INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Alzheimer's Disease: An Overview

G.V. Srivani*, Kothagadi Veena, Thakur Vaishnavi, Poddutoori Manaswini, Sangem Varsha, S. K. Kovid

Department of pharmacognosy, Pulla Reddy Institute of Pharmacy, Dundigal, Hyderabad, Telangana, India, 502313.

ARTICLE INFO

Published: 15 Jan. 2025
Keywords:
Senile dementia, Aberrant proteins, senile plaques, intricate interactions.
DOI:
10.5281/zenodo.14651398

ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, is a striking example of the connection between neurophysiological abnormalities and higher-order cognitive deficiencies. Since its initial description in 1906, research into the pathophysiology and etiology of AD has led to the illumination of an incredibly complex set of genetic and molecular mechanisms for the disease's progression, characterized by much more than the neuropathological hallmarks of beta- amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) Aging is the most obvious risk factor for developing AD. There is a genetic basis for AD, of course this relation is not complete but it is significant biomarkers, improved methods for disease diagnosis and the prediction of future decline, and identifying novel genetic AD risk. While there is no cure for AD, there are a variety of treatment options which can modulate disease progression and improve quality of life for patients.

INTRODUCTION

Alzheimer's disease (AD) is a neurological condition that worsens over time and causes memory loss, cognitive decline, behavioral abnormalities, and ultimately death Dementia is caused by several things. The most prevalent type of dementia is Alzheimer's disease (AD) Neuropathologically, the disease is characterized by the accumulation of aberrant proteins that lead to the development of intracellular neurofibrillary tangles (NFTs) and extracellular senile plaques. Amyloid-β (Aβ), which is neurotoxic, is the main component of senile plaques [(1).] AD is the sixth most common cause of death for older adults (2). Alois Alzheimer, a German psychiatrist, identified a rare type of mental illness in 1906 that affected Augustine Deter and was typified by "progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence" [(2).] Neuropathologically, the

***Corresponding Author:** G.V. Srivani
Address: *Department of pharmacognosy, Pulla Reddy Institute of Pharmacy, Dundigal, Hyderabad, Telangana, India, 502313.*
Email ✉: srivani.2021@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

disease is characterized by the accumulation of aberrant proteins that lead to the development of intracellular neurofibrillary tangles (NFTs) and extracellular senile plaques. Amyloid-β (Aβ), which is neurotoxic, is the main component of senile plaques [3]. Despite decades of encouraging research on Alzheimer's disease, there are currently no effective disease-modifying medications available. This could be partly caused by the intricate interactions between tau and amyloid abnormalities, neuroinflammation, and cerebrovascular impairment, as well as the considerable difficulties in diagnosing and staging Alzheimer's disease [4]. However, AD can manifest in two ways: the frequent late-onset AD (LOAD), sometimes referred to as senile dementia, which develops after age 65 as a result of ageing, and the uncommon early-onset dementia leading to AD (EOAD), which occurs before age 65 [5]. As life expectancy rises globally, Alzheimer's disease is the only illness predicted to increase in incidence at an alarming rate, in contrast to other conditions like cancer and heart disease that significantly affect healthcare today [6].

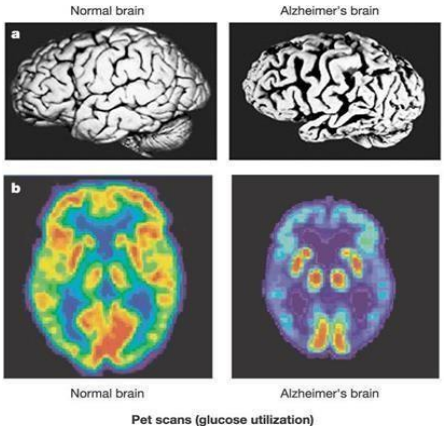

Figure-1

Epidomology:

The frequency of dementia is expected to increase by 2050, with two-thirds of those affected residing in low- and middle-income nations, according to an estimate made by Alzheimer's Disease International in 2018.By 2050, the prevalence of dementia is expected to increase across Europe, according to the latest recent research. While there is less compelling evidence for ftfg in frequency, there is growing evidence that dementia incidence is declining in high- income nations [7]. Dementia is the most common cause of mortality in England and Wales, making up 11.6% of all recorded deaths in 2015.According to recent research, dementia may be becoming less common in western nations, especially among men and in Low and middle-income nations, which exhibit trends of rising rates of diabetes, hypertension, and cardiovascular illness, are predicted to see the most increases in dementia incidence in the upcoming years [8]. People 65 and older have a yearly incidence rate of 1% for AD, while those 85 and older have an incidence rate of about 8%. Cholinesterase inhibitor treatment, caregiver stress reduction, community support, delaying institutionalization, lifestyle planning, and legal concerns all depend on early detection of AD

(9). the social, environmental, and genetic elements that contribute to this neurological degeneration's development. The main risk factor for Alzheimer's disease development is thought to be aging; only 1-6 percent of cases are early-onset AD (EOAD), which is defined by onset between the ages of 30 and 65. However, the ε4 allele of the Apolipoprotein E (ApoE) gene, present in about 40% of AD patients, is the most significant genetic

risk factor. The fact that DNA from HSV-1, an infection that is known to be a risk factor for AD, has been found in the brains of people with the ApoE-ε4 allele shows how risk factors can influence one another
(10).

Pathophysiology:

The pathophysiology of Alzheimer's disease has been thoroughly investigated since it was discovered and classified, which has confirmed the two main neuropathological motifs— plaques and neurofibrillary tangles—that were initially discovered in the early 1900s by Alois Alzheimer and Oskar Fischer. The first kind, known as senile plaques, are extracellular clumps of beta-amyloid protein (Aβ), which is created when amyloid precursor protein (APP), a crucial membrane glycoprotein, is cleaved by proteases. While β-secretase and γ-secretase can differently cleave APP to yield Aβ peptides of varying lengths [(11).] It is still unknown what exactly causes Alzheimer's disease. Scientists' amyloid cascade theory is now the main theory explaining the pathophysiology of AD. The primary cause of Alzheimer's disease, according to the theory, is the build up of toxic amyloid beta-protein (Aβ) in the central nervous system (CNS). Aβ may build up and form a structure rich in β-Sheet if there are extracellular abnormalities in Aβ levels in the brain [(12).] Amyloid plaques are extracellular deposits mostly made up of two by products of APP metabolism, improperly folded Aβ with 40 or 42 amino acids (Aβ40 and Aβ42). Because Aβ42 is more insoluble and fibrillizes more quickly than Aβ40, it is more prevalent in plaques. In general, amyloid deposition develops in the Iso cortex and only later affects subcortical areas; it does not always progress in a stereotyped manner. Amyloid plaques affect the entorhinal cortex and hippocampus forms less than NFTs do[(13).] The brain recognizes these plaques as foreign material and triggers an immunological and inflammatory response by triggering the production of cytokines and activating microglia, which ultimately results in cell death and neurodegeneration. The α, β, and γ secretases enzymatically cleave the amyloid precursor protein (APP) to produce the Aβ peptides that make up the Aβ plaque [(14).]

Hypothesis Of Pathophysiology of Alzheimer's Disease

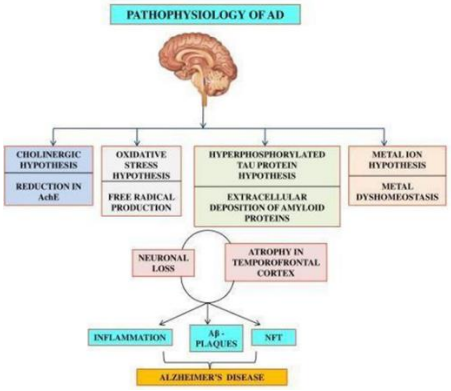

Figure-2

Risk Factors:

The chance of developing AD is increased by several acquired factors. These include the most frequently reported risk factor, cerebrovascular diseases, diabetes, hypertension, obesity, and dyslipidemia[(15).]

The most significant risk factor is age. According to a recent study that examined 1246
participants between the ages of 30 and 95, the risk rose with age, especially in APOE ε4 carriers and after the age of 70. Consequently, it may influence the risk of AD as people age. In cognitively normal people, age dramatically raises the probability of

ligand retention in amyloid PET. In addition to APOE, several genes have recently been shown to substantially alter the risk for AD on a genome-wide level. Through genome-wide association investigations, variations in genes related to endocytosis, inflammatory response, and lipid metabolism have been found. ABCA7, CLU, CR1, CD33, CD2AP, EPHA1, BIN1, PICALM, MS4A, CASS4, CELF1, DSG2, FERMT2, HLA-DRB5-DBR1, INPP5D, MEF2C, NME8, PTK2B, SLC24H4-RIN3, SORL1, and ZCWPW1 are among the genes that have polymorphisms in or close to them that are linked to AD risk [16]. Carrying at least one APOE ε4 allele and being older than 65, albeit this is not a set age, are the highest risk factors for Alzheimer's disease.27 Furthermore, especially after the age of 80, women are more prone than males to get Alzheimer's disease.20 Despite sharing a similar amyloid β burden, women are considerably more likely to have a larger tau load [17]. Furthermore, the foods that influence the general risk factors for AD, such as insulin resistance (IR) and inflammation, can be determined once they are understood. Every method can advance our knowledge of how nutrition and dietary factors impact AD risk [18].

Cardiometabolic factors have been identified as critical among the several other potentially modifiable risk factors for AD that have been shown in numerous studies, in addition to the hereditary factors. High blood pressure, diabetes, obesity, high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) cholesterol, and the development of AD have all been associated with cardiometabolic risk factors [19].

Diagnosis:

Late-onset the symptoms of AD usually appear after the age of 60 and progress gradually from modest memory impairment to severe cognitive decline, ultimately leading to total disability and death. Even though biomarkers like plasma Aβ, CSF Aβ and tau, amyloid imaging for AD, and cognitive decline prediction have advanced significantly in recent years [3–5], studies of plasma Aβ in particular have yielded conflicting results, and there are currently no conclusive diagnostic tests or biological markers of the disease. A clinical examination serves as the basis for the diagnosis during life [20].

A diagnostic evaluation that includes the following components is recommended by the Expert Panel for patients who are suitable for aducanumab treatment:

1) a thorough history that is adequate to determine the type and duration of cognitive symptoms, functional changes, and behavioral status;
2) objective confirmation of cognitive decline through standardized testing.
3) a thorough neurological and physical examination
4) a review of all current medications and supplements
5) adequate laboratory testing, such as a complete blood count, electrolyte panel, thyroid stimulating hormone, lipids and triglycerides, liver function tests, and serum vitamin B12 level ,to rule out other concurrent conditions that may contribute to cognitive deterioration[21].

MRS is an imaging method that develops and quantitatively analyzes certain nuclei and related compounds using the magnetic resonance principle and chemical shift events. High resolution, no bone aberrations, no ionizing radiation damage, multidirectional and multiparameter imaging, and the capacity to visualize brain regions without the need for contrast agents are some of the benefits of this technology (Chen et al., 2019). Chemical compounds can be distinguished based on their variations on the MRS spectral peak line due to variations in chemical shifts. Because the area of

the formant in MRS is proportional to the number of resonance nuclei, the compound's concentration can be observed. Acquired using head MRI are not very useful for diagnosing AD, and they don't show many signs of the physiological and metabolic alterations linked to AD [22].

Biomarkers:

Alzheimer's disease medication development, biomarkers can also be very helpful in choosing the best therapeutic candidates for costly and time-consuming phase 3 clinical trials. Together with a positive impact on the clinical course, biomarkers will be crucial in demonstrating In that a medication has an impact on the disease's underlying pathophysiology, which is necessary to classify the medication as having a disease-modifying effect [23]. In the recently developed diagnostic criteria for AD, biomarkers play a crucial role in determining the pathophysiological mechanisms behind cognitive impairment or in assisting in the prediction of the time it will take for dementia to develop. In 1998, an international consensus committee on genetic and biochemical indicators of AD proposed criteria for a meaningful biomarker (The National Institute on Aging Working committee, 1998; Ronald and Nancy Reagan Research Institute of the Alzheimer's Association, 1998) [24]. There are two types of AD biomarkers: topographic biomarkers and pathophysiologic biomarkers. These two categories of biomarkers can help doctors recognize, distinguish, and diagnose AD symptoms. Pathophysiologic markers linked to AD lesions include amyloid positron emission tomography (PET), amyloid and tau protein concentrations in cerebrospinal fluid (CSF), and plasma levels of amyloid, tau, and other protein biomarkers. Topographic biomarkers are associated with the regional consequences of AD pathology, including tau PET, regional hypometabolism on fluorodeoxyglucose (FDG)-PET, and regional/local atrophy on structural magnetic resonance imaging (MRI)[25]. The density of the pathological lesions is addressed in relation to the subject's age in another study about age and how it affects the severity of AD Furthermore, a number of studies have found the age marker to be a primate factor . Alongside the aforementioned, AD can also be classified as early onset familial AD, in which the illness primarily manifests before the age of 60. In this instance, AD is inherited autosomally dominantly and manifests as a genetic disease. At the same time, if neuronal damage and amyloid-β (Aβ) biomarkers were also tested affirmatively, biomarkers that indicate a high chance of AD owing to MCI could be more accurate. We can only obtain an intermediate chance of AD due to MCI based only on the Aβ protein evaluation. Patients will be presumed to have a lesser risk of developing AD if there is just one biomarker of neurologic impairment and Aβ cannot be measured [26].

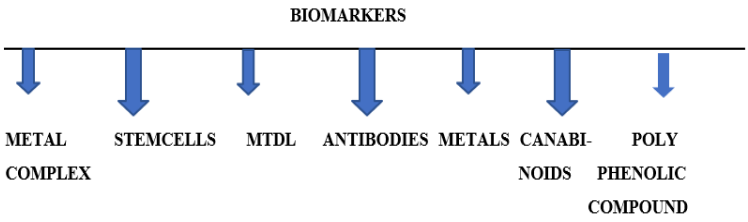

Figure-3

Treatment:

There are already an estimated 24 million cases of Alzheimer's disease worldwide, and by 2050, there will be four times as many people with dementia overall[27].

Despite being a public health concern, AD is currently exclusively treated with two groups of approved medications: antagonists of N-methyl d-aspartate (NMDA) and cholinesterase enzyme inhibitors (naturally occurring, synthetic, and hybrid analogues[28]. In order to slow the course of cognitive symptoms as well as behavioral and psychosocial symptoms of dementia (BPSD), current medication treatments for AD are symptomatic rather than curative. The four approved medications (donepezil, memantine, galantamine, and rivastigmine) are members of the anticholinesterase inhibitor and anti-glutaminergic medicine groups. The oral or transdermal routes are used to administer these medicines [29]. As supplemental treatments to memantine or cholinesterase inhibitors, the standard of care, a number of DMTs are presently undergoing clinical trials. The DMTs can be added to a background standard-of-care therapy because of these research [30]. Delaying the onset and progression of Alzheimer's disease is the general goal of treatment Such medication aims to enhance the patient's overall health and well-being as well as their ability to perform more comfortably in daily life [31]. Delaying the onset of dementia and the ensuing loss of function is a real possibility, but the absence of a longer-lasting benefit is most likely caused by AChE inhibitors' inability to substantially change the underlying disease process. Vitamin E has not been proven to be effective in slowing the progression of MCI to AD, despite the theory that oxidative stress is one step involved in the pathogenesis of Alzheimer's disease [32]. The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are recommended therapy for patients with mild, moderate, or severe AD dementia as well as Parkinson's disease dementia. Memantine, which has activity as both a non-competitive N-methyl-D-aspartate receptor antagonist and a dopamine agonist, is approved for use in patients with moderate-to- severe AD attempts are still being done to target and balance the neurotransmitter abnormalities. The fact that AD-related pathologic alterations start to appear so early, nearly ten years before the person exhibits symptoms, is a significant disadvantage of the lack of a targeted treatment for the underlying disease [33].

CONCLUSION:

Several biomarkers are proposed for the early diagnosis and longitudinal monitoring of AD with imaging techniques, but all these biomarkers have their limitations regarding specificity, reliability and sensitivity. Future perspectives. Future research should focus on expanding the employment of imaging techniques and identifying novel biomarkers that reflect AD pathology in the earliest stages. AD dementia incidence and prevalence are high worldwide and likely underestimated. Recent studies show that the risk of AD dementia is significant among older people with normal pathology and increases with progression from normal pathology to neurodegeneration and MCI. Studies of AD remain challenged by disease classification due to differential diagnosis, multiple biomarkers and neuropsychiatric tests ,and variation in consensus criteria. As new DMTs are introduced, clinicians will require combinations of diagnostic approaches to identify patients with preclinical AD and MCI due to AD and to assess the impact of treatment on slowing progression.

REFERENCES

1. Wieke M. van Oostveen1 and Elizabeth C. M. de Lange 2,Imaging Techniques in Alzheimer's Disease: A Review of Applications in Early Diagnosis and Longitudinal Monitoring https://doi.or/10.3390/ijms2204211
2. Mohammad KHANAHM DI 1, Dariush D.FARHUD 2,3, Maryam MALMIR Genetic of Alzheimer's Disease: A Narrative Review Article http://ijphtums.ac.ir

3. Martha Clare Morris, S.D.1, Christy C. Tangney, Ph.D.2, Yamin Wang, Ph.D.1, FranM. Sacks, M.D.5, David A Bennett, M.D.3,4, and Neelum T. Aggarwal, M.D.3,4 MIND Diet Associated with Reduced Incidence of Alzheimer's Disease DOI:10.1016/j.jalz.2014.11.00
4. Emily B. Buttona ,b, Je´roˆme Roberta,b, Tara M. Caffreya,b, Jianjia Fana,b, Wenchen Zhaoa,b, and Cheryl L. Wellington a ,b.HDL from an Alzheimer's disease perspective Volume 30 Number 3 June 2019 www.co-lipidology.com
5. Tan Sook Ling,1 Shanthini Chandrasegaran,1 Low Zhi Xuan,1 Tong Li Suan,1 Elaine Elaine,1 Durrgashini Visva Nathan,2 Yam Hok Chai,1 Baskaran Gunasekaran,1 and Shamala Salvamani The Potential Benefits of Nanotechnology in Treating Alzheimer's Disease https://doi.org/10.1155/2021/5550938
6. Adam S. Fleisher, MD, MAS Introduction Behavioural Neurology 21 (2009) 1 DOI 10.3233/BEN-2009-024
7. Amir Abbas Tahami Monfared . Michael J. Byrnes Leigh Ann White . Quanwn Zhang Alzimer's Disease : Epidemiology and Clinical Progression https://doi.org/10.1007/s40120-022-00338-8
8. Rishi S . Madnani Alzheimer's disease: a mini-review for the clinician DOI 10.3389/fneur.2023.1178
9. Alzheimer's disease C. A. Lane, J. Hardy, J. M. Schott https://doi.org/10.1111/ene.13439
10. Christiane Reitz. Genetic diagnosis and prognosis of Alzheimer's disease: challenges and opportunities doi:10.1586/14737159.2015.1002469.
11. Armand S. Schachter & Kenneth L. Davis . Alzheimer's disease https://doi.org/10.31887/DCNS.2000.2.2/asschachter
12. Rishi S. Madnani Chen Ma 1,2 , Fenfang Hong 1, and Shulong Yang 3,4,†Amyloidosis in Alzheimer's Disease: Pathogeny,Etiology, and Related Therapeutic Directionshttps://doi.org/10.3390/molecules27041210Alzheimer's disease: a mini- review for the clinician DOI 10.3389/fneur.2023.1178588
13. C. A. Lane J. Hardy, J M. Scott Alzheimer's disease https://doi.org/10.1111/ene.13439
14. Sahil Khan1, Kalyani H. Barve1and Maushmi S. Kumar1 Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease DOI: 10.2174/1570159X1866620052814242
15. Marcos Vinícius Ferreira Silva1, Cristina de Mello Gomide Loures1, Luan Carlos Vieira Alves1, Leonardo Cruz de Souza 2 , Karina Braga Gomes Borges1 and Maria das Graças Carvalho1 Alzheimer's disease: risk factors and potentially protective measures http://doi.org/10.1186/s12929-019-0524-y
16. Marta Crous-Bou1, Carolina Minguillón1, Nina Gramunt1,2 and José Luis Molinuevo1,2* Alzheimer's disease prevention: from risk factors to early intervention DOI 10.1186/s13195-017-0297-z
17. Bruno Duboisa1, Harald Hampela,b,1, Howard H. Feldmanc,1, Philip Scheltensd, Paul Aisene, Sandrine Andrieuf , Hovagim Bakardjiang, Habib Benalih, Lars Bertrami,j, Kaj Blennowk, Karl Broichl, Enrica Cavedob,m, Sebastian Crutchn, Jean-François Dartigueso, Charles Duyckaertsp, Stéphane Epelbauma, Giovanni B. Frisoniq,r , Serge Gauthiers, Remy Genthont, Alida A. Gouwf,u, Marie-Odile Habertv,w, David M. Holtzmanx,y, Miia Kivipeltoz,aa, Simone Listab, José-Luis Molinuevoab ,ac , Sid E. O'Bryantad, Gil D. Rabinoviciae, Christopher Roweaf, Stephen Sallowayag ,ah ,ai, Lon S. Schneideraj, Reisa Sperlingak,al , Marc Teichmanna, Maria C. Carrilloam, Jeffrey

Cummingsan, Cliff R. Jack Jrao, Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria doi:10.1016/j.jalz.2016.02.002.
18. Philip Scheltens, Bart De Strooper, Miia Kivipelto, Henne Holstege, Gael Chételat, Charlotte E Teunissen, Jeffrey Cummings, Wiesje M van der Flier Alzheimer's disease doi:10.1016/S0140-6736(20)32205-4.
19. William B. Granta,∗ and Steven M. Blakeb Diet's Role in Modifying Risk of Alzheimer's Disease: History and Present Understanding DOI 10.3233/JAD-230418
20. Giuseppe Pasqualetti a, Tony Thayanandan a, Paul Edison a,b,* Influence of genetic and cardiometabolic risk factors in Alzheimer's disease http://doi.org/10.1016/j.arr.2022.101723
21. J Cummings 1, P Aisen 2, LG Apostolova 3, A Atri 4, S Salloway 5, M Weiner 6Aducanumab: Appropriate Use Recommendations doi: 10.14283/jpad.2021.41
22. Hong-Mei Zeng 1,2, Hua-Bo Han 3, Qi-Fang Zhang 4, Hua Bai Application of modern neuroimaging technology in the diagnosis and study of Alzheimer's disease doi: 10.4103/1673-5374.286957
23. Bruno Dubois1,2†, Christine A. F. von Arnim3*†, Nerida Burnie4,5, Sasha Bozeat6 and Jeffrey Cummings7 Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variant https://doi.org/10.1186/s13195-023-01314- 6
24. Ajit Kumar Thakur,1 Parul Kamboj,1 Kritika Goswami,1 Karan Ahuja2 Pathophysiology and management of alzheimer's disease: an overview DOI: 10.15406/japlr.2018.07.0023
25. Weili Xu, Camilla Ferrari and Hui-Xin Wang Epidemiology of Alzheimer's Disease http://dx.doi.org/10.5772/5439
26. Vasileios Mantzavinos 1,2, Athanasios Alexiou 1,Biomarkers for Alzheimer's Disease Diagnosis doi: 10.2174/1567205014666170203125942
27. Zeinab Breijyeh 1, Rafik Karaman 1 ,Comprehensive Review on Alzheimer's Disease: Causes and Treatment doi: 10.3390/molecules25245789
28. Elodie Passeri 1,2, Kamil Elkhoury 1, Margaretha Morsink 3, Kerensa Broersen 3, Michel Linder 1, Ali Tamayol 4, Catherine Malaplate 2, Frances T Yen 2,†, Elmira Arab-Tehrany 1,4,,† Alzheimer's Disease: Treatment Strategies and Their Limitations doi: 10.3390/ijms232213954
29. Jeffrey L Cummings a,*, Gary Tong b, Clive Ballard c Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherap Options (doi: 10.3233/JAD-180766)
30. Sahil Khan1, Kalyani H. Barve1 and Maushmi S. Kumar1 ,Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease (DOI: 10.2174/1570159X18666200528142429
31. Bartosz Twarowski and Mariola Herbet *Alzheimer's Disease—Patho mechanism, Diagnosis and Treatment: A Review https://doi.org/10.3390/ijms24076518
32. Judith Neugroschl, MD and Sophia Wang, MD Mount Sinai School of Medicine, New York, NY Alzheimer's Disease: Diagnosis and Treatment Across the Spectrum of Disease Severity (doi :10.1002/msj.20279.)
33. Jason Weller, Andrew Budson1,2 Current understanding of Alzheimer's disease diagnosis and treatment (doi: 10.12688/f1000research.14506.1).

HOW TO CITE: G.V. Srivani*, Kothagadi Veena, Thakur Vaishnavi, Poddutoori Manaswini, Sangem Varsha, S. K. Kovid, Alzheimer's Disease: An Overview, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 1, 1169-1176. https://doi.org/10.5281/zenodo.14651398