# A Review on Clinical Management and Alzheimer's Disease Treatment Techniques

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**Abstract**

The main form of dementia, Alzheimer's disease, causes severe cognitive and functional deficits and has significant societal and financial costs. This study explores the intricate mechanisms underlying Alzheimer's disease, emphasizing key players like as brain inflammation, tau protein tangles, amyloid-β plaque accumulation, and synaptic price. Important risk factors are discussed, such as advanced age and genetic predispositions like the APOE ε4 variant, as well as the vital role biomarkers play in facilitating early diagnosis and directing treatment. Current therapeutic paradigms that are taken into consideration include pharmacological treatments that target amyloid pathology, including as monoclonal antibodies, acetylcholinesterase inhibitors, and NMDA receptor antagonists. Non-pharmacological methods like cognitive training and rehabilitation are also being studied. The therapeutic potential of traditional and Ayurvedic medicines is also highlighted due to its neuroprotective and antioxidant properties. The study highlights the pressing need for innovative, multimodal treatment approaches that address the complex pathophysiology of AD in order to enhance patient outcomes and quality of life. This synopsis will guide future research efforts by offering a solid foundation for enhancing our understanding of and strategy for treating Alzheimer's disease.

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**Keywords**

Alzheimer, Neuroprotective, Amyloid-β, Donepezil, Aducanumab, Ashwagandha

**Introduction**

Dementia is a type of genetic mental retardation disorder that significantly impairs a patient's capacity to live, study, work, and communicate. It is a major cause of mortality and disability among the elderly [1]. Alzheimer's disease (AD) is the neurological disorder that causes dementia in the elderly population most often globally [2]. Pathogenic tau protein-based clusters of fibrillations are the hallmark of Alzheimer's disease (AD). Despite the fact that tau illness frequently coexists with neuroinflammation, there is presently insufficient preclinical data to support a clear causal relationship in the formation of tau tangles [3]. Both dementia and moderate cognitive impairment (MCI) affect millions of individuals globally, causing both financial and

health problems. A significant rise in the number of cases is predicted by 2050 [4]. Young people with Alzheimer's disease and MCI have trouble comprehending words. The effects of new pharmaceutical and non-pharmacological treatments, such logical training and rehabilitation, on cognitive processes are promising [5]. Early identification is a critical element of improved sickness management. Pretrained convolutional neural networks (CNNs) trained on large datasets, such as ImageNet, have been used to classify AD. As a result, scientists may start developing more accurate models [6].

High prevalence, chronicity, and multimorbidity are characteristics of AD that may negatively impact a patient's functionality and quality of life [7]. The different plants and their chemical makeup are explained in the (Fig. 1)

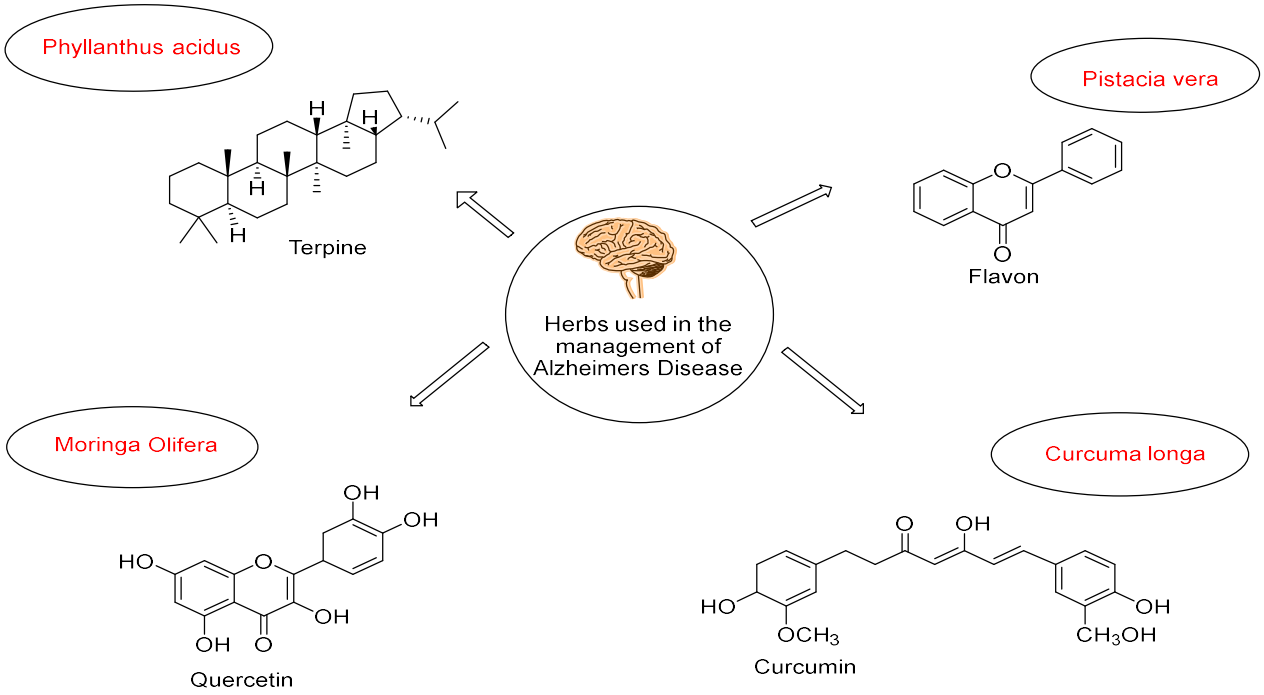


**Figure.1** Various chemical compositions and botanicals are utilised in Alzheimer's disease treatment.

**Pathophysiology**

Neuropathological features include extracellular senileamyloid-β (Aβ) peptides, which form plaques, and neurofibrillary tangles (NFTs) for cells, which are paired helical filaments that were enhanced phosphorylation (PHFs) from the microtubule-associated protein tau (MAPT) [8]. Plaques of Aβ are composed of several Aβ peptides, including the 40 and 42 amino acid products

(Aβ40 and Aβ42), which are created when the Aβ precursor protein (APP) is successively cleaved by γ-secretases and BACE-1, the β-site APP-cleaving enzyme [9]. When the illness first appears, there are extraneuronal Aβ deposits, intraneuronal NFTs, and neurotic threads in the entorhinal cortex and hippocampus, two crucial regions for memory and learning. However, in addition to tau and Aβ pathologies, other mechanisms, including as microglia-mediated inflammation and synaptic dysfunctions, are also significant in the pathophysiology of AD and may be linked to declining cognitive capacities [10,11]. The main risk factors for AD, a late-onset, sporadic disorder that typically affects persons 65 years of age or beyond, are ageing and possessing the Apolipoprotein E (ApoE) ε4 allele [12]. Conversely, those under 65 with the rare early-onset forms of AD usually have a good family history and a mostly autosomal inheritance pattern [13].These individuals have mutations in the genes PSEN1, PSEN2, or APP, which encode the proteins presenilin-1, presenilin-2, and APP, respectively. All of them have an impact on how APP is developed and handled, which raises the quantity of Aβ peptide that is generated or aggregated [14]. The failure of disease-modifying drugs may be explained by the complex biology of the condition and the limitations of earlier clinical research done on registered individuals with mild-to-moderate AD or without Aβ pathogenicity [15]. As a result, a biomarker may help develop AD medications more effectively and encourage a more customised approach to treatment [16] Consequently, a biomarker might aid in the more efficient development of AD drugs and promote a more individualised treatment plan [16]. It would be a useful tool for medical and epidemiological research, as well as for tracking the effectiveness of therapy and determining the stage at which the disease is developing. The National Institute on Ageing and Alzheimer's Association (NIA-AA) has updated its guidelines for the diagnosis of pre-clinical, AD, and moderate cognitive impairment (MCI) dementia, including imaging into the categories of biological indicators and AT(N). Based on this classification, the diagnostic markers may be separated into three groups: Aβ accumulation (A), tau (T) in fibrillary tissue, and neurodegeneration (N) [17, 18].Group N displays atrophy on magnetic resonance imaging (MRI), elevated CSF total tau (t-tau), and fluorodeoxyglucose (FDG)-PET hypometabolism, whereas Group T now has greater levels of cerebral circulation tau PET ligand binding and phosphorylated tau at threonine 181 (p-tau). There is now a low amount of Aβ42 in the CSF or Aβ ligand binding in PET in the first group [19]. A summary of the pathophysiology's mediators may be seen in Figure 3.

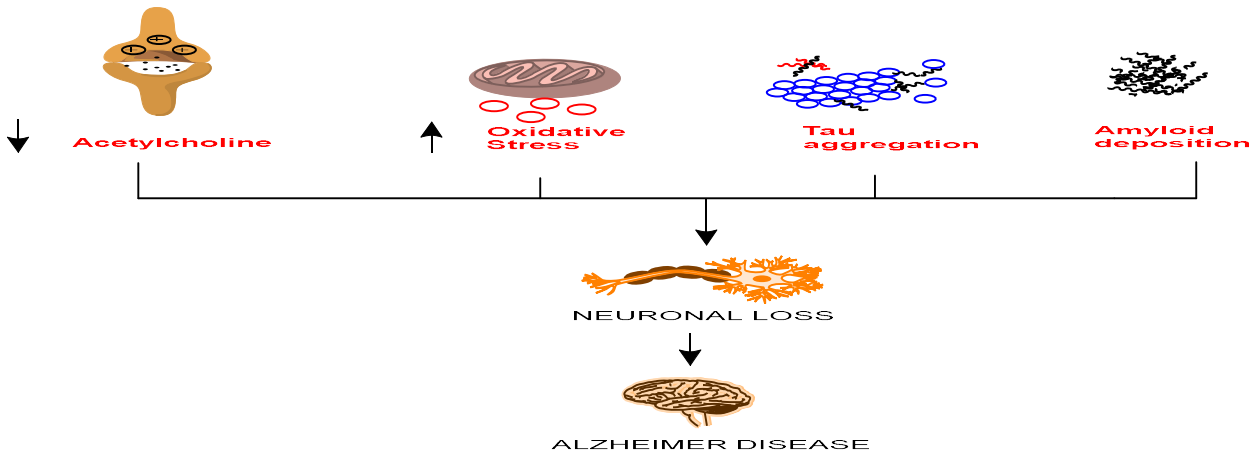


**Fig.2 Pathophysiology of Alzheimer's disease**

## Epidemiology

Globally, dementia is expected to affect almost 152 million people by the middle of the century, with low- and medium-income nations seeing the biggest increases in dementia cases [20]. Data from 2020 [21] suggests that by 2050, the number of Americans over 65 who have Alzheimer's disease might rise sharply from 5.8 million to 13.8 million. Community-dwelling studies conducted in China and Japan in the last several decades have undoubtedly shown a rise in the prevalence of AD (22, 23). The age-standardized death rate was higher than that of males, and the age-specific total incidence was 1.17 times higher than that of men, indicating that women's domination was not only attributable to their longer lifespans (24). Additionally, with a 146.2% rise in mortality between 2000 and 2018, AD rose to become the sixth leading cause of death among older Americans. Carers would notably have more negative emotional effects and mental pressures (25). But in Chinese cities, the prevalence of AD in those aged 65 and over rose from 3.5% to 4.8% after post-hoc adjustment of overall negative screening errors (26).

## Current approaches to treat Alzheimer's Disease

Alzheimer's disease can be treated using either Ayurveda or Allopathy. Despite the increase in frequency over the previous ten years and the associated financial expenses, there is presently no effective strategy to prevent or slow the development of AD. So far, the US Food and Drug Administration (FDA) has only authorised six drugs: memantine, galantamine, aducanumab, donepezil, rivastigmine, and a synthetic combination of donepezil and memantine. The only one of them, aducanumab, is used to eliminate Aβ plaques; the other five are used to treat symptoms

and function as antagonists of the N-methyl-D-aspartate receptor (NMDA-receptor) or by irritating the cholinergic system.
In **Allopathy,** there are certain drugs:

**1)Aducanumab**

A chimeric protein that specifically targetssoluble strands and monomers of b-amyloid peptides, aducanumab is used to treat Aβ plaques. It is advised to provide IV dose of 10 mg/kg over at intervals of at least 21 days, and once every four weeks (27).The FDA only recently approved this medication in April 2021 because it is believed to slow the progression of AD by acting on SP. The outcomes of three clinical trials, which offer compelling proof of the treatment's efficacy, served as the foundation for this approval. For a year, 165 participants in the first, multicenter, randomised, Double-blind, multiple-dose, placebo-controlled investigation of one year, PRIME (NCT01677572), received monthly from intravenous(IV) drawconcentrations 1 mg kg−1 of aducanumab, 3, 6, or 10. As measured according to the Acute Impairment RatingSum scores for the MMSE, or Mini Mental State Examand the number of boxes (CDR-SB) for the maximum dosage,this study showed thatThere was a dose-time-dependent reduction in Aβ plaques and an improvement in AD clinical symptoms (28).However, because of interactions with the CHMP the product's marketing authorization to treat Alzheimer's disease has been canceled by the European Medicines Agency,declaring that there is insufficient data to provide an optimistic assessment of the product's effectiveness.Due to an FDA revision, the studies indicate that this medicine is only available before beginning treatment, people in this situation need to obtain a brain MRI to check for superficial siderosis, microhemorrhages, and cerebral oedema, these MRI scans had to be performed again at 7 and 12 months [29].

**2) Acetylcholinesterase Inhibitors (AChE)**

In September 1993, the FDA authorised tacrine, the first medication in this class. It is an acridine-derived cholinergic that raises acetylcholine levels in different parts of the brain by acting as a central inhibitor of acetylcholinesterase [30]. It inhibits pseudocholinesterase more effectively than acetylcholinesterase does. Dr. Williams Summer conducted the first tacrine test in AD in 1989. Its main advantages are its capacity to penetrate the blood-brain barrier and administered intravenously and orally. But as its application grew, doubts about its efficacy arose because of inconsistent clinical trial outcomes [31,32,33,34].Tacrine was found to have a palliative

impact on people with mild to moderate dementia, but it had no effect on the progression of the underlying neurodegeneration.Its usage was stopped in 2013 because of numerous negative side effects, including hepatic cytotoxicity and the reported prevalence of clumsiness, diarrhea, vomiting, nausea, and loss of appetite [35].

**3) Donepezil**

Donepezil is a centrally located, non-competitive inhibitor of the enzyme acetylcholinesterase that hydrolyzes acetylcholine, and is a cholinergic drug composed of piperidine. Additionally, donepezil contributes to the pathophysiology ofAD at the level of molecules and cells by reducingearly inflammatory cytokine production, blocking many aspects of glutamate-induced excitotoxicity, and triggering a preventative isoform of ACG, and lessening the effects of oxidative stress [36] regarding the therapeutic treatment for moderate to severe AD, it was approved in 1996 [37]. Donepezil is available as a tablet, liquid, or jelly that can be taken orally or administered topically. For mild to severe dementia, 5 mg per day is recommended as a starting dose, with a rise to 10 mg per day for 4–6 weeks" People with moderate to severe dementia may be given a dosage of 23 mg per day as long because the 10 mg dosage has been taken by them for a minimum of three months [37].

**4)Galantamine**

The tertiary is quinoline alkaloid galantamine functionsas an inhibitor of acetylcholinesterase that is selective, competitive, and reversible. Additionally, it increases the intrinsic activity of acetylcholine on nicotinic receptors [37]. The FDA authorized this medication in 2001 [39]. Oral administration is used, and dosages of 4, 8, 12, 16, and 24 mg can be taken as extended-release capsules (once daily) or as a solution with rapid release (twice daily). It is advised to begin therapy with a dosage of 8 mg daily and increase 4–8 weeks later, to a maintenance dosage of 16 mg twice day [40]. The capacity of galactosamine to function at the level of the central nervous system while exhibiting little peripheral system activity makes it an extremely intriguing candidate for use in AD. Accordingly, a number of substances that help galantamine enter the brain have been connected to it, such as chitosan, solid lipid nanoparticles, and hydroxyapatite particles that contain cerium [41–43].Clinical investigations on this pathology have demonstrated that this medication can help Individuals with mild to moderate AD with their behavioraland symptoms related to

cognition, including such as restlessness, nervousness, lack of inhibition, and irregular motions [44,45,46].

Ayurvedic medicine is the name given to Indian traditional medicine, and researchers have created several medications and surgery methods to treat a broad range of ailments and Studies on medicinal herbs revealed. The various Ayurvedic herbs has been mentioned below:

**1)Ashwagandha**(Withania somnifera) Ashwagandha in Ayurveda, ashwagandha is widely used as an aphrodisiac, nervine tonic, and a "adaptogen" that aids with stress management [47, 48]. The component of ashwagandha that is most commonly utilized is the root. It is a member of the Solanaceae family, which includes nightshades. It is considered to have anti-oxidant, anti-free radical, and immune-boosting qualities and belongs to the rasayana, or rejuvenating, group [49]. Because of its relaxing properties, ashwagandha may be particularly helpful for AD patients, unlike other tending to be stimulating adaptogens [50]. The entire alkaloid extract from ashwagandha roots showed a relaxing effect on the central nervous system (CNS) in a number of mammalian species, suggesting that this herb might be utilised to promote relaxation [51].

**2)Turmeric**(Curcuma *longa)*particularly helpful for AD patients as opposed to other stimulatory adaptogens [50]. The entire alkaloid extract from ashwagandha roots showed a relaxing effect on the central nervous system (CNS) in a number of animal species. Turmeric, which comes from the rhizome and root, is used in Asian traditional medicine as well as as a spice and colouring. Water-soluble curcuminoids, such as curcumin, and turmerone oil are believed to be the active ingredients [52]. The primary curcuminoid that gives turmeric roots their yellow hue is curcumin [52–55]. The Indian medical system has long utilised turmeric, which possesses antibacterial, antiseptic, and anti-inflammatory properties, to treat a wide range of ailments. This multipurpose spice aids in liver detoxification, cholesterol balancing, allergy prevention, digestive stimulation, and immune building [56]. According to other research, turmeric's non-steroidal anti-inflammatory qualities are linked to a lower risk of AD [57]. In fact, curcumin decreased the quantity of plaque deposition in elderly mice that have developed plaque deposits similar to AD [58,59,60].

**3)Brahmi** (*Bacopa monnieri*)In Ayurvedic medicine, Bacopa, another name for Brahmithrives in moist, swampy areas and is a plant that grows bitterly. In addition to treating rheumatism, asthma, epilepsy, and sleeplessness, it is also used as a diuretic, cardiotonic, and nerve tonic [61,62]. The

primary constituents of Bacopa monnieri (BM) are saponins and triterpenoid bacosaponins, which comprise bacosides A and B, bacosaponins A, B, and C, and bacopasides III to V. Other saponin glycosides include the jujubogeninbisdesmosidesbacopasaponins D, E, and F. Other components include polyphenols, betulic acid, alkaloids, plant sterols, and sulfhydryl compounds that have antioxidant action [63,64,65].BM may function by reducing divalent metals, scavenging reactive oxygen species, restricting lipoxygenase activity, and reducing the generation of lipid peroxides [66]. BM was formerly used to improve cognitive [67].

**4)Gotu kola** (*Centella asiatica)* Gotu Kola is among the essential herbsthat restores brain and nerve cells as per the Ayurvedic medical system. It is also thought to have the ability to improve memory, lifespan, and intelligence [68,69].Considering that Asiaticoside derivatives, such as asiatic acid and asiaticoside, have been shown to prevent beta-amyloid cell death, lower free radical concentrations, and lessen hydrogen peroxide-induced cell death in vitro, Beta-amyloid toxicity and AD may be treated and prevented using gotu kola [70]. In the brains of PSAPP (APP/Sw × PS1M146L) mice, gotu kola extracts restored beta-amyloid pathology and altered the elements of the oxidative stress response [71–72].

**Phytoconstituents Reported for the management of Disease:**

Over time, AD has continued being the most prevalent kind of dementia, raising concerns worldwide, particularly among the elderly [73]. This neurodegenerative disease interrupts a patient's social and professional life [74]. The rise in the number of persons with unworthy medical conditions is a significant problem. Alzheimer's patients receive a lot of medical attention, but attempts to reverse the neurological condition appear futile. However, many medications can have adverse effects that exacerbate the patient's medical issues. Synthetic medications that regulate neurotransmitter enzymes, such as cholinesterase inhibitors or NMDA receptors, are used to treat Alzheimer's disease; nevertheless, this approach has not produced a perfect therapeutic answer [75].Since the beginning of time, traditional medicine has been practiced all across the world. Amnesia, dementia, AD, and other ailments have reportedly been treated with these natural therapies, which include medicinal plants and herbs. Herbal remedies originated in the cultures of ancient Egypt, India, and China [76].

**Ginseng**

One of the plants used to treat AD is ginseng (Panax ginseng /Araliaceae) [77]. In China, Japan, and Korea, this well-liked herb is utilized to improve memory and energy levels. Commonly referred to as Chinese ginseng,20(S)-protopanaxadiol, a byproduct of the triterpenoid dammarane, ginsenosides (saponins), ameliorate mitochondrial dysfunction, boost the release of neurotrophic factors, and stop amyloid-beta (A$\beta$) from aggregating and removing A$\beta$ from neurones [78]. Ginsenosides, which are found in ginseng, have high AChE inhibitory effects and can effectively reduce the symptoms of AD, according to molecular enzyme research [79]. By activating phosphatidic acid receptors involved in haemolysis, the bioactive glycoprotein glutinin decreases the generation of A$\beta$ and enhances learning and memory [80,81] g sA$\beta$PP$\alpha$ in the body and reducing the deposition of A$\beta$ plaque [83]. By encouraging oxidative stress, autophagy, anti-inflammatory mechanisms, and anti-apoptosis management, it also lessens AD symptoms, per a number of in vitro and in vivo studies [82]. Gintonin has long been known to help treat AD because it affects the cholinergic system and neutrophilic components by modifying lysophosphatidic acid receptors connected to G proteins, which lessens the extent of plaque development. Studies show that gintonin-administered mice showed better memory impairment by releasin.

***Moringa olifera***

AD is treated locally using *Moringa olifera*, a plant of the moringaceace family. This might be due to its many bioactive components. Phytochemicals including flavonoids, alkaloids, saponins, tannins, and isothiocyanates are abundant in Moringa olifera [84]. By increasing the synthesis of SOD and catalase, which reduces the quantity of lipid peroxides, these phytochemicals improve brain function [85]. In experimental rats with hyperhomocysteinemia, it also reduces the production of tau hyperphosphorylation and improves the stabilization of monoamine levels [86].

**Glycyrrhiza glabra**

Alzheimer's disease is treated using this plant, which is a member of the Fabaceae family and contains coumarins, isoflavonoids, saponins, flavonoids, and stilbenoids [87]. Collectively, these phytochemicals prevent cytotoxicity, ROS production, and GSH activity. When administered

orally for six weeks to an albino rat that is one month old, the glycyrrhiza glabra plant extract demonstrated enhanced memory and learning ability [88]. In addition, Tapia-Rojas's study [89] found that glycyrrhiza inflata extract, a distinct species of glycyrrhiza, significantly prevented radical-scavenging and Aβ aggregation [90]. Both mitochondrial biogenesis and oxidative stress were reduced. The plant extract's licochalcone A and liquiritigenin may be responsible for this [91].

**Curcuma plants**

The Zingiberaceae family includes Curcuma longa. Alzheimer's patients can benefit from its anti-inflammatory, anti-amyloidogenic, and antioxidant qualities [92]. The ability of plant extracts from Curcuma longa to prevent fibril formation and Aβ aggregation has been demonstrated in studies involving experimental mice. Additionally, the testing results demonstrated improved cognitive capabilities and a decrease in oxidative stress. This could be caused by COX (cyclooxygenase)−2 and inducible nitric oxide synthase (iNOS), which are activated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [93].

**Therapeutic Strategies to Target Alzheimer:** In this (Fig. 3) presents various approaches to treating or managing Alzheimer's disease which categorizes those strategies into six areas:

Anti – amyloids (AChEI, Secretases, Immunotherapy

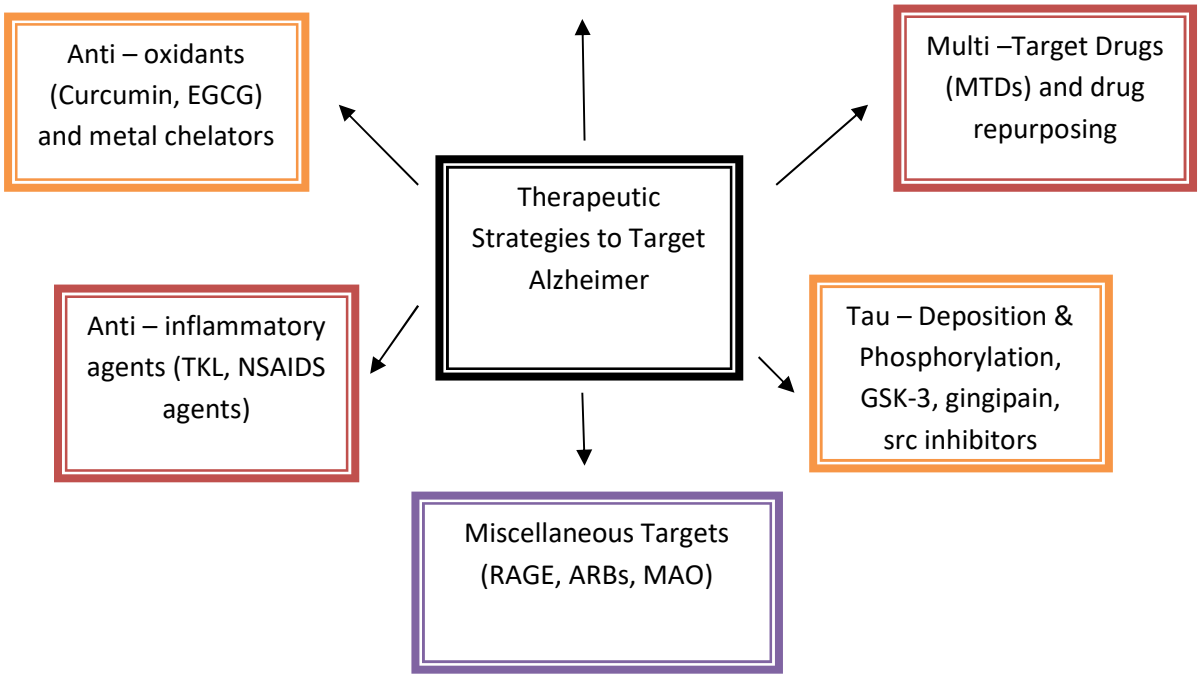


**Fig. 3 Targeted strategies for the management of Alzheimer's disease**

**Discussion**

In this paper we focused on Alzheimer's disease (AD), its pathophysiology, and therapeutic approaches. The paper highlights that AD is characterized by neurofibrillary tangles and amyloid-β plaques 2, making it the leading cause of dementia and disability among elderly populations. The paper discusses how AD cases are projected to reach 152 million globally by mid-century, with low and medium-income countries experiencing the highest growth. Women show a higher prevalence, with 1.17 times greater age-specific rates than men. The review explores various treatment approaches, including traditional medicines and modern therapeutics. It particularly emphasizes biomarker-based diagnosis, using the AT(N) classification system for better disease monitoring. The paper also addresses the challenges of current treatments, noting that while synthetic medications targeting neurotransmitter enzymes are common, they haven't provided perfect therapeutic solutions. The research underscores an urgent need for innovative, multimodal

therapeutic approaches to address AD's complex pathology. By 2050, a significant increase in AD cases is projected, with estimates suggesting up to 13.8 million Americans over 65 could be affected, highlighting the pressing need for advanced treatments. Biomarker-based approaches show promise for future drug development and personalized medicine. The paper suggests that future clinical trials should focus on early-stage AD patients and consider Aβ pathology for more successful disease-modifying treatments. The review also points to the potential of integrating traditional medicines with modern approaches, particularly exploring neuroprotective and antioxidative properties of Ayurvedic medicines. This synthesis aims to guide future research efforts toward enhancing patient outcomes and quality of life. The paper faces several constraints in its data and approach. There is insufficient preclinical proof that the formation of tau tangles and neuroinflammation are directly causally related, despite their frequent co-occurrence. Regarding treatment efficacy, the paper acknowledges limitations in current therapeutic approaches, noting that there is currently no proven cure to stop or halt the course of AD.The available drug data shows limitations, particularly with Aducanumab, where study results weren't consistently replicable. The epidemiological data presents geographical limitations, with most detailed prevalence studies focused on specific regions like Chinese cities, showing limited global representation. Additionally, the paper highlights limitations in current diagnostic approaches, as early detection remains challenging despite its importance in disease management. The review also notes limitations in clinical trial data, particularly regarding variations in disease progression and treatment responses.

**Conclusion**

One of the most complicated diseases is Alzheimer's. and ever-growing global health challenges, accompanied by multifaceted pathology and rapid increased prevalence. This review emphasizes that the amyloid-β plaques with tau protein tangles, neuroinflammation, and synaptic dysfunction represent an intricate interplay in AD pathophysiology; it also emphasizes the importance of biomarkers and advanced imaging technologies in early detection. Current pharmacological interventions,such as NMDA receptor antagonists and acetylcholinesterase inhibitors, merely alleviate symptoms; they do not stop the course of the disease. In the same manner, emerging therapies such as monoclonal antibodies targeting amyloid pathology hold great promise but are limited in efficacy and accessibility. The therapeutic promise of traditional medicine, such as

Ashwagandha, turmeric, and ginseng, in association with modern therapies, offers a door to neuroprotective and antioxidative properties. Since AD largely affects women, and the burden this disease continues to impose on the personal, social, and economic fronts, this review calls for patient-centric innovative strategy that combines traditional and alternative therapeutic approaches. For future researches, early-stage intervention and personalization through refinement of therapeutic targets must be the goals, based on biomarkers. Though great strides in understanding AD's pathology have advanced diagnosis and management, there remains a place for improvement: limited preclinical evidence and disparities in global epidemiological data. This requires collaborative research investment and participation in precision medicine, ultimately through the merger of traditional knowledge, modern science, and technological innovation, transforming the care of AD and enhancing patient outcomes and quality of life as we emerge into this ever-escalating prevalence of this devastating disease.

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**Author Contributions:**

Nishant Goutam conceptualized the idea for the review article, designed the frame of work, and supervised the overall preparation of the manuscript. Abhishashi Sharma performed the literature search, compiled relevant data, conducted the analysis, and drafted the initial manuscript. Kanika Kaushal and Shivani contributed to the interpretation of the collected data, provided critical

insights, and assisted in refining the manuscript. All authors were involved in the critical revision of the work for intellectual content and have approved the final version of the manuscript for submission.

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