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A SYSTEMATIC REVIEW OF ALZHEIMER'S DISEASE: EXPLORING GENETIC AND ENVIRONMENTAL RISK FACTORS, BIOMARKERS, AND FUTURE PHARMACOTHERAPY FOR COGNITIVE DECLINE AND NEURODEGENERATION

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ABSTRACT

Background: Alzheimer's disease (AD) is the most prevalent form of dementia, affecting millions globally through progressive cognitive decline caused by neurodegeneration in cholinergic brain regions. Aging is the primary risk factor, but metabolic, genetic, and environmental influences, including inflammation and vascular dysfunction, significantly contribute to disease onset and progression. **Methodology:** This comprehensive review evaluates diagnostic methods, biomarkers, and genetic and environmental risk factors associated with AD, focusing on recent advancements (2022–2025). The study selection process prioritized clinical trials, systematic reviews, and meta-analyses related to AD pathophysiology, diagnostics, and therapeutic interventions while excluding research with ambiguous findings or lacking methodological rigor. A PRISMA flowchart illustrates the study selection process, ensuring transparency. Pharmaceutical and non-pharmacological interventions, along with multi-target therapeutic strategies, were critically analyzed. **Results and Discussion:** AD pathology is driven by amyloid-beta plaques and tau tangles, leading to synaptic dysfunction and neurodegeneration. Current treatments, including acetylcholinesterase inhibitors and NMDA receptor antagonists, offer symptomatic relief but are ineffective in halting disease progression. Emerging therapies such as monoclonal antibodies (Lecanemab, Donanemab), tau inhibitors, and neuroinflammation modulators show potential in slowing cognitive decline and preserving neuronal health. Advances in biomarker-based diagnostics (e.g., p-tau217) and AI-powered precision medicine have improved early detection and personalized treatment strategies, though challenges in cost, accessibility, and regulatory approval persist. **Conclusion:** A multisystem approach combining pharmacotherapy, biomarker-driven diagnostics, and AI-assisted personalized medicine is essential to optimize AD treatment effectiveness. Future research should focus on developing innovative, multidisciplinary treatment strategies to enhance patient outcomes and quality of life.

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INTRODUCTION

Alzheimer's disease (AD) represents a progressive form of neurodegeneration that stands as the primary dementia cause of dementia in the world since it affects 60–80% of dementia patients [1],[2]. Daily functioning depends heavily on the extent of disease progression as well as the brain regions affected by the disability and the severity of its stage [3],[4]. The symptoms of AD include various manifestations that include depression alongside apathy and difficulties in communication and disorientation, combined with judgment deterioration, along with swallowing problems, walking impairments, and behavioral patterns [5]. AD cases continue to increase quickly throughout the world. The worldwide dementia population is expected to reach 55 million people by 2025, since AD represents the leading type among dementia forms. The prevalence of AD is anticipated to soar from its current 55 million cases to reach more than 152 million patients by 2050 because of increasing elderly populations, together with lifestyle alterations and genetic risks [6],[4]. The combination of insufficient healthcare access and late diagnosis will cause the most significant rise in Alzheimer's disease cases throughout low- and middle-income nations [7]. COVID-19 became a crucial factor in increasing dementia patient mortality, which underscores the necessity of new disease management approaches [8]. The diagnosis of AD depends on the identification of amyloid-beta (Aβ) plaques and tau protein tangles, which are visible in molecular analyses. The pathological deposits of proteins cause harm to cellular structures and disrupt synapses, resulting in significant brain cell death and progressive cognitive decline [9].

Two essential biomarkers for AD diagnosis and disease tracking include neurofilament light chain (NfL) which detects axonal damage and phosphorylated tau at residue 217 (p-tau217) which provides specific tau pathology assessment [10],[11]Research shows that elevated measurements of NfL reflect the extent of neurodegenerative damage but p-tau217 identifies explicitly Alzheimer's disease from other dementia types The urgent necessity for effective therapeutic measures gains strong support from recent research which confirmed complex neuronal processes between Aβ and tau that result in neuronal damage which show in **Figure 1** shows that AD patients currently do not have access to any therapeutic drugs that can completely reverse their neuronal dysfunction.

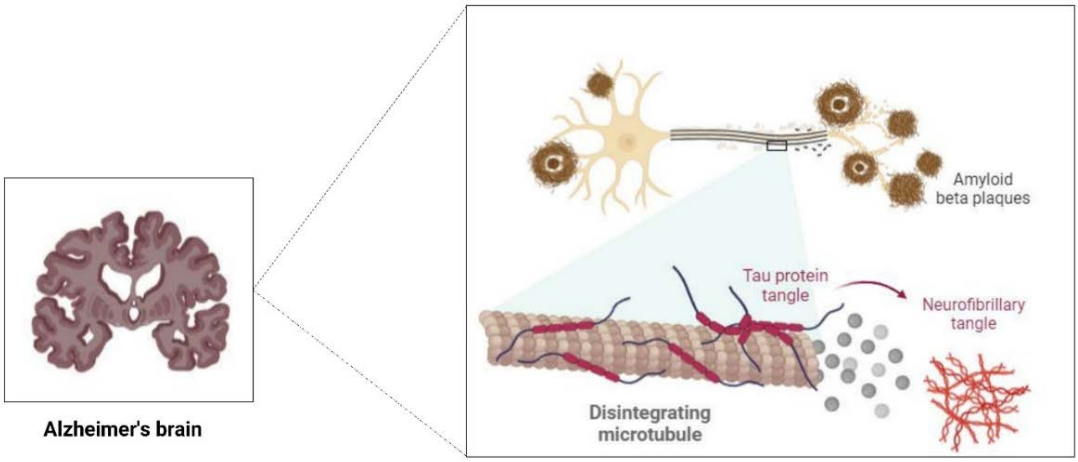

Figure 1: The pathogenic characteristics of Alzheimer's disease: the picture depicts tau protein tangles and beta amyloid plaques in the neural network. That has suffered from Alzheimer's disease. Amyloid deposits are found between neurons, while tau aggregates destroy microtubules within them, leading to the formation of neurofibrillary tangles. These abnormal protein clumps give rise to neuronal damage and cognitive impairment [12],[13].

Therapeutic research now investigates how natural products and specific metabolite interventions can protect brain cells. Multi-omics research investigates treatment strategies that may impact neurovascular signaling pathways, aiming to develop novel therapeutic methods. The cellular pathways involved in AD expression appear to vary based on biological sex, according to recent findings on how unfavorable glycemic and lipemic conditions influence disease progression [7]. This review conducts a detailed assessment of the diagnostic elements, along with biomarkers of NfL and p-tau217, alongside genetic factors,

environmental triggers, and therapeutic interventions used to manage AD. Researchers focus on newly developed treatment approaches with disease-reducing abilities.

Diagnostic Parameters for Alzheimer's Disease

Accurate and early diagnosis of Alzheimer's disease (AD) is essential for effective disease management, treatment planning, and improving patient outcomes. A combination of clinical assessments, neuropsychological tests, and biomarker evaluations is commonly employed to identify and monitor the progression of the disease. These diagnostic tools offer insights into cognitive decline, structural brain changes, and pathological markers, including amyloid-beta and tau proteins. Table 1 summarizes the key diagnostic parameters used in Alzheimer's disease, highlighting their clinical significance and associated observations.

Table 1: Diagnostic Parameters for Alzheimer's disease: Tests, Significance, and Remarks

Diagnostic Parameter	Description	Tests or Methods Used	Significance	Remarks	Ref
Neurophysiological Assessment	Assessment of cognitive functions and daily living activities through neuropsychological tests.	Neuropsychological tests (e.g., MMSE, MoCA)	Helps identify cognitive impairment and memory loss.	Essential for initial screening.	[14]
Magnetic Resonance Imaging (MRI)	Imaging technique to visualize brain structure and identify abnormalities associated with AD.	MRI scans	Aids in detecting brain atrophy and other structural changes related to AD.	Non-invasive method.	[15]
Vitamin B12 Level	Assessment of serum vitamin B12 concentration and serum homocysteine levels.	Blood tests for vitamin B12 and homocysteine levels	Low vitamin B12 levels are linked to neurogenic complications and increased AD risk.	Important for ruling out deficiencies.	[16]
Clinical History and Family History	Review of patient's medical and family background related to neurodegenerative diseases.	Patient interviews and medical history review	Provides context for genetic predisposition and environmental factors influencing AD risk.	Critical for comprehensive assessment.	[17], [18]
NINCDS-ADRDA Diagnostic Criteria	Established in 1984 to assess symptoms like dementia, memory loss, aphasia, apraxia, and agnosia for diagnosing AD.	Clinical evaluation using established criteria	Standardizes diagnosis and highlights specific cognitive deficits related to AD.	Neuro-pathological examination is impractical in living individuals.	[19]
Mini-Mental State Examination (MMSE)	A bedside assessment tool used to evaluate cognitive impairment and changes in mental status.	Structured questionnaire	Quick screening tool to gauge cognitive function and memory.	Widely used in clinical settings.	[20], [21]
Exclusion of Other Neurodegenerative Diseases	Diagnostic process to rule out other conditions such as frontotemporal dementia and Parkinson's disease.	Differential diagnosis using clinical assessments	Ensures accurate diagnosis by excluding similar conditions presenting with dementia-like symptoms.	Necessary for targeted treatment.	[22]
Exclusion of Treatable Causes of Cognitive Decline	Identification of reversible factors contributing to dementia symptoms, including depression and drug intoxication.	Blood tests, thyroid function tests, and mental health evaluations	Critical for ensuring that potential reversible causes are addressed before confirming AD.	Helps in treatment planning.	[23], [24]

BIOMARKER IN ALZHEIMER'S DISEASE

CSF Biomarkers Related to AD Pathogenesis

Cerebrospinal fluid (CSF) represents a close link to the brain's extracellular environment and is an ideal medium in which to detect AD biomarkers. The neurovascular impairment and blood-brain barrier (BBB) dysfunction that contribute to neurodegenerative disorders can lead to reflecting biochemical parameters in CSF [25]. Aβ42, t-tau, and p-tau are theretofore known for their extremely sensitive and definitive biomarkers for AD. These key pathogenic molecules act as over 80% specific and sensitive markers for symptomatic cases [26]. Indicate that levels of CSF Aβ42 are decreased in cognitively normal individuals who are at risk of developing AD, and that these patients might have already had lower levels of CSF Aβ42 before the onset of sporadic dementia. Provide information that denotes that CSF Aβ42 levels are lower among cognitively intact individuals who are at risk for developing AD, and that sporadic dementia patients may already have reduced CSF Aβ42 levels before the dementia onset. [27],[28],. Moreover, it has also been demonstrated that t-tau levels are predictive of cognitive decline, particularly in elderly female populations.

The levels of another amyloid peptide, CSF Aβ40, do not seem to differ appreciably between an AD patient and controls, thus suggesting that the Aβ42 Aβ40 ratio may be a more efficacious approach than Aβ42 alone in distinguishing AD from dementia in Parkinson's disease (PDD) or dementia with Lewy bodies (DLB) [29],[30],. According to research, impaired Aβ42/40 and Aβ42/38 ratios may serve as investigative indicators that differentiate AD from other dementias. Familial AD cohorts provide evidence that Aβ42 levels during precocious elevations may decrease (or at least plateau) up to 25 years before symptom onset. In comparison, PET amyloid deposition and t-tau CSF levels can precede the expected onset of symptoms up to 15 years [31].

These outcomes suggest that CSF Aβ42 decline represents a key biomarker for identifying preclinical familial and sporadic AD. However, CSF collection is an invasive procedure, potentially dangerous, and not suited for screening healthy individuals [32]. Alongside neuroimaging tools such as volumetric assessments of the hippocampus and fluorodeoxyglucose (FDG) PET and amyloid PET, FCMT029 is incorporated in the NIA-AA criteria for inclusion of individuals in the diagnosis of Alzheimer's disease (AD), for determining the later stages of AD, and for differentiation between normal aging and the mild forms of cognitive impairment.

Marking shifts in A1 42 and tau proteins in CSF, the NIA-AA criteria for diagnosing AD, assessing the later stages of AD, and differentiating between it and normal aging versus mild cognitive impairment (MCI) include changes in biomarkers where the alterations are complemented with volumetric imaging and neuroimaging, such as those with fluorodeoxyglucose (FDG) PET and amyloid PET [33],[34].

CSF Neurodegeneration Biomarkers

Neurodegeneration has been defined by changes in axons, synapses, and the activation of glial cells. Neurofilament light chain (NF-L), a protein of neurofilaments in axons, is released into CSF and plasma during numerous neurodegenerative diseases. Increased levels of CSF NF-L have been reported in vascular dementia (VaD), normal pressure hydrocephalus, multiple sclerosis, and amyotrophic lateral sclerosis. In frontotemporal dementia and late-onset Alzheimer's disease, there can be intra-species differences that indicate diagnostic criteria since CSF NF-L levels taken alone would signal those conditions [35],[36],[37].

Therefore, CSF NF-L can be viewed as a likely biomarker for the detection of neurodegenerative diseases, but not specific for AD. Zetterberg et al. explain that CSF NF-L levels are elevated in AD and MCI, indicating that increased CSF NF-L levels correlate with poorer cognitive performance and brain atrophy in individuals with AD and MCI. Another such example is visinin-like protein 1, a calcium sensor protein that is also found overexpressed in other injuries to the brain, including AD. Bringing changes in early AD suggests that it could also become a marker for diagnosis or progression in the disease.

However, the evidence is inconsistent for VILIP-1 in CSF regarding AD versus DLB, and this warrants further investigation [38]. Pre- and postsynaptic proteins, including neurogranin, SNAP-25, and synaptotagmin, were detected in the cerebrospinal fluid of AD patients. There are other markers worth characterizing among the best in the molecular changes that accompany AD, and they include the Ca2+/calmodulin-dependent protein kinases and their substrate neurogranin, found primarily in dendritic spines, which are increased in the CSF of AD patients and MCI patients progressing to AD.

SNAP-25 fragments were also detected in higher concentrations in individuals with AD and MCI. Still, their levels decreased over time, suggesting that SNAP-25 fragments could potentially be used to differentiate AD from other forms of dementia. These synaptic biomarkers may serve as adjunctive markers of AD or MCI but are not definitive [39],[40],[41],[42].

Blood-Based Biomarkers for AD Pathogenesis

Aβ42 and Aβ40, which are the most commonly studied blood-based markers, are often examined as they measure symptomatic and prodromal disease. Nevertheless, studies reveal inconsistent results regarding the evidence of at least some of these markers in the plasma of AD patients. AD patients and those developing AD within three years had higher plasma Aβ42 levels, which Mayeux et al. reported would double the rate of developing AD. However, van Oijen et al. did show that higher levels of plasma Aβ40 correlated with higher dementia risk, and a lower Aβ42/Aβ40 ratio was linked with cognitive decline in dementia free older adults [43],[44],[45],[46]. However, hippocampal volume and amyloid PET scans differentiate AD/MCI from other dementias using magnetic resonance imaging (MRI).

The Aβ42/Aβ43 ratio has been suggested as a potential blood biomarker for AD diagnostics in several studies [47]. In addition, the ratios of Aβ42/APP699-711 and Aβ42/Aβ40 are predictive of brain amyloid burden. Another set of ratios that distinguish AD from healthy, such as Aβ42/Aβ40 and plasma t-tau/Aβ42, have been validated [48],[49],[50]. Therefore, the lower levels of CSF Aβ42 in AD patients indicate less plasma Aβ42 in AD patients and amyloid-positive MCI. Therefore, in combination with Aβ42/Aβ40 and Aβ42/Aβ43, as well as Aβ42/APP669-711 and Aβ42/t-tau and Aβ42/p-tau181, the combination of these measures may enhance diagnostic accuracy for AD [51],[52].

Blood p-tau Markers

Plasma tau has become an attractive biomarker of AD, given its invasiveness and cost compared to CSF tau analysis. Numerous studies have quantified tau levels in AD and other forms of progressive dementia and MCI [53]. The difference in plasma tau concentrations compared to CSF has led to the development of an ultra-sensitive assay. We found that plasma t-tau levels were elevated in AD patients relative to MCI or healthy controls. Still, there were no differences between MCI patients who progressed to AD and those with stable MCI. Plasma t-tau could reflect the pathological progression of AD, or age relations matched controls, and thus be a biomarker in symptomatic individuals [54],[55]. A novel ultrasensitive immunoassay is used to quantify plasma p-tau181 and has shown significantly higher levels in AD and Down syndrome subjects than in normal controls.

Studies such as those have shown that as the disease progresses in patients with AD and MCI who later develop AD, plasma p tau 181 levels increase and can differentiate AD from all other dementia, including frontotemporal dementia, vascular dementia, and multiple system atrophy [56],[57].

Neurofilament light chain (NfL)

Neurofilament Light Chain (NfL) is a structural protein found in neuronal axons, playing a crucial role in maintaining axonal integrity. When neurons are damaged or degenerate, NfL is released into the cerebrospinal fluid (CSF) and blood, making it a valuable biomarker for neurodegenerative diseases, including Alzheimer's disease (AD) [58]. Unlike amyloid-beta (Aβ42) and tau, which are more specific to AD pathology, NfL serves as a general marker of neurodegeneration, reflecting axonal damage and neuronal loss. Increased levels of NfL in CSF and blood correlate with cognitive decline, brain atrophy, and disease severity in AD patients. Furthermore, its presence in blood (plasma/serum) makes it a promising non-invasive biomarker for monitoring disease progression. While NfL is not exclusive to AD, elevated levels help distinguish AD from normal aging and other neurodegenerative disorders such as frontotemporal dementia and multiple sclerosis. Due to its strong association with neurodegeneration, NfL is being explored for early diagnosis, disease monitoring, and therapeutic response assessment in clinical trials [22],[59].

Phosphorylated tau 217

Phosphorylated tau 217 (p-tau217) is a particular and sensitive biomarker for AD. P-tau217 has shown a stronger correlation with amyloid plaque deposition and tau pathology compared to previous tau biomarkers, such as p-tau181, making it a superior predictor of disease onset and progression [60]. Recent studies indicate that p-tau217 can detect AD pathology up to two decades before the onset of clinical symptoms, making it one of the most promising early diagnostic tools. Elevated levels of p-tau217 in CSF and blood plasma have been linked to amyloid accumulation in the brain, even in preclinical AD stages. Unlike

other phosphorylated tau isoforms, p-tau217 demonstrates higher specificity for distinguishing AD from other tauopathies, such as frontotemporal dementia (FTD) and progressive supranuclear palsy (PSP) [61].

Additionally, p-tau217 has emerged as a potential non-invasive blood-based biomarker, reducing the reliance on costly and invasive lumbar punctures for CSF analysis. Advances in ultrasensitive blood biomarker detection technologies have enhanced their clinical applicability, enabling early-stage screening and risk assessment in asymptomatic individuals. AI-driven diagnostic models are increasingly integrating p-tau217 alongside Aβ42/Aβ40 ratios and neuroimaging data to enhance diagnostic precision and monitor disease progression.

Given its strong predictive capabilities, p-tau217 is also being utilized as a biomarker for patient stratification in clinical trials, helping identify individuals who are most likely to benefit from targeted AD therapies [62]. (p-tau217) as a highly specific and sensitive biomarker for AD. P-tau217 has shown a stronger correlation with amyloid plaque deposition and tau pathology compared to previous tau biomarkers, such as p-tau181, making it a superior predictor of disease onset and progression.

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Pharmacological Management of Alzheimer's Disease and Mechanisms

The treatment of Alzheimer's disease (AD) primarily focuses on alleviating symptoms and slowing disease progression, as there is currently no definitive cure. Various drug classes have been developed to target specific aspects of the disease pathology, including neurotransmitter regulation and the aggregation of amyloid-beta.

Understanding the mechanisms of these therapeutic agents helps in selecting appropriate treatment regimens for individual patients. **Table 2** outlines the major types of drugs used in the management of Alzheimer's disease, detailing their mechanisms of action and representative examples.

Table 2: Types of drugs used for Alzheimer's disease (AD) treatment, along with their mechanisms of action and examples:

Type of Drug	Mechanism of Action	Examples	Ref
Cholinesterase Inhibitors	Inhibit the interruption of acetylcholine, increasing its levels in the brain in **Figure 2**	Donepezil, Rivastigmine, Galantamine	[64]
NMDA Receptor Antagonists	Regulate glutamate activity to stop excitotoxicity	Memantine	[65]
Anti-inflammatory Agents	Reduce inflammation in the brain	NSAIDs, Corticosteroids	[66]
Antioxidants	Combat oxidative stress and protect neurons	Vitamin E, Ginkgo biloba	[67]
Beta-amyloid Targeting Agents	Aim to reduce amyloid plaque formation	Aducanumab, Lecanemab	[68]
Tau-targeting Agents	Target tau protein aggregation	TPI 287, Biologics in development	[69]
Neuroprotective Agents	Protect against neuronal cell death	Cerebrolysin, Riluzole	[70]
Hormonal Treatments	Modulate hormones that may influence AD progression	Estrogen therapy	[71]
Other Experimental Therapies	Explore various novel targets and mechanisms	Anti-diabetic drugs, anti-viral agents	[72]

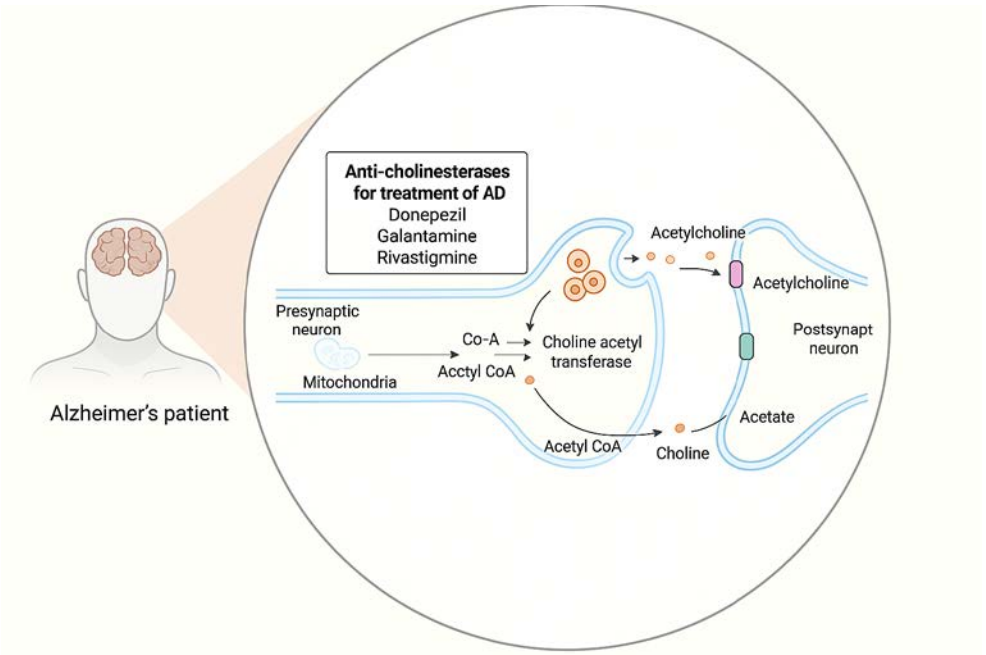

Figure 2: Mechanism of anti-cholinesterase drugs in Alzheimer's disease treatment: They are such drugs that include Donepezil, Galantamine, and Rivastigmine. These function by inhibiting the enzyme acetylcholinesterase, thereby increasing the amount of acetylcholine present in the synaptic cleft, as observed in patients with dementia and Alzheimer's disease [73],[74],[64].

NEUROPATHOLOGICAL CHANGES IN ALZHEIMERS DISEASE

The significant changes noted in AD involve a gradual formation of beta-amyloid (Aβ) plaques from the neocortex, over limbic structures, diencephalon, basal ganglia, to the brainstem and cer ebellum, and NFT from the transentorhinal region to the limbic system and finally to the neocortex [75]. The Consortium to Establish a Registry for Alzheimer's Disease, also known by its acronym CERAD, measures the density of neuronal plaques. Moreover, these neuropathological changes effectively reflect the pathological state of AD neurons, indicating a significant stage in the disease's progression and highlighting that all AD individuals have at least one other potential pathogenic alteration (which may lead to clinical markers and disease progression) [76].

In smaller cohorts, Lewy body pathology, including limbic predominant age-related TDP-43 encephalopathy (LATE), chronic traumatic encephalopathy (CTE), and ageing-related tau astrogliopathy (ARTAG) lesions, has been well characterized but remains to be studied in larger cohorts [77]. Furthermore, AD is also facilitated by vascular pathology, which makes an essential contribution to the pathogenesis of the disease. Still, due to a lack of clinical evidence, progress in assessing these modifications as clinical markers and disease progression has been slowed [78].

Amyloid-β Peptide:

Extracellular plaques contain a principal component of Aβ. The genetic materials in the genes APP and their conversion by β- and γ-secretase into the autosomal dominant form of AD form the basis for the amyloid cascade hypothesis, which is the favored pathogenic feature of AD, as illustrated in **Figure 3** [79]. It has been observed that the brains of patients suffering from Alzheimer's disease exhibit a varied deposition of Aβ in their neural networks, which can range from diffuse, or "lake-like," amyloid to compact, coarse-grained, cotton-wool-like, and senile plaques [80].

Even if these Aβ plaques are generally less harmful individually and can be found in cognitively normal individuals with little or no accompanying tau pathology, they are, in many respects, related to forms of neurofibrillary tangles and are associated with cognitive dysfunction. Millions of Aβ plaques form within the neocortex during the fifth phase of their development; they subsequently spread to the limbic areas, including the cingulate gyrus, the amygdala, the entorhinal cortex, and the subiculum, during the second phase.

This also progresses through subcortical areas, such as the basal ganglia and thalamus (phase 3). During stage four (late stage), the brainstem-like midbrain, pons, and medulla oblongata are affected. In contrast, the final stage (phase five) is a condition in which the cerebellar cortex is affected [81],[61],[82]. There are phases 4 and 5 related to dementia, but phases 1 and 2 are primarily reported in asymptomatic individuals. Especially in the early stages of disease, exerting symptoms do not necessarily occur where Aβ plaque is distributed in brain regions. There are compositional variants of the Aβ deposits formed with various co-agglutinating proteins, such as Apolipoprotein E (APOE), Clusterin (APOJ), or Midkine, that can interfere with the neighboring cells and the cells' pathways involved in disease processing, driving the disease [98]. CAAs are most often the cerebral and leptomeningeal blood vessel deposits of Aβ, which are commonly seen in AD patients. The beta-amyloid deposition is combined with cystatin C, gelsolin, prion protein, and transthyretin in this context of ADNC; this is CAA. The vascular Aβ deposition may lead to the destruction of blood vessel walls, causing cerebral haemorrhage of either micro-bleeds or extensive lobar hemorrhages [84].

Impaired perivascular drainage pathways (PDPs) appear, therefore, to be the primary cause of sporadic AD, and the PDPs can thus be used as biomarkers for the use of Aβ as a clearance route in the brain. However, CAA also suffers some of its adverse consequences, as seen with other therapeutic approaches targeting Aβ using monoclonal antibodies in antibody-treated individuals, including amyloid-related imaging abnormalities such as brain edema and hemorrhage. The multiple neuropathological studies on CAA presented in this evaluation assess the intensity of impairment on vascular wall integrity and the distribution of CAA throughout brain regions. It is, however, predicted that more severe pathogenesis would be associated with more severe consequences, such as micro- or macrohemorrhage or infarcts [85].

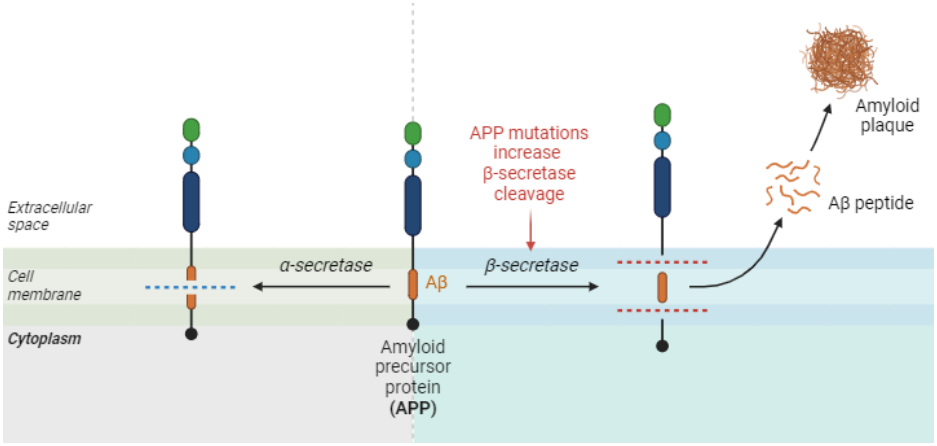

Figure 3: Treatment of Amyloid Precursor Protein (APP) and Formation of Amyloid-β (Aβ) Peptides: The diagram shows Amyloid Precursor Protein (APP) and its crucial role in the development of Alzheimer's disease. APP, a transmembrane protein, can be processed through two distinct pathways. In the non-amyloidogenic pathway, α-secretase cleaves APP within the Aβ region, preventing the formation of toxic Aβ peptides and generating soluble APP-α (sAPP-α), which has neuroprotective properties. Conversely, in the amyloidogenic pathway, β-secretase cleaves APP at a site that leads to the production of Aβ peptides, particularly Aβ42, which is highly prone to aggregation. The diagram highlights that mutations in APP can enhance β-secretase activity, increasing Aβ peptide production and accelerating amyloid plaque formation. These plaques are a hallmark of Alzheimer's disease, contributing to neuronal dysfunction, neuroinflammation, and progressive cognitive decline. Maintaining a balance between α-secretase and β-secretase activity is essential for regulating APP processing and preventing neurodegenerative changes associated with Alzheimer's disease. [86],[87].

Microtubule-Associated Protein (MAP)

The subsequent principal pathogenesis in AD is the formation of NFTs, aggregates of the microtubule-associated protein tau. The characteristic pattern of spreading has been identified using whole-hemisphere 100-µm-thick sections and silver staining procedures. An adjuvant factor that contributes to the pattern of spreading in AD has been established using topographically representative postmortem whole-hemisphere 100-µm-thick sections and silver staining methods [88]. Initially, the entorhinal and stage I areas are followed by the density and the two

subiculum (HPC) layers (II), while the stages involve the transentorhinal regions of the hippocampus. NFT enters the entorhinal cortex and then the HPC layer, with a sector corresponding to CA1 (III) [89]. The above pathological changes become pronounced in CA1–CA4 sectors of the HPC layer and later spread to the adjacent inferior temporal cortex (ITC). For this reason, the NFT pathology spreads to other neocortical areas, such as the STC and frontal cortex (stage IV), which are also collectively termed 'limbic stages' as the formation of the hippocampus is severely affected. That is when the late stages present with aggregates spreading on secondary association areas (SAAs) and primary cortical areas (PCAs), which are mentioned as isocortical stages [90],[91].

The section of the occipital cortex is analyzed to assess this progression of neuropathology and confidently assign stages V and VI, indicating the involvement of this pathology in the peristriate and striate regions of the occipital cortex, respectively. The highest association with clinical dementia is V and VI, and stages I and II are often seen in clinically asymptomatic patients [92],[93],[94],[95]. Therefore, the low prion-like tau function appears to be associated with a longer lifespan, as indicated by 100 postmortem brain tissues from individuals with either sporadic or inherited AD. Furthermore, together, prion-like Aβ and prion-like tau proteins were found [93],[96]. This was mirrored in the tau prion progression, such that the age was inversely proportional to tau concentration itself; i.e., subjects who died young of AD had less prion-like tau at death, although NFTs increased [97].

While tau phosphorylation may affect tau coalescence or exert toxicity, it remains unproven whether impaired prion-like tau in elderly AD individuals represents tau that has become inamenable to formation and/or clearance activities or tau that has converted from prion-like tau to the inert amyloid state, such as insoluble tau. Henceforth, the development of a therapeutic target of AD for prions will not be realized [98].

Neurite Amyloid Plaques

A particular type of plaque, known as a neurofibrillary tangle or senile plaque, is caused by the interaction of Aβ and tau. Aβ depositions are known to associate with dystrophic neurites, highlighting the interaction within cellular organelles, including lysosomes, and with lysosomal proteins and aggregated forms of tau in these structures [99]. Many of the markers for neurotic plaques include silver staining with tau antibodies against lysosomal proteins (LAMP1, Cathepsin D), as well as axonally transported neuronal proteins (APP, BACE1). The density of these markers is used to assess the age and symptoms of dementia. The neurotic plaques of a 75-year-old patient are uncertain evidence for AD. Still, the frequent plaques found in younger patients are interpreted as a diagnosis of AD. Axonally transported neuronal proteins (APP, BACE) [100].

The density of neurofibrillary plaques increases with age, coinciding with the onset of dementia symptoms. The neurotic plaques in patients aged 75 years are considered uncertain evidence of AD, but frequent plaques in younger patients are deemed to indicate a diagnosis of AD [93],[101]. Enhanced tau phosphorylation has been used as a marker for neurofibrillary tangles, and the risk-associated variants of inducing receptor generation on myeloid cells (TREM) 2 can be used to support the phospho-tau hypothesis [102]. This evidence is also supported by another animal study which implies the importance of Aβ plaques for their connection with tau dystrophic neurites later worsening of neuronal tau pathology, and the particular plaque can be seen as a key frontier between Aβ and tau pathology in AD and is a potential site of AD pathomorphic alteration [103].

ENVIRONMENTAL INFLUENCES AND NEUROTOXIC METALS

Many environmental factors influence brain health. Elements in our environment, at large (such as air pollution and water quality, affect brain function and health outcomes [104]. Exposure to air pollution particulate matter, especially fine particulate matter (PM2.5), has been linked to increased oxidative stress and inflammation in the brain. These effects also elevate the risk of cognitive decline and neurodegenerative diseases, including Alzheimer's disease, as well as the potential for neuronal damage [105].

Water contaminated with toxic metals like lead, mercury, and arsenic, along with other specific metals shown in Table 3, can also pose serious threats to neurological health. These metals are neurotoxic and, in time, can be accumulated in the brain, causing neurological function impairment, memory deficits, and, more severely, neurodegeneration [106]. Air pollution and water quality, when interacting, can lead to elevated levels of oxidative stress, inflammation, and neuronal damage, all of which are

recognized risk factors for neurodegenerative diseases. These environmental influences must be understood and mitigated for populations exposed to these risks to promote brain health and reduce disease burden from neurological disorders [107].

SPECIFIC METALS LINKED TO ALZHEIMER'S

Table 3: Summarizing the specific metals linked to Alzheimer's disease and their effects:

Metal	Impact on Alzheimer's Disease	Common Sources	Ref
Al	Promotes amyloid plaque formation, enhances beta-amyloid aggregation, and increases oxidative stress, leading to neuronal damage. Cumulative exposure can contribute to Alzheimer's onset and progression.	Aluminium cookware, certain antacids, antiperspirants, drinking water with high aluminium levels	[108]
Lead	Causes long-term neurotoxic effects, disrupts synaptic function, impairs neuronal communication, and induces oxidative stress and inflammation. Linked to cognitive decline and increased Alzheimer's risk with exposure	Old paint, contaminated soil, drinking water from lead pipes	[109]
Mercury	Crosses the blood-brain barrier, leading to neurotoxicity, oxidative stress, and inflammation. Methylmercury accumulates in the brain, disrupting neuronal function, while elemental mercury from dental amalgams releases vapour absorbed into the bloodstream.	Contaminated fish (methyl mercury), dental amalgams (elemental mercury)	[110]

Mechanisms of Metal-Induced Neurotoxicity

Oxidative Stress

Oxidative stress is the imbalance between the body's capacity to detoxify oxidative intermediates or to repair the harm they cause versus the amount of reactive oxygen species (ROS) that are generated [111]. ROS producing metals like aluminum, lead, and mercury may all produce hydroxyl radicals, superoxide anions, and hydrogen peroxide. ROS have the potential to be very damaging to lipids, proteins, and DNA within cells, which can cause neuronal death and damage to neurons. The brain is particularly vulnerable to oxidative stress, as it is a high-oxygen-consuming, high-lipid-containing tissue with relatively low levels of antioxidant defenses. Mitochondrial impairment due to prolonged exposure to oxidative stress can aggravate neuronal damage and lead to Alzheimer's disease [112].

Inflammation

Exposure to neurotoxic metals causes chronic activation of microglia, the resident immune cells of the central nervous system (CNS). This results in a sustained inflammatory response in the brain and the release, by activated microglia, of proinflammatory cytokines, chemokines, and other inflammatory mediators. The result of this neuroinflammation can directly damage neurons and establish a toxic environment conducive to further neuronal injury and death. Furthermore, chronic inflammation can weaken the blood-brain barrier and allow more neurotoxic substances into the brain to aggravate neurodegenerative processes [113],[114].

Amyloid Plaque Formation

A hallmark of Alzheimer's disease is the presence of amyloid plaques, primarily composed of beta-amyloid (Aβ) peptides. Beta-amyloid aggregation is promoted by aluminum, which accelerates the formation of amyloid plaques [115]. Because of this, the metal can react with the Aβ peptides, increasing their propensity for embedding and stability toward aggregation, thereby producing plaques. Plaques can interfere with cell signaling, disrupt synaptic function, and cause neuronal toxicity. High levels of aluminum in the brain have also been linked with greater amyloid burden and the development of Alzheimer's pathology [116].

Neuronal Apoptosis

This is controlled cell death, the process by which we eliminate unhealthy or superfluous cells through apoptosis. Neurotoxic metals can induce apoptosis in neurons through different pathways in which neurotoxic agents exert their prolonged effects [117]. For example, lead and mercury can disrupt calcium homeostasis, upregulate proapoptotic proteins such as Bax, p53, and activate apoptotic signaling pathways.

Finally, these metals can also affect the mitochondria, causing their malfunction and leading to the release of cytochrome c, as well as the activation of caspases and proteases, which execute apoptosis. Loss of neurons is one process in Alzheimer's disease that neuronal apoptosis contributes to and exacerbates cognitive decline and functional impairment [118].

PREVENTIVE MEASURES

Reduce Exposure

Reducing exposure to products that include high levels of aluminum can help minimize the risk of being a victim of Alzheimer's disease [119]. This includes being cautious of other items that may contain aluminum, as well as alternatives to aluminum-based antiperspirants and the avoidance of aluminum cookware. However, reducing daily aluminum intake should help to protect against neurotoxicity related to aluminum [120].

Dietary Choices

Resolving to reduce exposure to neurotoxic metals starts in the kitchen. Although mercury is pervasive in many types of marine fish, limiting your consumption of fish with higher mercury levels, such as shark and swordfish, and opting for safer choices like salmon, trout, and sardines can significantly reduce your mercury intake. And because mercury can have a connection with Alzheimer's, ensuring a diet low in mercury can help protect against mercury-induced neurotoxicity [118].

Regulations and Policies

They need to advocate for stronger environmental regulation of industrial emissions of neurotoxic metals, such as lead and mercury. These harmful metals can be reduced by policies that target the reduction of emissions from factories, waste dumpsites, and other industrial sources. If they support regulatory measures, they can help increase cleaner air, water, and soil, thereby reducing the public's exposure to neurotoxic compounds [121]. Prevention depends on educating communities about the risks of metal exposure and engaging in healthy lifestyle choices. Thus, public health campaigns can help inform the public about the sources and dangers of neurotoxic metals and encourage them to adopt behaviors that limit their exposure. The community can spread knowledge & help prevent practices that harm the community's neurological health [122].

FUTURE PERSPECTIVES

The future perspectives of Alzheimer's disease (AD) drug research focus on innovative approaches that address the underlying causes and aim to improve patient quality of life. Here are some key areas of exploration:

Amyloid-beta (Aβ) and tau protein accumulation

Amyloid-beta (Aβ) and tau protein accumulation remain central to AD pathology. With the recent approvals of anti-amyloid drugs like Lecanemab and Donanemab, researchers are now exploring combined therapeutic approaches that simultaneously reduce amyloid plaques and tau tangles to achieve better disease modifying effects. Novel dual-targeting agents & tau aggregation inhibitors are studied to enhance synaptic function & neuroprotection while minimizing adverse effects [123].

Neuroinflammation Modulation

Chronic neuroinflammation plays a crucial role in AD progression, driven by overactivation of microglial cells and pro-inflammatory cytokines. Future therapies aim to modulate microglial activity, reduce oxidative stress, and enhance anti-inflammatory signaling to prevent neuronal damage. Drug candidates targeting pathways like TREM2 activation, complement system inhibition, and IL-1β suppression are being investigated for their potential to slow neurodegeneration [124]

Gene Therapy and CRISPR

Gene editing tools, such as CRISPR, have provided new ways to modify our genetic risk factors for Alzheimer's, for example, through the APOE gene. The goal of research is to reduce the expression of these genes or mitigate their harmful effects [125].

Stem Cell Therapy

There is a promising area in regenerative medicine, particularly with stem cells, that holds potential for replacing damaged neurons and restoring cognitive function. Stem cell-based therapies are being investigated in AD patients in clinical trials for their use and safety [126].

Synaptic Plasticity and Neuroprotection

Inhibition of cognitive decline could be achieved by drugs that enhance synaptic plasticity and provide neuroprotection. In the future, AD treatments may become dependent on agents that promote the growth and health of neurons [127].

Artificial Intelligence (AI) for Personalized Treatment

AI and machine learning algorithms are becoming integral to personalized medicine in AD. By analyzing biomarker profiles, genetic data, and neuroimaging results, AI can identify individual patient subtypes, predict disease progression, and tailor drug responses for optimized therapeutic strategies. AI-driven platforms are also enhancing drug discovery, improving clinical trial efficiency, and facilitating early treatment monitoring, making precision medicine a reality for AD management [128].

Early Diagnosis and Preventive Therapies

Early intervention is crucial for effective treatment of AD. Biomarkers, imaging, and cognitive assessments are being utilized to enhance these early diagnostic tools, thereby allowing for the development of more effective preventative therapies that slow the progression of the disease to symptoms [129].

Lifestyle and Multimodal Approaches

Future research calls for a multifaceted approach, combining pharmacological treatments with lifestyle interventions such as diet, exercise, cognitive training, and sleep management, with a focus on the whole person [130]. A PRISMA flowchart is illustrated in Figure 4.

CONCLUSION

Alzheimer's disease (AD) remains a leading cause of mortality, disability, and cognitive decline worldwide, placing a substantial burden on healthcare systems and caregivers. Despite decades of research, the complex and multifactorial nature of AD pathology, involving amyloid-beta plaques, tau hyperphosphorylation, neuroinflammation, synaptic dysfunction, and oxidative stress, continues to challenge the development of effective disease-modifying therapies. Currently, available pharmacological treatments, such as acetylcholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and NMDA receptor antagonists (Memantine), provide only symptomatic relief without addressing the underlying neurodegenerative processes. In contrast, emerging therapeutic approaches aim to slow disease progression by targeting multiple disease pathways rather than a single molecular mechanism. Monoclonal antibodies (Lecanemab, Donanemab) have shown promise in reducing amyloid burden, but challenges related to long-term efficacy, adverse effects, and high costs limit their widespread use. Future research must focus on more effective and safer anti-amyloid and tau therapies while expanding therapeutic strategies beyond these classical targets. A significant gap in AD research remains the lack of definitive biomarkers for early detection, disease monitoring, and personalized treatment selection. Recent advancements in biomarker discovery, particularly p-tau217, neurofilament light chain (NfL), and blood-based markers, offer hope for less invasive and more accessible diagnostic methods. Additionally, AI-driven models integrating multi-omics data (genomics, proteomics, and metabolomics) have the potential to revolutionize early diagnosis, risk assessment, and treatment optimization. However, the standardization and validation of AI-driven diagnostics in clinical settings remain a challenge, requiring further refinement and regulatory approval.

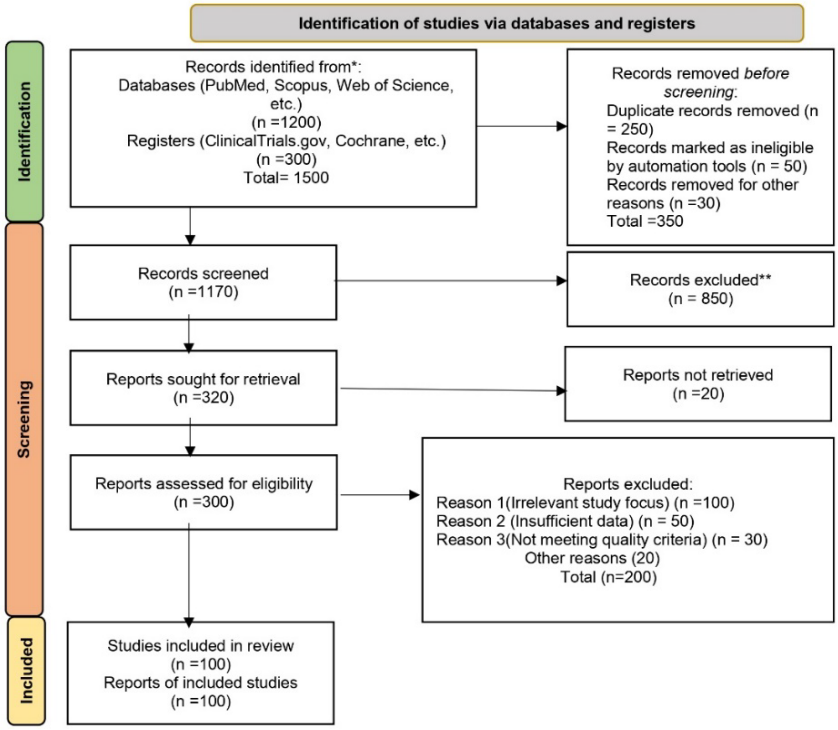

Figure 4: PRISMA Flow Diagram for Study Selection Process

Beyond pharmacological treatments, regenerative medicine and neuroprotection strategies are gaining traction. Stem cell-based therapies are being investigated for their potential to restore neuronal function and repair damaged neural circuits; however, concerns regarding immune rejection, ethical considerations, and long-term safety must be addressed. Gene therapy and CRISPR-based interventions targeting APOE4 and other genetic risk factors are promising but require extensive clinical validation before becoming mainstream treatments. Furthermore, the role of senolytics, nanomedicine, and neuroimmune modulation is being actively explored for their potential to enhance neuronal resilience and slow AD progression. The integration of personalized medicine is essential for the future of AD treatment. AI and machine learning technologies are helping to classify patient subtypes, predict drug responses, and optimize individualized therapeutic regimens. Future studies should prioritize multimodal approaches that combine pharmacotherapy with non-pharmacological strategies, such as cognitive training, exercise, dietary interventions, and sleep management, to create comprehensive treatment plans tailored to each patient's disease profile.

Additionally, traditional medicine and plant-derived compounds have shown potential neuroprotective and anti-inflammatory effects, suggesting a complementary role in AD management. Botanical extracts rich in polyphenols, flavonoids, and secondary metabolites warrant further preclinical and clinical investigations to evaluate their effectiveness in modulating oxidative stress, neuroinflammation, and synaptic function. Despite advancements in AD research, significant challenges persist in the accessibility, affordability, and real-world application of novel therapies. Future research must focus on developing cost-effective, globally accessible treatments that address the growing prevalence of AD, particularly in aging populations. Expanding large-scale cohort studies and clinical trials will be crucial in validating emerging therapies and refining precision medicine approaches.

In conclusion, the future of AD management lies in a multidisciplinary, patient-centered approach that integrates biomarker-driven diagnostics, targeted pharmacological interventions, regenerative medicine, and AI-driven precision therapy. Collaboration between researchers, clinicians, and healthcare policymakers will be essential to accelerate the development of innovative treatments and improve outcomes for AD patients worldwide.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Debraj Dey, Abu Shoeb, and Deepannita Roy Mukherjee were responsible for designing and planning the study, as well as its objectives. Pinki Biswas and Saikat Santra conducted the work and gathered data. Deepannita Roy, Abu Shoeb, and Pinki Biswas drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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