Chu C, Qin Q, Shen H, Wen L, Tang Y. Lipid metabolism and oxidative stress in patients with alzheimers disease and amnestic mild cognitive impairment. Brain Pathol. 2024 Jan;34(1):e13202. doi: 10.1111/bpa.13202, PMID 37619589.
64. Kalra J, Kumar P, Majeed AB, Prakash A. Modulation of LOX and COX pathways via inhibition of amyloidogenesis contributes to mitoprotection against β-amyloid oligomer induced toxicity in an animal model of alzheimers disease in rats. Pharmacol Biochem Behav. 2016 Jul-Aug;146-147:1-12. doi: 10.1016/j.pbb.2016.04.002, PMID 27106205.
65. Molinuevo JL, Ayton S, Batrla R, Bednar MM, Bittner T, Cummings J. Current state of alzheimers fluid biomarkers. Acta Neuropathol. 2018 Dec;136(6):821-53. doi: 10.1007/s00401-018-1932-x, PMID 30488277.
66. Khan SS, Bloom GS. Tau: the center of a signaling nexus in alzheimers disease. Front Neurosci. 2016 Feb 9;10:31. doi: 10.3389/fnins.2016.00031, PMID 26903798.
67. Skillback T, Rosen C, Asztely F, Mattsson N, Blennow K, Zetterberg H. Diagnostic performance of cerebrospinal fluid total tau and phosphorylated tau in creutzfeldt jakob disease: results from the swedish mortality registry. JAMA Neurol. 2014 Apr 1;71(4):476-83. doi: 10.1001/jamaneurol.2013.6455, PMID 24566866.
68. Pereira JB, Janelidze S, Smith R, Mattsson Carlgren N, Palmqvist S, Teunissen CE. Plasma GFAP is an early marker of amyloid-β but not tau pathology in alzheimers disease. Brain. 2021 Nov 1;144(11):3505-16. doi: 10.1093/brain/awab223, PMID 34259835.
69. Baldacci F, Lista S, Cavedo E, Bonuccelli U, Hampel H. Diagnostic function of the neuroinflammatory biomarker YKL-40 in alzheimers disease and other neurodegenerative diseases. Expert Rev Proteomics. 2017;14(4):285-99. doi: 10.1080/14789450.2017.1304217, PMID 28281838.
70. Wallin AK, Blennow K, Zetterberg H, Londos E, Minthon L, Hansson O. CSF biomarkers predict a more malignant outcome in alzheimer disease. Neurology. 2010 May 11;74(19):1531-7. doi: 10.1212/WNL.0b013e3181dd4dd8, PMID 20458070.
71. Chandra A, Farrell C, Wilson H, Dervenoulas G, DE Natale ER, Politis M. Aquaporin-4 polymorphisms predict amyloid burden and clinical outcome in the alzheimers disease spectrum. Neurobiol Aging. 2021 Jan 1;97:1-9. doi: 10.1016/j.neurobiolaging.2020.06.007, PMID 33068891.
72. Lan YL, Zhao J, MA T, LI S. The potential roles of aquaporin 4 in alzheimers disease. Mol Neurobiol. 2016 Oct;53(8):5300-9. doi: 10.1007/s12035-015-9446-1, PMID 26433375.
73. Crews L, Tsigelny I, Hashimoto M, Masliah E. Role of synucleins in alzheimers disease. Neurotox Res. 2009 Oct;16(3):306-17. doi: 10.1007/s12640-009-9073-6, PMID 19551456.
74. Serrano Pozo A, Das S, Hyman BT. APOE and alzheimers disease: advances in genetics pathophysiology and therapeutic approaches. Lancet Neurol. 2021 Jan 1;20(1):68-80. doi: 10.1016/S1474-4422(20)30412-9, PMID 33340485.
75. Ghosh G, Neely BA, Bland AM, Whitmer ER, Field CL, Duignan PJ. Identification of candidate protein biomarkers associated with domoic acid toxicosis in cerebrospinal fluid of california sea lions (Zalophus californianus). J Proteome Res. 2024 May 28;23(7):2419-30. doi: 10.1021/acs.jproteome.4c00103, PMID 38807289.
76. OU Yang MH, XU F, Liao MC, Davis J, Robinson JK, Van Nostrand WE. N-terminal region of myelin basic protein reduces fibrillar amyloid-β deposition in Tg-5xFAD mice. Neurobiol Aging. 2015;36(2):801-11. doi: 10.1016/j.neurobiolaging.2014.10.006, PMID 25457550.
77. Smith AS, Subramanian J, Doderer J, Moskovitz J. Methionine oxidation of clusterin in alzheimers disease and its effect on clusterins binding to beta amyloid. Neurosci Lett. 2024 Jun 9;836:137874. doi: 10.1016/j.neulet.2024.137874, PMID 38857696.
78. XU M, LI J, Xia L, DU Y, WU B, Shi X. PCSK6 exacerbates alzheimers disease pathogenesis by promoting MT5-MMP maturation. Exp Neurol. 2024 Apr 1;374:114688. doi: 10.1016/j.expneurol.2024.114688, PMID 38216110.
79. Lombardi P, Karadayian AG, Guerra JI, Bustamante J, Rodriguez DE Lores Arnaiz GR, Lores Arnaiz S. Mitochondrial bioenergetics and cytometric characterization of a synaptosomal preparation from mouse brain cortex. Mitochondrion. 2023 Nov 1;73:95-107. doi: 10.1016/j.mito.2023.10.002, PMID 37944836.
80. Marwarha G, Dasari B, Prasanthi JR, Schommer J, Ghribi O. Leptin reduces the accumulation of Aβ and phosphorylated tau induced by 27-hydroxycholesterol in rabbit organotypic slices. J Alzheimers Dis. 2010 Jan 1;19(3):1007-19. doi: 10.3233/JAD-2010-1298, PMID 20157255.
81. Niedowicz DM, Studzinski CM, Weidner AM, Platt TL, Kingry KN, Beckett TL. Leptin regulates amyloid β production via the γ-secretase complex. Biochim Biophys Acta. 2013;1832(3):439-44. doi: 10.1016/j.bbadis.2012.12.009, PMID 23274884.
82. Lilamand M, Bouaziz Amar E, Dumurgier J, Cognat E, Hourregue C, Mouton Liger F. Plasma leptin is associated with amyloid CSF biomarkers and alzheimers disease diagnosis in cognitively impaired patients. J Gerontol A Biol Sci Med Sci. 2023 Apr 1;78(4):645-52. doi: 10.1093/gerona/glac234, PMID 36441007.
83. Liu W, HU Q, Zhang F, Shi K, WU J. Investigation of the causal relationship between osteocalcin and dementia: a men delian randomization study. Heliyon. 2023 Oct 1;9(10):e21073. doi: 10.1016/j.heliyon.2023.e21073, PMID 37916108.
84. Abdullah M, Kimura N, Akatsu H, Hashizume Y, Ferdous T, Tachita T. Flotillin is a novel diagnostic blood marker of alzheimers disease. J Alzheimers Dis. 2019 Jan 1;72(4):1165-76. doi: 10.3233/JAD-190908, PMID 31683489.
85. Galasko D, Montine TJ. Biomarkers of oxidative damage and inflammation in alzheimers disease. Biomark Med. 2010 Feb 1;4(1):27-36. doi: 10.2217/bmm.09.89, PMID 20383271.
86. Dassati S, Waldner A, Schweigreiter R. Apolipoprotein D takes center stage in the stress response of the aging and degenerative brain. Neurobiol Aging. 2014 Jul 1;35(7):1632-42. doi: 10.1016/j.neurobiolaging.2014.01.148, PMID 24612673.
87. Gonzalez Palomo AK, Fernandez Macias JC, Rangel Ramirez VV, Jimenez Avalos JA, Cortes Garcia JD. Transcriptomics applied in research of non-communicable diseases. In: Transcriptomics from aquatic organisms to humans. CRC Press; 2021 Dec 13. p. 91-124. doi: 10.1201/9781003212416-5.
88. Vyas S, Kothari SL, Kachhwaha S. Nootropic medicinal plants: therapeutic alternatives for alzheimers disease. J Herb Med. 2019 Sep-Dec;17-18:100291. doi: 10.1016/j.hermed.2019.100291.

89. Shabbir U, Rubab M, Tyagi A, OH DH. Curcumin and its derivatives as theranostic agents in alzheimers disease: the implication of nanotechnology. Int J Mol Sci. 2020 Dec 27;22(1):196. doi: 10.3390/ijms22010196, PMID 33375513.
90. Peng Y, Tao H, Wang S, Xiao J, Wang Y, SU H. Dietary intervention with edible medicinal plants and derived products for prevention of alzheimers disease: a compendium of time tested strategy. J Funct Foods. 2021 Jun 1;81:104463. doi: 10.1016/j.jff.2021.104463.
91. Shi Y, Ghetti B, Goedert M, Scheres SH. Cryo EM structures of chronic traumatic encephalopathy tau filaments with PET ligand flortaucipir. J Mol Biol. 2023 Jun 1;435(11):168025. doi: 10.1016/j.jmb.2023.168025, PMID 37330290.
92. Parikh NH, Parikh PK, Rao HJ, Shah K, Dave BP, Prajapati BG. Current trends and updates in the treatment of alzheimers disease in: alzheimers disease and advanced drug delivery strategies. Amsterdam: Elsevier; 2024. p. 373-90. doi: 10.1016/B978-0-443-13205-6.00014-5.
93. Cullen NC, Novak P, Tosun D, Kovacech B, Hanes J, Kontsekova E. Efficacy assessment of an active tau immunotherapy in alzheimers disease patients with amyloid and tau pathology: a post hoc analysis of the "ADAMANT" randomised placebo controlled double blind multi-centre phase 2 clinical trial. E Biomedicine. 2024 Jan 1;99:104923. doi: 10.1016/j.ebiom.2023.104923, PMID 38101301.
94. Crestini A, Carbone E, Rivabene R, Ancidoni A, Rosa P, Tata AM. A systematic review on drugs acting as nicotinic acetylcholine receptor agonists in the treatment of dementia. Cells. 2024 Jan 26;13(3):237. doi: 10.3390/cells13030237, PMID 38334629.
95. Elrosasy A, Zeid MA, Negida A. Sodium oligomannate (GV-971) safety and efficacy in the treatment of alzheimers disease: a systematic review and meta-analysis of randomized controlled trials (P11-9.005). Neurology. 2024 Apr 14;17 Suppl 1:102. doi: 10.1212/WNL.0000000000205757.
96. Niu Y, Lin P. Advances of computer aided drug design (CADD) in the development of anti azheimers disease drugs. Drug Discov Today. 2023 Aug 1;28(8):103665. doi: 10.1016/j.drudis.2023.103665, PMID 37302540.
97. Perna A, Montine KS, White LR, Montine TJ, Cholerton BA. Paradigm shift: multiple potential pathways to neurodegenerative dementia. Neurotherapeutics. 2023 Oct 1;20(6):1641-52. doi: 10.1007/s13311-023-01441-w, PMID 37733209.
98. Soderberg L, Johannesson M, Nygren P, Laudon H, Eriksson F, Osswald G. Lecanemab aducanumab and gantenerumab binding profiles to different forms of amyloid beta might explain efficacy and side effects in clinical trials for alzheimers disease. Neurotherapeutics. 2023 Jan 1;20(1):195-206. doi: 10.1007/s13311-022-01308-6, PMID 36253511.
99. Danieli MG, Antonelli E, Longhi E, Gangemi S, Allegra A. The role of microbiota and oxidative stress axis and the impact of intravenous immunoglobulin in systemic lupus erythematosus. Autoimmun Rev. 2024 Aug 24;23(9):103607. doi: 10.1016/j.autrev.2024.103607, PMID 39187222.
100. Abdallah AE. Review on anti-alzheimer drug development: approaches challenges and perspectives. RSC Adv. 2024;14(16):11057-88. doi: 10.1039/D3RA08333K, PMID 38586442.
101. Aljassabi A, Zieneldien T, Kim J, Regmi D, Cao C. Alzheimers disease immunotherapy: current strategies and future prospects. J Alzheimers Dis. 2024 Mar 14;98(3):755-72. doi: 10.3233/JAD-231163, PMID 38489183.
102. Hovakimyan A, Chilingaryan G, King O, Capocchi JK, Chadarevian JP, Davtyan H. mRNA vaccine for alzheimers disease: pilot study. Vaccines (Basel). 2024 Jun 14;12(6):659. doi: 10.3390/vaccines12060659, PMID 38932388.
103. YU HJ, Dickson SP, Wang PN, Chiu MJ, Huang CC, Chang CC. Safety tolerability immunogenicity and efficacy of UB-311 in participants with mild alzheimers disease: a randomised double blind placebo controlled phase 2a study. EBiomedicine. 2023 Aug 1;94:104665. doi: 10.1016/j.ebiom.2023.104665, PMID 37392597.
104. Guan L, Han Y, Yang C, LU S, DU J, LI H. CRISPR-Cas9 mediated gene therapy in neurological disorders. Mol Neurobiol. 2022 Feb;59(2):968-82. doi: 10.1007/s12035-021-02638-w, PMID 34813019.
105. Martinez Torres NI, Cardenas Bedoya J, Torres Mendoza BM. Acute combined cerebrolysin and nicotinamide administration promote cognitive recovery through neuronal changes in the hippocampus of rats with permanent middle cerebral artery occlusion. Neuroscience. 2024 Jun 21;549:76-83. doi: 10.1016/j.neuroscience.2024.05.006, PMID 38734304.
106. Karvelas N, Bennett S, Politis G, Kouris NI, Kole C. Advances in stem cell therapy in alzheimers disease: a comprehensive clinical trial review. Stem Cell Investig. 2022 Feb 21;9:2. doi: 10.21037/sci-2021-063, PMID 35280344.
107. Gao G, LI C, MA Y, Liang Z, LI Y, LI X. Neural stem cell derived extracellular vesicles mitigate alzheimers disease like phenotypes in a preclinical mouse model. Signal Transduct Target Ther. 2023 Jun 14;8(1):228. doi: 10.1038/s41392-023-01436-1, PMID 37311758.
108. Ahmad M, Shafaq Z, Rajput AR, Bughio R. Glial cell line derived neurotrophic factor GDNF gene expression analysis: unveiling neuronal protection mechanisms in alzheimers disease management. JHRR. 2024;4(2):16-21. doi: 10.61919/jhrr.v4i2.766.
109. Mortensen C, Thomsen MT, Chua KC, Hammer HS, Nielsen F, Potz O. Modeling mechanisms of chemotherapy induced peripheral neuropathy and chemotherapy transport using induced pluripotent stem cell derived sensory neurons. Neuropharmacology. 2024 Nov 1;258:110062. doi: 10.1016/j.neuropharm.2024.110062, PMID 38972371.
110. Jing L, Cheng S, Pan Y, Liu Q, Yang W, LI S. Accumulation of endogenous mutant huntingtin in astrocytes exacerbates neuropathology of huntington disease in mice. Mol Neurobiol. 2021 Oct;58(10):5112-26. doi: 10.1007/s12035-021-02451-5, PMID 34250577.