Applied Chemical Engineering (2023) Volume 6 Issue 3
doi: 10.24294/ace.v6i3.2338

REVIEW ARTICLE

Receptor-based approaches and therapeutic targets in Alzheimer's disease along with role of AI in drug designing: Unraveling pathologies and advancing treatment strategies

Mohsina Patwekar[1,*], Faheem Patwekar[1], Daniyal Shaikh[1], Shaikh Rohin Fatema[1], Sunil J. Aher[2], Rohit Sharma[3,*]

[1] *Luqman College of Pharmacy, Gulbarga 585102, Karnataka, India*

[2] *Sanjivani College of Pharmaceutical Education and Research, Kopargaon 423601, Maharashtra, India*

[3] *Department of Rasa Shastra and Bhaishajya Kalpana, Faculty of Ayurveda, Banaras Hindu University, Varanasi 221005, Uttar Pradesh, India*

*** Corresponding authors:** Mohsina Patwekar, Mohsina.patwekar@gmail.com; Rohit Sharma, rohitsharma@bhu.ac.in

ABSTRACT

Alzheimer's disease (AD) is a prevalent cause of dementia in the elderly, characterized by progressive cognitive decline and neurodegeneration. This review focuses on the etiology of AD, the role of various receptors [TNF (Tumor necrosis factor) receptor, nAChR (Neuronal nicotinic acetylcholine receptors), NMDARs (N-Methyl-D-aspartate receptors), APOE (Apolipoprotein E) receptor, and amyloid-beta receptor], and risk factors contributing to its development. AD progresses through mild, moderate, and severe stages, each exhibiting distinct symptoms. The hallmark pathologies are neurofibrillary tangles and amyloid plaques, comprised of hyperphosphorylated tau protein and amyloid-beta peptides, respectively. Current pharmacotherapeutic options alleviate symptoms but lack a complete cure. To address the challenges in developing effective AD treatments, researchers have turned to artificial intelligence (AI) and computational approaches in drug design. AI techniques, including machine learning and molecular docking, enable the analysis of large datasets and prediction of molecular interactions between potential drug candidates and target receptors. Virtual screening and molecular modeling aid in identifying novel therapeutic compounds. Predictive modeling and optimization algorithms optimize drug properties and predict efficacy. AI also facilitates the repurposing of existing drugs by analyzing their interactions with AD-related receptors and pathways. Clinical trial optimization using AI algorithms enhances patient selection, treatment monitoring, and outcome prediction. Integrating AI into AD drug design holds tremendous promise for accelerating the discovery of effective interventions. By leveraging AI's capabilities, researchers can efficiently analyze extensive data, predict drug-target interactions, and optimize drug properties, leading to the identification of novel AD treatments. However, further research and validation are needed to translate AI-driven drug design approaches into clinically viable solutions for AD patients. Through continued advancements in AI and collaborative efforts, the development of targeted and advanced therapies for AD is within reach.

Keywords: Alzheimer's disease; receptors; computational approach; artificial intelligence

ARTICLE INFO

Received: 1 July 2023
Accepted: 28 August 2023
Available online: 31 October 2023

1. Introduction

The first person to describe a dementing ailment that would eventually be recognized as AD was the German neuropathologist Dr. Alois Alzheimer. A severe form of dementia known as Alzheimer disease (AD) causes issues with memory, language, and behavior[1]. According to the 1992 definition provided by the World Health Organization (WHO)[2], dementia is a phenomenon that is caused by a brain disorder that is usually long or progressing. A variety of higher brain functions, including memory, reasoning, understanding,

computation, learning, language, and judgment, are impaired. They typically coexist with changes in social conduct, emotional control, or motivation. Dementia has several origins, including AD and cerebrovascular disease[2]. Cognitive decline, impaired memory and eventually dementia are inescapable neurological symptoms of AD, which is brought on by the death of brain cells. In those 65 and older, it causes dementia the most frequently[3,4]. The disease goes through three primary stages, each with its own difficulties and signs. By identifying the disease phases at this time, medical experts can predict future symptoms and possible treatments for AD cases that are both sporadic and hereditary. The symptoms of AD vary in severity and are specific to each individual instance. Both familial and sporadic occurrences of AD can be attributed to the inheritance of specific genes. The most prevalent form of AD, known as sporadic AD, has a relationship to the apolipoprotein 4 (APOE 4) allele, with homozygotic conditions carrying a higher risk[5,6]. The sickness goes through three primary stages, each with its own difficulties and signs. By figuring out what stage the disease is now at, medical practitioners can predict future symptoms and possible treatments. The degree of AD symptoms varies and is unique to each incidence. Specific genes can be passed down through families, which can explain AD cases that are both sporadic and genetic. The apo lipoprotein 4 (APOE4) allele and the most common kind of AD, known as sporadic AD, both have a link, with homozygotic circumstances bearing a greater risk. A few of the numerous etiological factors for AD include genetics, environmental factors, and ordinary lifestyle choices **Figure 1**[7]. The neocortex and hippocampal portions in brain, which are sensitive and essential for memory and cognition, play crucial roles in learning, forming new memories, spatial navigation, and the integration of sensory information[8].

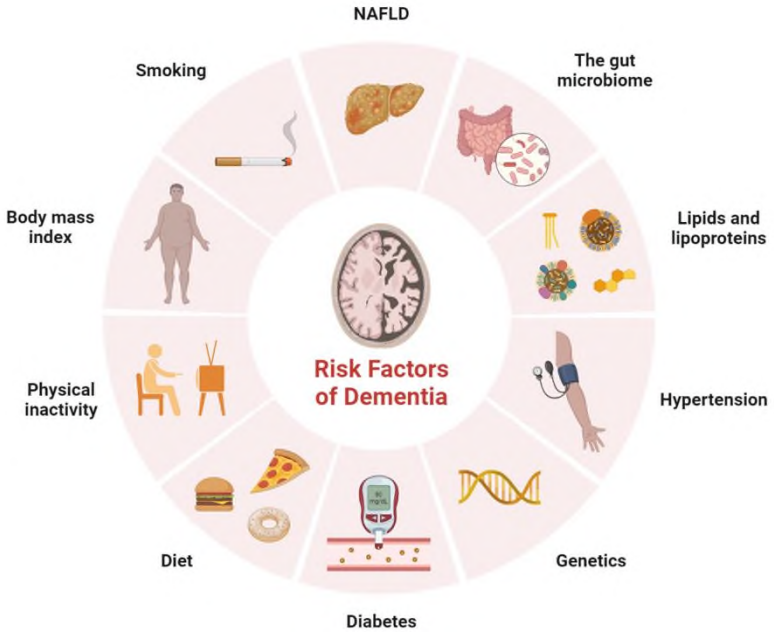

Figure 1. The elements that contribute to Alzheimer's disease.

AD may have more than one definition, depending on its intended application. Numerous elements, including clinical trials for novel therapies, epidemiological research, or pathological examinations, might be used to make a clinical diagnosis[9]. The National Institute of Health's Work Group disorders of the communication and Nervous system, in conjunction with the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), formulated diagnostic criteria for Alzheimer's disease, which were widely embraced[10]. Based on this criterion, the diagnosis of AD is divided into 3 parts: definite, feasible as well likely. The existence of dementia must be determined by clinical examination, recorded by a standardized mental health evaluation, and verified by neuropsychological testing in order for AD to be considered probable. These must show cognitive defects in two or more domains, along with memory loss and other cognitive decline in time even in the absence of delirium. There must be no other systemic or brain disorders that might

account for the gradual losses in memory, cognition, and the onset must occur between the ages of 40 and 90. Characteristics that, albeit not necessary, support a likely AD diagnosis progressive deficits in particular cognitive abilities like language, praxis, and perceptual recognition; impairments in daily living activities; a ancestry of AD, specific if it has been confirmed pathologically; as well normal or nonspecific results on common tests like spinal fluid analysis, electroencephalography, and computerized tomography. A likely diagnosis of AD is supported by mental and behavioral problems, weight loss, and, in more severe cases, increased muscular tone, myoclonus, aberrant gait patterns, and seizures. When a second systemic or brain disease is present but is not thought to be the source of the dementia, when the conventional clinical syndrome is present but there are changes in the onset, appearance, or clinical course, when a single, persistent brain disease is there but not thought to be the dementia's primary cause, and when any of these circumstances apply, the diagnosis of possible AD is made. If no other known reason is present, a gradual cognitive deterioration is discovered. AD has been shown to be unlikely if there is a rapid apoplectic onset, localized neurologic abnormalities, seizures, or gait problem in the early or starting phases of the illness. According to research, these variables have a moderate to exceptional degree of reliability[11,12]. The fatalities in other neurodegenerative diseases like Parkinson's disease, up to 80% of the neurons may need to be faulty before a symptomatic threshold is crossed and clinically noticeable issues appear[13].

2. Different variables involved in Alzheimer's disease along with the correlation of receptors

2.1. Molecular genetics of Alzheimer's disease and aging

Ageing can impact the body's auto-healing process, including those in the brain, as several studies have shown. Additionally, as people age, a certain heart-related risk factors, like excessive Blood pressure, cardiac disorder, and too much low density lipoprotein—become increasingly common[3]. Approximately 5% of AD affects persons between the ages of 65 and 74. The likelihood increases to 50% for people above 85. The main factor for AD is age, and it is also one of the risk factors that cannot be altered[14].

AD is a neurodegenerative disorder which occurs primarily in older adults, particularly those over the age of 65. It is identified by the progressive loss of cognitive function, including memory loss, confusion, and difficulties with language and problem-solving. While AD involves complex alteration in the brain, with an increase in abnormal protein deposits. Receptors play a crucial role in transmitting signals and mediating communication between cells in the brain and throughout the body[8]. One important receptor system affected by AD is the cholinergic system, specifically the cholinergic receptors. Cholinergic receptors are involved in the transmission of signals mediated by the neurotransmitter acetylcholine, which is crucial for learning, memory, and attention. Another receptor system affected in AD is the glutamatergic system, it involves receptors which respond to the neurotransmitter glutamate. Glutamate receptors are essential for normal synaptic function and plasticity, which are critical for learning, memory processes. In AD, its evidence of dysregulation of glutamate receptors, including alterations in their expression and function. This dysregulation can lead to abnormal excitatory activity, impaired synaptic function, and neuronal damage, further contributing to the cognitive loss[13].

Additionally, AD involves the deposition of abnormal protein, like amyloid plaques and tau tangles. These deposits can also interact with receptors and disrupt their normal functioning. For example, amyloid beta, the main component of plaques, has been shown to bind to several receptors, including NMDA (N-methyl-D-aspartate) receptors, nicotinic acetylcholine receptors, metabotropic glutamate receptors, leading to altered signaling and neuronal dysfunction.

The link between age, receptors, and AD is complex and multifaceted. Aging plays the major risk factor in the disease, the exact mechanisms underlying receptor dysfunction and their contribution to disease progression are still being investigated.

The NMDA (N-methyl-D-aspartate) receptor is a type of glutamate receptor is important in synaptic plasticity, learning, and memory cycle. It is one of the major receptor subtypes involved in excitatory neurotransmission in the brain[12].

The function and regulation of NMDA receptors can be affected in several ways:

- Age-related changes: NMDA receptor function can be influenced by normal aging processes. As individuals age, there can be alterations in the structure and composition of NMDA receptors, including alter expression levels of receptor subunits. These age-related changes can affect the sensitivity and responsiveness of NMDA receptors to glutamate, that contributes to cognitive loss as well as age-related memory impairments.
- Amyloid beta interaction: In AD, the deposition of amyloid beta plaques can interact with NMDA receptors. Amyloid beta can bind to NMDA receptors and disrupt their normal function. This interaction may lead to increase Ca^{+} in nervous system, triggering a series of events which lead to neuronal dysfunction and cell morbidity.
- Tau pathology: Another importance of AD is the formation of tau tangles, which aggregates of abnormal tau protein within neurons. Tau pathology can affect NMDA receptor activity by disrupting synaptic function and impairing the trafficking of receptors to the cell membrane. This can lead to altered synaptic transmission and develop to cognitive impairment.
- Excitotoxicity: In AD, the dysregulation of glutamate signaling, including NMDA receptor activity, can lead to excitotoxicity, which lead to the excessive action of glutamate and NMDA receptors, resulting in an intake of Ca^{++} ions and which destroy neurons. Excitotoxicity can promote to neurodegeneration and cognitive loss.

Understanding the intricacy in NMDA receptors and AD is crucial for developing targeted therapeutic interventions. Researchers are investigating strategies to modulate NMDA receptor activity and restore the balance of excitatory neurotransmission to mitigate detrimental effects of NMDA receptor dysregulation in AD. These efforts aim to increase cognition and potentially lowers the progression of AD[13].

2.2. Correlation of socioeconomic determinants of dementia along with education and Alzheimer's disease

It is hypothesized that greater education causes the brain to form more synaptic connections, while the precise explanation of this link is unknown. As the condition worsens, the brain develops a "synaptic reserve" that gives patients the ability to compensate for the death of neurons. People with less education tend to be at a greater risk since they are not familiar with the typical causes[15,16]. More years of schooling, in the opinion of some experts, produce a "cognitive reserve" that helps people to more effectively adjust for brain abnormalities that might result in signs of AD or another dementia. In order to compensate for early Alzheimer's disease-related brain alterations, the cognitive reserve theory states that education improves the relation in brain neurons and offers the brain the capacity to employ alternate neuron-to-neuron communication routes to complete cognitive tasks[17].

2.3. Association between alcohol and Alzheimer's disease

Alcohol abuse clearly has a negative impact on the brain, and little to more alcohol consumption has been linked to increased brain shrinkage and decreased brain sizes[18,19]. Study indicating that heavier drinkers in between 20 to 40 years have a chance of dementia and AD in old age that was more than three times higher,

especially among bearers of the APOE 4 genotype, highlights the harmful effect of heavy alcohol consumption[20].

AD and increase alcohol intake can have separate and combined effects on various receptors in the brain. While alcohol can have acute effects on receptor function. While some points which provide insights into the potential effects of AD and alcohol on certain receptors:

- GABA receptors: Gamma-aminobutyric acid (GABA) receptors are inhibitory receptors which act by regulating neuronal excitability. Chronic alcohol consumption can affect GABA receptors, leading to increased inhibitory signaling and tolerance development. In Alzheimer's disease, alterations in GABA receptor function have also been reported, although the exact mechanisms are not fully elucidated. These changes in GABA receptors may act in cognitive impairments in both chronic alcohol use disorder and Alzheimer's disease[16].
- Glutamate receptors: Glutamate is excitatory neurotransmitter, and receptors like NMDA and AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors, are crucial for synaptic transmission and plasticity. Chronic alcohol consumption can affect glutamate receptor function, leading to adaptive changes in receptor expression and signaling. In AD, improper regulation of glutamate receptors, including NMDA receptors, has also been observed, contributing to excitotoxicity and neuronal damage. The combined effects of chronic alcohol consumption and Alzheimer's disease on glutamate receptors may exacerbate excitotoxicity and neuronal dysfunction[13].
- Dopamine receptors: Alcohol consumption can impact dopamine receptors, which act in reward and motivation pathways. Acute alcohol intake can increase dopamine release, contributing to satisfactory effects of alcohol. Chronic alcohol consumption, however, may cause dopamine receptor modifications that culminate in tolerance and dependence. In Alzheimer's disease, alterations in dopamine receptor signaling have been reported, potentially contributing to behavioral and neuropsychiatric symptoms commonly seen in the disease[14].

Alcohol consumption is a modifiable problem for dementia, including AD. The use of alcohol in excess over extended periods of time raises the risk of cognitive decline and neurodegeneration. The pathogenic mechanisms that underlie Alzheimer's disease, such as neuroinflammation and oxidative stress, can also be made worse by alcohol misuse[13,14].

Given complexity of alcohol's effects on receptors and the interaction with AD, it is important to promote responsible alcohol consumption and seek professional medical advice for personalized guidance regarding alcohol use[13,17].

2.4. Effects of smoking on Alzheimer's disease

Numerous follow-up investigations, in contrast to cross-sectional research, discovered a considerably elevated chance of AD related with smoking, particularly in noncarriers of the APOE €4 genotype[21–23]. Numerous epidemiological investigations into the connection between smoking and AD have been conducted, with many of these investigations coming to contradictory conclusions. Generally speaking, case-control or cohort studies have been used in this epidemiological research. In general, case-control work demonstrates that smoking is linked to a lower chance of developing AD. Cohort studies, on the other hand, frequently demonstrate that smokers have a higher chance of acquiring AD than do non-smokers[24].

Alzheimer's disease and smoking can both have separate effects on various receptors in the brain. Here are some points into potential effects of AD and smoking on certain receptors:

- Nicotinic acetylcholine receptors (nAChRs): These are a type of acetylcholine receptor that works in cognitive function, learning, and memory. Nicotine, the primary addictive component of tobacco, binds to and activates nAChRs. Chronic smoking increases the upregulation of nAChRs in brain, as the receptors adapt to chronic nicotine exposure. In AD, cholinergic neurons are lost and decreased

cholinergic transmission, including the activity of nAChRs. The combined actions of smoking and AD on nAChRs are complex, as nicotine's effects can modulate cholinergic signaling but smoking itself is linked with increased risk for cognitive loss and dementia[22].

- Dopamine receptors: Smoking affects the release and reuptake of various neurotransmitters, including dopamine. Nicotine stimulates the release of dopamine, leading to the rewarding and reinforcing effects of smoking. Chronic smoking can lead to adaptations in dopamine receptors, resulting in tolerance and dependence. In Alzheimer's disease, alterations in dopamine receptor signaling have been observed, potentially contributing to behavioral and neuropsychiatric symptoms of disease. The combined action of smoking with Alzheimer's disease on dopamine receptors are not yet fully understood but may interact to further dysregulate dopamine signaling[23].
- Serotonin receptors: These play a role in mood regulation and cognitive processes. Smoking has been shown to affect serotonin receptors and serotonin transporter function. However, the specific effects of smoking on serotonin receptors and their interaction with AD are still being investigated. Changes in serotonin receptor signaling have been implicated in mood disturbances and neuropsychiatric symptoms observed in AD[22,24].

Given the detrimental health effects associated with smoking, including its potential impact on receptors and the risk of cognitive decline, it is highly recommended to quit smoking or avoid smoking altogether. Seeking professional medical advice and support for smoking cessation can significantly improve overall health outcomes and potentially reduce the risk of AD and different cognitive impairments[21–24].

2.5. Molecular genetics of Alzheimer's disease

The APOE α4 allele is the primary genetic vulnerability component, acceleration of Aβ accumulation in the brain was likely what first made it a risk factor for AD[25,26]. However, using the α4 form raises the likelihood of getting Alzheimer's and the age at when it strikes. More people are at risk if they inherit two α4 genes[17].

AD has a significant genetic component, with certain genetic variations linked to the high risk of developing the disease. These factors can affect various receptors in the brain, contributing to the propagation of AD. Here are some key points regarding the correlation between Alzheimer's genetics and receptors:

- Amyloid precursor protein (APP) and amyloid beta (Aβ) receptors: Genetic mutations in the APP genes involved in the processing of APP, such as presenilin 1 (PSEN1) and presenilin 2 (PSEN2), can lead to the overproduction or deposition of amyloid beta protein. Amyloid beta is a vital factor of amyloid plaques observed in AD. Receptors such as NMDA, nicotinic, metabotropic glutamate receptors can interact with amyloid beta, leading to altered signaling and neuronal dysfunction[18].
- Apolipoprotein E (APOE) and cholesterol receptors: The APOE gene has 3 types: ε2, ε3, and ε4. The APOE ε4 type is the major genetic factor for late-onset AD. APOE is linked in cholesterol metabolism, and APOE receptors play a role in the transport of lipids, including cholesterol. Disruptions in cholesterol homeostasis can impact neuronal function and develop of Alzheimer's pathology[20,22].
- Tau and microtubule-associated protein (MAP) receptors: Genetic variations can influence function of tau protein and MAPs. Mutations in the MAPT (Microtubule Associated Protein Tau) gene, which encodes tau, lead to abnormalities in tau protein, resulting in the neurofibrillary tangles in AD. Tau interacts with various receptors, including NMDA receptors, influencing synaptic function and neuronal health[17].
- Cholinergic receptors: Genetic factors can influence the expression and function of cholinergic receptors, such as nicotinic acetylcholine receptors and muscarinic acetylcholine receptors. Variations in genes in cholinergic signaling, like cholinergic receptor genes (CHRNA) and choline acetyltransferase (CHAT), can impact cholinergic neurotransmission, contributing to cognitive impairments seen in AD.

Genetic variations linked with a high risk of AD; they do not guarantee the development of the disease (**Table 1**). Studying the genetic correlations with receptors in AD provides insights into the underlying mechanisms and potential targets for therapeutic interventions[17,25,26].

Table 1. A tabular representation of the correlation between Alzheimer's disease, genetics, and their effects and drawbacks in correlation with receptors.

Genetic factors	Receptors	Effects	Drawbacks
APP, PSEN1, PSEN2	NMDA receptors	Altered signaling, neuronal dysfunction	Accumulation of amyloid beta, neurodegeneration
	Nicotinic		
	Acetylcholine		
	Receptors		
	Metabotropic		
	Glutamate		
	Receptors		
APOE	Cholesterol	Disruptions in neuronal function, lipid metabolism	High prevalence of late-onset AD
	Receptors		
MAPT	NMDA receptors	Abnormal tau protein, neurofibrillary tangles	Tauopathies, cognitive decline
Cholinergic receptor	Nicotinic	Altered cholinergic neurotransmission	Cognitive impairments, loss of memory
Genes (CHRNA, CHAT)	Acetylcholine		
	Receptors		
	Muscarinic		
	Acetylcholine		
	Receptors		

2.6. Peripheral cholesterol, metabolic disorders and Alzheimer's disease

Certain dietary components is having role in reducing the incidence of AD, according to studies conducted in both animal and human models[27] consuming lots of fatty acids raises the risk of obesity, which increases the chance of AD[28,29]. According to a recent study, a high-fat diet can result in damage that resembles the pathology of AD, including cognitive decline, potentiated beta-secretase processing of APP, and mitochondrial damage linked to insulin resistance[30–32].

Local high-density lipoproteins (HDL) transport cholesterol into the brain; In the adult brain, astrocytes produce 1° cholesterol to a greater amount than neurons do. LDL levels are increased by Cardiovascular disorder, which has systemic changes linked to oxidation and nitration, is increased by hypercholesterolemia[33,34]. AD risk factors have been proposed to include high blood and plasma cholesterol levels[35,36].

Alzheimer's disease, obesity, and hypercholesterolemia (high cholesterol levels) can all have effects on various receptors in body and brain as well. Few effects of each condition with respect to receptors are below.

2.6.1. Alzheimer's disease and receptors

a) Cholinergic receptors: AD is characterized by a progressive loss of cholinergic neurons with reduced cholinergic transmission in brain. This leads to impaired signaling through cholinergic receptors, such as nicotinic and muscarinic receptors. Consequently, cognitive impairments and memory deficits are observed due to the crucial role of cholinergic signaling in learning and memory processes **(Figure 2)**.

b) Glutamate receptors: Dysregulation of glutamate receptors, particularly NMDA receptors, occurs in AD. Abnormal deposition of amyloid beta plaques disrupts glutamate signaling, leading to excitotoxicity and neuronal damage. Alterations in NMDA receptor activity and function contribute to cognitive decline and synaptic dysfunction in AD[27,28].

2.6.2. Obesity and receptors

a) Leptin receptors: In obesity, there is often resistance to the actions of leptin, leading to decreased sensitivity of leptin receptors. This resistance can disrupt the normal signaling of leptin receptors, impairing the regulation of diet and energy spend.

b) Insulin receptors: Obesity is commonly linked with insulin resistance, which can affect insulin receptor signaling. They are involved in various functions, including neuronal survival, synaptic plasticity, and cognitive processes. Insulin resistance in obesity may lead to impaired insulin signaling through insulin receptors, potentially contributing to cognitive impairment and increased risk of neurodegenerative diseases[30,32].

2.6.3. Hypercholesterolemia and receptors

a) Cholesterol receptors: Hypercholesterolemia is characterized by elevated levels of cholesterol in the blood. Cholesterol receptors, such as LDL receptors, work for the uptake and regulation of cholesterol in various cells, including those in the brain. High cholesterol levels, the receptors may become dysregulated, leading to altered cholesterol homeostasis. Disruptions in cholesterol receptor function can have detrimental effects on neuronal health, synaptic function, and cognitive processes[31].

b) Serotonin receptors: Hypercholesterolemia has been associated with alterations in serotonin receptors. It plays a role in mood regulation and cognitive function. Elevated cholesterol levels can impact the function and expression of serotonin receptors, potentially contributing to mood disorders and cognitive impairments[30,32].

The relationships described here are complex, and the specific effects on receptors may vary depending on individual factors and the interplay of various physiological processes. While these conditions have implications for receptor function, the mechanisms and their contributions to disease development and progression are still areas of ongoing research[27–32].

2.7. Type 2 diabetes mellitus (T2DM) and Alzheimer's disease

Hyperglycemia causes an increase in glucose production, impaired pancreatic beta-cell synthesis of insulin, and insulin resistance are the hallmarks of T2DM[37]. Another common condition linked to fat and ageing is T2DM, which is regarded as separate problem[38]. Diabetes is linked with neurodegeneration because high blood sugar levels and insulin resistance may affect the brain's oxidative stress pathways and neuro inflammatory signals[39] (**Table 2**).

The mechanisms and interactions involved are complex and the specific effects may vary depending on individual factors. Additionally, this table does not encompass all potential effects and drawbacks linked with T2DM and AD[38,39].

2.8. Traumatic brain injury (TBI) and Alzheimer's disease

According to recent studies, even moderate, frequent TBI may promote neurodegenerative disease. TBI is the impairment of normal brain function brought on by a head injury, shock, or anything inserted into the skull. AD risk rises with moderate to severe TBI and other dementias. Auto accidents are the primary cause of half of all moderate or severe TBIs. High risk of Alzheimer's is linked with moderate TBI and other dementias when compared to persons who have not experienced a head injury, while a severe TBI is linked to a 4.5 times greater risk[17].

Table 2. Tabular representation of the effects of type 2 diabetes mellitus on Alzheimer's disease with respect to receptors.

T2DM effects on Alzheimer's	Receptors	Effects	Drawbacks
Insulin resistance	Insulin	Impaired insulin signaling, reduced insulin sensitivity	Altered glucose metabolism in the brain, neurodegeneration
	Glutamate (NMDA)	Excitotoxicity, synaptic dysfunction	Neurodegeneration, cognitive decline
	Cholinergic	Reduced cholinergic transmission, cognitive impairments	Memory deficits, impaired learning
Advanced glycation end products (AGEs)	RAGE (receptor for AGEs)	Increased inflammatory response, oxidative stress	Neuroinflammation, neuronal damage
	Glutamate (NMDA)	Excitotoxicity, synaptic dysfunction	Neurodegeneration, cognitive decline
	Cholinergic	Reduced cholinergic transmission, cognitive impairments	Memory deficits, impaired learning
Oxidative stress	Glutamate (NMDA)	Excitotoxicity, synaptic dysfunction	Neurodegeneration, cognitive decline
	Cholinergic	Reduced cholinergic transmission, cognitive impairments	Memory deficits, impaired learning
	Insulin	Impaired insulin signaling, reduced insulin sensitivity	Altered glucose metabolism in the brain, neurodegeneration

2.9. Hypertension and Alzheimer's disease

According to study, having high blood pressure in your middle years increases your risk of developing AD[40]. There may be connection between AD and high BP since many research have linked it to brain atrophy and the creation of NFTs (intracellular neurofibrillary tangles)[41].

2.9.1. Alzheimer's disease and receptors

a) Cholinergic receptors: Cholinergic receptors, including nicotinic and muscarinic receptors, play important part in learning, memory, and cognitive processes. In AD, the dysfunction of cholinergic receptors leads to impaired synaptic transmission and cognitive decline.

b) Glutamate receptors: Dysregulation of glutamate receptors, particularly NMDA receptors, occurs in AD. Abnormal increase of amyloid beta plaques disrupts glutamate signaling, leading to excitotoxicity and neuronal damage. The altered function of glutamate receptors leads to synaptic dysfunction and cognitive failure.

c) Insulin receptors: Insulin receptors in the brain are involved in various functions, including synaptic plasticity, neuronal survival, and cognitive processes. In AD, insulin resistance and reduced insulin signaling have been observed, leading to impaired insulin receptor function. This disruption can contribute to neuronal dysfunction and impaired cognition.

2.9.2. Hypertension and receptors

a) Adrenergic receptors: Hypertension is characterized by chronically elevated BP. Increased sympathetic activity in hypertension activates adrenergic receptors, including alpha-1 and beta-1 receptors. Prolonged stimulation of adrenergic receptors can contribute to vascular remodeling, increased vascular resistance, and further elevation of blood pressure.

b) Renin-angiotensin system (RAS) receptors: Hypertension often involves dysregulation of the renin-angiotensin system. Activation of angiotensin II receptors, such as AT1 receptors, can lead to vasoconstriction, sodium and water retention, and increased blood pressure. Chronic activation of RAS receptors contributes to sustained hypertension.

c) NMDA receptors: Hypertension is linked with higher activity of NMDA receptors in certain brain regions. Overactivation of NMDA receptors can lead to calcium influx and excitotoxicity, potentially damaging neurons and contributing to cognitive impairment.

Both AD and hypertension are complex conditions with various underlying mechanisms. The effects on receptors described here represent some of the known relationships observed in scientific research. However, the interactions between these conditions and receptors are multifaceted and may vary among individuals. Further research is necessary to fully elucidate the intricate connections between AD, hypertension, and their impact on receptor function[40,41].

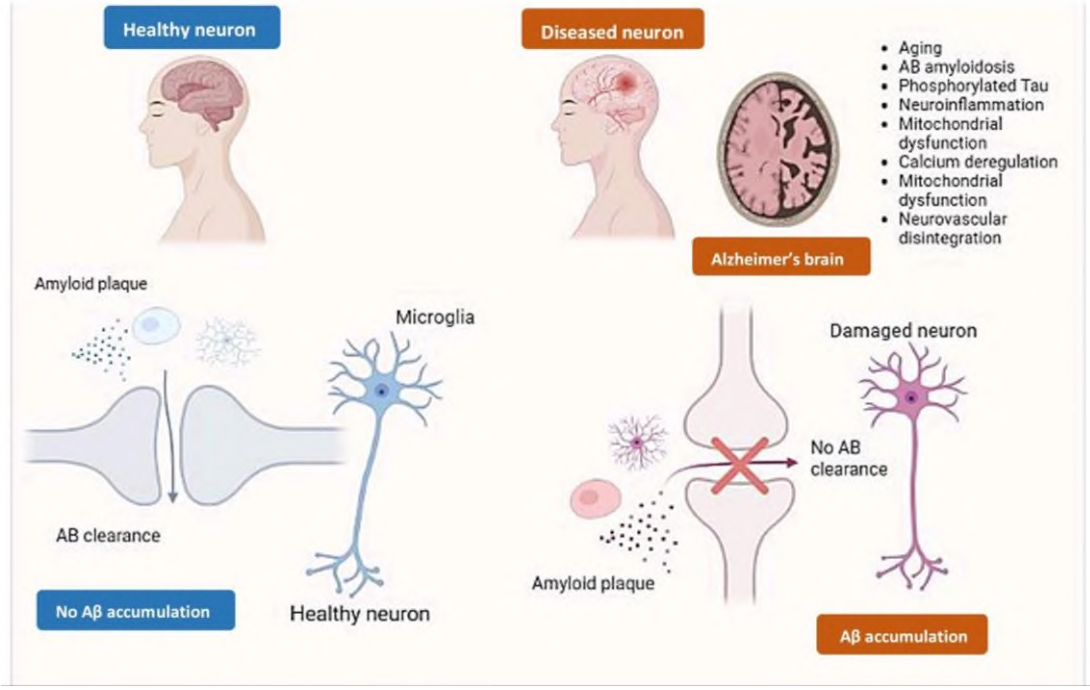

Figure 2. The physiological characteristics of neurons in **(a)** healthy; and **(b)** Alzheimer's disease-affected brains.

3. Stage and symptom in Alzheimer's disease

Different stages and conditions, symptoms of the Alzheimer's disease are displayed in **Figure 3**[42,43].

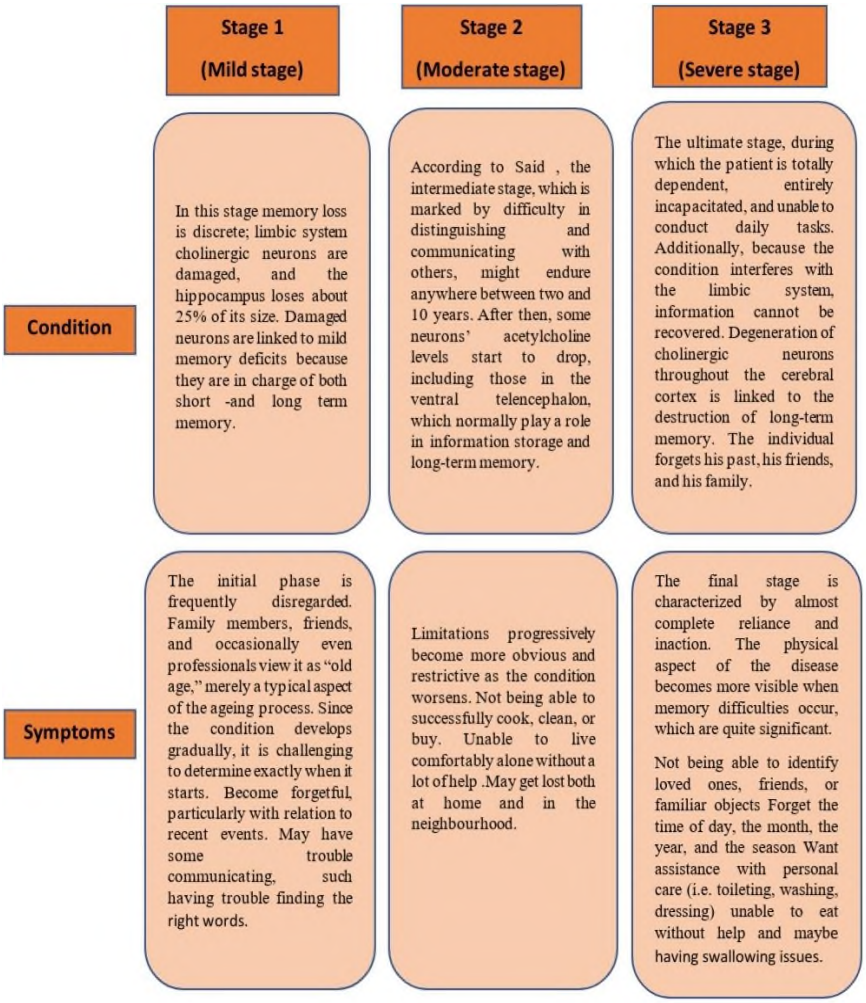

Figure 3. Sign and symptoms of Alzheimer's disease.

4. Receptors

Effect of various receptors along with there role is given in **Table 3**.

Table 3. Effect of various receptors along with their role.

Receptors	Role
nAChR	Another recurrent feature of AD is a reduction in cholinergic neurons in the forebrain[44–46]. The two distinct kinds of acetylcholine receptors that are released by cholinergic neurons are nAchRs and mAchRs, often known as ionotropic and metabotropic receptors, respectively. Five unique subunits (α, β, ɣ and £), each of which is expressed by a separate gene, make up the pentameric structure of nAchRs, which are ligand-gated ion channels[47,48]. Because they are strongly expressed in the brain areas where AD neuropathology develops, the 2 principal nAChR subtypes expressed in the CNS—a7 and a4b2—are involved in the emergence of this dementia[49].
NMDARs	NMDARs are important mediators of brain plasticity because unique neuronal activity patterns may be transformed into long-lasting changes in synapse and function, which hypothesized to underpin higher cognitive capacities[50]. The main excitatory neurotransmitter in human brain, glutamate, is a ligand for the N-methyl-D-aspartate receptor. Majority of NMDAR subgroup are distinct in that they need the opening of the channel by Mg^{2+} to be relieved at the same time as presynaptic glutamate release and a sizable postsynaptic membrane depolarization[51]. Ischemic stroke, seizures, and neurodegenerative diseases like Parkinson's, Huntington's and AD are all correlated with abnormal NMDAR activity[52]. NMDAR is crucial for synaptic plasticity and neuronal persistence. But overzealous NMDAR activation promotes cell death and excitotoxicity[53].

Table 3. (*Continued*).

Receptors	Role
TNFR1	The two main TNF receptors are TNFR1 and TNFR2. To produce its biological action, TNF binds with them. On chromosome 12p13.31, there is a gene called TNFR1 that produces a 55/60 kDa membrane receptor and contains 10 exons. A membrane receptor with a 75/80 kDa molecular weight is encoded by the TNFR2 gene, which has 10 exons and is found at chromosome 1p36.22. Study found that individuals having dementia of the Alzheimer type (DAT) have both kinds of receptors on their T cells than usual. This may demonstrate that DAT patients have an active systemic immune system as compared to healthy people[54–60].
Amyloid-beta receptor	An extracellular protein deposit that, when stained with Congo red and seen with circularly polarized light, exhibit green birefringence is what is traditionally referred to as an amyloid fibril, also known as an amyloid. This pattern is a result of the cross beta-sheet secondary structure connected to amyloid fibrils[61]. Amyloid-beta was found to be the primary elements of amyloid plaques in 1984[62]. Although beta deposition in the medial parietal cortex is the 1st stage in AD progression, tau aggregates in the medial temporal lobe precede it in older adults with cognitive intact brain[63]. Studies on cells and experiments on animals have shown that oligomeric, soluble α-beta plaques, not insoluble amyloid plaques, are what have the detrimental effect[64,65]. The updated amyloid cascade theory suggests that soluble oligomeric α-beta gathering are the direct cause of the neurodegenerative triad[66]. Oligomers of α-beta1-42, which is assumed to be in charge of the early cognitive impairments in AD, are most synaptotoxic forms[67].
APOE receptor	A significant apolipoprotein and cholesterol transporter in the brain is called APOE. Triglycerides and other lipids are delivered to the CNS and plasma by the 34 kDa APOE protein, which binds to APOE receptors on cell surfaces[68]. The allele 4 of the APOE gene has a substantial risk for developing late-onset AD[69,70]. The LDLR family, which is primarily in charge of making APOE-lipoprotein particles, carries lipids like cholesterol to the brain's neurons[71,72]. The liver and brain express large amounts of this LDLR-related protein that is LRP1 which is different from LRPs, which binds more than 30 ligands, including App, APOE, tissue-type plasminogen activator, and 2 macroglobulin[73]. When affected by A peptides[74-77] various APOE isoforms connect to APOE receptors in different ways. These findings established that A peptides can conflict with APOE's typical work in brain lipid metabolism, which would add to the pathogenesis of AD[78–80].

With AD, the link between synapse loss and cognitive deterioration. At the top of the image is a control synapse. The pleiotropic effects of the β-amyloipeptide (Aβ) are shown by a "Alzheimer's disease synapse" at the bottom of the picture. Rings are used to depict synaptic vesicles. By diminishing dendritic spine density and changing the ratio of long-term potentiation to long-term depression, the experimental application and expression of Aβ, in particular oligomers, reduce synaptic plasticity. Oligomers may inhibit baseline synaptic transmission when used in high doses. N-methyl-D-aspartate (NMDAr) and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor endocytosis is made easier by Aβ (AMPAr). Additionally. Aβ interacts with the p75 neurotrophin receptors (p75NTr). The levels of BDNF are already inhibited by the tyrosine kinase B receptor (trkBr), also known as the BDNF receptor. Nerve growth factor (NGF) and brain-derived neurotrophic factor levels are already inhibited by the tyrosine kinase B receptor (trkBr), also known as the BDNF receptor (BDNF). Nicotinic acetylcholine (ACh) receptor (nAChr) signalling as well as presynaptic terminal ACh release are both impacted by Aβ. Mild cognitive impairment causes the loss of hippocampal synapses, but it also increases the size of the synaptic profiles that are still there. The acronym for amyloid precursor protein includes tyrosine kinase Aβ receptor (trkAr), phosphorylated calcium-calmodulin-dependent protein kinase 2 (pCaMKII), cyclic AMP response element-binding protein (pCREB), and voltage-gated calcium channel (VGCC) (APP) (**Figure 4)**.

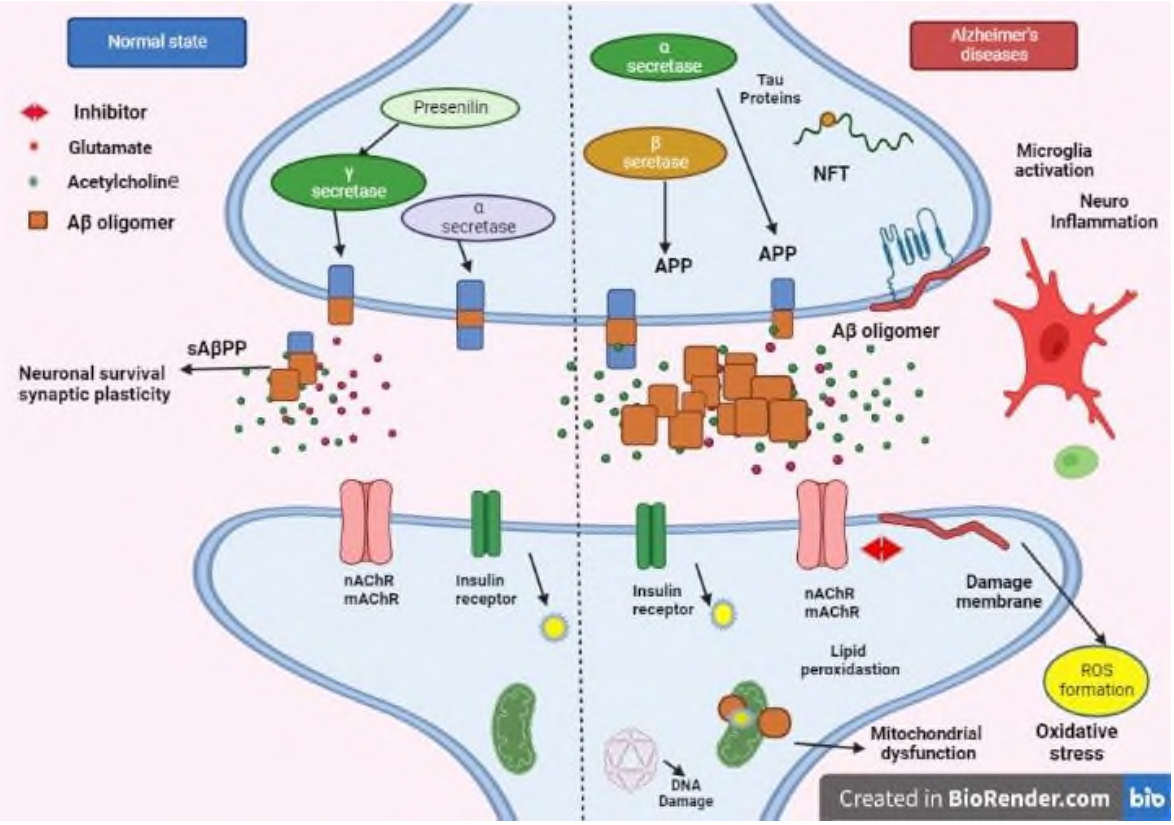

Figure 4. Dysfunction of the synapses in Alzheimer's disease.

5. Diagnoses of Alzheimer's disease

Variants of Alzheimer's disease along with the multicenter clinicopathological correlation in dementia

Patients with AD who have been diagnosed for over 50 years and whose autopsy results finally confirm the diagnosis have been documented with atypical clinical presentations[77]. Many patients complicate clinical diagnostics due to comorbid conditions. The ratio of hippocampal neurofibrillary tangle density to neocortical tangle density can be used to classify three primary subgroups of AD[78]. In this way, "limbic predominate AD" and "hippocampal sparing AD" are characterized as two atypical AD subtypes. Hippocampal sparring AD sometimes manifests at a younger age and degenerates cognitively more quickly than usual AD. In contrast, limbic predominate AD frequently manifests later in life and degrades cognition more gradually. It's interesting to note that 30% of instances with hippocampal sparing may appear clinically differently. In these situations, there may be localized or asymmetrical enhanced cortical atrophy, which frequently results in clinical symptoms other than problems in episodic memory. Although executive function, visuospatial, and linguistic abnormalities are all seen in AD, they are not often the clinical manifestation. Those who have main progressive[79]. Posterior cortical atrophy is another unusual clinical symptom that can accompany AD with hippocampal sparing (PCA). PCA can also be brought on by prion disease and corticobasal degeneration, in addition to AD[80]. Progressive executive impairment is most typically associated with frontotemporal lobar degeneration, but AD, particularly hippocampal-sparing AD, can also present in this fashion[81]. Genetic study of APOE indicates that hippocampus sparing AD and typical or limbic dominant AD are more closely related[79](**Table 4**).

Table 4. Illustrating different variants of Alzheimer's disease.

Variant	Description	Characteristics
Early-onset AD	Occurs before the age of 65 and represents a small proportion of all AD cases.	Strong genetic component, often caused by mutations in APP, PSEN1, or PSEN2 genes.
Late-onset AD	The most common form of AD, typically developing after the age of 65.	Complex interaction of genetic, environmental, and lifestyle factors.
Familial AD	A subset of AD cases with a clear pattern of inheritance, typically autosomal dominant.	Caused by mutations in APP, PSEN1, or PSEN2 genes.
Sporadic AD	The majority of AD cases, lacking a clear familial pattern of inheritance.	Likely caused by a combination of genetic, environmental, and lifestyle factors.
Early-onset familial AD	A rare form of AD with an onset before age 50 and a strong genetic basis.	Typically caused by highly penetrant mutations in APP, PSEN1, or PSEN2 genes.
Late-onset sporadic AD	The most common form of AD with a late onset, influenced by both genetic and environmental factors.	Associated with genetic risk factors such as APOE ε4 allele.

6. Comparison of neuropathologic criteria for the diagnosis of Alzheimer's disease

Every neuropathological alteration associated with AD is abnormal, according to the pathologic diagnosis of AD. The 2012 National Institute on Aging-Association Alzheimer's Guidelines are the most recent set of criteria for the neuropathological evaluation of Alzheimer's disease[82-84]. Since Alzheimer initially identified the neuropathological symptoms of the condition, such as amyloidal plaques and hyper phosphorylated NFTs, in 1907, the pathophysiology of AD has been a contentious subject. Several ideas have been put out to explain this complicated condition in light of the numerous causation factors. These include the tau hypothesis, the inflammatory theory, the cholinergic hypothesis, and the A hypothesis. The most often used Aβ hypotheses during the past 20 years, according to recent study[85,86]. Recent research has further emphasized the significance of Aβ oligomers in synaptic dysfunction, indicating that they are largely the sole signal among many others that compromises the integrity of brain processes additionally, the development of amyloid plaques in older age seems to be a very late process. So as a result[87]. Current research has highlighted the significance of Aβ oligomers in synaptic dysfunction, demonstrating that, among many other signals, they are primarily the only ones that compromise the integrity of brain functions. Amyloid plaque development in old age also seems to be a somewhat late process[88]. Recent research has demonstrated that both neurons and their accompanying astrocytes work together to create Aβ 42 oligomers. But because Aβ42 plaques, which are predicted to form in the late stages, draw microglia, their significance in the process cannot be discounted[87,88]. Microglial activation results in the production and release of proinflammatory cytokines such as IL-1b, TNF-a, and IFN-g. These cytokines then drive the neighboring astrocyte-neuron to produce more amounts of Aβ 42 oligomers, which stimulates further Aβ 42 synthesis and dispersion[89]. Aβ-oligomers also kill oligodendroglia (OLGs), which is related to the neurons-astrocyte complex. The neuronal and vascular degeneration in AD brains is considered to be caused by aggregates of Aβ oligomers[88,90]. Due to their low reduced glutathione (GSH) content and high iron concentration, which impairs their ability to scavenge oxygen radicals, OLGs are particularly susceptible to oxidative stress[91]. Additionally, it has been shown that membranes rich in cholesterol, such as those present in OLGs and myelin, are more vulnerable to damage by Aβ 42 oligomers[92]. Aβ 42 oligomers engage a number of membrane receptors on neurons and astrocytes, including the p75 neurotrophin receptor (p75NTR), frizzled receptor, insulin receptor, NMDA glutamate receptor, and 7 nicotinic ach receptor, according to earlier studies on the pharmacology of Aβ receptors (a7n). IGF-1R (insulin-like growth factor-1 receptor) neuroprotective signaling is activated by Aβ 42 monomers[93]. The proteases neprilysin and insulin degrading enzyme (IDE), absorption by astrocytes and microglia, passive flow into the cerebrospinal fluid, and soluble form of the low-density lipoprotein are some of the methods used to remove

Aβ oligomers from the protein 1 linked to low-density lipoprotein receptors (LRP1)[94]. Studies on the impact of NO on IDE-mediated Aβ degradation suggest that higher NO levels found in AD may reduce IDE enzyme activity, which may encourage the buildup of Aβ oligomers in the brain and the onset of AD[95].

7. Several therapeutic pharmacological targets exist for Alzheimer's diseases

7.1. Focusing on A protein (anti-amyloid)

There is anti-amyloid medicines tackle a number of APP metabolism-related issues (**Table 4**)[96].

7.2. Focusing on amyloid transport

According to study, LRP expression declines with ageing, reducing Aβ oligomers' ability to leave the brain quickly[97]. According to study, LRP expression declines with ageing, worsening Aβ oligomer export and prolonging their stay in the brain[98]. It has been previously documented that Aβ oligomers bind to the blood-brain barrier's multiligand receptor (RAGE) with a high affinity, facilitating their entry into the CNS and helping to promote CNS entry, inflammation, and neuronal death[99].

7.3. Change in secretes enzyme activity

According to research, cell surface receptors (muscarinic/GABA agonists) and the activation of signaling cascades like PKC (protein kinase C) control the activity. Bryostatin 1, a powerful PKC activator and anti-cancer medication, is now undergoing phase II clinical studies. Another potential method for inhibiting APP processing is β-secretes[100]. Another β-secretase inhibitor with promising preclinical findings is GRL-8234[101].

7.4. Aiming to reduce amyloid aggregation

Monomeric Aβ is bound by glycosaminoglycan tramiprosate, which prevents oligomerization and aggregation. The medicine has finished its phase II testing. The anti-oligomerization characteristics of ELND005 (scyllo-inositol) have also been investigated since they significantly reduced insoluble Aβ oligomers and reversed cognitive impairment in transgenic mice[102]. Aβ phase II study has just been completed. Initially isolated from ovine colostrum, colostrunin (CLN) is a proline-rich polypeptide complex. It not only significantly influences cognition, learning, and memory, but it also has strong immunoregulatory properties[103]. Colostrinin dissolves pre-formed fibrils and has a potent anti-Aβ peptide aggregation inhibitory action[104].

7.5. Focusing on amyloid clearance

Degrading enzymes for Aβ oligomers are less abundant in AD, which might lead to Aβ buildup[98]. Experimental evidence shows that the quantities of Aβ oligomers in the plasma and brain of transgenic mice are decreased by inhibitors of plasminogen activator inhibitor 1[105]. Earlier studies have shown that somatostatin, a peptide hormone, regulates the clearance of Aβ oligomers by activating neprilysin[106].

7.6. Therapy for vaccination using amyloid

Immunization with Aβ oligomers is a key component of amyloid-based immunotherapy. This immune response prevents Aβ oligomers from aggregating and leads to their ejection from the body[107]. In 2001, Tuppo and Arias[100] financed the first clinical trial utilizing active immunization, which used aggregated synthetic Ab42 peptide administered in QS21 adjuvant. These studies focus that delivery of the Ab42 peptide resulted in anti-Aβ antibodies, reduced CSF tau levels, and slowed cognitive decline[108]. The therapeutic immunization potential of the APPswe/PS1dE9 vaccine was investigated in double transgenic mice and other animal models with AD-like illness[109].

7.7. Focus on tau protein

In order to maintain the microtubules and guarantee ideal neuronal function, particularly with regard to axonal form, development, and polarity, neuronal cells frequently manufacture the tau protein. Consequently, focusing therapy on tau protein may be more successful[110].

7.8. Phosphorylation of tau is prevented

One of the crucial enzymes that phosphorylates tau is glycogen synthase kinase 3 (GSK3). Lithium and valproate are said to inhibit GSK3 in tests, and when taken orally, they lessen tau pathology[111].

7.9. Microtubule stabilization as a target

Microtubule stabilizer paclitaxel is reported to improve fast axonal transit, microtubule density, and motor performance in an AD experimental model[112]. It has been discovered that epothilone D, a microtubule stabilizer known for its capacity to traverse the blood-brain barrier, considerably reduces microtubule pathology[113].

7.10. Vaccination therapy based on tau

Another method to promote the immune system's removal of tau tangles is tau-based immunotherapy[91]. The possibility of treating tau illness by activating the immune system has been emphasized by recent studies on active vaccination. Although the precise mechanism is yet unknown, using the JNPL3 mouse P301S tauopathy model, passive immunotherapy is successful in avoiding intracellular tau pathology and associated symptoms[114].

7.11. NMDA receptor antagonism

Synaptic plasticity, neuronal development, cognition, learning, and memory are all regulated by glutamatergic neurons[115]. The NMDA receptor is blocked by memantine, an uncompetitive NMDA antagonist, by tying it up in an open state. Memantine therapy improves spatial learning in AD animal models, guards against Ab-induced neurotoxicity, lowers apoptosis, reduces free radical-mediated damage, and reverses synaptic degeneration according to experimental findings. Memantine is the only medication that has received clinical approval for treatment in AD in the USA and Europe[116,117]. It is expected that cholinergic neurons would first get affected by the illness before the glutamatergic system is damaged by excitotoxicity[118]. In the USA and Europe, only memantine has been used for therapeutic use in individuals with AD. Cholinergic neurons show early illness involvement in[119, 120] before glutamatergic system degradation and excitotoxic degeneration, early disease involvement of cholinergic neurons is predicted.

7.12. Multiple-targeted ligands

Owing to the intricacy of the underlying mechanics AD, substances with multiple potential targets (multi-target directed ligands) interact with various mechanisms to treat symptoms and slower the effects. Examples of such compounds include AChEIs that have antioxidant properties and drugs that simultaneously inhibit AChE and BACE[121] (**Table 5**).

8. Additional pharmacotherapeutic techniques

8.1. Drugs that reduce cholesterol

Statins have been shown to have pleiotropic effects, including dose-dependent advantages for cognition, memory, and neuroprotection. Statins are also known to protect 1° cortical neurons against glutamate damage[122] (**Table 6**).

Table 5. Illustrating several therapeutic pharmacological targets for Alzheimer's disease based on different approaches.

Therapeutic approach	Target	Description
Anti-amyloid therapy	Aβ protein	Targeting the accumulation and aggregation of amyloid-beta (Aβ) protein to prevent plaque formation and deposition.
Amyloid transport modulation	Amyloid transport proteins	Enhancing the clearance and removal of Aβ protein from the brain through modulation of transport mechanisms.
Secretase enzyme activity	β-secretase (BACE) and γ-secretase	Modulating the activity of secretase enzymes involved in Aβ production to reduce the generation of amyloid-beta peptides.
Amyloid aggregation inhibition	Aβ aggregation	Preventing the aggregation and formation of Aβ oligomers and fibrils, which are implicated in neurotoxicity and plaque formation.
Amyloid clearance enhancement	Amyloid clearance mechanisms	Enhancing the clearance of Aβ protein from the brain through various mechanisms, such as immune-mediated clearance or activation of microglial phagocytosis.
Immunotherapy/vaccination	Amyloid-beta protein	Developing therapeutic vaccines or antibody-based treatments that stimulate the immune system to target and clear amyloid-beta protein.
Tau protein modulation	Tau protein	Targeting the phosphorylation and aggregation of tau protein to prevent the formation of neurofibrillary tangles.
Phosphorylation inhibition	Tau protein phosphorylation	Modulating enzymes involved in the abnormal phosphorylation of tau protein to reduce its aggregation and neurotoxic effects.

Table 6. Illustrating additional pharmacotherapeutic techniques for Alzheimer's disease.

Pharmacotherapeutic technique	Description
Acetylcholinesterase inhibitors	Inhibit the breakdown of acetylcholine, a neurotransmitter involved in memory and cognition, to increase its availability in the brain. These drugs can help alleviate cognitive symptoms in AD.
NMDA receptor antagonists	Block NMDA receptors to modulate glutamate activity, aiming to reduce excitotoxicity and neuronal damage associated with AD.
Anti-inflammatory agents	Target neuroinflammation by inhibiting inflammatory processes and reducing the release of pro-inflammatory cytokines.
Antioxidants	Counteract oxidative stress and reduce free radical damage through the supplementation of antioxidants.
Insulin sensitizers	Enhance insulin signaling and sensitivity in the brain, aiming to improve glucose metabolism and neuronal function.
Anti-amyloid antibodies	Monoclonal antibodies that target and clear amyloid-beta (Aβ) plaques in the brain, potentially slowing disease progression.
Tau protein stabilizers	Aim to prevent the abnormal aggregation and phosphorylation of tau protein, reducing the formation of neurofibrillary tangles.
Neuroprotective agents	Promote neuronal survival and protect against neurodegeneration by targeting various pathways involved in cell death and neuroprotection.
Calcium channel blockers	Regulate calcium influx into neurons, potentially protecting against excitotoxicity and reducing neuronal damage.
Neurotransmitter modulators	Modulate the levels and activity of neurotransmitters such as serotonin, dopamine, and norepinephrine to enhance cognitive function and alleviate symptoms.

8.2. Gonadotropins with neuroprotective properties

Such hormones as progesterone, estrogen, and testosterone are renowned for their neuroprotective abilities. It is widely known that as people age, their concentrations rise while luteinizing hormone (LH), which promotes the illness process, declines. Studies have revealed that women who have previously taken HRT (hormone replacement therapy) have a reduce chance of developing Alzheimer's disease, but current usage is ineffective unless it lasts more than 10 years. The risk of AD is decreased by low dosage estrogen treatment, according to a new study[123].

8.3. Neurogenesis

Since cholinergic neurons are sensitive to and dependent upon nerve growth factor (NGF), neurotrophic factors are administered in an effort to preserve neurogenesis and cell survival in neurodegenerative illnesses. When neurotrophic factors are used as a treatment, preclinical studies have demonstrated positive outcomes.

8.4. Anti-inflammatory therapy

In addition to inhibiting cyclooxygenase (COX), NSAIDs are used to treat neuroinflammation associated with disease processes. These drugs have positive effects via preserving Ca^{2+} homeostasis, focusing on several pathways including PPAR, Rho-GTPases, and g-secretase.

8.5. Caspase blockers

In preclinical trials, caspase inhibitors—both selective and non-selective—proved beneficial for neuroprotection.

8.6. Nucleic acid drugs substance

The novel method for treating neurodegenerative illnesses that uses choices based on nuclear factor k-B (NF-kB) decoys or plasmid DNA (pDNA) or antisense oligodeoxy nucleotides. They are now undergoing preclinical research and preliminary clinical testing. Another method is to provide neurotrophic factors by utilizing naked pDNA that has the insertion of the genes for neurotrophic factors. pDNA is used as a DNA vaccine because of the molecule's immunogenicity, which stimulates dendritic cells and fosters a T-cell response[124].

8.7. Multiple-targeted ligands

Because the processes underlying AD are complicated, drugs with several possible targets (also known as multi-target directed ligands) interact with a variety of systems to provide symptomatic and disease-modifying effects. Examples include compounds that block AChE and BACE concurrently or AChEIs with antioxidant characteristics[123].

8.8. Current pharmacotherapeutic options for Alzheimer's disease (AD)

Acetylcholinesterase inhibitors (AChEIs): Drugs like donepezil, rivastigmine, and galantamine work by increasing the levels of acetylcholine, a neurotransmitter that's reduced in AD. These drugs help improve cognitive function, especially in the early stages of the disease.

N-methyl D-aspartate receptor antagonists (NMDARs): Memantine is an NMDAR antagonist that regulates glutamate activity, a neurotransmitter linked to excitotoxicity in AD. Memantine helps manage moderate to severe AD symptoms and may slow cognitive decline[124,125].

AI-driven drug design holds immense promise in revolutionizing the discovery of new treatments for Alzheimer's disease (AD). However, like any advanced technology, it comes with potential challenges and risks that need to be considered.

Data bias and quality: Training data is a major component of AI models. The predictions and results may also be biased if the data utilized to train the AI systems is biased or lacking. The produced treatments for AD may not be appropriate to all patients if the training data is biased toward a certain subset of patients.

AI models occasionally overfit the training data, which makes them highly good at forecasting outcomes based on the training data but may fail to generalize to new, unknown data. This can result in the identification of medication candidates that are ineffective or false positives.

Lack of human oversight: Relying only on AI forecasts without human knowledge could lead to missing important details that human researchers might otherwise notice[122,123].

9. Role of AI in drug designing of Alzheimer's disease

The role of artificial intelligence (AI) in drug designing for Alzheimer's disease (AD) is increasingly significant and holds great promise for accelerating the discovery and development of effective treatments. AI techniques, such as machine learning and deep learning, are revolutionizing the drug discovery process by enabling researchers to analyze vast amounts of data, identify patterns, and make predictions with enhanced speed and accuracy[125].

AI can be employed at various stages of drug design for Alzheimer's.

9.1. Data analysis and integration

AI algorithms can analyze and integrate diverse data sources, including genomics, proteomics, and clinical data, to identify potential biomarkers, therapeutic targets, and disease pathways associated with AD. This helps in gaining a comprehensive understanding of the disease and identifying novel drug targets (**Table 7**)[126].

Table 7. Tabular form detailing the key aspects of data analysis and integration in drug designing for Alzheimer's disease (AD).

Data analysis and integration in AD drug design	Description
Genomic data analysis	Analyzing DNA sequencing and gene expression data to identify genetic risk factors, disease-related genes, and dysregulated pathways associated with AD.
Proteomic data analysis	Analyzing protein expression profiles to identify differentially expressed proteins, protein-protein interactions, and post-translational modifications relevant to AD pathology.
Clinical data integration	Integrating demographic information, cognitive assessments, medical history, and imaging data to understand disease progression, identify clinical phenotypes, and correlate with molecular signatures.
Bioinformatics and data mining	Utilizing bioinformatics tools and data mining techniques to extract knowledge from large-scale biological datasets, predict protein structures and functions, identify drug targets, and uncover molecular pathways and networks associated with AD.

9.2. Virtual screening and molecular modeling

AI-based computational methods, including molecular docking, molecular dynamics simulations, and structure-based drug design, can efficiently screen large databases of chemical compounds to identify potential drug candidates with high affinity and specificity for target proteins involved in AD pathogenesis, such as amyloid-beta or tau proteins (**Table 8**)[126].

9.3. Predictive modeling and optimization

Machine learning algorithms can analyze drug-target interactions and predict the efficacy, safety, and pharmacokinetic properties of potential drug candidates. These predictions aid in prioritizing lead compounds and optimizing their chemical structures to enhance drug-like properties and reduce the likelihood of adverse effects (**Table 9**)[127].

Table 8. Tabular form detailing the key aspects of virtual screening and molecular modeling in relation to receptors in Alzheimer's disease.

Virtual screening and molecular modeling in AD	Description
Receptor selection	Identifying relevant receptors involved in AD pathogenesis, such as amyloid-beta (Aβ) receptors, tau protein receptors, cholinergic receptors, glutamate receptors, etc.
Compound library	Creating a database of chemical compounds for virtual screening. This library can include approved drugs, natural compounds, small molecules, or compound databases obtained from various sources.
Ligand preparation	Preparing the chemical structures of the compounds in the library by optimizing their conformations, assigning appropriate charges, and generating 3D models.

Table 8. (*Continued*).

Virtual screening and molecular modeling in AD	Description
Protein structure preparation	Obtaining protein structures of the selected receptors through experimental methods (X-ray crystallography, cryo-electron microscopy, etc.) or using computational techniques (homology modeling, ab initio modeling, etc.).
Molecular docking	Performing molecular docking simulations to predict the binding affinity and interaction between the compounds in the library and the target receptors. This technique evaluates the complementary fit between the ligand and receptor, considering factors such as hydrogen bonding, electrostatic interactions, and hydrophobic interactions.
Binding site prediction	Identifying and predicting the binding sites on the receptor proteins where the ligands interact and form stable complexes. This information helps in understanding the key interaction residues and guiding the design of ligands with improved binding affinity and specificity.
Scoring and ranking	Scoring and ranking the ligand-receptor complexes based on their docking scores or energy calculations. This step helps prioritize the compounds with the most favorable binding interactions for further analysis and experimental validation.
Molecular dynamics simulations	Performing molecular dynamics simulations to study the dynamic behavior of the ligand-receptor complexes over time, providing insights into the stability, flexibility, and conformational changes of the complexes. This analysis aids in understanding the binding mechanism and can guide optimization of ligands for enhanced efficacy and reduced side effects.
Virtual screening hit validation	Validating the hits obtained from virtual screening through additional computational methods, such as pharmacophore modeling, quantitative structure-activity relationship (QSAR) analysis, or molecular mechanics calculations. This step helps filter out false positives and prioritize the most promising compounds for further experimental evaluation.

Table 9. Tabular form detailing the key aspects of predictive modeling and optimization in Alzheimer's disease (AD) research.

Predictive modeling and optimization in AD	Description
Data integration	Integrating diverse data sources, including genomics, proteomics, clinical data, and imaging data, to build comprehensive datasets for predictive modeling.
Feature selection	Identifying relevant features or variables from the integrated dataset that contribute significantly to AD prediction or drug response. This helps reduce dimensionality and improve the accuracy and interpretability of the predictive models.
Machine learning algorithms	Utilizing various machine learning algorithms, such as logistic regression, random forests, support vector machines (SVM), or deep learning models, to develop predictive models for AD-related outcomes, such as disease progression, diagnosis, treatment response, or patient stratification.
Model training and evaluation	Splitting the dataset into training and testing sets and training the predictive models using the training data. The models are then evaluated on the testing set to assess their performance in terms of accuracy, sensitivity, specificity, and other relevant metrics.
Cross-validation	Performing cross-validation techniques, such as k-fold cross-validation or leave-one-out cross-validation, to assess the robustness and generalizability of the predictive models. This helps estimate their performance on unseen data and mitigate overfitting.
Model optimization	Tuning the hyperparameters of the predictive models to optimize their performance. This can be done using techniques like grid search, random search, or Bayesian optimization, aiming to find the best set of parameters that yield the highest predictive accuracy or other desired metrics.
Model interpretation	Analyzing the trained models to understand the important features and their contributions to the predictions. This provides insights into the underlying factors associated with AD and can guide further investigations or inform personalized treatment strategies.
External validation	Validating the predictive models on external datasets or independent cohorts to assess their generalizability and reproducibility. This helps determine the reliability and applicability of the models beyond the initial training dataset.

Predictive modeling and optimization techniques in AD research leverage machine learning algorithms and statistical methods to analyze integrated data, develop accurate predictive models, and optimize their performance. These approaches aid in identifying relevant biomarkers, predicting disease outcomes, optimizing treatment strategies, and guiding personalized medicine efforts in the fight against Alzheimer's disease.

9.4. Repurposing existing drugs

AI algorithms can analyze large-scale drug databases and clinical data to identify approved drugs or investigational compounds that may have therapeutic potential for AD. This approach accelerates the drug development process by repurposing existing drugs, which have already undergone safety testing and may require less time and resources for further evaluation (**Table 10**)[128].

Table 10. Tabular form detailing the key aspects of repurposing existing drugs for Alzheimer's disease (AD) and their receptor actions.

Repurposing existing drugs for AD	Description
Drug repurposing approach	Utilizing existing drugs approved for other indications to potentially treat AD by repurposing them for their known pharmacological actions and mechanisms of action.
Target receptors	Identifying the specific receptors or molecular targets that the repurposed drugs act upon to exert their therapeutic effects in AD. These receptors can include cholinergic receptors, glutamate receptors, GABA receptors, serotonin receptors, insulin receptors, or amyloid-beta receptors, among others.
Mechanisms of action	Understanding the specific mechanisms of action by which the repurposed drugs interact with the target receptors to modulate biological pathways and processes relevant to AD pathogenesis. This can involve receptor activation, inhibition, modulation of signaling pathways, or regulation of neurotransmitter release.
Drug screening and selection	Conducting in vitro or in silico screenings to identify potential candidates among existing drugs that exhibit desirable receptor interactions and have the potential to affect AD-related pathological processes.
Preclinical evaluation	Performing preclinical studies, such as cell-based assays or animal models, to assess the efficacy and safety of repurposed drugs in targeting the identified receptors and modulating AD-related molecular pathways.
Clinical trials and evaluation	Conducting clinical trials to evaluate the repurposed drugs' effectiveness and safety in AD patients. These trials assess the drugs' impact on cognitive function, disease progression, biomarker profiles, and overall patient outcomes.
Receptor-related therapeutic outcomes	Assessing the specific therapeutic outcomes achieved through receptor modulation, such as improvement in cognitive function, reduction in neuroinflammation, regulation of amyloid-beta production or clearance, enhancement of synaptic plasticity, or modulation of tau protein phosphorylation.
Combination therapies	Exploring the potential synergistic effects of combining repurposed drugs targeting different receptors or pathways to achieve enhanced therapeutic outcomes in AD. This can involve simultaneous or sequential administration of multiple drugs with complementary actions.
Safety and side effects	Monitoring and evaluating the safety profile and potential side effects associated with the repurposed drugs, taking into consideration their known profiles from their approved indications and potential off-target effects resulting from receptor interactions.
Regulatory considerations and market approval	Addressing regulatory requirements and seeking market approval for repurposed drugs as AD treatments, considering the existing safety and efficacy data, as well as any necessary modifications or additional studies required to support their new indication.

Repurposing existing drugs for AD offers the advantage of leveraging known pharmacological properties and established safety profiles. By targeting specific receptors and modulating relevant pathways, these repurposed drugs hold the potential to provide novel therapeutic options for AD.

9.5. Clinical trial optimization

AI can assist in optimizing clinical trial design by leveraging patient data, real-world evidence, and predictive modeling to identify patient populations that respond to specific treatments. This helps in better trial outcomes and reducing costs associated with unsuccessful trials (**Table 11**)[129].

Table 11. Tabular form detailing the key aspects of clinical trial optimization specific to Alzheimer's disease (AD).

Clinical trial optimization in AD	Description
Trial design	Determining the optimal trial design, including study objectives, patient population, sample size calculation, randomization methods, and allocation of treatment groups. This involves considering the specific AD stage (mild, moderate, or severe), target population (early-onset, late-onset, genetic mutations), and the type of intervention (new drug, repurposed drug, non-pharmacological interventions).
Biomarker selection	Identifying and selecting appropriate biomarkers, such as amyloid-beta (Aβ) levels, tau protein, neuroinflammation markers, neuroimaging (PET, MRI), or cerebrospinal fluid (CSF) biomarkers, to assess disease progression, treatment response, and safety endpoints. Incorporating biomarkers into the trial design helps evaluate target engagement, disease modification, and monitor treatment effects more accurately.
Patient recruitment	Developing strategies for efficient patient recruitment, including collaboration with research sites, clinics, and patient registries, as well as utilizing online platforms and social media to reach potential participants. Implementing robust screening and eligibility criteria to ensure enrollment of suitable participants and minimize dropout rates during the trial.
Endpoint selection	Defining relevant clinical endpoints and outcome measures to assess treatment efficacy, such as cognitive function (using validated scales like ADAS-Cog, MMSE), activities of daily living (ADL), neuropsychiatric symptoms (NPI), global clinical impression (CGI), or quality of life (QoL) assessments. Selecting appropriate surrogate endpoints or biomarker-based outcomes that can serve as early indicators of treatment response or disease modification.
Data collection and management	Establishing standardized procedures for data collection, including electronic data capture (EDC) systems, case report forms (CRFs), and source documentation. Implementing rigorous data management and quality control measures to ensure accurate and reliable data collection, storage, and analysis. Compliance with data protection and privacy regulations (e.g., GDPR, HIPAA) is essential to maintain data integrity and participant confidentiality.
Statistical analysis plan	Developing a comprehensive statistical analysis plan (SAP) outlining the statistical methods and procedures for data analysis. This includes specifying primary and secondary endpoints, statistical tests, treatment effect estimation, handling missing data, and adjustment for multiple comparisons. Adhering to the pre-specified SAP reduces bias and enhances the validity and interpretability of the trial results.
Adaptive trial designs	Exploring adaptive trial designs, such as adaptive randomization, sample size re-estimation, Bayesian approaches, or interim analyses, to optimize trial efficiency, flexibility, and to increase the chances of detecting treatment effects. Adaptive designs allow for modifications based on accumulating data while maintaining statistical rigor and ensuring participant safety.
Site management and monitoring	Implementing robust site management and monitoring procedures to ensure compliance with the protocol, regulatory guidelines, and good clinical practice (GCP). Conducting regular site visits, monitoring data quality, verifying participant informed consent, and providing training and support to investigators and site staff.
Regulatory compliance	Adhering to regulatory requirements and guidelines, obtaining necessary approvals from regulatory agencies (e.g., FDA, EMA), and following the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for conducting clinical trials. Ensuring proper documentation, reporting adverse events, and meeting ethical standards throughout the trial process.
Patient engagement and retention	Implementing strategies to enhance patient engagement.

10. Limitations and challenges

Limited efficacy: These medications do not offer a cure or stop the underlying illness progression; instead, they mainly treat symptoms and may halt cognitive deterioration.

Temporal efficacy: Efficacy tends to be more evident in the early stages of AD, whereas its influence is generally less pronounced in the later stages. Acetylcholinesterase inhibitors might have negative side effects such diarrhea, vomiting, and nausea. NMDAR antagonists may cause confusion, hallucinations, and nausea. Variability in response: These medications' effectiveness varies greatly and depends greatly on how each patient reacts to them. Impact in the short term: Although these medications may have an effect on the disease's progression in the short term, this is not always the case. Limited illness modification: The underlying illness process is not modified by the available medications. They merely offer temporary respite and don't stop or

stop the neurodegenerative processes that lead to AD. High cost and accessibility: Due to financial limitations or problems with the healthcare system, some patients may not be able to afford these medications or have restricted access to them. Need for combinatorial therapy: Due to the intricacy of AD, single-drug therapies frequently fall short. Although a combination of medications that target various routes may be more beneficial, this presents difficulties for safety, tolerance, and possible drug interactions. Ethical considerations: Deciding when to initiate or discontinue these medications, particularly in advanced stages, involves ethical considerations surrounding the patient's quality of life and potential benefits[120,122,126].

11. Conclusion and perspective

This publication provides further information on the pathophysiology and development of AD illness as well as an understanding of the numerous receptors, their functions, and prospective treatment targets. There is an abundance of information available regarding this complex condition, but there aren't many options for managing it. Unfortunately, the current treatment choices (AChEIs and memantine) primarily target the disease's symptoms rather than its underlying cause. Conversely, the vaccine strategy continues to be promising because of the behavioral alteration shown in mice and the potential that the amyloid accumulates in the brain could be targeted and neutralized through an effective immunization approach, thereby offering a potential avenue for halting or slowing the progression of Alzheimer's disease. The behavioral benefits seen in animal, however, and the amyloid reserved in preclinical studies of illness might be removed after Aβ immunization, indicate that the vaccination technique is still a viable one. Another appealing alternative is vaccination, which is said to promote the elimination of tau and Aβ oligomers on an internal level. Moreover, certain novel techniques are now being studied, including DNA immunization, NOS modulation, and caspase inhibition. It's difficult to predict if the right use of several non-targeted methods, such as anti-inflammatory therapy, metal chelation, antioxidant supplements, and epigenetic alterations, would enhance clinical outcomes because it has been documented that their effects are more detrimental. Where did we go wrong, considering the anti-amyloid and antioxidant research that failed? Failure of the drug compound, experimental design, omission of biomarkers from trials, incomplete data reporting, population heterogeneity, inappropriate dosage, inappropriate timing, and last but not least antioxidant therapy may be benefit in the early stages. Such factors include a lack of knowledge about the pharmacokinetics and bioavailability of the medicine.

In conclusion, AD is a complex neurodegenerative disorder with various pathological mechanisms and clinical manifestations. Understanding the effects of AD on receptors and exploring therapeutic targets is crucial for developing effective treatments. Several receptors, such as cholinergic, glutamate (NMDA), insulin, and amyloid beta receptors, are implicated in the disease process. Changes in receptor function contribute to cognitive decline, synaptic dysfunction, and neurodegeneration observed in AD.

Moreover, the correlation between AD and other factors, such as genetics, obesity, hypertension, smoking, and T2DM further highlights the intricate nature of the disease. Genetic variants can influence the risk and onset of AD, while comorbidities like obesity, hypercholesterolemia, hypertension, and T2DM can impact receptor activity and contribute to disease progression.

To combat AD, various pharmacotherapeutic techniques are being explored. These include targeting amyloid-beta (Aβ) protein through anti-amyloid therapies, amyloid transport modulation, secretase enzyme activity changes, and inhibition of Aβ aggregation. Additionally, therapies focusing on tau protein, such as preventing phosphorylation and stabilizing tau, are being investigated. Other approaches involve enhancing amyloid clearance, vaccination against amyloid, and modulating neurotransmitters and neuroprotective pathways. A lot of study is done in relation of AD and developing therapeutic strategies, the field is still evolving, and effective treatments remain a challenge. More research has to be done to explore the complexities of AD, identify novel therapeutic targets, and develop interventions that can effectively halt the disease.

In summary, AD involves alterations in various receptors and their signaling pathways, leading to cognitive impairments and neurodegeneration. Factors such as genetics, comorbidities, and lifestyle choices can impact receptor activity and contribute to disease development. Therapeutic interventions targeting amyloid-beta, tau protein, neuroinflammation, and oxidative stress are being investigated. However, the effective pharmacotherapies for AD remain a complex and ongoing research endeavor.

In conclusion, optimizing clinical trials specific to AD is crucial for the successful treatments. By carefully designing trial protocols, selecting appropriate endpoints, and incorporating biomarkers, researchers can enhance the accuracy and reliability of the trial outcomes. Efficient patient recruitment strategies and robust data collection and management systems help ensure the timely enrollment of suitable participants and accurate data collection. Statistical analysis plans and adaptive trial designs allow for flexibility and efficient utilization of resources, increasing the chances of detecting treatment effects. Compliance with regulatory guidelines and ethical standards is essential for patient safety and data integrity. Moreover, maintaining patient engagement and retention throughout the trial process fosters meaningful participation and minimizes attrition rates.

Optimizing clinical trials in AD involves a multidisciplinary approach, incorporating expertise from clinical researchers, statisticians, data managers, and regulatory professionals. By implementing these strategies, researchers can enhance the efficiency, reliability, and interpretability of clinical trial results, ultimately advancing the development of novel therapies for same. As mentioned in this study, several interesting clinical trials are now being carried out. These studies might identify brand-new treatment targets and contribute to cracking the complex AD puzzle.

Conflict of interest

The authors declare no conflict of interest.

References

1. Hane FT, Robinson M, Lee BY, et al. Recent progress in Alzheimer's disease research, part 3: Diagnosis and treatment. *Journal of Alzheimer's Disease* 2017; 57(3): 645–665. doi: 10.3233/JAD-160907
2. Khan MM, Ahsan F, Ahmad U, et al. Alzheimer disease: A review. *World Journal of Pharmacy and Pharmaceutical Sciences* 2016; 5(6): 649–666. doi: 10.20959/wjpps20166-7045
3. Bhushan I, Kour M, Kour G, et al. Alzheimer's disease: Causes & treatment—A review. *Annals of Biotechnology* 2018; 1(1): 1002. doi: 10.33582/2637-4927/1002
4. Wortmann M. Dementia: A global health priority-highlights from an ADI and World Health Organization report. *Alzheimer's Research & Therapy* 2012; 4: 40. doi: 10.1186/alzrt143
5. Povova J, Ambroz P, Bar M, et al. Epidemiological of and risk factors for Alzheimer's disease: A review. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czech Republic* 2012; 156(2): 108–114. doi: 10.5507/bp.2012.055
6. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *The Lancet* 2006; 368(9533): 387–403. doi: 10.1016/S0140-6736(06)69113-7
7. Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: Prevalence, management, and risk factors. *The Lancet Neurology* 2008; 7(9): 812–826. doi: 10.1016/S1474-4422(08)70169-8
8. Platzer K, Yuan H, Schütz H, et al. *GRIN2B* encephalopathy: Novel findings on phenotype, variant clustering, functional consequences and treatment aspects. *Journal of Medical Genetics* 2017; 54(7): 460–470. doi: 10.1136/jmedgenet-2016-104509
9. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. Alzheimer's disease: Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology* 1998; 51(1 Suppl 1): S65–S67. doi: 10.1212/wnl.51.1_suppl_1.s2
10. Seripa D, Matera MG, Franceschi M, et al. The RELN locus in Alzheimer's disease. *Journal of Alzheimer's Disease* 2008; 14(3): 335–344. doi: 10.3233/jad-2008-14308
11. Blacker D, Albert MS, Bassett SS, et al. Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease: The National Institute of Mental Health Genetics Initiative. *Archives of Neurology* 1994; 51(12): 1198–204. doi: 10.1001/archneur.1994.00540240042014

12. Lopez OL, Swihart AA, Becker JT, et al. Reliability of NINCDS‐ADRDA clinical criteria for the diagnosis of Alzheimer's disease. *Neurology* 1990; 40(10): 1517–1522. doi: 10.1212/wnl.40.10.1517
13. DeMaagd G, Philip A. Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis. P T. 2015 Aug;40(8):504-32. PMID: 26236139; PMCID: PMC4517533.
14. Alzheimer's Association. 2019 Alzheimer's disease facts and figures. *Alzheimer's & Dementia* 2019; 15(3): 321–387. doi: 10.1016/j.jalz.2019.01.010
15. Gantela P, Ilankumaran S, Arunachalam M, et al. Analysis of Alzheimer disease with K means algorithm and PSO segmentation. In: Proceedings of the 2022 IEEE 2nd Mysore Sub Section International Conference (MysuruCon); 16 October 2022; Mysuru, India. pp. 1–6.
16. Savova GK, Masanz JJ, Ogren PV, et al. Mayo clinical text analysis and knowledge extraction system (cTAKES): Architecture, component evaluation and applications. *Journal of the American Medical Informatics Association* 2010; 17(5): 507–513. doi: 10.1136/jamia.2009.001560
17. Zhao L. CD_{33} in Alzheimer's disease—Biology, pathogenesis, and therapeutics: A mini-review. *Gerontology* 2019; 65(4): 323–331. doi: 10.1159/000492596
18. Ding J, Eigenbrodt ML, Mosley Jr TH, et al. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2004; 35(1): 16–21. doi: 10.1161/01.STR.0000105929.88691.8E
19. Paul CA, Au R, Fredman L, Massaro JM, et al. Association of alcohol consumption with brain volume in the Framingham study. *Archives of Neurology* 2008; 65(10): 1363–1367. doi: 10.1001/archneur.65.10.1363
20. Anttila T, Helkala EL, Viitanen M, et al. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: A prospective population based study. *BMJ* 2004; 329(7465): 539. doi: 10.1136/bmj.38181.418958.BE
21. Ott A, Slooter AJ, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: The Rotterdam study. *The Lancet* 1998; 351(9119): 1840–1843. doi: 10.1016/s0140-6736(97)07541-7
22. Merchant C, Tang MX, Albert S, et al. The influence of smoking on the risk of Alzheimer's disease. *Neurology* 1999; 52(7): 1408–1412. doi: 10.1212/wnl.52.7.1408
23. Aggarwal NT, Bienias JL, Bennett DA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology* 2006; 26(3): 140–146. doi: 10.1159/000091654
24. Almeida OP, Hulse GK, Lawrence D, Flicker L. Smoking as a risk factor for Alzheimer's disease: Contrasting evidence from a systematic review of case-control and cohort studies. *Addiction* 2002; 97(1): 15–28. doi: 10.1046/j.1360-0443.2002.00016.x
25. Ridge PG, Ebbert MTW, Kauwe JSK. Genetics of Alzheimer's disease. *BioMed Research International* 2013; 2013: 254954. doi: 10.1155/2013/254954
26. Myers A, Holmans P, Marshall H, Kwon J, Meyer D, Ramic D, Shears S, Booth J, DeVrieze FW, Crook R, Hamshere M. Susceptibility locus for Alzheimer's disease on chromosome 10. Science. 2000 Dec 22;290(5500):2304-5.
27. Noviandy TR, Maulana A, Idroes GM, et al. Integrating genetic algorithm and LightGBM for QSAR modeling of acetylcholinesterase inhibitors in Alzheimer's disease drug discovery. *Malacca Pharmaceutics* 2023; 1(2): 48–54. doi: 10.60084/mp.v1i2.60
28. Barnard ND, Bunner AE, Agarwal U. Saturated and trans fats and dementia: A systematic review. *Neurobiology of Aging* 2014; 35: S65–S73. doi: 10.1016/j.neurobiolaging.2014.02.030
29. Morris MC, Tangney CC. Dietary fat composition and dementia risk. *Neurobiology of Aging* 2014; 35(Suppl 2): S59–S64. doi: 10.1016/j.neurobiolaging.2014.03.038
30. Maesako M, Uemura M, Tashiro Y, et al. High fat diet enhances β-site cleavage of amyloid precursor protein (APP) via promoting β-site APP cleaving enzyme 1/adaptor protein 2/clathrin complex formation. *PLoS One* 2015; 10(9): e0131199. doi: 10.1371/journal.pone.0131199
31. Knight EM, Martins IVA, Gümüsgöz S, et al. High-fat diet-induced memory impairment in triple-transgenic Alzheimer's disease (3xTgAD) mice is independent of changes in amyloid and tau pathology. *Neurobiology of Aging* 2014; 35(8): 1821–1832. doi: 10.1016/j.neurobiolaging.2014.02.010
32. Patwekar M, Patwekar F, Mezni A, et al. Assessment of antioxidative and alpha-amylase potential of polyherbal extract. *Evidence-Based Complementary and Alternative Medicine* 2022; 2022: 7153526. doi: 10.1155/2022/7153526
33. Dias IHK, Polidori MC, Griffiths HR. Hypercholesterolaemia-induced oxidative stress at the blood-brain barrier. *Biochemical Society Transactions* 2014; 42(4): 1001–1005. doi: 10.1042/BST20140164
34. Lim WLF, Martins IJ, Martins RN. The involvement of lipids in Alzheimer's disease. *Journal of Genetics and Genomics* 2014; 41(5): 261–274. doi: 10.1016/j.jgg.2014.04.003
35. Mittelman MS, Roth DL, Coon DW, Haley WE. Sustained benefit of supportive intervention for depressive symptoms in caregivers of patients with Alzheimer's disease. *American Journal of Psychiatry* 2004; 161(5): 850–856. doi: 10.1176/appi.ajp.161.5.850

36. Kosari S, Badoer E, Nguyen JCD, et al. Effect of western and high fat diets on memory and cholinergic measures in the rat. *Behavioural Brain Research* 2012; 235(1): 98–103. doi: 10.1016/j.bbr.2012.07.017
37. Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: A key role for oxidative stress in brain. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 2014; 1842(9): 1693–1706. doi: 10.1016/j.bbadis.2014.06.010
38. Mittal K, Katare DP. Shared links between type 2 diabetes mellitus and Alzheimer's disease: A review. *Diabetes & Metabolic Syndrome* 2016; 10(2 Suppl 1): S144–S149. doi: 10.1016/j.dsx.2016.01.021
39. Rosales-Corral S, Tan DX, Manchester L, Reiter RJ. Diabetes and Alzheimer disease, two overlapping pathologies with the same background: Oxidative stress. *Oxidative Medicine and Cellular Longevity* 2015; 2015: 985845. doi: 10.1155/2015/985845
40. Joas E, Bäckman K, Gustafson D, et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension* 2012; 59(4): 796–801. doi: 10.1161/HYPERTENSIONAHA.111.182204
41. Birnbaum JH, Bali J, Rajendran L, et al. Calcium flux-independent NMDA receptor activity is required for Aβ oligomer-induced synaptic loss. *Cell Death & Disease* 2015; 6(6): e1791. doi: 10.1038/cddis.2015.160
42. Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, et al. Alzheimer's disease: A review from the pathophysiology to diagnosis, new perspectives for pharmacological treatment. *Current Medicinal Chemistry* 2018; 25(26): 3141–3159. doi: 10.2174/0929867323666161213101126
43. World Health Organization. mhGAP: Mental Health Gap Action Programme: scaling up care for mental, neurological and substance use disorders. World Health Organization; 2008.
44. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *The Lancet* 1976; 2(8000): 1403. doi: 10.1016/s0140-6736(76)91936-x
45. McGeer PL, McGeer EG, Suzuki J, et al. Aging, Alzheimer's disease, and the cholinergic system of the basal forebrain. *Neurology* 1984; 34(6): 741–745. doi: 10.1212/wnl.34.6.741
46. Muir JL. Acetylcholine, aging, and Alzheimer's disease. *Pharmacology Biochemistry and Behavior* 1997; 56(4): 687–696. doi: 10.1016/s0091-3057(96)00431-5
47. Gotti C, Clementi F. Neuronal nicotinic receptors: From structure to pathology. *Progress in Neurobiology* 2004; 74(6): 363–396. doi: 10.1016/j.pneurobio.2004.09.006
48. Karlin A. Emerging structure of the nicotinic acetylcholine receptors. *Nature Reviews Neuroscience* 2002; 3(2): 102–114. doi: 10.1038/nrn731
49. Wevers A, Schröder H. Nicotinic acetylcholine receptors in Alzheimer's disease. *Journal of Alzheimer's Disease* 1999; 1(4–5): 207–219. doi: 10.3233/jad-1999-14-503
50. Quazi A, Mohsina FP, Faheem IP, Priya S. Silico ADMET analysis, molecular docking and in vivo anti diabetic activity of polyherbal tea bag formulation in streptozotocin-nicotinamide induced diabetic rats. *International Journal of Health Sciences* 2022; 6(S3): 343–372. doi: 10.53730/ijhs.v6nS3.5189
51. Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. *Nature* 1984; 309(5965): 261–263. doi: 10.1038/309261a0
52. Liu J, Chang L, Song Y, et al. The role of NMDA receptors in Alzheimer's disease. *Frontiers in Neuroscience* 2019; 13: 43. doi: 10.3389/fnins.2019.00043
53. Wang R, Reddy PH. Role of glutamate and NMDA receptors in Alzheimer's disease. *Journal of Alzheimer's Disease* 2017; 57(4): 1041–1048. doi: 10.3233/JAD-160763
54. Fuchs P, Strehl S, Dworzak M, et al. Structure of the human TNF receptor 1 (p60) gene (TNRF1) and localization to chromosome 12p13. *Genomics* 1992; 13(1): 219–224. doi: 10.1016/0888-7543(92)90226-I
55. Loetscher H, Pan YC, Lahm HW, et al. Molecular cloning and expression of the human 55 kd tumor necrosis factor receptor. *Cell* 1990; 61(2): 351–359. doi: 10.1016/0092-8674(90)90815-v
56. Santee SM, Owen-Schaub LB. Human tumor necrosis factor receptor p75/80 (CD120b) gene structure and promoter characterization. *Journal of Biological Chemistry* 1996; 271(35): 21151–21159. doi: 10.1074/jbc.271.35.21151
57. Schall TJ, Lewis M, Koller KJ, et al. Molecular cloning and expression of a receptor for human tumor necrosis factor. *Cell* 1990; 61(2): 361–370. doi: 10.1016/0092-8674(90)90816-w
58. Smith CA, Davis T, Anderson D, et al. A receptor for tumor necrosis factor defines an unusual family of cellular and viral proteins. *Science* 1990; 248(4958): 1019–1023. doi: 10.1126/science.2160731
59. Perry RT, Collins JS, Wiener H, et al. The role of TNF and its receptors in Alzheimer's disease. *Neurobiology of Aging* 2001; 22(6): 873–883. doi: 10.1016/s0197-4580(01)00291-3
60. Bongioanni P, Romano MR, Sposito R, et al. T-cell tumour necrosis factor-alpha receptor binding in demented patients. *Journal of Neurology* 1997; 244(7): 418–425. doi: 10.1007/s004150050115
61. Sipe JD, Cohen AS. Review: History of the amyloid fibril. *Journal of Structural Biology* 2000; 130(2–3): 88–98. doi: 10.1006/jsbi.2000.4221
62. Glenner GG, Wong CW. Alzheimer's disease: Initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications* 1984; 120(3): 885–890. doi: 10.1016/s0006-291x(84)80190-4

63. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. *Nature Reviews Neuroscience* 2018; 19(11): 687–700. doi: 10.1038/s41583-018-0067-3
64. Lacor PN, Buniel MC, Furlow PW, et al. Aβ oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. *Journal of Neuroscience* 2007; 27(4): 796–807. doi: 10.1523/JNEUROSCI.350106.2007
65. Shankar GM, Bloodgood BL, Townsend M, et al. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *Journal of Neuroscience* 2007; 27(11): 2866–2875. doi: 10.1523/ JNEUROSCI.4970-06.2007
66. Wu HY, Hudry E, Hashimoto T, et al. Amyloid beta induces the morphological neurodegenerative triad of spine loss, dendritic simplification, and neuritic dystrophies through calcineurin activation. *Journal of Neuroscience* 2010; 30(7): 2636–2349. doi: 10.1523/JNEUROSCI.4456-09.2010
67. Palop JJ, Mucke L. Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: From synapses toward neural networks. *Nature Neuroscience* 2010; 13(7): 812–818. doi: 10.1038/nn.2583
68. Mahley RW. Apolipoprotein E: Cholesterol transport protein with expanding role in cell biology. *Science* 1988; 240(4852): 622–630. doi: 10.1126/science.3283935
69. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proceedings of the National Academy of Sciences* 1993; 90(5): 1977–1981. doi: 10.1073/pnas.90.5.1977
70. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small G, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993 Aug 13;261(5123):921-3.
71. Herz J, Bock HH. Lipoprotein receptors in the nervous system. *Annual review of biochemistry* 2002; 71(1): 405–434. doi: 10.1146/annurev.biochem.71.110601.135342
72. Pitas RE, Boyles JK, Lee SH, et al. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. *Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism* 1987; 917(1): 148–161. doi: 10.1016/0005-2760(87)90295-5
73. Herz J, Kowal RC, Goldstein JL, Brown MS. Proteolytic processing of the 600 kd low density lipoprotein receptor‐related protein (LRP) occurs in a trans‐Golgi compartment. *The EMBO Journal* 1990; 9(6): 1769–1776. doi: 10.1002/j.1460-2075.1990.tb08301.x
74. Ritchie K, Touchon J. Heterogeneity in senile dementia of the Alzheimer type: Individual differences, progressive deterioration or clinical sub-types? *Journal of Clinical Epidemiology* 1992; 45(12): 1391–1398. doi: 10.1016/0895-4356(92)90201-w
75. Murray ME, Graff-Radford NR, Ross OA, et al. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. *The Lancet Neurology* 2011; 10(9): 785–796. doi: 10.1016/S1474-4422(11)70156-9
76. Weintraub S, Wicklund AH, Salmon DP. The neuropsychological profile of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine* 2012; 2(4): a006171. doi: 10.1101/cshperspect.a006171
77. Slattery CF, Crutch SJ, Schott JM. Phenotypical variation in Alzheimer's disease: Insights from posterior cortical atrophy. *Practical Neurology* 2015; 15(1): 2–4. doi: 10.1136/practneurol-2014-000955
78. Beffert U, Aumont N, Dea D, et al. Beta‐amyloid peptides increase the binding and internalization of apolipoprotein E to hippocampal neurons. *Journal of Neurochemistry* 1998; 70(4): 1458–1466. doi: 10.1046/j.1471-4159.1998.70041458.x
79. Hone E, Martins IJ, Jeoung M, et al. Alzheimer's disease amyloid-beta peptide modulates apolipoprotein E isoform specific receptor binding. *Journal of Alzheimer's Disease* 2005; 7(4): 303–314. doi: 10.3233/jad-2005-7406
80. LaDu MJ, Falduto MT, Manelli AM, et al. Isoform-specific binding of apolipoprotein E to beta-amyloid. *Journal of Biological Chemistry* 1994; 269(38): 23403–23406.
81. McDonald C. Clinical heterogeneity in senile dementia. *The British Journal of Psychiatry* 1969; 115(520): 267–271. doi: 10.1192/bjp.115.520.267
82. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. *Alzheimer's Research & Therapy* 2013; 5(1): 1–4. doi: 10.1186/alzrt155
83. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & Dementia* 2012; 8(1): 1–13. doi: 10.1016/j.jalz.2011.10.007
84. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Archives of Neurology* 1985; 42(11): 1097–1105. doi: 10.1001/archneur.1985.04060100083029
85. Mirra SS, Heyman A, McKeel D, et al. The consortium to establish a registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991; 41(4): 479–486. doi: 10.1212/wnl.41.4.479
86. Kumar A, Dogra S. Neuropathology and therapeutic management of Alzheimer's disease—An update. *Drugs of the Future* 2008; 33(5): 433–446. doi: 10.1358/dof.2008.033.05.1192677

87. Hardy J. The amyloid hypothesis for Alzheimer's disease: A critical reappraisal. *Journal of Neurochemistry* 2009; 110(4): 1129–1134. doi: 10.1111/j.1471-4159.2009.06181.x
88. Dal Prà I, Chiarini A, Gui L, et al. Do astrocytes collaborate with neurons in spreading the "infectious" aβ and Tau drivers of Alzheimer's disease? *The Neuroscientist* 2015; 21(1): 9–29. doi: 10.1177/1073858414529828
89. Rosenmann H. Immunotherapy for targeting tau pathology in Alzheimer's disease and tauopathies. *Current Alzheimer Research* 2013; 10(3): 217–228. doi: 10.2174/1567205011310030001
90. Mohsina FP, Faheem IP, Priya S, Husain SMA. Evaluation of anti diabetic activity of ichnocarpus frutescens L. *International Journal of Advances in Pharmacy and Biotechnology* 2018; 4(2): 1–2. doi: 10.38111/ijapb.20180402001
91. Roth AD, Ramírez G, Alarcón R, Von Bernhardi R. Oligodendrocytes damage in Alzheimer's disease: Beta amyloid toxicity and inflammation. *Biological Research* 2005; 38(4): 381–387. doi: 10.4067/s0716-97602005000400011
92. Mohsina FP, Quazi A, Faheem IP, et al. Botanical, ethnopharmacological, phytochemical & pharmacological standards of plant ichnocarpus frutescens. *Research & Review: Drugs and Drugs Development* 2022; 4(1): 1–2. doi: 10.46610/RRDDD.2022.v04i01.001
93. Chaturvedi V, Goyal S, Mukim M, et al. A comprehensive review on Catharanthus roseus L. (G.) Don: Clinical pharmacology, ethnopharmacology and phytochemistry. *Journal of Pharmacological Research and Developments* 2022; 4(2): 17–36. doi: 10.46610/JPRD.2022.v04i02.003
94. Xu Y, Yan J, Zhou P, et al. Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease. *Progress in Neurobiology* 2012; 97(1): 1–13. doi: 10.1016/j.pneurobio.2012.02.002
95. Selkoe DJ. Alzheimer's disease: Genes, proteins, and therapy. *Physiological Reviews* 2001; 81(2): 741–766. doi: 10.1152/physrev.2001.81.2.741
96. Wenk GL. Neuropathologic changes in Alzheimer's disease. *Journal of Clinical Psychiatry* 2003; 64 (Suppl 9): 7–10.
97. Boncristiano S, Calhoun ME, Kelly PH, et al. Cholinergic changes in the APP23 transgenic mouse model of cerebral amyloidosis. *Journal of Neuroscience* 2002; 22(8): 3234–3243. doi: 10.1523/JNEUROSCI.22-08-03234.2002
98. Yasojima K, McGeer EG, McGeer PL. Relationship between beta amyloid peptide generating molecules and neprilysin in Alzheimer disease and normal brain. *Brain Research* 2001; 919(1): 115–121. doi: 10.1016/s0006-8993(01)03008-6
99. Braak H, Del Tredici K. Alzheimer's pathogenesis: Is there neuron-to-neuron propagation? *Acta Neuropathologica* 2011; 121(5): 589–595. doi: 10.1007/s00401-011-0825-z
100. Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. *The International Journal of Biochemistry & Cell Biology* 2005; 37(2): 289–305. doi: 10.1016/j.biocel.2004.07.009
101. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 1999; 400(6740): 173–177. doi: 10.1038/22124
102. Zlokovic BV. Clearing amyloid through the blood-brain barrier. *Journal of Neurochemistry* 2004; 89(4): 807–811. doi: 10.1111/j.1471-4159.2004.02385.x
103. Sagare A, Deane R, Bell RD, et al. Clearance of amyloid-beta by circulating lipoprotein receptors. *Nature Medicine* 2007; 13(9) :1029–1031. doi: 10.1038/nm1635
104. Yan SD, Bierhaus A, Nawroth PP, Stern DM. RAGE and Alzheimer's disease: A progression factor for amyloid-β-induced cellular perturbation? *Journal of Alzheimer's Disease* 2009; 16(4): 833–843. doi: 10.3233/JAD-2009-1030
105. Shinde MU, Patwekar M, Patwekar F, et al. Nanomaterials: A potential hope for life sciences from bench to bedside. *Journal of Nanomaterials* 2022; 2022: 5968131. doi: 10.1155/2022/5968131
106. Chang WP, Huang X, Downs D, et al. β-Secretase inhibitor GRL-8234 rescues age-related cognitive decline in APP transgenic mice. *The FASEB Journal* 2011; 25(2): 775–784. doi: 10.1096/fj.10-167213
107. Janusz M, Zablocka A. Colostral proline-rich polypeptides-immunoregulatory properties and prospects of therapeutic use in Alzheimer's disease. *Current Alzheimer Research* 2010; 7(4): 323–333. doi: 10.2174/156720510791162377
108. Jacobsen JS, Comery TA, Martone RL, et al. Enhanced clearance of Abeta in brain by sustaining the plasmin proteolysis cascade. *Proceedings of the National Academy of Sciences* 2008; 105(25): 8754–8759. doi: 10.1073/pnas.0710823105
109. Saito T, Iwata N, Tsubuki S, et al. Somatostatin regulates brain amyloid β peptide $A\beta_{42}$ through modulation of proteolytic degradation. *Nature Medicine* 2005; 11(4): 434–439. doi: 10.1038/nm1206
110. Scarpini E, Bruno G, Zappalà G, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: A randomized, double blind, placebo controlled withdrawal trial. *Journal of Alzheimer's Disease* 2011; 26(2): 211–220. doi: 10.3233/JAD-2011-110134
111. Hock C, Nitsch RM. Clinical observations with AN-1792 using TAPIR analyses. *Neurodegenerative Diseases* 2005; 2(5): 273–276. doi: 10.1159/000090368
112. Nicoll JAR, Wilkinson D, Holmes C, et al. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: A case report. *Nature Medicine* 2003; 9(4): 448–452. doi: 10.1038/nm840

113. Buée L, Bussière T, Buée-Scherrer V, et al. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Research Reviews* 2000; 33(1): 95–130. doi: 10.1016/s0165-0173(00)00019-9
114. Engel T, Goñi‐Oliver P, Lucas JJ, et al. Chronic lithium administration to FTDP‐17 tau and GSK‐3beta overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre‐formed neurofibrillary tangles do not revert. *Journal of Neurochemistry* 2006; 99(6): 1445–1455. doi: 10.1111/j.1471-4159.2006.04139.x
115. Zhang B, Maiti A, Shively S, et al. Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model. *Proceedings of the National Academy of Sciences* 2005; 102(1): 227–231. doi: 10.1073/pnas.0406361102
116. Pange SS, Patwekar M, Patwekar F, et al. A potential notion on Alzheimer's disease: Nanotechnology as an alternative solution. *Journal of Nanomaterials* 2022; 2022(2): 6910811. doi: 10.1155/2022/6910811
117. Chai X, Wu S, Murray TK, et al. Passive immunization with anti-tau antibodies in two transgenic models: Reduction of tau pathology and delay of disease progression. *Journal of Biological Chemistry* 2011; 286(39): 34457–34467. doi: 10.1074/jbc.M111.229633
118. Butterfield DA, Pocernich CB. The glutamatergic system and Alzheimer's disease: Therapeutic implications. *CNS Drugs* 2003; 17(9): 641–652. doi: 10.2165/00023210-200317090-00004
119. Miguel-Hidalgo JJ, Paul IA, Wanzo V, Banerjee PK. Memantine prevents cognitive impairment and reduces Bcl-2 and caspase 8 immunoreactivity in rats injected with amyloid β1-40. *European Journal of Pharmacology* 2012; 692(1-3): 38–45. doi: 10.1016/j.ejphar.2012.07.032
120. Hellweg R, Wirth Y, Janetzky W, Hartmann S. Efficacy of memantine in delaying clinical worsening in Alzheimer's disease (AD): Responder analyses of nine clinical trials with patients with moderate to severe AD. *International Journal of Geriatric Psychiatry* 2012; 27(6): 651–656. doi: 10.1002/gps.2766
121. Ni R, Marutle A, Nordberg A. Modulation of α7 nicotinic acetylcholine receptor and fibrillar amyloid-β interactions in Alzheimer's disease brain. *Journal of Alzheimer's Disease* 2013; 33(3): 841–851. doi: 10.3233/JAD-2012-121447
122. Bösel J, Gandor F, Harms C, et al. Neuroprotective effects of atorvastatin against glutamate‐induced excitotoxicity in primary cortical neurones. *Journal of Neurochemistry* 2005; 92(6): 1386–1398. doi: 10.1111/j.1471-4159.2004.02980.x
123. Yue Y, Hu L, Tian QJ, et al. Effects of long‐term, low‐dose sex hormone replacement therapy on hippocampus and cognition of postmenopausal women of different apoE genotypes. *Acta Pharmacologica Sinica* 2007; 28(8): 1129–1135. doi: 10.1111/j.1745-7254.2007.00618.x
124. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacological Reports* 2015; 67(2): 195–203. doi: 10.1016/j.pharep.2014.09.004
125. Vatansever S, Schlessinger A, Wacker D, et al. Artificial intelligence and machine learning‐aided drug discovery in central nervous system diseases: State‐of‐the‐arts and future directions. *Medicinal Research Reviews* 2021; 41(3): 1427–1473. doi: 10.1002/med.21764
126. Krishnamurthy N, Grimshaw AA, Axson SA, et al. Drug repurposing: A systematic review on root causes, barriers and facilitators. *BMC Health Services Research* 2022; 22(1): 970. doi: 10.1186/s12913-022-08272-z
127. Diaz V, Rodríguez G. Machine learning for detection of cognitive impairment. *Acta Polytechnica Hungarica* 2022; 19(5): 196–213.
128. Arrué L, Cigna-Méndez A, Barbosa T, et al. New drug design avenues targeting Alzheimer's disease by pharmacoinformatics-aided tools. *Pharmaceutics* 2022; 14(9): 1914. doi: 10.3390/pharmaceutics14091914
129. Narayanan RR, Durga N, Nagalakshmi S. Impact of artificial intelligence (AI) on drug discovery and product development. *Indian Journal of Pharmaceutical Education and Research* 2022; 56(3): S387–S397.