Degenerative Neurological and Neuromuscular Disease

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REVIEW

Review of Pharmacotherapeutic Targets in Alzheimer's Disease and Its Management Using Traditional Medicinal Plants

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and impaired daily functioning. While there is currently no cure for AD, several pharmacotherapeutic targets and management strategies have been explored. Additionally, traditional medicinal plants have gained attention for their potential role in AD management. Pharmacotherapeutic targets in AD include amyloid-beta (Aβ) aggregation, tau protein hyperphosphorylation, neuroinflammation, oxidative stress, and cholinergic dysfunction. Traditional medicinal plants, such as *Ginkgo biloba, Huperzia serrata, Curcuma longa* (turmeric), and Panax ginseng, have demonstrated the ability to modulate these targets through their bioactive compounds. *Ginkgo biloba*, for instance, contains flavonoids and terpenoids that exhibit neuroprotective effects by reducing Aβ deposition and enhancing cerebral blood flow. *Huperzia serrata*, a natural source of huperzine A, has acetylcholinesterase-inhibiting properties, thus improving cholinergic function. *Curcuma longa*, enriched with curcumin, exhibits anti-inflammatory and antioxidant effects, potentially mitigating neuroinflammation and oxidative stress. Panax ginseng's ginsenosides have shown neuroprotective and anti-amyloidogenic properties. The investigation of traditional medicinal plants as a complementary approach to AD management offers several advantages, including a lower risk of adverse effects and potential multi-target interactions. Furthermore, the cultural knowledge and utilization of these plants provide a rich source of information for the development of new therapies. However, further research is necessary to elucidate the precise mechanisms of action, standardize preparations, and assess the safety and efficacy of these natural remedies. Integrating traditional medicinal-plant-based therapies with modern pharmacotherapies may hold the key to a more comprehensive and effective approach to AD treatment. This review aims to explore the pharmacotherapeutic targets in AD and assess the potential of traditional medicinal plants in its management.

Keywords: Alzheimer's disease, acetylcholinesterase, amyloid beta, tau protein, traditional medicine, Ayurvedic herbs, acetylcholinesterase inhibitors, neurodegenerative disorders, cognition

Introduction

Alzheimer's disease (AD) is one of the most prevalent types of dementia, a neurocognitive disease that causes memory loss and a behavioral disorder that affects daily life. Dr. Alois Alzheimer, a German psychiatrist, made the initial diagnosis of the illness in 1901 and noted abnormalities in the patient's cognitive abilities. After performing an autopsy, he noted shrinkage of the patient's brain and atrophied nerve cells, diagnosing the condition as AD.[1] Nearly 50 million people worldwide are currently impacted by AD. A World Health Organization study reported that 152 million people will be suffering from AD worldwide by 2050.[2] World economies are affected by dementia, with a cost of USD 1.3

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trillion in 2019.[3,4] Furthermore, In 2017, 4 million people died due to obesity and obesity-related complications, with 41.9% of the US population being deemed obese.[5] Recently research has linked the obesity epidemic to multiple detrimental chronic conditions. As of 2020, 55 million people have been diagnosed with dementia, and by 2050.[6,7] This number is expected to increase to 139 million because of the steady rise in obesity prevalence.[8] The prevalence is predicted to be 58% in low- and middle-income nations, which is expected to increase to 63% in 2030 and 68% in 2050. South Asian nations, like China and India, where a case is reported every four seconds, have the highest anticipated rates of AD cases. India currently has 4 million cases of this dreadful and fatal disease on record.[9] Dementia is a result of AD in older people. India has a growing elderly population as a result of longer lifespans and decreasing fertility rates. A substantial increase in dementia prevalence is anticipated as a result of 19.1% of the population being over the age of 60, as dementia is the primary cause of impairment in older individuals. As the number of elderly individuals increases, it follows that the burden of dementia will increase. Therefore, South Asian nations like China and India will significantly contribute to the rise of dementia due to their vast populations.[10]

Short-term memory loss, psychiatric symptoms, cognitive dysfunctions, physical disability, behavioral problems, and early mortality are frequently the first clinical signs of this condition.[11] AD's characteristic symptoms are progressive loss of memory, poor managerial tasks, and difficulty accomplishing everyday work.[12] Furthermore, 20–30% of patients with early AD experience severe mood and depressive symptom irregularities.[13] Significant memory loss, hallucinations, confusion, and a lack of independence are common in people with advanced AD.[14] Cholinergic, amyloid, tau, excitotoxicity, Apolipoprotein E (ApoE), oxidative stress, cAMP Response Element-Binding Protein (CREB) signaling mechanisms, insulin resistance, and others are currently recognized clinical and physiological symptoms.[15] Only drugs that alleviate symptoms, such as acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, and rivastigmine) and N-methyl D-aspartate (NMDA) receptor blockers (memantine), have been given FDA approval for clinical use for AD patients.[16–18] Because no single drug has been identified to control the symptoms of AD, management is thought to be difficult. The majority of existing AD treatments address neurological and behavioral problems that may impede the disease's progression. There is a need for research into alternative therapy strategies for AD because the current system of AD treatment has some limitations, such as unpleasant effects, limited efficacy, and low patient compliance.[19] Due to its natural approach and absence of side effects in comparison to contemporary allopathic methods, herbal and traditional therapies, like traditional Indian medicine (Ayurveda) and traditional Chinese medicine (TCM), are being explored.[20]

Although the direct research data on symptoms of AD or dementia have not been specifically reported in the Ayurvedic literature, the signs of memory loss and amnesia are available in it.[21,22] Numerous Ayurvedic medicinal herbs with nootropic properties have demonstrated potential effectiveness in neuropsychopharmacology and have been demonstrated to be neuroprotective via neural network regeneration.[23,24] Traditional Ayurvedic treatments for illnesses related to memory and neurodegenerative disorders have been validated by researchers.[25,26]

Bearing in mind all of these points, the review delivers a brief statement and understanding of the various pathogenesis factors involved in the progression of dementia and AD. In addition, clear data concerning the application of phytocompounds in the treatment of AD and its related symptoms are scattered. We aim to link this space and provide research data concerning the same. Thus, this report focuses on highlighting the different traditional medicinal herbs, phytoconstituents, and therapeutic uses in AD as beneficial involvements that might head the advance of novel potential molecules for AD. In addition, this paper mentions FDA-approved herbs and future prospects.

Current Pathogenesis Involved in AD

It has been suggested that a variety of factors, including low levels of the neurotransmitter acetylcholine (ACh), deposition of the amyloid-β (Aβ) peptide, accumulation of hyperphosphorylated tau microtubule protein, excitotoxic hypothesis, oxidative stress, ApoE hypothesis, glycogen synthase kinase hypothesis, and the chronic inflammation hypothesis, play significant functions in the pathophysiology of AD. Some potential hypotheses have been established to examine the AD mechanism processes in light of these significant factors.[27–29]

The Cholinergic Hypothesis

AD is characterized by a loss of cognitive function in the brain's ACh neurotransmitter-producing neurons. The most widely accepted pathophysiology of AD is the severe degeneration of cholinergic neurons, which eventually changes into gradual loss in the later stages of the illness. Research has reported that cholinesterase is a category of serine hydrolase, which has two types: AChE and butyrylcholinesterase (BChE).[30,31] Firstly, the AChE hydrolyzes the ACh neurotransmitter into acetic acid and choline to regulate cognitive functioning.[32,33] Memory loss, reduced attention, and cognitive deterioration are all brought on by the low levels of ACh in cholinergic synapses.[34] In addition, the nucleus basalis of Meynert (NBM) cholinergic neurons are located in the substantia innominate and along the ventral extent of the basal forebrain. In the 1970s, the NBM was recognized as the cholinergic center in the brain with neurons sending cholinergic inputs to the neocortex.[35] Based on the cholinergic hypothesis, neuronal damage of NBM declines the concentration of cortical ACh subsequently causing cognitive impairments.[36] Mesulam et al described the 4 cholinergic cell groups (Ch1–Ch4) in the basal forebrain during the experiment on AChEE and choline acetyltransferase.[37] Among them, more than 90% of neurons of NBM are cholinergic with Ch4 which contributes to the greater cholinergic network in the basal forebrain for the production of ACh.[38,39] Acetyl CoA, which is produced from the breakdown of glucose (glycolysis) or citrate (pyruvate-oxidase system), catalyzes the biosynthesis of ACh.[40] Further, the vesicular ACh transporter (VAChT) in nerve endings carries ACh into synaptic vesicles, which serve as storage vesicles. After synthesis, ACh is released through depolarization of the neuronal membrane at the neural synapse, where it is hydrolyzed by AChE into choline and acetate.[41] This occurs in the presence of extracellular calcium ions. The reuptake mechanism transports the choline back to the presynaptic neuron, as mentioned in Figure 1.[42] In addition, AChE exists in two molecular forms: (1) an asymmetric form that is preferentially localized in the neuromuscular junction; and (2) a globular form that is anchored to the membrane of the hydrophobic domain. Globular membrane-bound tetrameric form G4 is more predominant in the brain than the monomeric G1 form.[43,44] However, during AD, the ratio of G1 and G4 is disturbed by the selective loss of the G4 form in the hippocampal and cortex regions of the brain. Therefore, the predominantly available monomeric G1 form could be an appropriate target for AChEIs.[45,46]

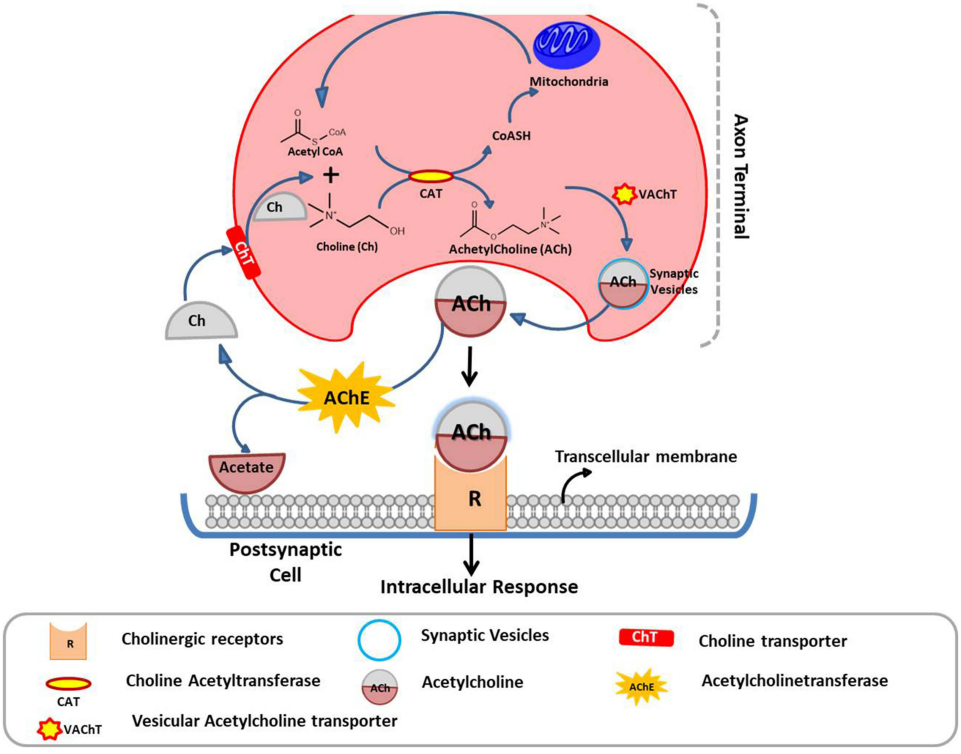

Figure 1 Biosynthesis of acetylcholine and cholinergic transmission.

BChE is the non-specific type of enzyme that catalyzes choline ester hydrolysis, which is also known as pseudo or non-neuronal cholinesterase. BChE is predominantly found in plasma, with approximately 99% of total plasma cholinesterase,[15] while AChE is primarily located in neural tissues. Structurally, BChE shares 65% amino acid sequence homology with AChE, apart from functional similarities.[47] In addition, the BChE level was reported to be increased more exponentially than AChE over the course of AD progression.[48,49] As such, BChE plays a significant role in cholinergic transmission and is involved in the hydrolysis of ACh, which makes BChE an important therapeutic target in AD.[50] However, recent studies have indicated that the inhibition of BChE might also have some role in the treatment of AD. However, there are still numerous challenges, as specific BChEIs could result in adverse effects because of the peripheral inhibition of ACh, and specific AChEIs without BChE inhibition properties may not be disease-modifying.[18,51,52]

The Amyloid Hypothesis

For many years, this hypothesis has been a key idea and the accepted pathogenic cause of AD. α-secretase, which has neuroprotective effects, produces amyloid precursors protein along with the C83-subunit (non-amyloidogenic pathway), and BACE-1, which generates APP along with the C99-subunit (amyloidogenic pathway), cleaves APP (amyloid precursor protein) under normal conditions.[53] Then, the secretase enzymes split the subunits into the Aβ-42 peptide, which builds up amyloid peptides into an insoluble neurotoxic Aβ sheet and causes the death of neuronal cells; It also substantiates cognitive dysfunctions. It is typically identified by an amyloid cascade, which refers to a variety of pathophysiologic abnormalities caused by excessive amyloid-level accumulation in the brain.[54,55]

APP is a substrate of Aβ peptides that are typically broken by the α- and γ-secretase enzymes, as depicted in Figure 2. The 42 amino acids produced by BACE-1's cleavage and γ-secretase's subsequent action aggregate extracellularly to form an insoluble toxic peptide known as Aβ plaque. Additionally, plaque deposition originates through the gradual growth of Aβ monomer in the brain due to an increase in production. Cognitive dysfunctions are facilitated by a complicated chain of events that include inflammatory responses, microglia activation, and Aβaggregation. Additionally, AChE causes cognitive dysfunctions by causing the aggregation and deposition of insoluble Aβfibrils by generating an AChE-A complex.[56,57] Necroptosis and NLRP3 inflammasome are the common simulatory factors for

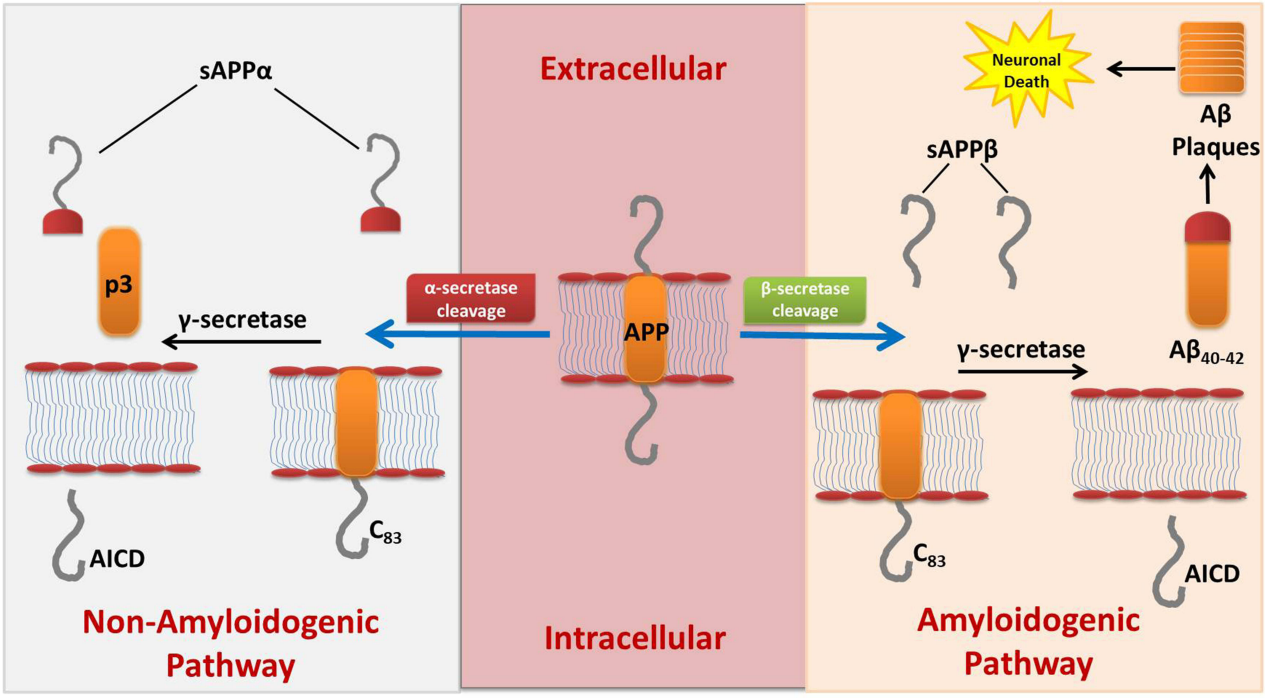

Figure 2 α-, β-, and γ-secretase pathway.

neuroinflammation found in the AD brain which leads to apoptosis and autophagy resulting in neuronal cell death.[58] Aggregates of tau and Aβ are responsible factors leading to neurotoxicity, in excess results in inflammation and neuronal cell death.[59] Several other genetic factors could give rise to Aβ production and deposition. Genetic mutation and polymorphism of presenilins (PSEN1 and PSEN2) are the most important factors that could raise the levels of Aβ.[60] PSEN1 and PSEN2 encode for presenilin 1 and 2 genes, respectively. Presenilins are the catalytic subunit of γ-secretase responsible for cleavage of APP to Aβ.[61] Some theories also indicate that Aβ could initiate the pathological processes of AD, such as propagation of tau aggregation, downstream toxicity, and neurodegeneration, but it is not necessarily responsible for disease progression.[62]

Tau Protein Hypothesis

The stabilization of microtubules, which is crucial for maintaining cell integrity, is caused by the tau protein. A tau protein, which has 84 sites comprising serine/threonine/tyrosine, phosphorylates the microtubules in the axonal membrane to stabilize them in normal conditions.[63] The excessive hyperphosphorylation of tau protein in AD is facilitated by the overstimulation of kinases and inactivation of phosphatases. These hyperphosphorylated states create pairings in knots, which are known as paired helical filaments. These filaments then give rise to insoluble intracellular NFTs (Neurofibrillary tangles), which interrupt neuronal plasticity and cognitive impairment (Figure 3).[64] In addition, many molecular parameters have been investigated to express the function of tau–tau interactions and their hyperphosphorylation in AD.[65] The various factors are involved in the activation of alarming signals that affect the cascade of events in microglial cells and astrocytes, leading to the release of NF-kB and overproduction of pro-inflammatory mediators, such as TNF-α and interleukins (ILs), causing the inflammatory reactions in brain cells and neuritic injury as well as causes neuronal death.[15] The inflammatory mediators also stimulate the MAP kinase and cyclin-dependent kinase-5 (CDK-5) and subsequently produce tau phosphorylation.[66,67] Studies have found that overstimulation of kinases and inactivation of phosphatases could direct the initiation of tau hyperphosphorylation.

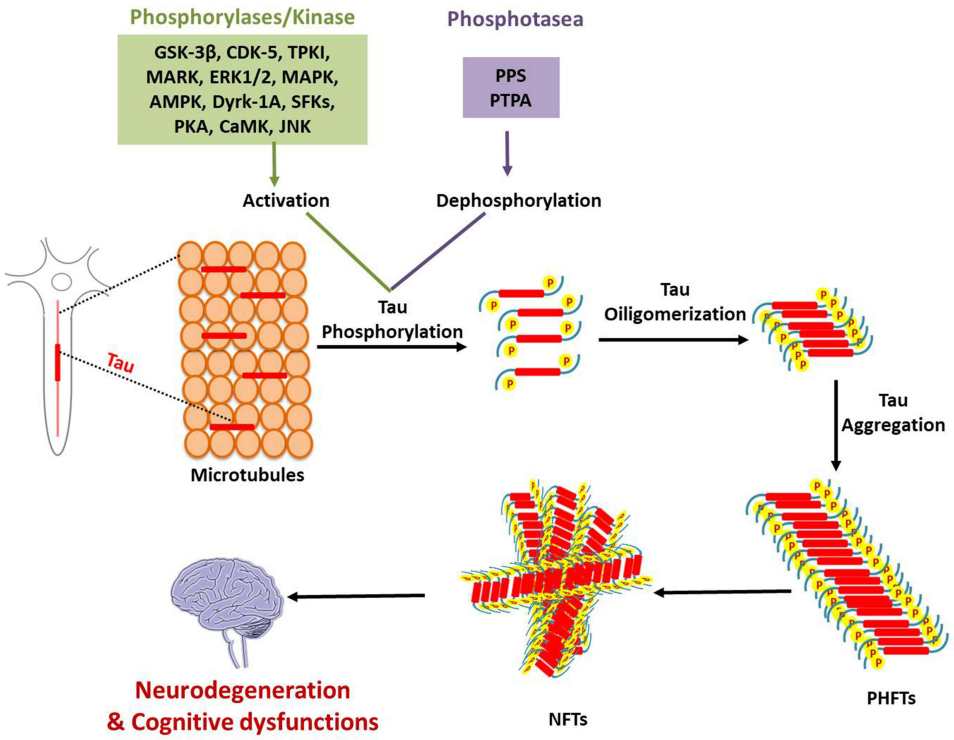

Figure 3 Tau hypothesis cascade.

Glutamatergic or Excitotoxic Hypothesis

N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors are generally two kinds of glutamate receptors that operate as excitatory neurotransmitters in the hippocampus and cortex. In healthy individuals, glutamate binds to NMDA receptors, which causes depolarization and inhibits calcium and sodium ions from entering resting neuronal cells by blocking cationic channels. When receptors are overstimulated in AD conditions, calcium enters the cells, delaying neuronal transmission and causing neurodegeneration, neuritic injury, and cell death.[68] In addition, excitotoxicity is highly increased with the reduction in the level of intracellular energy during AD. The reduced glucose metabolism and ATP-dependent membrane transport lead to impaired neuronal functionalities and an imbalance in sodium and calcium levels in neuronal cells.[69] The excessive calcium influx was also reported for initiating other mediators, such as the generation of free radicals and inflammatory mediators (such as prostaglandins and leukotrienes), through the activation of phospholipase A2 (PLA2) enzyme.[70] The idea of slowing down excitotoxicity has not gone away but is limited to only symptomatic relief in AD. Still, several researchers continue to believe that blocking excitotoxicity might be more beneficial in AD.

Oxidative Stress Hypothesis

Due to their higher oxygen consumption rates, higher lipid contents, and lower levels of antioxidant enzymes compared to those of other organs, neurons are more susceptible to free radicals (also known as reactive oxygen species, or ROSs, or reactive nitrogen species, or RNSs), which harm neuronal cells.[71] Numerous mechanisms, including the buildup and deposition of Aβ-peptides, lipid peroxidation, protein oxidation, DNA oxidation, and mitochondrial dysfunctions, potentiate the oxidative damage of neurons in AD circumstances.[72] The literature has also established that oxidative stress has a role in AD-related neurodegeneration and aging.[73] The main negative variables that cause oxidative stress are an imbalanced generation of free radicals (ROS and RNS) and a lack of antioxidant enzymes. Protein oxidation and lipid peroxidation are brought on by the generation of excessive free radicals, which ultimately results in reduced cognitive processes. By accumulating and depositing Aβ, the ROSs and RNSs play a vital role in AD progression.[74] The brain is more susceptible to oxidative stress than other organs owing to its high oxygen consumption rate, high lipid concentration, and lack of antioxidant enzymes.[71] Numerous causes, including defective mitochondrial energy metabolism,[75] DNA oxidation,[76] Ca^{2+} homeostasis, abnormal protein accumulation, altered proteasome functions, membrane damage, and an abundance of trace elements and transition metals (including aluminum, mercury, copper, zinc, and iron), contribute to oxidative damage in the brain.[77] In addition, oxidative stress rapidly activates the microglia because it's the key factor of neuroinflammation. The stimulation and accumulation of activated microglia surrounding the damaged zone results in the secretion of various inflammatory, cytotoxic elements and free radicals that are responsible for neuroinflammation and neurodegeneration. Thus, oxidative stress and neuroinflammation are interconnected and show an essential function in the progression of AD.[78,79] Also, There is still much research effort that needs to be taken to simplify the complex oxidative stress hypothesis and its correlation with AD. However, its role in the early stage of AD cannot be ignored.

Apolipoprotein E Hypothesis

The ApoE is the glycoprotein consisting of 299 amino acid residues that are generated by astrocytes, and it also shows a key function in the transportation of cholesterol through ApoE receptors.[80] These types of receptors are associated with the low-density lipoprotein (LDL) gene family and are situated on chromosome number 19. The ApoE gene is generally found in three polymorphic forms (ApoE2; ε2, ApoE3; ε3, ApoE4; ε4), which are known as alleles.[81] In addition, numerous studies have noted the existence of the ApoE ε4 allele, which is mostly responsible for the pathogenesis of AD. On the other hand, the ε2 allele reduces the risk of occurrence of AD. The advanced AD stage is typically linked to genetic risk factors affecting the late onset of AD. In the etiology of AD, ε4 decreases the Aβ clearance and increases Aβ aggregation, including neuroinflammation, tauopathy, and a reduced rate of glucose metabolism, which are also linked to the ApoE ε4 allele.[82]

Glycogen Synthase Kinase Hypothesis

GSK-3 is kind of a microtubule-binding serine/threonine kinase enzyme found in both α- and β-isoforms. GSK-3β is the decisive type of kinase-dependent enzyme concerned with the hyperphosphorylation of microtubule tau protein allied with AD. It also encourages the production of senile plaques and Aβ peptide deposits and ultimately causes cognitive dysfunctions.[83] In addition, GSK-3β is assessed as a valuable diagnostic biomarker for the diagnosis of AD at the early stage.[84] Various studies have also displayed that the connection between GSK-3β and oxidative stress causes neuroinflammation and AD.[85] GSK-3β has been recognized as the mechanism of apoptosis and cell death by controlling several transcription parameters, including heat shock factor-1 (HSF-1), cyclic-AMP-response element-binding protein (CREB), and nuclear factor kappa B (NF-kB).[86] These transcription factors have shown an important function in neurodegeneration and proved the connection of GSK-3β in the progression of AD.[87]

The Chronic Inflammation Hypothesis

The chronic inflammatory state is also connected with Aβ to enhance the chances of neuronal injury and neurodegeneration.[88] Plaque deposition promotes microglia, which are susceptible to neuronal damage and neurodegenerative diseases, to become inflamed.[89] In AD, it triggers the release of inflammatory chemicals, such as cytokines, ROSs, and proteinases, which ultimately result in the death of neuronal cells.[90] A study further reported that augmented COX-2 expression causes the NMDA-mediated receptor excitotoxicity. Evidence shows that the risk of AD declines considerably in the person taking non-steroidal anti-inflammatory drugs (NSAIDs).[91] In addition, NSAIDs with antithrombotic activity have also been observed to defend against the injury of neurons and might be a beneficial and satisfying strategy to cure AD.[92] The current literatures recommendthat COX-1/2 gene expression and Aβ aggregation are not interconnected and that the valuable outcomes of NSAIDs could be because of diverse processes other than COX inhibition.[41,92,93] Therefore, there is still a prerequisite to try this approach to attain the extra scientific result.

Current Neurotherapeutics for AD

There is currently no treatment for AD. There are numerous drugs, nevertheless, that have been shown to relieve the disease's symptoms. The Food and Drug Administration (FDA) has recommended cholinesterase inhibitors (ChEIs) and NMDA receptor antagonists in the past to treat the symptoms of AD. Additionally, promising therapy alternatives are now being tested in humans, although their safety, efficacy, and benefits have not yet been discovered.

The Cholinesterase Inhibitors

ACh is an essential cholinergic neurotransmitter in the control of memory and learning processes. Three ChEIs (donepezil, rivastigmine, and galantamine) have been given USFDA approval to treat AD symptoms by increasing ACh levels because they are responsible for inhibiting ChEs by hydrolyzing ACh (Table 1).[94] Although the first USFDA approved another drug, tacrine, its use is restricted due to severe adverse effects, such as loss of appetite, diarrhea, cramping of the smooth muscle in the abdomen, vomiting, nausea, and hepatotoxicity (Figure 4).[95]

On the other hand, donepezil is generally prescribed for the treatment of all the stages of the disease. The other two drugs (rivastigmine and galantamine) are only used to manage mild to moderate AD.[96] Donepezil is a highly selective

Table 1 USFDA-Approved Medicines for the Management of AD

Drug	Half-Life (h); T_{max} (h)	Absorption (%)	Distribution& Protein Binding (%)	Type	Treatment Stage
Rivastigmine	2; 0.8–1.7	40	40	AChE and BChE inhibitor	Mild to moderate
Galantamine	5–7; 0.5–1.5	85–100	18	AChE and BChE inhibitor	Mild to moderate
Donepezil	60–90; 3–5	100	96	Selective AChE inhibitor	All stages
Memantine	60–80; 3–7	100	45	NMDA Receptor Antagonist	Moderate to severe

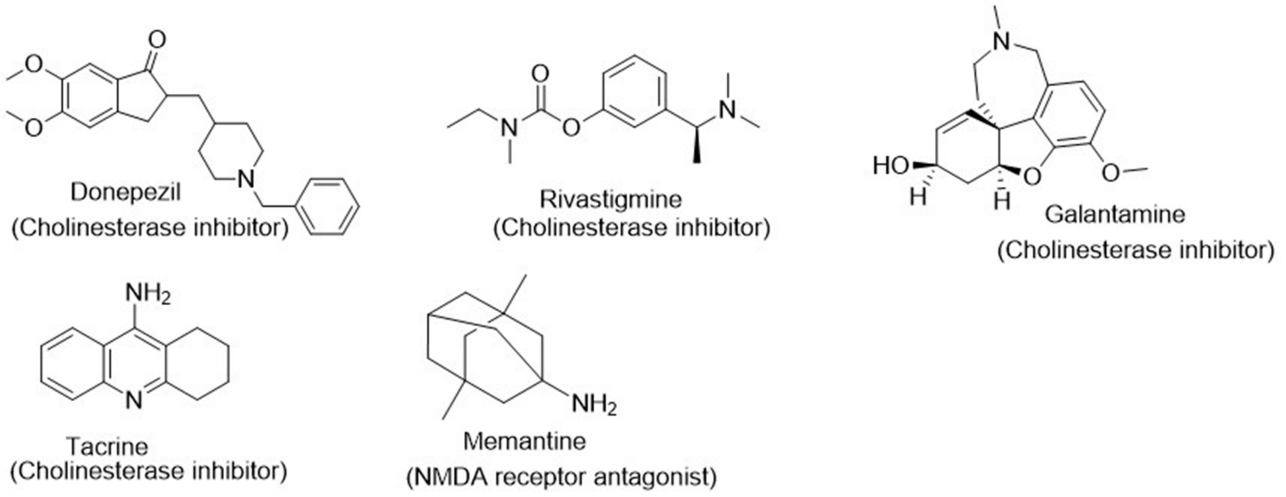

Figure 4 Chemical structures of FDA-approved drugs for the treatment of AD.

AChE inhibitor having lesser cholinergic side effects and is well-tolerated compared to others. This drug also shows a high affinity because of its strong binding affinity with the CAS and PAS residues of AChE.[97] Rivastigmine also has dual cholinesterase inhibitory potency with more selectivity for BChE over AChE. It has a relatively long duration of action and is hydrolyzed to form a phenolic cleavage product and a carbamoylated side product at the esteratic site of AChE. This carbamoyl derivative leaves the active site very slowly. Hence, the drug has been called a 'pseudo-irreversible' AChE inhibitor.[98] Also, galantamine has a dual mode of action on ChEs and is shown as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs). It binds to distinct sites on α subunits of nAChRs and potentiates the frequency of channel opening in response to ACh and nicotine agonist stimulation without interfering with the binding of these ligands to the receptors.[99,100] These marketed drugs show the most frequent adverse reactions, such as appetite loss, vomiting, increased bowel frequency, and nausea, which prevent their use in more advanced stages of the disorder. These drugs only alleviate symptoms, and they cannot halt disease progression. Therefore, they have restricted the possibility of AD intervention. There is no potential among anti-AD drugs, and the suitable medicine is chosen depending on the dosage form, route of administration, and acceptance of the AD patient.

In addition, a naturally derived cholinergic inhibitor, huperzine (source—*Huperzia serrata*), showed potential efficacy with high oral bioavailability (>96%) against AChE in a reversible manner. China has approved it for the treatment of AD.[101] It also showed modest activities in the USA during Phase II, but a clinically considerable effect was observed in AD. Another plant-derived product, galanin (source—rhizomes of *Alpinia officinarum*), has shown significant potential inhibition action against AChE,[102] but toxicity studies have not been conducted to date.

Other than the naturally derived cholinergic inhibitors, many hybrid ChEIs have been developed, such as the donepezil–AP2238 hybrid, which has a potential binding affinity against the CAS and PAS regions of AChE, whereas AP 2238 hybrid has inhibited the AChE with greater ability to inhibit Aβ deposition in comparison to donepezil.[103] There have been numerous hybrid derivatives (donepezil–tacrine hybrid, tacrine–ferulic acid hybrid, and tacrine–8-hydroxy-quinoline hybrids) reported in the literature.

Other than these ChEIs, muscarinic receptor agonists (drugs that mimic the pharmacological action of ACh) have been included for treatment via stimulation of these receptors (muscarinic receptor 1; M1 and muscarinic receptor 4; M4) to improve neurocognitive symptoms.[104] However, these strategies have been unsuccessful at clinical trial phases because of serious adverse effects. Nicotinic receptor agonists have also been developed to enhance learning and memory in AD patients by halting neurodegeneration.[105] These antagonistic problems created very thoughtful queries regarding the effective utilization of receptor-based agonists for the management of AD.[106]

NMDA Receptor Antagonist

The NMDA antagonist "memantine" is advised for the treatment of moderate to severe AD because it blocks the NMDA receptor and protects the nerves from overstimulation (Table 1 and Figure 4). When other ChEIs are co-administered, memantine also displays neurotoxicity and psychological issues that are exacerbated.[107] However, during the advanced stage of AD, it is the least successful in providing a total cure or altering the underlying disease process. A few non-competitive NMDA receptor blockers (Neramexane and Ifenprodil) also halted the dysfunction of transmission of nerve impulses and inhibited the Aβ-induced aggregation in AD.[108] They showed rapid off-rate kinetics, uncompetitive inhibition property, and little affinity to maintain the role of the receptor.[109] NMDA receptor antagonists exhibited therapeutic effects earlier but were then unsuccessful in clinical trials because of their side effects and nonselective blocking of the NMDA receptor.

Therefore, comprehensive information and significant scientific knowledge about the composite structure of the NMDA receptor are required to design and develop potential inhibitors against its receptor. The literature suggests that the crystal structure has an extracellular N-terminal domain and agonist-binding domain with various subunits, such as GluN1, GluN2, and GluN3. The GluN1 subunit is mostly joined by many GluN2 subunits. In the agonist-binding domain, GluN2 binds to glutamate residue, while GluN1 and GluN3 bind to glycine.[110]

Current Approaches to Treat AD

Instead of using single-target therapies, different multi-targeted ligand methods are currently being used to treat AD. AChE inhibitors, 5-HT6 antagonists, microtubule stabilization, anti-tau immunotherapy, AChE inhibitors, Aβ aggregation inhibitors, tau aggregation and hyperphosphorylation inhibitors, chelate metal ions inhibitors, and agents that scavenge free radicals simultaneously are some of the targets that are currently receiving more attention.[111] Although these current methods are only partially effective in managing AD,[68] current neurotherapeutics put more emphasis on reducing its symptoms than on slowing the disease's progression.

Current Scenarios of Drugs in Clinical Trials

Several initiatives have been made over the past 20 years towards the discovery of novel therapies for the successful management of AD. Although metrifonate and tesofensine were found to be effective in treating AD, they were removed from clinical studies due to their higher-dose toxicity and lack of clinical efficacy. In phase studies, natural huperzine A, a ChEI, had a negligible impact. A nutraceutical supplement called huperzine A is used to improve memory.[112] Some disease-modifying compounds have been reported to have failed in clinical trials, including gantenerumab, crenezumab from Roche, solanezumab from Eli Lilly, and bapineuzumab from Pfizer.[113]

Function of Traditional and Complementary Remedies

Adopting an integrated strategy can improve the health of the AD brain because although allopathic or chemical-based medications generally reduce the symptoms, they have limited effectiveness and severe adverse side reactions.[114] A few alternative therapies include acupuncture, meditation, yoga, dietary advice, and vitamins that are employed to alleviate and manage the warning signs of AD and other related disorders. Popular culinary spices, like ginger, cinnamon, sage, turmeric, and rosemary, have phytochemicals that can help prevent AD and neurodegenerative disorders.[115] It should be noted that no evidence-based recommendations are currently available due to the lack of significant studies on the overall therapeutic advantages and mechanisms of these interventions. On the other hand, TCM and Indian Ayurvedic herbal systems have recognized a variety of medicinal herbs and plants that may be brought into play to revive the neurocognitive side reactions. For example, *Panax notoginseng* containing ginsenosides (Rg1 and Rb1) generally enhanced learning and remembrance abilities in AD mice.[116] Notoginsenoside R1 has been reported to improve neuronal excitability, synaptic plasticity, and memory impairment and to decrease Aβ-induced toxicity.[117] Furthermore, some herbal extracts, like galantamine and huperzine, are also identified to be successful treatments for avoiding AD etiology.[118] Alongside medicinal formulations and dosage forms, Ayurveda has aided numerous exceptional medication processes in the management of AD, and it is also consulted in this review paper.[21]

Principle of AD in Ayurveda

Ayurveda is an ancient science of life with an integrated approach to health and customized healing. It is one of the healthcare systems, and it is a customized, comprehensive medical system with strong logical and philosophical underpinnings that seeks to cultivate and bring harmony to people's minds, bodies, and souls. According to Ayurveda, *Tridosha* (three matters of the universe: *asvata* (wind), *pitta* (bile), and *Kapha* (phlegm)) and *Triguna* (integral elements of the mind) are bioenergies that modulate the biological and psychobehavioral processes in human beings. The imbalance of *Tridosha* and *Triguna* may create a detrimental effect on the *Indriya* (mental and motor systems), *Manas* (psyche), and *Buddhi* (intellect); subsequently, it will deteriorate the learning ability.[119] AD cannot be precisely compared to any medical issue as defined in Ayurveda. However, in Ayurvedic medicine, classic *Smritinasha* (memory loss) is observed as a prodromal sign of *Jara* (aging). In *Jaravastha* (old age; begins at the age of 60), the abilities to store memory and other mental skills degrade spontaneously. *Smritibhramsha* (disrupted cognition) is also defined as a sign of disease, while Smriti is attenuated by Rajas (zeal) and *Tamas* (ambiguity). Hence, dementia might be considered *Jarajanya, Smriti bhramsha* based on Ayurvedic theories.[120] Ayurveda characterizes neurological disorders as *Vata Vyadhi*, which are crucial to manage due to their seriousness and treated with intensive *panchakarma* (biopurification) and supportive remedies administered by competent medical professionals.[121] The detection and appropriate clinical treatment of symptoms of neurocognitive diseases involve a comprehensive clinical understanding. There are two Ayurvedic strategies for the treatment of AD. One is the establishment of a healthy balance of *Tridosha* and *Triguna* for supporting mental abilities, and the second is the encouragement of healthy aging with *Rasayana* (rejuvenation) medicines or psychological therapies.[122,123]

Ayurveda's Approaches to Treating AD

The standard care in Ayurveda for the management of mental illness is in two ways; one is the pharmacological method, also known as *Yuktivyapashraya Chikitsa* (rationale therapy/medical treatment), and the second is the non-pharmacological method, which is also known as *Daivavyapashraya Chikitsa* (spiritual healing/mantra therapy) as well as *Satvavajaya Chikitsa* (psychotherapy/counseling/yoga/meditation).[124] These therapy techniques are frequently used in Indian Ayurveda to mitigate AD behavior, such as anger, aggression, despondency, restlessness, and wandering. The objectives of Ayurvedic *Rasayana* therapy include extending life and improving memory, physical stamina, senses, physical beauty, and linguistic ability.[125] Ayurveda has also suggested that a controlled lifestyle, a healthy diet, psychological support, *Rasayanas*, and psychotherapies are the most efficient strategies to halt and treat AD and other neurological diseases (Figure 5).

Figure 5 Ayurveda's approaches to treating AD.

Different principles govern how the medical systems of modern medicine and Ayurveda operate. Recently marketed synthesized drugs only provide symptomatic relief for 1 to 4 years for the treatment of mild-moderate AD. These synthetic regimens show many types of adverse effects, and they also do not halt the factors that are responsible for disease progression.[41,48,72,126] On the other hand, Ayurvedic treatment uses a holistic approach (it cares for one's psychological, physical, religious, and cultural well-being) and balances the Tridosha to treat the illness's fundamental causes in the body, making the cure irreversible and permanent. When used appropriately, Ayurvedic ideas can offer effective AD control and therapy.[21]

Ayurvedic Medicinal Plants Used in AD

Different kinds of medicinal plants and their formulations have been used since ancient times to enhance remembrance and cognitive abilities (Figure 6). These plants have therapeutic potential, the capacity to inhibit AChE activity, anti-inflammatory and antioxidant qualities, the capacity to prevent Aβ protein aggregation, and the capacity to hyperphosphorylate the tau proteins. They also have chelating activities for redox metals. Medicinal plants with bioactive components have shown potential beneficial effects against dementia and AD.[127] Additionally, natural chemicals differ in both their action and structure; it is not pretentious to discover anti-AD remedies from natural herbal products.[128] Additionally, the FDA now only approves a few medicines for the treatment and diagnosis of AD.[129] Here, we are more focused on mainly current studies on the prospective benefits of employing a variety of traditional medicinal plants and their phytoconstituents to treat AD.

Thus, the therapeutic value of the important Ayurvedic single medicinal plants is discussed and shown in Table 2 concerning their various mechanisms, such as anti-inflammatory properties, antioxidant properties, anti-ChEs properties, anti-Aβ aggregation, anti-tau aggregation, microtubule stabilizing, β-secretase inhibition, free radical scavenger neuroprotective properties, antiapoptotic properties, and nootropic and memory-enhancing properties.[130]

In addition, there are currently five FDA-approved medicinal plants that can be used against AD. Among them, rivastigmine, which is derived from the plant Physostigma venenensis (Leguminosae), was given the brand name Exelon by the FDA in 2000, and it is intended to inhibit AChE activity in the hippocampal and cortex regions.[225] Furthermore, the FDA approved galantamine, also known as Razadyne, in 2001.[226] It is derived from the Amaryllidaceae plant *Lycoris radiata* and has two main effects; the reversible inhibition of the AChE activity and the allosteric potentiating of neuronal nicotinic ACh receptors. Its goal is to prevent cognitive deficits and allied oxidative stress through the lowering of the deposition of Aβ plaque.[227] Resveratrol, which is derived from the *Vitis vinifera* (Vitaceae), is currently undergoing Phase III clinical research.[228] Huperzine A, which is derived from the Lycopodiaceae plant *Huperzia serrata*, is currently undergoing phase III clinical research.[229] Its primary use is to restore cognitive impairment through reversible AChE

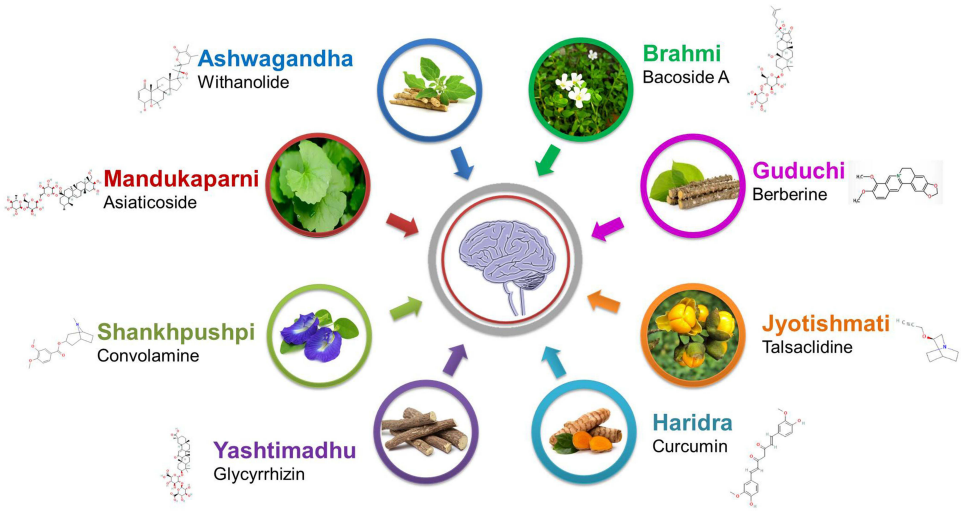

Figure 6 Phytoconstituents of Ayurvedic medicinal plants used for AD.

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Table 2 Medicinal Plants and Their Phytoconstituents Effective Against AD.[21]

Plant Sources	Plant Part	Active Constituents	AD Drug Target	Model Used	References
Acorus calamus (Acoraceae)	Whole plant extract	β-Asarone, α-asarone	It inhibits AChE activity and increases the GSH while reducing oxidative stress markers (SOD & LPO).	Enzyme, rat and mouse	[131–133]
Ginkgo biloba (Ginkgoaceae)	Leaf extract	Ginkgolide B, flavonoids	It inhibits Aβ deposition and improves the cytochrome P-450 enzyme system through the free-radical-scavenging property (antioxidant).	Mice	[134,135]
Crocus sativus ten (Iridaceae)	Stigma dry powder	Crocin, safranin, carotenoids, Safranal	It inhibits Aβ and tau protein deposition by reducing oxidative stress. It also inhibits the cognitive dysfunctions to maintain the hippocampal synaptic plasticity and fibrillogenesis in AD.	Cell and tissue	[134]
Hancornia speciosa Gomes (Apocynaceae)	Fruit extract	Phenolic compounds, rutin	It blocks the ChEs and increases the ACh, reducing oxidative stress by inhibiting the generation of NO & LPO.	Enzyme	[136]
Ecklonia cava (Lessoniaceae)	Extract of seaweed	Dieckol, Phlorofucofuroeckol-A	It decreases inflammatory cytokine levels (NF-kB andSTAT3) andAD markers (glial fibrillary acidic protein, Aβ, β-secretase).	Enzymes& peptide	[137]
Syagrus romanzoffiana (Cham.) Glassman (Arecaceae)	Extract of leaf and fruit	Phenols & fatty acids	It inhibits AChE activity in the cerebral cortex and cerebellum of rats and exhibits the nootropic effect.	Rat	[138]
Nonea micrantha (Boraginaceae)	Whole plant Extract	Flavonoids	It inhibits AChE activity along with scavenging free radicals.	Enzyme	[139]
Convolvulus pluricaulis Choisy (Convolvulaceae)	Whole plant Extract	Triterpenoids, flavonol glycosides, anthocyanins, and steroids	It reduces mRNA expression of the M1 receptor, Choline acetyltransferase, and NGF-TrkA receptor.	Rats	[140]
Rhodiola rosea (Crassulaceae)	Root & rhizome extract	Salidroside, rosavins, and p-tyrosol	It down-regulates the expression of the following genes, such as ALOX5AP, DPEP2, and LTC4S. Also, inhibits the leukotriene biosynthesis signaling path to reduce inflammation and neurotoxicity in AD.	Human T98G neuroglia cells	[141]
Ficus carica mesocarp (Moraceae)	Mesocarp extract	C-Sitosterol	It improves neuronal bioactivity by reducing oxidative stress in AD.	Enzyme& cells	[142]
Psidium guajava (Myrtaceae)	Leaf & fruit extract	Phenolic and flavonoid molecules	It blocks ChEs and also shows free-radical-scavenging activity.	Enzymes	[143,144]
Olea europaea (Oleaceae)	Leaf	Oleuropein, hydroxytyrosol	It inhibits Aβ and tau protein deposition by decreasing oxidative stress as well as neuroinflammation (NF-κB and Nrf2 modulation).	Enzyme and cells	[145]

Sargassum sagamianum (Sargassaceae)	Seaweed extract	Ring-fused 3β-acetoxyandrost-5-ene derivatives (S) −4,4a,5,6,7,8-(hexahydronaphthalen-2-one)-fused 3β-acetoxyandrost -5-ene	It selectively inhibits BChE and shows a neuroprotective effect by regulating mitochondrial potential.	Enzymes	[146]
Curcuma longa (Zingiberaceae)	Rhizome extract	Curcumins	It is a multitargeted phytoconstituent that inhibits ChEs and Aβ protein. Also, it maintains the structure of neurons and synaptic plasticity by deferring neuronal impairment, neurogenesis pathway, and neuroinflammation.	Enzyme, cells and rodents	[147]
Thunbergia grandiflora Roxb (Acanthaceae)	Leaf extract	Phenolics and flavonoids	It decreases the level of ChEs and also inhibits LPO levels from showing antioxidant activity to restore cognitive dysfunction.	Enzymes	[148]
Mangifera indica (Anacardiaceae)	Leaf & seed kernel extract	Isomangiferin & pentagalloyl glucose	It reverses the cognitive function by inhibiting AChE and Aβ as well as also showing radical-scavenging properties.	Enzymes	[149]
Andrographis paniculata (Acanthaceae)	Active compound	3,4-di-o-caffeoylquinic acid, apigenin, and 7-o-methyl wogonin	It inhibits ChEs, Aβ, and BACE-1.	In silico software and enzymes	[150]
Semecarpus anacardium (Anacardiaceae)	Leaf extract	Flavonoids, phenols	It improves learning and memory by blocking AChE & also decreases the oxidative stress markers.	Enzymes	[151]
Coriandrum sativum (Apiaceae)	Leaf extract, volatile oil	Petroselinic acid, linalool, fatty acids	It inhibits the AChE to increase the ACh level in the brain. It possesses antioxidant activity by reducing catalase and elevating GSH levels in the hippocampus region.	Enzymes & rat	[152]
Ferula asafoetida (Apiaceae)	Whole plant extract, resins	Umbelliferone, ferulic acid, coumarins, and other terpenoids	It inhibits AChE in the brain. Furthermore, it exhibits free- radical-scavenging activity.	Enzymes	[153,154]
Acanthopanax trifoliatus and Eleutherococcus senticosus (Araliaceae)	Whole Plant extract	Polyphenols, flavonoids	It inhibits lipid peroxidation and also scavenges the free radicals in the rat brain.	Stress markers	[155]
Sarcococca saligna (Buxaceae)	Whole plant extracts	Salignenamide-E, 2-hydroxysalignarine-E, axillaridine-A	It increases the ACh level by inhibiting AChE and BChE.	Enzymes	[156]
Sarcococca hookeriana (Buxaceae)	Whole plant extracts	Hookerianamine-A, phulchowki-amideA	It selectively blocks AChE to increase the ACh.	Enzymes	[156]
Buxus papillosa (Buxaceae)	Leaf	Buxakashmir-amine	It selectively blocks BChE to increase the ACh.	Enzymes	[155,157,158]

(*Continued*)

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Table 2 (Continued).

Plant Sources	Plant Part	Active Constituents	AD Drug Target	Model Used	References
Bauhinia forficate and Copaifera langsdorffii (Fabaceae)	Fruit extract	Polyphenols	It inhibits the AChE to increase the ACh level.	Enzymes	[159,160]
Clitoria ternatea (Fabaceae)	Root extracts	Quercetin and myricetin glycosides	It improves cognitive behavior	Rats & cells	[161,162]
Mentha piperita, Salvia longifolia, Betonica officinalis, Satureja Montana, Chamaedrys Moench, Clerodendrumcephalanthus, Teucrium polium, and Thymus vulgaris (Lamiaceae)	Aerial part and leaf extracts	Carotenoids, phenolic acids, rosmarinic acid, chlorogenic acid, caffeic acid	It displays AChE-inhibitory activity and controls the oxidative stress parameters.	Enzymes	[163]
Lavandula angustifolia (Lamiaceae)	Aerial part extract	Linalool, tannins, linalyl acetate, camphor, coumarins, triterpenes, flavonoids	It is capable of regulating the production of APP and GLT1 proteins, reducing oxidative stress, protecting neurodegeneration apoptosis, and significantly improving cognitive dysfunction in AD. It also scavenges the free radical.	Rats & cells	[164–166]
Lycopodie llacernu, Lycopodie llariofrio (Sodiro), Lycopodium clavatum, and Huperzia selagovar. serrata (Lycopodiaceae)	Whole plant extract	Huperzine A	It decreases the level of ACh and shows free-radical-scavenging activity.	Enzymes	[167,168]
Rehmannia glutinosa f. lutea (Plantaginaceae)	Root extract	Catapols, 5-hydroxymethyl furfural, bacopasaponin	It upregulates the expression of NGF in the neurons of the hippocampus. It reduces the Aβ-induced neurotoxicity. It exhibits neuroprotective activity.	Peptides & fly (Drosophila)	[169]
Bacopa monnieri (Plantaginaceae)	Leaf extracts	Brahmine, herpestine	It increases the ACh level through inhibition of AChE, activates choline acetyltransferase, and also reduces the Aβ plaques.	Enzyme, peptides, cells, and rats	[170,171]
Ashwagandha/ Withania somnifera	Roots	Sitoindoside IX, Sitoindoside X, Withanolides, withanols	It reduces the Aβ toxicity in SK-N-MC cells, lipid peroxidation, and elevates the conc. of SOD, catalase, and ascorbic acid. It also blocks the AChE in neuronal cell culture and regenerates axons, dendrites, and synapses.	Enzymes, peptides, and cells	[172]
Saururus chinensis hort. ex Loudon (Saururaceae)	Whole plant extract	Flavonoids, alkaloids, αpinene, cinnamic acid, camphene, safrole, β-caryophyllene, linalool, and humulene	It inhibits LPS-activated neuroinflammation in BV-2 microglia cells by controlling the NF-κB signaling pathway and also scavenges the free radicals.	Cells	[173,174]
Ziziphus jujuba Lam (Rhamnaceae)	Whole plant extract	Flavonoids, polysaccharides, phenolics, terpenes	It inhibits the Aβ deposition and exhibits antioxidant activity through scavenging the free radicals.	Peptide	[175]

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Nigella sativa (Ranunculaceae)	Seed extract	Thymoquinone, phenols	It blocks the AChE to increase the ACh and strengthens the neuroprotective action in neuronal injury via toluene exposure.	Rats & oxidative stress markers	[176–178]
Sesamum indicum (Pedaliaceae)	Seed extract	Sesamin, sesaminol, terpenes, flavonoids	It inhibits the AChE and generation of the free radical.	Rats	[179]
Lawsonia inermis (Lythraceae)	Leaf extract	Phytol, pseudoephedrine, aspidofractinine-3-methanol, phenol, 2.6-bis(1,1-dimethylethyl)-4-methyl	It inhibits the AChE activity in the hippocampus region and increases the nootropic effect. It also possesses the scavenging ability against the free radicals.	Mice & oxidative stress markers	[180]
Panax notoginseng (Araliaceae)	Root extract	Ginsenoside Rg1	It inhibits the expression of inflammatory factors TNF and Toll-like receptors. It also reduces the secretase enzymes.	Enzyme, peptide and cell	[181,182]
Ginkgo biloba (Ginkgoaceae)	Leaves extract	Ginkgetin, bilobalide, ginkgolide	It increases the ACh level through inhibition of AChE.	Enzymes	[183,184]
Dipsacus asper Wall (DAW) (Caprifoliaceae)	Bark extract	Akebia saponin D	It shows neuroprotective action against $A\beta_{25\text{-}35}$-induced cytotoxicity in PC-12 cells and may be beneficial in the treatment of AD.	Peptides, cells, and rats,	[111,185]
Paeonia suffruticosa (Paeoniaceae)	Plant extract	1,2,3,4,6-Penta- O-galloyleta-d-glucopyranose	It inhibits both types of $A\beta_{1\text{–}40}$ and $A\beta_{1\text{–}42}$ aggregation and also destabilizes Aβ fibrils.	Peptide & transgenic mice	[186]
Polygala tenuifolia (Polygalaceae)	Root extract	Tenuifolin	It possesses inhibitory activity against β-secretase enzymes and maintains neuronal plasticity. Also, it reduces the Aβ formation in cultured cells.	Peptide& cultured cell lines	[187]
Radix Salviae miltiorrhizae (Lamiaceae)	Rhizoma extract	Triterpenoids, Tanshinone	It shows AChE inhibitory activity and reduces the Aβ toxicity.	Rats	[188,189]
Monascus purpureus (Monascaceae)	Fermented red mold rice	Monascus fermented red rice	It inhibits enzymes, such as AChE and secretase, and scavenges the free radicals.	Enzyme, peptides and Mice	[189,190]
Uncaria rhynchophylla (Rubiaceae)	Stem with hooks	Triterpene esters, muscarinic acids	It reduces the Aβ aggregation and stabilizes Aβ fibril. It also inhibits the tau hyperphosphorylation, maintains the synaptic function, and reduces the neuronal loss.	Peptides & Mice	[191,192]

(*Continued*)

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Table 2 (Continued).

Plant Sources	Plant Part	Active Constituents	AD Drug Target	Model Used	References
Bacopa monnieri (Scrophulariaceae)	Whole plant extract	Bogenines, steroids, Triterpene	It regulates the MARK4 to reduce the kinase activity. It also increases the ACh to improve learning and memory.	Rats	[193,194]
Salvia officinalis (Lamiaceae)	Aerial parts extract	Essential oils having cineole and thujone	It shows inhibitory action against AChE and scavenges the free radicals to elevate cognitive functions and treat mild-moderate AD. Now, it is in the clinical phase.	Enzyme, and Human	[195,196]
Melissa officinalis (Lamiaceae)	Whole plant extract	Terpenes, tannins, eugenol, rosmarinic acid	It displays inhibition action against the AChE and shows antioxidant activity.	Rats & humans	[197,198]
Murraya koenigii (Rutaceae)	Leaves extract	Carbazole alkaloids, Scoponin	It reduces the ChEs action in the hippocampus region of the brain to increase the nootropic effect.	Enzyme, mice and oxidative stress markers	[199,200]
Cassia obtusifolia (Legumes)	Seed extract	Gluco-obtusifolin, Obtusifolin	It increases the ACh level through inhibition of AChE.	Mice	[201,202]
Centella asiatica (Umbellifers)	Extract of whole plant	Triterpene glycosides, saponins	It increases the ACh level through inhibition of AChE and also reduces the formation of Aβ plaques.	Mice, peptide and oxidative stress markers	[203]
Fungus Ganoderma lucidum (Ganodermataceae)	Ethanol extract	Ganoderic acid (Triterpene glycoside)	It preserves the neuronal plasticity and decreases the Aβ-induced apoptosis. It may be beneficial in the treatment of AD and dementia.	Peptide, and cortical neuronal culture	[204]
Desmodium gangeticum (Legumes)	Aqueous extract	Aminoglucosyl- glycerolipids, cerebrosides	It inhibits AChE from elevating the ACh to improve the working memory. It also exhibits neuroprotective action and free-radical-scavenging activity.	Mice	[205]
Lycium barbarum (Solanaceae)	Whole plant extract	Polysaccharides	It reverses Aβ and homocysteine-induced apoptosis to treat AD.	Peptide, and rat cortical neurons	[206]
**Yokukansan*	Extracted from 7-medicinal herbs	Composition of crude herbs	It reduces the Aβ-induced neurotoxicity and enhances motor activity.	Tg2576 mice	[207]
***Zokumei-to*	Combination of 9 crude drugs	Composition of crude herbs	It reduces Aβ-induced neurotoxicity and eliminates neuronal loss.	Mice & peptide	[208]

Guggulu/ Commiphora whighitti	Resin	Guggulsterones, manusumbionic acid	It inhibits AChE to increase the ACh to show a nootropic effect. It also scavenges free radicals.	Mice& oxidative stress markers	[209]
Ardraka/ Zingiber officinale	Rhizome	Zingerone; (4-hydroxy-3-methoxyphenyl-yl-2-butanone)	It inhibits the Aβ deposition, tau hyperphosphorylation mRNA expression of LPS, TNF-α, IL-1β, and decreased levels of TNF-α, IL-1β, COX-2, MIP-1α, MCP-1, and IP-10. Thus, it enhances the working memory.	Enzymes, peptide, rats, and cell lines	[210]
Amalaki /Emblica officinalis	Fruit	Tannins, Phyllembelin, Pectins, Vitamin C	It inhibits the AChE activity to enhance the ACh level in the brain.	Mice	[211]
Brahmi/ Bacopa monnieri	Roots & leaves	Bacoside A	It inhibits the AChE to increase the ACh level in the brain and scavenge the free radicals.	Rats	[212]
Guduchi/ Tinospora cordifolia	Stem	Tinosporine, Giloin, Tinosporide, Magnoflorine	It blocks ChEs from showing a nootropic effect in AD. It also scavenges the free radicals to show neuroprotective activity.	Rats & Humans	[213]
Harinda/ Curcuma longa	Roots/ rhizomes	Curcumin	It blocks stimulatory proinflammatory cytokines, such as TNF-α and IL-1β. It also prevents Aβdeposition, oxidative stress markers, and neurotoxicity in AD.	Proinflammatory cytokines parameters	[214]
Jatamansi/ Nardostachys jatamansi	Roots & rhizomes	Jatamansic acid, Jatamansone, Jatamansinol, Valeranone	It inhibits the AChE, BChE, GSK3β, and Keap1.	Rodents	[215]
Falgu/ Ficus carica	Fruit	Anthocyanin, triterpenoids, coumarins	It inhibits the AChE action to improve the nootropic effect and also shows potential chelating and radical-scavenging properties.	Mice	[216]
Paatha/ Cissampelos pareira	Whole vine	Hayatine, hayatidine, berberine	It suppresses the AChE and free radical activity. Also, it diminishes the oxidative stress markers in the hippocampus.	Mice	[217]
Kushmanda/ Benincasa hispida	Fruit	Triterpenes, sterols, and glycosides	It increases the ACh level and reduces the oxidative stress markers (SOD, catalase, MDA) while increasing the GSH level. It also reduces inflammatory cytokines, such as TNF-α and IL-1β, and reduces $AlCl_3$-induced AD in rats.	Rats	[218]

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Table 2 (Continued).

Plant Sources	Plant Part	Active Constituents	AD Drug Target	Model Used	References
Nithyakalyani/ Catharanthus roseus	Dried root	Serpentine, ajmalicine, catharanthine	It shows potential inhibitory action against AChE and also exhibits low cholinergic receptor affinity.	Rats	[219]
Puga/ Areca catechu	Fruit	Arecaidine, Arecoline,	It reduces AChE action and increases the ACh in the brain, and it also shows agonistic activity on the muscarinic-2 receptor.	Rats	[220,221]
Shatavari/ Asparagus racemosus	Fresh tuber	Sarsasapogenin	It acts as a multitargeted ligand to inhibit ChEs, Aβ aggregates, BACE1, and MAO-B. It also shows neuroprotective activity on PC12 cells against $A\beta_{42}$ and H_2O_2-induced cytotoxicity.	Enzymes, peptide, cells	[222]
Glycyrrhiza glabra	Root extract	Glycyrrhizin; 2.2′,4′-Trihydroxychalcone	It improves spatial learning and memory-enhancing activities.	Mice	[132]
Shalparni/ Desmodium gangeticum	Root extract	Aminoglucosyl-glycerolipids, cerebrosides, pterocarpan, pterocarpanoids, gangetin, gangetinin, desmodin	It reduces the brain AChE in scopolamine-induced AD at doses of 50, 100, and 200 mg/kg, *p.o.* Thus, it improves learning and memory.	Mice	[205]
Aparajita/ Clitoria ternatea	Root extract	Inositol, cyclohexen, 1-methyl-4-(1-methylethylideme)	It enhances the ACh level in the hippocampus region to improve the nootropic action at a dose of 100 mg/kg.	Rat	[223]
Dadima/ Punica granatum	Flower, fruits	Anthocyanin compounds	It prevents oxidative stress and reduces $A\beta_{42}$-induced cytotoxicity. It also maintains mitochondrial homeostasis in cultured neuronal cells.	Rat, peptide	[224]

Notes: *Atractylodes Lancea rhizome, Poria sclerotium, Cnidium rhizome, Uncaria hook, Japanese angelica root, Bupleurum root, and Glycyrrhiza.**Armeniacae Semen (Prunus armeniacaL.), Ephedrae Herba (Ephedra sinica Stapf), Cinnamomi Cortex (Cinnamomum cassia Blume), Ginseng Radix (Panax ginseng C.A. Meyer), Angelicae Radix (Angelica acutiloba Kitagawa), Cnidii Rhizoma (Cnidium officinale Makino), Zingiberis Siccatum Rhizoma (Zingiber officinale Roscoe), Glycyrrhizae Radix (Glycyrrhiza uralensis Fisch.), and Gypsum Fibrosum (gypsum).

Abbreviations: AD, Alzheimer's disease; ACh, acetylcholine; AChE, acetylcholinesterase; BChE, Butyrylcholinesterase; Aβ, amyloid beta; NO, nitric oxide; GSH, glutathione; CAT, catalase; SOD, superoxide dismutase; MDA, malondialdehyde; MAO, monoamine oxidase; COX, cyclooxygenase; LPO, Lipid peroxidation; STAT, Signal transducer and activator of transcription; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells; NGF-TrkA, Nerve Growth Factor-Tropomyosin-related kinase A receptor; BACE1, Beta-site APP-cleaving enzyme 1; GLT-1, Glutamate transporter 1; NGF, Nerve growth factor; LPS, Lipopolysaccharide; TNF, Tumor necrosis factor; MARK4, Microtubule affinity-regulating kinase 4; IL, Interleukins; MIP-1α, Macrophage inflammatory protein-1α; MCP-1, Monocyte chemoattractant protein-1; GSK3β, Glycogen synthase kinase 3 beta; KEAP1, Kelch-like ECH-associated protein 1; Nrf2, Nuclear factor erythroid.

blocking. Curcumin is derived from *Curcuma longa* (Zingiberaceae), possesses anti-amyloidogenic, anti-inflammatory, anti-ChE, and anti-secretase properties, and is in a clinical trial II.[214]

Ayurvedic Herbal Formulations Employed in AD

Ayurveda provides several herbal preparations under the name Medhya (cognition) Rasayana to treat cognitive and mental disorders like AD.[230] The four *Medhya rasayana* that are known to foster intelligence are *Shankhapushpi* (*Convolvulus pluricaulis), Mandukaparni* (*Centella Asiatica), Guduchi* (*Tinospora cordifolia*), and *Yashtimadhu* (*Glycyrrhiza glabra*).[21] These four *Medhya rasayana* inhibit the ChEs to increase the ACh, reduce the Aβ plaques, and scavenge the free radicals. In addition, the literature has reported that *Shankhapushpi* reduced the mRNA expression of the M1 receptor, CAT, and NGF-TrkA receptor in the cerebral cortex of rats. It improved the spatial learning and memory-enhancing activities in in vivo models, such as the elevated plus maze, Hebb–William maze, and Morris water maze. It is speculated that a variety of single *Rasayana* medications and combinations may affect AD through different mechanisms, including nutritive, adaptogenic, regenerative, and immunological modulatory mechanisms, which also refer to their subcellular activity. Rasayana drugs affect the neuroendocrine and immune systems, improve host strategy, supply a rich source of antioxidants, renovate youth, strengthen and restore cognitive abilities, and improve intellectual disabilities as well as other physiological impacts on the body.[230]

Other than single herbal preparations, Ayurvedic polyherbal formulations are employed to treat both dementia and neurodegeneration.[21] Among them, the traditional uses of *Saraswata churna*, a sort of *churna* (herbal powder) formulation, are to enhance intelligence, memory, and poetic ability, because *churna* inhibits the AChE, Aβ protein deposition, scavenging of the free radicals, and the NMDA receptor. The *Asava/Arishta* (fermentative drinks) formulation of *Saraswata rishta* is also used to treat a variety of mental illnesses, dementia, and mental disorders. A study reported its beneficial memory-enhancing activities by inhibiting AChE to increase the ACh, provide a reduction in Aβ aggregation, and provide the neuroprotective potential through scavenging the free radicals, and, subsequently, enhancing the cerebral blood flow in the brain. *Manasamitra Gutika* is a vati/ Guggulu concoction (tablets/pills) used to treat speech abnormalities, hysteria, insanity, and mental retardation. *Abana* is another polyherbal formulation (tablet) that is reported to increase the ACh level by inhibiting the brain AChE. It improved cognitive function without any oral toxicity in the scopolamine-induced AD mice model. In addition, *BR-16A* (Mentat) is a composition of 26 medicinal plants and is also explored as *Medhya rasayana* in Ayurveda to cure cognitive dysfunction in aging conditions. It was reported to reverse the colchicine- or scopolamine- or ibotenic-acid-induced cognitive impairment in the AD model in a dose-dependent manner. *Trasina* is an Indian formulation prepared using six medicinal plants, and it exhibited a potential nootropic effect against colchicine- and ibotenic-acid-induced AD at doses of 200 and 500 mg/kg, *P.O. Trasina* inhibits the AChE to increase the ACh level, increase the CAT activity, and provide high binding affinity towards muscarinic receptors in the rat brain to improve the overall anti-AD activity. Furthermore, commonly used *Ghrita* (medicated cow ghee) polyherbal preparations include *Brahmi Ghrita, Chetasa Ghrita, Kushmanda Ghrita*, and *Siddharthaka Ghrita* used to cure insanity, dementia, and mental retardation.[231] Among them, *Brahmi Ghrita* was reported to decrease the AChE activity and MDA level (via its free-radical-scavenging property). It also reduced the transfer latency and escape latency in the scopolamine-induced AD (elevated plus maze and Morris water maze test at doses of 50 and 100 mg/kg, *p.o*), and then ultimately reversed the cognitive dysfunctions in in vivo rat models. Thus, polyherbal formulations generally have broad-spectrum medicinal value because of their effectiveness at lower doses and safety at higher doses. Hence, polyherbal formulations show a greater risk-benefit proportion.

Future Prospects

The current medical system still falls short when it comes to treating neurodegenerative diseases because of intricate brain circuitry and our incomplete knowledge of the CNS's structure and functions. We need all-inclusive treatment to control such broad-spectrum pathological concerns of neurocognitive diseases, which are caused by many parameters, including genetic and environmental. Over the past few decades, there has been an increase in enthusiasm for alternative and herbal remedies for AD, and there is some anticipation that these treatments will soon be integrated synergistically with traditional therapy. The current study supports the idea that conventional herbal and holistic therapies might be

helpful as therapeutic choices for AD. Ayurvedic nootropic medicinal plants/herbs and formulations have free-radical-scavenging abilities, thereby reducing the toxicity of Aβ and neurons and inhibiting inflammation. These properties regulate and boost the immune and neuroendocrine systems, enhance the ability for learning, restoration, and mental power, revitalize brain functions, and alleviate AD-related neurodegenerative etiology. The Ayurvedic Rasayana treatment has a primary goal of improving oxygenation, which leads to increasing neurogenesis by reviving homeostatic equilibrium. The potential synergistic therapeutic methods might increase oxygenation and restore neurons' degeneration. Systems of Ayurveda have incredible clinical understanding and knowledge. This information could support the improvement of vision together with successful remedial management to reduce morbidity and control the diseases at preventative, helpful, and therapeutic levels, although more research is required. The main basis for employing Ayurvedic medications is based generally on conventional practice, with very few scientific studies on the effectiveness, safety, or signal transduction pathways. However, recently, efforts have commenced towards the authentication of data of biological, toxicological, and medical claims, as well as to record Ayurvedic nootropic medications, and this is essential for their level of quality assessment and widespread adoption. In the pharmaceutical industry, the medication development approach for neurocognitive conditions is getting costlier and riskier and is extremely ineffective, which leads to severe problems. A design transfer from a single-target to a multi-target ligands strategy, principally for complicated illnesses, is being noticed. It is expected that comprehensive scientific information of Ayurveda has come together with modern-day sciences and can give novel useful leads for neurocognitive disorders. The amalgamation of Ayurveda and modern science might play a significant function in novel treatment, therapeutic innovation, and development methods. There are concerns regarding the employment of herbal medicines as a substitution or supplement for current medicine because of their effectiveness, purity, safety, or interaction with other medications. The post-market research might be explored for any side reactions of herbal drugs. It is very challenging to afford active phytochemicals from herbs in high quantities. Additionally, there is no proper scientific data on the standardization process, mode of action, or quality control of these formulations. Scientists and researchers could explore these new ideas in the future. Unfortunately, there have been current data available on toxicological, pharmacological, and clinical research on the therapeutic value of traditional medicinal plants and polyherbal mixtures in AD that are unusual and inconclusive. This incapability to manage confusion can create problems of incorrectness and inaccuracy. Taking these factors into account, some of the following suggestions are reasonable to arrive at a concrete ending; first include comprehensive, well-stratified multi-center investigations with reliable neurological evaluations; second, to determine whether the combined use of conventional medicinal plants along with modern medicines improves the effectiveness of medications or enhances their therapeutic efficacy against the management of AD. Furthermore, the present overview not only provides the significance of a comprehensive conventional and contemporary scientific strategy for developing new drugs for AD-related diseases but also upgrades the knowledge on the pathogenesis of AD.

Conclusions

There are currently no effective medications or treatments for AD, which is the most prevalent neurocognitive disease worldwide. With their wide variety and abundance of pharmacological principles, natural remedies may show significant functions in the development of novel chemical entities. Plants' secondary metabolites, like alkaloids, flavonoids, and phenolic acids, are essential in either encouraging regeneration or avoiding neurodegeneration. Several herbal medicines and particular herbal medicinal parts have exhibited substantial promise for the amelioration of AD. Furthermore, several medicinal herbs and plants have been available with identical taxonomic backgrounds that showed almost similar pharmacological characteristics. However, given the fact that research in neurocognitive diseases, like AD, presents significant scientific challenges, it is a highly important field for the investigation of traditional medicinal methods, and natural remedies could warrant a safe, reliable, and effective strategy for its treatment.

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