Pharmacological Approaches and Herbal Interventions for Alzheimer's Disease: A Comprehensive Review

Praful Kumar Majhi*, Prasanna Kumar Pradhan, Surendra Gohil, Goutam Ghosh, Bharat Bhusan Subudhi.

Email: Praful1509@gmail.com*

Address: School of Pharmaceutical Sciences, SOA Deemed to be University, Kalinga Nagar, Ghatikia, Bhubaneswar-751003*

Abstract

This review comprehensively examines herbal interventions and pharmacological approaches for treating Alzheimer's disease (AD). Active constituents and mechanisms of action of various herbal drugs, including Withania somnifera, Bacopa monnieri, Ginkgo biloba, and Curcuma longa, are discussed, highlighting their anti-inflammatory, antioxidant, and neuroprotective properties. Allopathic drugs such as cholinesterase inhibitors (Donepezil, rivastigmine) and memantine are also explored, emphasizing their mechanisms of action and side effects. Non-drug therapies, including cognitive-oriented interventions, physical exercise, and brain stimulation techniques, are reviewed, showcasing their potential to enhance cognitive function and neuroplasticity. Additionally, combination therapies are discussed to target multiple aspects of AD pathology. Overall, this review provides valuable insights into alternative treatment approaches for AD, emphasizing the potential of herbal interventions in improving cognitive function and addressing AD pathology. Also, it can provides a new direction for repurposing combination of allopathic and herbal drugs.

Keywords: Alzheimer's disease, combination therapy, herbal drugs, cognitive function, disease progression, neurodegenerative disorder.

1. Introduction

The Global Problem of Alzheimer's Disease and Dementia: Prevalence, Projections, and Regional Variations

Alzheimer's is a neurodegenerative disorder that primarily affects memory, cognition, and behavior, leading to the progressive decline of cognitive function and other mental abilities [1]. Memory impairment is a common symptom characterized by difficulties remembering recent events, new information, and details from the past. Cognitive dysfunction, including attention, perception, language, and problem-solving difficulties, is also prevalent. Executive dysfunction is another common feature causing issues with planning, organizing, and completing tasks [1].

Besides cognitive symptoms, Alzheimer's disease can manifest as alterations in personality and behavior, including irritability, anxiety, depression, modified social behavior, and impaired decision-making capabilities [1]. It is essential to know that although Alzheimer's disease is the leading cause of dementia in older individuals, other types of dementia can produce comparable symptoms. Getting medical advice is crucial to receive an accurate diagnosis and proper treatment. [1].

Dementia is a significant global health challenge, mainly affecting older adults. It refers to a decline in cognitive abilities that interferes with daily activities. As of September 2021, the global number of individuals with dementia surpassed 55 million, and approximately 10 million new cases are diagnosed annually. More than 60% of individuals with dementia reside in low- and middle-income countries. Dementia ranks as the seventh leading cause of death globally, impacting cognitive, functional, and social abilities, necessitating caregiver or healthcare assistance. With aging people, the number of persons living with dementia will likely rise [3]. Projections suggest that by the year 2050, the number of individuals affected by Alzheimer's disease and other dementias is estimated to reach 152 million [4].

The global number of dementia cases is expected to rise significantly from 574 lakhs in 2019 to 1528 lakhs in 2050. However, it is anticipated that the age-standardized prevalence of dementia will remain relatively stable despite the substantial increase in the projected number of affected individuals. Women are projected to have a higher prevalence of dementia than men, both in 2019 (1.69 ratio) and in 2050 (1.67 ratio). Geographically, the increases in projected dementia cases vary across countries and regions. The regions of high-income Western Europe and the Asia Pacific are expected to have the most minor percentage changes. In contrast, the Middle East, North Africa, and eastern sub-Saharan Africa are expected to experience significant increases in dementia cases. The projected case increases are attributed to population growth and aging, while their regional significance varies [4].

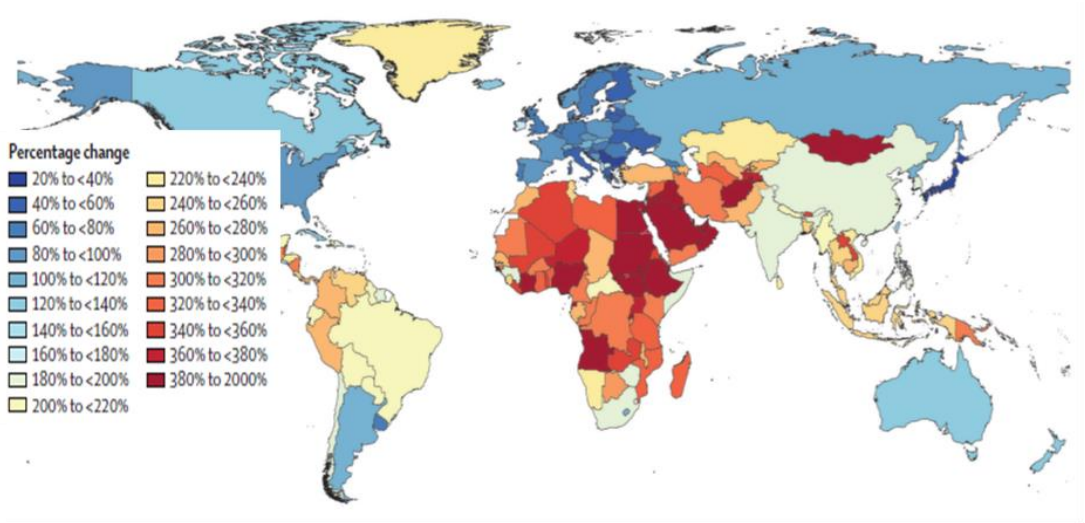

Figure 1: The all-age number of individuals with dementia is expected to undergo varying percentage changes between 2019 and 2050

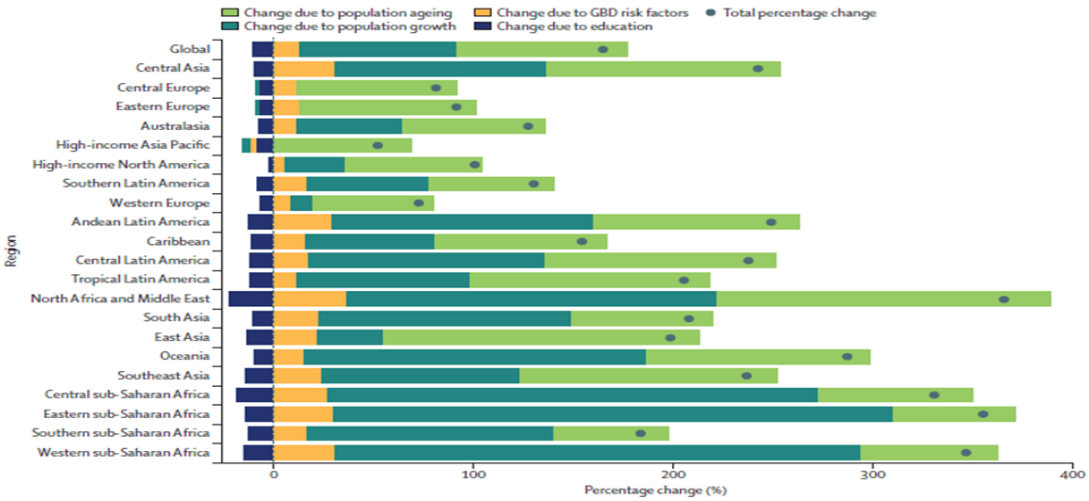

Figure 2: Percentage variation in the number of individuals with dementia, both at a global level and across different world regions, from 2019 to 2050 [4]

2. Advancing Research and Therapeutic Approaches for AD and Dementia

The projected growth in AD and dementia can be attributed to population aging and various risk factors, including hypertension, obesity, Diabetes, physical inactivity, hearing loss, smoking, depression, low education level, and social isolation [5]. While the precise mechanisms that connect these risk factors to dementia are not entirely comprehended, embracing a healthy lifestyle is generally advantageous for overall well-being and can potentially lower the risk of developing dementia.

Despite increased research efforts, there are currently no known cures for Alzheimer's disease. Available treatments focus on symptom management and slowing disease progression but do not halt it entirely [5]. Ongoing research aims to understand the disease's mechanisms better and develop more effective therapies to target them.

Dementia is a multifactorial condition, often resulting from age-related neurodegeneration, genetic predisposition, and environmental factors. Managing dementia requires a multidisciplinary approach, including pharmacological interventions, nutrition and exercise interventions, cognitive stimulation and training, and medication reviews [6]. Recent studies provide evidence supporting the implementation of multi-modal interventions to deliver comprehensive care for individuals in danger of evolving dementia.

Even with the noteworthy public health impact of dementia, there are currently a limited number of approved medical treatments for Alzheimer's disease. These treatments address symptoms rather than altering the disease course [7]. Medical trials for AD have faced high failure rates, emphasizing the need for more research and development to identify effective treatments [7].

Based on ongoing research, the Common Alzheimer's Disease Research Ontology's Translational Research and Clinical Interferences group presents potential targets for AD and related dementias

[8]. Creating treatments for neurological disorders is difficult because of the intricate nature of the nervous system, the various reasons behind these diseases, the limited number of patients, and the barrier between the brain and blood. Nevertheless, scientists and organizations are pursuing sophisticated techniques like gene therapy, stem cell therapy, and neurostimulation to find solutions [9]. Accomplishing this goal necessitates teamwork and significant financial resources.

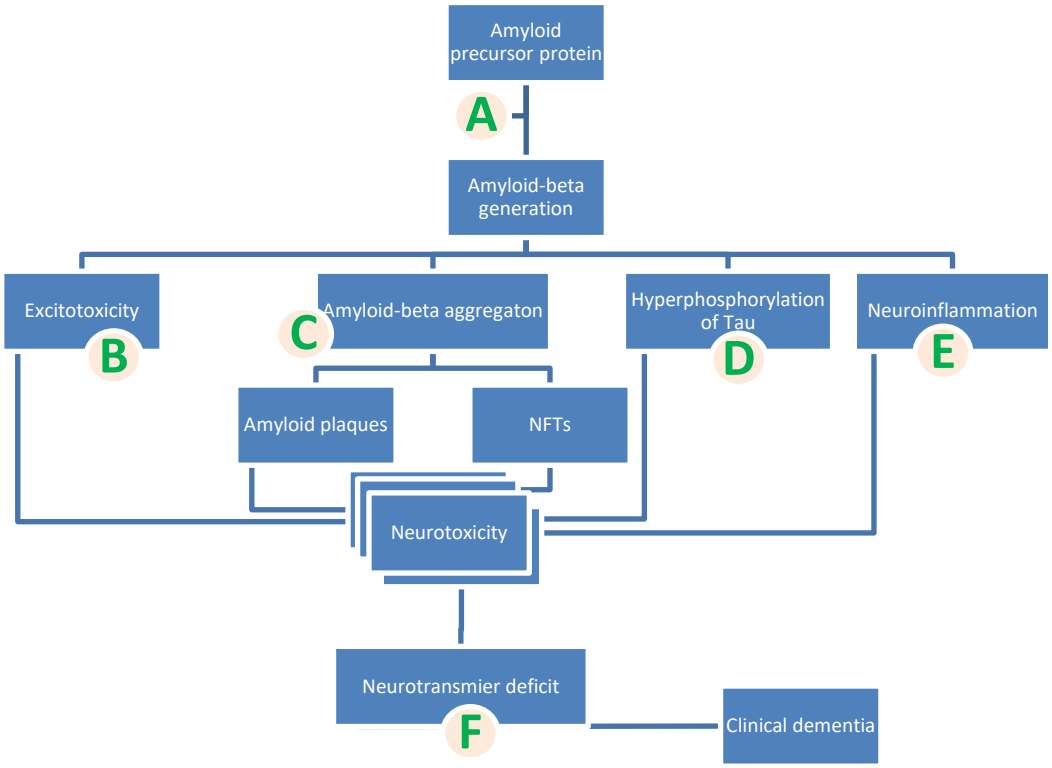

Figure 3: Aetiology of AD with beneficial targets.

Exploring Pathophysiological Mechanisms and Possible Beneficial Targets in AD

In 2021, the FDA approved seven new drugs for central nervous system (CNS) disorders and two for disorders related to the peripheral nervous system in the United States. Among the CNS disorders, the approved drugs covered a range of conditions such as von Hippel-Lindau disease, relapsing multiple sclerosis, migraine, schizophrenia, attention deficit-hyperactivity disorder (2 medicines approved), and Alzheimer's disease [7]. Notably, the approval of an Alzheimer's disease drug marked the initial such approval in the United States since 2003.

According to the amyloid hypothesis, when the amyloid precursor protein (APP) is not processed correctly, it creates amyloid beta (Aβ). Damage is caused to the connections between brain cells, leading to the loss of brain cells and the formation of amyloid plaques. Neurofibrillary tangles (NFTs) are also developed, comprising tau protein over-phosphorylated.[10]. Usually, tau protein stabilizes microtubules within neurons, but when hyperphosphorylated, it aggregates into NFTs,

disrupting normal cellular functions. It is believed that the accumulation of Aβ initiates this process, and toxic forms of tau can further enhance Aβ production through a response mechanism [11], [12].

Cholinergic Hypothesis: According to the cholinergic hypothesis, the decline in cognitive function in Alzheimer's disease is caused by decreased cholinergic neurons. The decrease mentioned in this context leads to reduced levels of acetylcholine. The choline acetyltransferase enzyme can cause problems with memory and learning by affecting the neurotransmitter responsible for these functions. Cholinesterase inhibitors, such as Donepezil, elevate acetylcholine levels and enhance cognitive function in certain AD patients. However, there is a continued need for novel treatments that target the underlying pathophysiology of AD, as the current interventions primarily focus on symptomatic relief. [13].

Glutamate Excitotoxicity: Excessive introduction to glutamate or overstimulation of its NMDA receptor can lead to glutamate excitotoxicity, which is believed to contribute to the progressive neurological loss observed in AD. This process is supposed to affect the cholinergic neurons, increasing calcium influx into cells [14].

Vascular Burden: It means states that the swelling impact of vascular risk factors, such as hypertension, Diabetes, and smoking on brain blood vessels, is associated with the change of both Alzheimer's disease (AD) and vascular dementia. Research has shown that certain factors affecting blood vessels can contribute to the buildup of amyloid-beta protein in the brain, a significant feature of Alzheimer's disease. By addressing vascular risk factors through lifestyle modifications and appropriate management of these conditions early, it may be possible to decrease the risk of both [15]-[19].

Insulin Dysregulation: Research has identified that insulin dysregulation and irregular insulin metabolism in the central nervous system contribute to the development of Alzheimer's disease (AD). Insulin, which can cross the blood-brain barrier and is produced in the central nervous system, may regulate tau pathology and beta-amyloid deposition in the brain. The link between Diabetes and AD is partially attributed to disrupted insulin metabolism in the CNS [20]-[22].

Apoe4 Allele: The Apo epsilon 4 (Apoe4) allele is a type of the apolipoprotein gene known genetic risk factor for Alzheimer's disease (AD). Individuals who carry one copy of the Apoe4 allele are more likely to develop Alzheimer's disease, while those with two copies have an even higher risk. The presence of Apoe4 may impact various aspects of AD pathology, including Aβ aggregation and clearance, neurotoxicity, synaptic function, hyperphosphorylation (tau), and neuroinflammation. Potential therapeutic approaches to Apoe4 include enhancing Aβ clearance, modulating Apoe4 levels, or converting Apoe4 to Apoe3. However, it is essential to note that clinical trials in this area are currently limited [23]-[25].

Neuroinflammation: Neuroinflammation, characterized by the buildup of glial cells in the central nervous system, is regarded as a central phenomenon in the pathophysiology of Alzheimer's disease. Amyloid neurofibrillary tangles and plaque trigger this immune response. It is now recognized that the brain has an active immune system that contributes to normal brain function and responds to injury and disease [26], [27]. Targeting the neuroinflammatory processes in the CNS holds promise as a strategy for developing novel therapies for AD [29].

Vitamin B5 Deficiency: It is crucial to emphasize that there is currently no scientific evidence available to back the assertion that a primary, acute deficiency of vitamin B5 (pantothenic acid) leads to AD, nor is there evidence to suggest that taking oral doses of vitamin B5 can reverse dementia or neurodegeneration in AD. AD is a multifaceted neurodegenerative disorder influenced

by various factors, and severe deficiencies of vitamin B5 are uncommon in developed countries due to its widespread presence in various foods [30].

Mitochondrial Dysfunction: Mitochondrial dysfunction, linked to aging and neurodegenerative conditions, involves mutations in mitochondrial DNA (mtDNA), heightened production of reactive oxygen species (ROS), and impaired biogenesis. The precise timeline of these events and their role in initiating neurodegeneration still need to be fully comprehended. However, it is believed that mitochondrial dysfunction contributes to Alzheimer's and Parkinson's diseases. Further investigation is necessary to expand a complete understanding of the sequential events and how they interact with other pathological processes [31], [32].

TDP-43: The transactive response DNA binding protein (TDP-43), known for its role in amyotrophic lateral sclerosis and frontotemporal lobar degeneration, has also been implicated in AD. Studies have identified TDP-43 residues in the brains of AD patients, suggesting a potential role in the disease's progression and clinical manifestations. Additional research is required to fully know AD's TDP-43 mechanisms and implications [33].

The Dual Role of Reactive Astrocytes in AD: Reactive astrocytes play beneficial and detrimental roles. They can clear amyloid beta (Ab) oligomers and aggregates. However, excessive activation of specific systems can lead to the overproduction of harmful molecules, reactive oxygen species (ROS), and inhibitory transmitters, making astrocytes neurotoxic. Proper regulation is crucial to maintain an appropriate oxidative status.

Balancing Astrocytic GABA Levels: Manipulating astrocytic GABA levels by regulating monoamine oxidase-B activity may improve cognitive impairments in AD. Balancing antioxidant mechanisms, Ab clearance, and neurotoxicity is essential in developing effective AD therapies [34].

MicroRNAs and their Regulatory Role: MicroRNAs, particularly microRNA-200a-3p (miR-200a-3p), have been studied in AD. The regulatory role of miR-200a-3p in proteins associated with Alzheimer's disease has been discovered, including PRKACB and BACE1. Through its regulatory function, miR-200a-3p has been shown to reduce amyloid-beta (Ab) production, tau hyperphosphorylation, cell apoptosis, and activating the Bax/caspase-3 axis. In AD patients, decreased levels of miR-200a-3p have been observed, indicating its potential as a peripheral biomarker for Alzheimer’s disease diagnosis and treatment [35].

Reactive Astrocytes and Microglia: Brain microglia, immune cells, have a dual role in AD. They can promote inflammation by releasing inflammatory mediators and contribute to spreading pathological proteins through exosomes, influencing disease progression. Microglia activation triggers the release of complement components, chemokines, free radicals, and inflammatory cytokines, which can contribute to the generation and aggregation of amyloid-beta. Investigating the roles of microglia, inflammation, and intercellular transmission of pathological proteins is vital for comprehending the causal mechanisms of Alzheimer's disease [36].

Dysregulation of Cell Cycle Control Machinery: Cyclin-dependent kinase 5 (Cdk5) and its complex with p35 show a role in suppressing the neuron's cell cycle. However, the aggregation of amyloid-beta triggers the dissociation of the Cdk5/p35 complex in AD, leading to dysregulation of the cell cycle control machinery and contributing to the pathogenesis of AD [37].

Calcium Signalling and Familial AD: Regulating calcium dysregulation in neurons is crucial in addressing familial AD—presenilin mutations, which account for around 90% of familial AD cases, impact calcium homeostasis. Modulating components involved in calcium regulation, such as the Sarco/endoplasmic reticulum ATPase (SERCA) pump, ryanodine receptors (RyR), plasma

membrane Ca2+ ATPase (PMCA), Na+/Ca2+ exchanger (NCX), and inositol 1,4,5-trisphosphate receptors (InsP3R), may help restore cellular calcium balance and have potential therapeutic implications. However, further research is needed to develop effective interventions [37].

3. Herbal Interventions in Traditional Medicine

Herbal interventions have been used in traditional medicine systems for centuries to overcome various ailments, including Alzheimer's disease (AD) and memory deficits. Medicinal plants contain a variety of compounds, such as alkaloids, sterols, triterpenes, polyphenols, tannins, flavonoids, and lignins, which have been identified through phytochemical studies to have pharmacological activities that may be beneficial for neurodegenerative disorders [9].

Herbal medicines are based on balancing the body's humor and promoting overall health and well-being. Traditional medicinal systems, such as Ayurveda, Homeopathy, Unani, and Siddha, combine herbs, minerals, and natural substances to prevent, protect, and cure diseases. These systems offer a holistic approach to healthcare, addressing the symptoms and underlying causes of the disease [39]. While herbal medicines can offer safe and effective treatment options, it is vital to use them under the guidance of a qualified practitioner and with appropriate safety measures in place. Not all herbal medicines are safe or effective for everyone, and their use should be personalized based on individual needs and health conditions. Before using any herbal product, it is essential to consult healthcare professionals to ensure their suitability and to avoid potential interactions with other medications or adverse effects.

Table 1 Herbal drugs used for the treatment of Alzheimer's disease

Name of Herbal Drugs	Biological Name and Family	Active Constitute	Mechanism of Action
Withania somnifera	Ashwagandha	Withanamides A and C	Inhibits acetylcholinesterase (AChE) and B-Site of Amyloid Precursor Protein Cleaving Enzyme (BACE1). It prevents fibril formation and protects neuronal cells from amyloid plaques [40].
Bacopa monnieri	Brahmi	Bacoside A	Reverses acetylcholine depletion, reduces choline acetyltransferase activity, and decreases muscarinic cholinergic binding in the Hippocampus and frontal cortex [41].
Tinospora cordifolia	Guduchi	Choline, Tinosporin, Isocolumbin, Palmatine	It exhibits anti-cholinesterase, neuroprotective, antioxidant, anti-amyloidogenic, and nootropic effects, improving cognitive deficits [42].

Name of Herbal Drugs	Biological Name and Family	Active Constitute	Mechanism of Action
Ginkgo biloba	Ginkgo	Bilobalide, ginkgolide, EGb 761	Promotes cell proliferation and neuroblast differentiation, inhibits membrane lipid peroxidation, attenuates beta-amyloid aggregate formation, and exhibits anti-inflammatory effects [43].
Curcuma Longa	Turmeric	Curcumin	Reduces plaque deposition in the brain, prevents the development and induces disaggregation of amyloid-beta plaques, modifies microglial activity, inhibits acetylcholinesterase, and acts as an antioxidant [44, 45].
Glycyrrhiza glabra	Liquorice	Glycyrrhizin, Glycyrrhetinic acid, Glabridin, Quercetin, Liquiritigenin, and others	It inhibits Aβ-induced neurotoxicity, exhibits neuroprotective effects, and improves cognitive impairment-related models [46, 47, 48, 49].
Apocynaceae, lesser periwinkle	Periwinkle	Vincacetine	It improves Aβ-induced memory impairment and exhibits neuroprotective, anti-inflammatory, antioxidant, and phosphodiesterase-one inhibitory effects [50, 51].
Crassulaceae Rhodiola Rosea	Rhodiola	Salidroside, rosavin, tyrosol	p-GSK-3β and PI3K/AKT signaling Upregulates, p-tau downregulates, deteriorates the irregular processing of APP, induces antioxidant enzymes, prevents caspase three activations, and increases activities of GSH-Px and SOD[52, 53, 54, 55, 56, 57].
Lamiaceae, Salvia Rosmarinus	Rosemary	Rosmarinic acid	Exhibits antioxidant potential, including lipid peroxidation inhibition and protection against oxidative cell death [58, 59].
Plantae, Lycopodiopsida	Clubmoss	Huperzine A	Possesses potent acetylcholinesterase inhibitory activity [60].
Rubiaceae, Uncaria tomentosa	Cats claw	Proanthocyanidin B2 (epicatechin-4β-8-epicatechin)	Prevents Aβ 1–40 amyloid fibril formation and reduces pre-formed Aβ 1–42 fibrils [61]. Continued:

Name of Herbal Drugs	Biological Name and Family	Active Constitute	Mechanism of Action
Coriandrum sativum	Coriander	Coumarin	It inhibits Aβ42-induced glial cell proliferation and extracellular signal-regulated kinase activation and reduces oxidative stress, improving spatial memory [62].
Panax ginseng	Ginseng	Ginsenosides	Exhibits anti-inflammatory, anti-neuroinflammatory, and neuroprotective effects [63, 64].
Coffea arabica	Coffee	Caffeine	Reduces hippocampal Aβ levels, decreases expression of PS1 and β-secretase-1, and diminishes Aβ production [65].
Magnolia Officinalis	Magnolia-bark	4-O-methyl honokiol	Attenuates acetylcholinesterase activity inhibits the scopolamine-induced increase of AChE activity and exhibits neuroprotective and antioxidant effects [66].
Zingiber officinale	Ginger	Shogaol and gingerol	Enhances rates of learning and memory [67].
Crocus sativus	Saffron	Safranal, Trans crocetin	It regulates glutamate levels, reduces oxidative stress, and modulates Aβ and tau protein aggregation [68].
Lepidium meyenii	Maca	Choline	It improves learning and memory, lowers lipid peroxidation, and inhibits acetylcholinesterase activity [69].
Ficus carica	Fig	Quercetin, Sitosterol	It improves learning ability, exhibits antioxidant action, and promotes neuronal bioactivity [70].
Celastrus paniculatus	Malkangani	Celapanine, celapanigine, celapagine, celastrine, paniculatine	Increases acetylcholine levels, protects neuronal cells from neurotoxicity, and improves memory performance [71].
Punica granatum	Pomegranate	Polyphenols	Reduces Aβ42 accumulation, protects against oxidative stress, improves cognitive performance, and suppresses Aβ-induced cell death [73].

Name of Herbal Drugs	Biological Name and Family	Active Constitute	Mechanism of Action
Convolvulus pluricaulis	Shankhpushpi	Alkaloids, glycosides, flavonoids, carbohydrates, proteins, sterols, gum, and mucilages	Exhibits nootropic, anxiolytic, tranquilizing, antidepressant, anti-stress, and anti-amnesia effects [74].
Nardostachys jatamansi	Jatamansi	Sesquiterpenes and coumarins	It inhibits acetylcholinesterase, exhibits neuroprotective and antioxidant effects, and enhances memory [75].

Table 2 Allopathic drugs used for the treatment of Alzheimer's disease

Name	IUPAC Name & Structure	Mechanism of Action	Side Effects
Donepezil	2-[(1-benzylpiperidin-4-yl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one	Inhibit acetylcholinesterase besides increases the availability of acetylcholine (ACh) at the synapse, enhancing cholinergic transmission [82].	diarrhea, Nausea, dizziness, malaise, insomnia, aggression, agitation, and abnormal dreams [83]
Rivastigmine	(S)-N-Ethyl-N-methyl-3-[1-(dimethyl amino) ethyl]-6-methoxyindan-2-carboxamide	Reversibly binds to upregulated acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), resulting in increased acetylcholine in the subcortical region of the brain [84].	Nausea, vomiting, sleep disturbances, muscle cramps, weakness; long-term use increases the risk of death compared to patients treated with donepezil [84]
Memantine	3,5-dimethyltricyclo [3.3.1.1^3,7^] decane-1,3,5-triamine	It acts as an open-channel blocker, collegial and low-affinity for NMDA receptors, preventing excessive activation of the receptors and protecting against neuronal cell death induced by excitotoxicity [85, 86].	Weight gain, confusion, hypertension, nervous system disorders, dizziness [87, 88]

Name	IUPAC Name & Structure	Mechanism of Action	Side Effects
Reserpine	(3β,16β,17α,18β,20α)-11,17-dimethoxy-18-[(1-methylethyl) oxide]-20-[(1-methylethyl) amino] yohimban-16-carboxylic acid	Acting as an adrenergic uptake inhibitor irreversibly blocks the vesicular monoamine transporter-2 (VMAT-2) within the adrenergic neurotransmission pathway. This action leads to the depletion of catecholamines from both peripheral and central synapses. [89].	Sleepiness, depression, nasal congestion, faintness, arrhythmias, Nausea, arrhythmias, headache, syncope, gastric ulceration, vomiting, diarrhea, loss of appetite, dry mouth, male impotence, gastrointestinal upset; severe adverse effects: bradycardia, chest pain, hypotension[90]
Tacrine	1,2,3,4-tetrahydroacridin-9-amine	Reversibly inhibits acetylcholinesterase, slowing down the breakdown of acetylcholine [ACh) in the brain. It inhibits butyrylcholinesterase activity and acts as a histamine N-methyltransferase inhibitor [89].	Hepatotoxicity is a significant side effect, causing liver toxicity [90]

4. Non-drug therapy approach for Alzheimer's disease AD

Dementia, primarily caused by Alzheimer's disease [91], currently lacks a definitive cure, prompting ongoing endeavors to develop disease-modifying therapies and symptomatic treatments. Disease-modifying therapies target amyloid-beta and tau proteins and aim to improve cognition but have not shown significant success in halting or reversing AD progression. Symptomatic treatments like acetylcholinesterase inhibitors (AChEIs) manage cognitive and behavioral symptoms but have limited effects on the underlying disease process. Ongoing research explores novel targets such as inflammation and synaptic dysfunction, and combination therapies are gaining interest [92]. However, effective disease-modifying therapies addressing the underlying causes are still needed.

AD remains an untreatable condition, and current therapies provide limited benefits. Multifocal and multidisciplinary interventions are recommended to maximize the effects of AD treatment [91, 92].

Cognitive-Oriented Interventions, Physical Exercise, and Brain Stimulation Techniques

Cognitive-oriented interventions have gained attention for AD and can be categorized into cognitive exercise, cognitive encouragement, and personalized cognitive restoration [93]. Cognitive training focuses on improving specific cognitive domains through structured activities and exercises [94]. Cognitive stimulation promotes overall cognitive function through engaging activities like discussions, puzzles, and music therapy [95]. Individualized cognitive rehabilitation addresses specific cognitive difficulties and functional impairments through personalized strategies [96]. These interventions promote neuroplasticity, improve cognitive function, and enhance well-being [97, 98].

Physical exercise interventions have shown beneficial effects on brain health and overall physical well-being in AD [97]. Regular exercise reduces brain atrophy, improves cardiovascular fitness, and decreases dementia risk [97]. Exercise also reduces psychological and behavioral symptoms of dementia and enhances daily living actions [99, 100]. It may positively impact cognitive function and brain structures like the Hippocampus [99, 100].

Brain stimulation techniques, including DBS, tDCS, rTMS, TPS, and iTBS, can regulate cognitive functions in neuropsychiatric diseases [101-105]. DBS involves implanting electrodes to modulate neuronal activity [101]. tDCS applies weak electrical currents to alter neuronal excitability [102]. rTMS uses magnetic fields to stimulate specific brain areas [103]. TPS and iTBS utilize pulsed electromagnetic fields [104, 105]. While these techniques show promise, further research is needed to establish their efficacy, safety, and optimal protocols [101-105].

Nutrition Supplementations:

A 24-month study involving nutrient supplementation in individuals with prodromal Alzheimer's disease revealed positive outcomes in terms of cognition, function, and brain structure measurements. The comprehensive formula utilized in the study included DHA, EPA, vitamins B12, B6, C, E, and folic acid [106]. Moreover, cognitive and psychosocial functioning have been positively influenced by essential amino acids such as Phe, Lys, Leu, His, Ile, Trp, and Val, which affect neurotransmitter synthesis [107]. Furthermore, the administration of combined metabolic precursors (CMAs) containing glutathione precursors and NAD+ has shown cognitive improvement in individuals with AD [108].

Nonpharmacological interventions for AD encompass cognitive stimulation, physical exercise, social engagement, environmental modifications, music and art therapy, multisensory stimulation, and caregiver support. These interventions aim to improve symptom control and enhance the excellence of life for caregivers and patients [109].

5. Combination Therapy for the treatment of Alzheimer's disease AD

Combination therapy is being explored as a treatment approach for AD to overcome monotherapy limitations. Targeting a single molecular target is unlikely to modify AD pathophysiology and disease progression effectively. High doses of a single drug can lead to severe side effects. Combination therapy involves using drugs with different mechanisms of action to produce synergistic effects and better outcomes. Combining therapy can modify disease progression more effectively by addressing multiple targets simultaneously.

Additionally, using multiple drugs may allow for lower individual doses, reducing the risk of severe side effects. However, developing and implementing effective combination therapies for AD requires careful consideration of drug selection, dosages, and potential interactions. Ongoing research in this area holds promise for finding more effective treatment approaches for AD [109].

Table 3 Clinical studies conducted on combination therapy involving cholinesterase inhibitors and memantine for treating Alzheimer's.

Therapy	Alzheimer's Disease Status	Effects of Therapy
Memantine + ChEIs	severe	No noticeable variations were found in the rates of changes in the total volume of the brain during the two periods of the study. Additionally, memantine administration was associated with improved executive functioning abilities and a reduction in atrophy of the right Hippocampus [110].
Memantine + Rivastigmine	Mild to moderate	There were no statistically significant variations in efficacy observed between the treatment groups. Additionally, the different test groups noted no apparent disparities in tolerability and safety.[111]
Memantine + Rivastigmine	Mild-to-moderate	No significant differences in tolerability were observed between the treatment groups. Additionally, there were no noticeable disparities in cognition or global functioning among the various treatment groups [112].
Memantine + ChEIs	Probable	The intervention significantly prolonged the time until admission to a nursing home.[113]
Memantine + Rivastigmine	Mild-to-moderate and moderate-to-severe	Secondary memory progress was accompanied by notable enhancements in attention and executive function [114]
Memantine + ChEIs	Moderate to severe	The therapy significantly improved multiple measures, such as the Severe Impairment Battery and Clinician's Interview-Based Impression of Change Plus data. Furthermore, it was deemed safe and well-tolerated [115].
Memantine + ChEIs	Mild to moderate	No statistically significant variances were observed among the memantine and placebo groups regarding the consequence measures [116].
Memantine + Donepezil	Moderate to severe	Compared to monotherapy, the combination treatment demonstrated significant enhancements in the Severe Impairment Battery, a lesser decline in the AD Cooperative Daily Living Inventory Study-Activities, and

		improvements in the Clinic person's Interview-Based Impression of Change Plus data. [117]
Memantine + ChEIs	severe	Cognitive and functional impairment progressed slower in individuals receiving cognitive training than those receiving cholinesterase inhibitors or no treatment.[118]
Memantine + Rivastigmine	Moderately severe	Swapping from galantamine or Donepezil to rivastigmine has shown potential for improving behavior and understanding. Additionally, memantine may offer further benefits in this regard. [119]
Dextromethorphan + Quinidine	Moderately severe	Dextromethorphan reduces neuronal damage as well as neurodegeneration. [138]

Combination Therapies for AD: Synergistic Approaches Targeting Multiple Aspects of AD Pathology

Combination therapy involving different drug combinations has shown promise in the treatment of Alzheimer's disease (AD). One example is the combination of galantamine and memantine, which can potentially have a synergistic neuroprotective effect by working together in a similar cascade of excitotoxic [120].

A combination of memantine and nitroglycerin, specifically in the form of nitro memantine, has shown promising results in Alzheimer's disease (AD) mouse models. This combination has been observed to reverse brain connection losses and also restore the synapses to normal levels in a few months of treatment. [121].

Hybrid compounds that combine the donepezil pharmacophore (benzylpiperidines) through the 8-hydroxyquinoline component of the clioquinol have been developed. These compounds were designed to provide various beneficial effects, such as stopping the aggregation of Aβ, neutralizing free radicals, binding to metal ions, and blocking cholinesterase activity. [122].

A hybrid compound that combines rivastigmine and rasagiline has demonstrated several beneficial effects in mice. It exhibits reversible inhibition of both butyrylcholinesterase and acetylcholinesterase and irreversible inhibition of monoamine oxidase-B. Additionally, this compound possesses antioxidant properties and has been shown to protect against motor function and memory impairments in mice [123].

These examples highlight the potential benefits of combining different drugs with distinct mechanisms of action to target multiple aspects of AD pathology and improve treatment outcomes. However, it is important to note that further research and clinical trials are needed to evaluate the safety and efficacy of these combination therapies in humans.

Further Approaches for Alzheimer's Disease with Combination Therapies

No effective agent exists to stop or delay Alzheimer's disease. Investigational drugs targeting underlying processes like beta-amyloid and tau are being studied, but challenges remain. Research continues to find treatments that can slow or halt disease progression.

Table 4 Combination Approaches for Alzheimer's Disease

Combination	Observations
PBT2 and ChEIs	• Combining PBT2 with cholinesterase inhibitors (ChEIs) in early AD improves executive functions and lowers cerebrospinal fluid Aβ42 levels more than ChEIs alone. Suggesting potential benefits in early-stage AD patients. [124]
ChEIs/NMDAR Antagonists and Noradrenaline Reuptake Inhibitors	• The combination of atomoxetine with cholinesterase inhibitors (galantamine, Donepezil, rivastigmine) or an NMDAR antagonist (memantine) was generally well borne by patients with mild to moderately severe AD. However, this combination therapy did not lead to significant improvements in the clinical efficacy compared to monotherapy alone [125]
Neurotrophic Agents	• Combined treatment with Donepezil, cerebrolysin, and peptidergic drug has shown advantages over monotherapy with Donepezil alone [126]
Antioxidative Factors	• Imbalances between oxidants and antioxidants have been strongly related to several diseases, including AD [127] • Combination trials involving omega-3 fatty acids, vitamin B groups, and vitamin E are ineffective in treating certain conditions, including Alzheimer's disease [128-130].
Anti-inflammatory Drugs	• Elevated inflammatory signals are commonly observed in Alzheimer's disease [131] • Combination therapies involving ibuprofen, celecoxib, rofecoxib, and naproxen are more effective in treating specific conditions, including Alzheimer's disease [132]-[134].
Antidiabetic Drugs	• There is a close relationship between diabetes mellitus and cognitive impairment, including Alzheimer's disease [135] • In individuals with both type 2 diabetes and mild-to-moderate Alzheimer's disease, add-on therapy with insulin has been found to significantly reduce functional and cognitive decline compared to regular therapy without insulin [136].

6. Conclusion

In conclusion, the use of pharmacological agents in the treatment of Alzheimer's disease (AD) aims to target the underlying mechanisms and symptoms associated with the disease. Donepezil, rivastigmine, memantine, reserpine, and tacrine are some drugs commonly used to manage AD.

Rivastigmine and Donepezil exert their effects by inhibiting the enzyme acetylcholinesterase (AChE), leading to increased levels of acetylcholine in the brain. This action enhances cholinergic transmission, contributing to the therapeutic benefits of Alzheimer's disease. Studies have

demonstrated that these medications can enhance cognitive abilities in individuals with AD. However, they may trigger negative symptoms like queasiness, throwing up, and sleep problems.

Memantine acts as an uncompetitive NMDA receptor antagonist, preventing excessive activation of the receptors and protecting against excitotoxicity-induced neuronal cell death. It is often combined with acetylcholinesterase inhibitors to provide additive therapeutic effects. However, memantine can cause side effects such as weight gain, confusion, and dizziness.

Reserpine acts as an adrenergic uptake inhibitor and blocks the vesicular monoamine transporter-2 (VMAT-2), depleting catecholamines from synaptic vesicles. While it can effectively reduce symptoms of AD, reserpine may cause side effects such as nasal congestion, drowsiness, and gastrointestinal upset.

Tacrine reversibly inhibits acetylcholinesterase and acts as a histamine N-methyltransferase inhibitor. It has been used for AD treatment but is associated with significant hepatotoxicity and liver toxicity.

These pharmacological agents provide options for managing AD symptoms and improving cognitive function. However, it is crucial to carefully monitor patients for potential side effects and consider individual patient characteristics when selecting the appropriate treatment. Future research and development of novel therapies are needed to provide more safe and effective options for Alzheimer's disease treatment. Multicomponent profile of Herbal drugs are safe and side effect free drugs. Based on mode of action or pharmacological effect repurposing of drugs i.e., in between allopathic drugs or in between allopathic and herbal drugs could be a novel approach for further development of suitable drug to potential management of Alzheimer disease.

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