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Review Article

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Holistic and Conventional Approaches in Alzheimer's Therapy: Exploring Herbal, Synthetic, and Alternative Interventions

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Abstract

Alzheimer's disease (AD) is a progressive and irreversible neurological condition characterized by a steady and progressive impairment of different domains or sectors of cognition, such as language, learning and memory, attention, and social skills. Kraepelin used the term Alzheimer's disease to describe the condition before it was first described by a German psychiatrist known as Alois Alzheimer in 1906. A study conducted in 2023 shows that 6.7 million of the American citizens aged 65 and over have Alzheimer's disease. It is also possible that by 2060, 13.8 million sufferers of Alzheimer's sufferers will exist unless significant progress is achieved in the field of science to prevent, treat, or cure the disease. Tau and amyloid-β (Aβ) are the defining molecules of Alzheimer's disease and form neurofibrillary tangles and senile plaques. The main clinical aim of Alzheimer disease is to reduce its development, because there is currently no treatment. Synthetic preparations, which only attenuate symptoms, include cholinesterase inhibitors and NMDA receptor inhibitors (donepezil, rivastigmine, galantamine, and memantine). Unlike synthetic drugs, herbal medicines are more flexible over time and produce fewer side effects, such as inability to sleep, developing withdrawal symptoms, and adversely affecting other vital organs that are common with synthetic drugs. The first objective of this paper was to establish a review of how AD is being treated by searching databases such as PubMed, Web of Science, ResearchGate, Mdpi, Google Scholar, Science Direct, Willey, and many other websites.

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1 Introduction : A broad spectrum of neurological conditions known as neurodegenerative disorders (NDDs) are defined by alterations in the structure and operation of the central nervous system (CNS). The most prevalent form of NDD is Alzheimer's disease (AD)[1]. First, before German psychiatrist Alois Alzheimer provided the first explanation of the condition in 1906, it was known as "Alzheimer disease by Kraepelin"[2]. An irreversible neurological condition, Alzheimer's disease (AD) is characterized by progressive and growing deficits in multiple areas of cognition, such as language, learning and memory, attention, and social skills. [3,4] Aphasia, agnosia, memory loss, visuospatial impairment, challenges with computation and critical thinking, and aberrations in personality and behaviour are its clinical characteristics[5,6]. Hallucinations, amnesia, and confusion are symptoms that may eventually result in infection, aspiration pneumonia, dysphagia, or starvation [7]. The patients' ability to perform daily tasks on their own is severely limited by progressive cognitive deterioration, which ultimately leaves them bedridden and requires round-the-clock care. Many elderly people experience growing social isolation and total dependence on others due to AD and dementia, which affect a rapidly aging population[8]. Some statistics show that, as people age, the prevalence of Alzheimer's disease increases significantly. Approximately 5.0% and 13.1% of persons aged 65 to 74 years and over 75 and 84 years, respectively, were diagnosed with Alzheimer's disease. Remarkably, 33.3% of individuals aged > 85 years suffer from Alzheimer's disease. The fact that Alzheimer's disease can affect anyone, especially those under 65, should not be overlooked[9,10]. Although those over 65 years of age are more likely to have Alzheimer's disease, children under 30 years of age can still be affected[11]. In the US, it is the seventh leading cause of mortality and accounts for almost 80% of all dementia cases. [12]. The 2023 study estimates that around 6.7 million Americans aged 65 and older suffer from Alzheimer's disease. By 2060, there could be 13.8 million Alzheimer's patients if no major advancements in medicine were made to prevent, stop, or cure the condition. Official death certificate statistics show that between 2000 and 2019, the mortality rate from Alzheimer's disease increased by approximately 145%. [9] Additionally, AD has created a significant issue; the World Health Organization estimates that the expense of providing additional care for patients with AD has skyrocketed to $600 billion annually due to the progressive decline in everyday activities and independent living[13]. Depending on when it first manifests, AD is classified into two types: early onset or familial AD (EOAD), which accounts for 1%–5% of AD cases, and late-onset AD (LOAD) or sporadic AD, which accounts for over 95% of AD cases. [14] Mutations in three autosomal dominant genes, presenilin-1 (PSEN1), presenilin-2 (PSEN2), and amyloid-β precursor protein (APP), are usually the cause of EOAD. Aβ generation and APP processing are mediated by PSEN1 and PSEN2, respectively, whereas the amyloid beta (Aβ) sequence is encoded by the APP gene[15]. The hallmarks of Alzheimer's disease include tau and amyloid-β (Aβ) peptides that form neurofibrillary tangles (NFTs) and senile plaques[16,17]. Affected people experience behavioral, cognitive, and functional impairments as a result of these protein aggregators, which also alter synaptic function and neurotransmitter levels and trigger oxidative and inflammatory responses that lead to cell death[18]. A recent study identified distinct pathways, such as mitochondrial failure, defective autophagy, and dysregulation of the gut-brain axis, caused by abnormalities in intestinal microbes that contribute to the course of Alzheimer's disease. The pathophysiology is complicated by genetic variations such as APOE4 and TREM2, which affect disease development and susceptibility[19]. Alternative therapeutic techniques are urgently needed because current pharmaceutical treatments remain unsuccessful and concentrate on symptoms rather than the course of the disease[13]. The main clinical objective of Alzheimer's disease is to slow its progression because there is currently no cure for it[20]. Among the synthetic formulations that only reduce symptoms are cholinesterase inhibitors and NMDA receptor inhibitors (donepezil, rivastigmine, galantamine, and memantine). [21–23]. Aβ-targeting antibodies, such as lecanemab and aducanumab, have recently received FDA approval[24–26]. Unlike synthetic drugs, herbal remedies are more flexible over time and have fewer adverse effects, including trouble sleeping, withdrawal syndromes, and negative effects on other vital organs, which are common issues with synthetic alternatives[27,28]. This review aims to present a comprehensive comparison between holistic approaches to managing Alzheimer's disease and contemporary medical therapy. To find the areas where medications can have the greatest effect, it first looks into how the disease affects the brain. Subsequently, the topic turns to conventional therapies, including synthetic drugs that have FDA approval, and examines their mechanisms of action, effectiveness, and drawbacks. The expanding interest in plant-based compounds and herbal treatments is also covered in this paper, with references to both contemporary scientific research and conventional wisdom. It also explores complementary therapies, such as music therapy and nutrition therapy, to prevent cognitive decline and support brain health. The evaluation encourages a more comprehensive and targeted plan by integrating the best features of both the strategies.

2. Pathophysiology of Alzheimer disease-

While the exact pathogenetic mechanisms underlying Alzheimer's disease remain unknown, it is widely believed that the main causes of the disease are excessive accumulation of insoluble amyloid β protein (Aβ), which forms senile plaques on blood vessel walls and in the extracellular space, and neurofibrillary tangles, which are aggregates of hyperphosphorylated tau protein[29–32]. Under a microscope, frequent lesions were shown to be senile plaques composed of aggregated amyloid-β42 (Aβ42) peptides and intracellular NFTs generated by hyperphosphorylated tau proteins in the neurons[33]. Based on these pathological indicators, Alzheimer's disease can be diagnosed accurately. In the brain, phosphorylated tau and β-amyloid accumulation damage synaptic function and

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eventually cause neuronal cell death[34]. The first stage of Aβ formation involves altered APP cleavage. The transmembrane protein, APP, has an extracellular domain. It is broken down by both amyloidogenic and nonamyloidogenic processes[35]. The large soluble ectodomain APP α and the C-terminal fragment α are produced when α (APPs-secretase, ADAM10, and ADAM17) cleaves APP at residues 16–17 of the Aβ sequence during the non-amyloidogenic process. [36] When sick, APP is broken down by β-secretase (BACE1) to create CTFβ and soluble APP β (αAPPβ). γ-Secretase breaks down CTFβ, leaving behind AICD and insoluble Aβ. Upon polymerization stimulation of kinases, the microtubule-binding tau protein is hyperphosphorylated and insoluble NFTs are formed. [35–37]. Along with tubulin construction and linking bridges between microtubules, hyperphosphorylation of the microtubule-associated tau protein is another important characteristic of Alzheimer's disease[38]. The generation of kinases and hyperphosphorylation of tau results in the formation of amyloid plaques and NFTs[39]. These NFTs are linked to the loss of signal processing and inter-neuronal communication, resulting in neuronal death. Oxidative stress is one of the main causes of NFT in Alzheimer's disease[40]. ROS and reactive nitrogen species imbalances are the primary causes of oxidative stress. Aβ deposition and excessive oxygen free radicals may trigger inflammation and activate microglia, which in turn may result in ROS production [41,42]. When these pathways are combined, they create a toxic stress environment that results in permanent neuronal death. Each of these mechanisms is essential to the onset and course of the disease. [43]

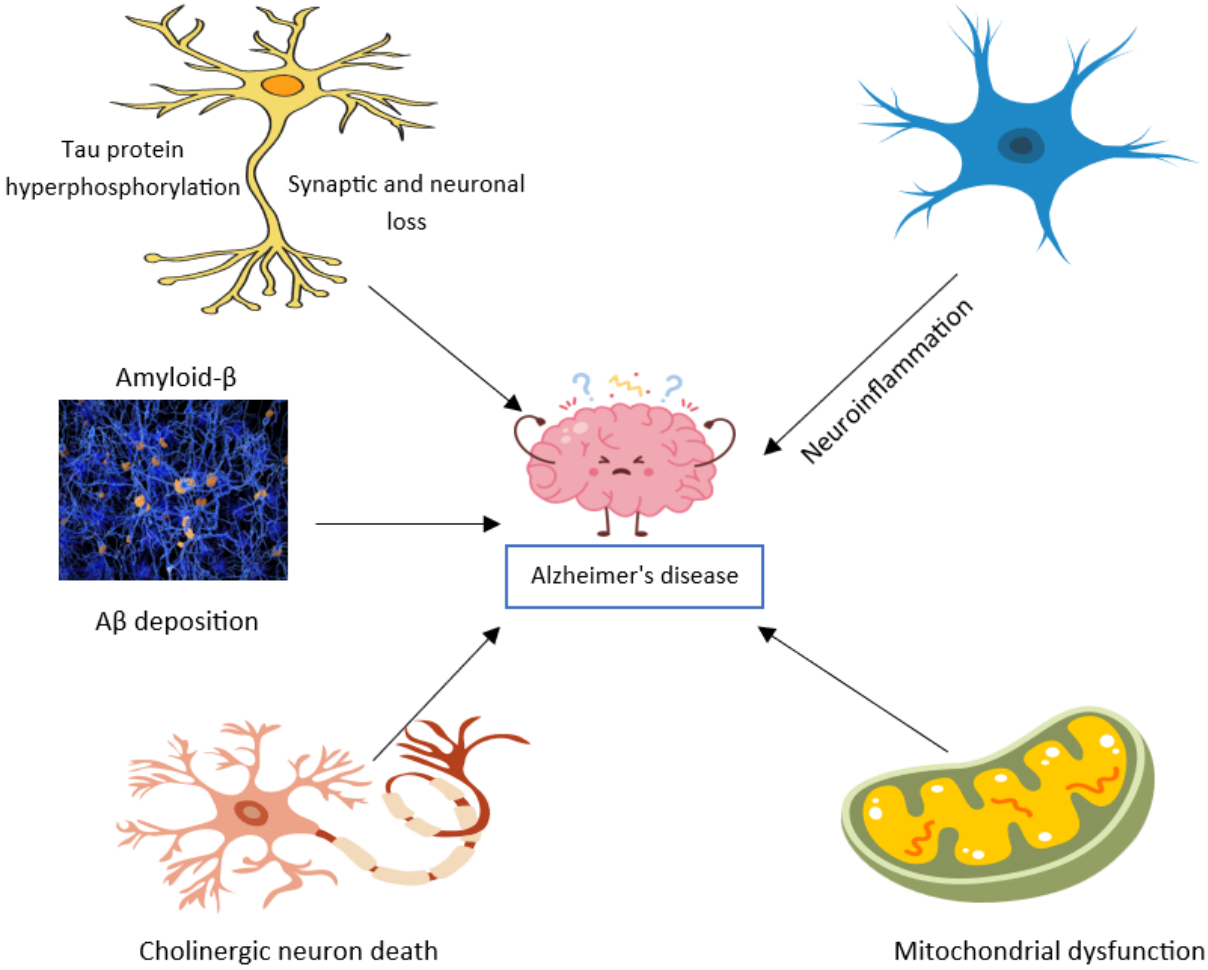

Fig. (1) pathophysiology of Alzheimer disease

2.1 Amyloid-β hypothesis-

Years (or even decades) before Alzheimer's disease symptoms manifest, Aβ deposition starts [44]. Alzheimer's causes Aβ to accumulate and form plaques by interfering with the normal Aβ clearance route.[44]. Amyloid proteins Amyloid beta (Aβ) is naturally produced by amyloid precursor protein (APP) and contains 36–43 amino acids.[45] Pathological production of APP occurs through the production of Aβ by β-secretase and γ-secretase. Under physiological conditions, APP is cleaved by α-secretase and not by β-secretase to produce soluble APP α fragments via a non-amyloid secretory route[46]. Elevated formation of Aβ plaques occurs when mutations alter the cutting pattern of

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APP, presenilin 1, presenilin 2, or APOE 4 genes[47,48]. This leads to the release of longer Aβ peptides, which are prone to aggregation too early. Hydrophobic and poisonous Aβ42 species have a higher likelihood of aggregation than Aβ40 monomers[49]. The acuity of cognitive impairment in patients with AD is related to the number of soluble oligomers in the brain, with the notable exception that the responses to soluble oligomers depend on the various alpha-entities that form them, especially Aβ40[50]. The soluble oligomers facilitate the proliferation of oxygen free radicals and are neurologically toxic. They are both significant and mostly dependent on the deregulation of the nerve cell activity of calcium homeostasis, which leads to their death[51]. Controversially, Aβ remains uncertain, but there are a few reports that, under physiological concentrations, Aβ might contribute to the regulation of synaptic plasticity[52]. A discrepancy between Aβ generation and clearance could cause aggregation, which could lead to AD. This is termed the amyloid cascade hypothesis, which may incorporate the genetic types of AD[53].

2.2 Neurofibrillary tangles hypothesis-

Neurofibrillary tangles (NFTs) are another important histological feature of AD brains. [54]. In addition to NFTs, neuropil threads (NT) are produced when the dendrites and axons of tangle-bearing neurons deteriorate. [55]. The microtubule-associated protein tau is organized into paired helical filaments, which make up the NFT[56]. A highly soluble cytoplasmic protein, tau, binds to tubulin during polymerization onto microtubules, promoting assembly and stability and enhancing axonal transport[57]. Under pathogenic circumstances, tau is excessively phosphorylated, especially by dysregulated kinases, such as GSK-3β and CDK5. [58]. As a result of hyperphosphorylation, the binding affinity of Tau for MTs decreases, causing the neuronal cytoskeleton to become unstable and eventually collapse[59]. Tau, which is hyperphosphorylated, quickly separates from microtubules and forms NFTs. [60] NFTs and microtubule dissociation result in oxidative stress, neuroinflammation, cytoskeletal and mitochondrial dysfunction, axonal transport deficits, and synaptic loss. Figure (2) [61,62] Because tau dysregulation is a critical component of neurodegeneration, attempts are being made to halt disease progression by developing therapeutic methods that target tau stabilization, kinase inhibition, or post-translational changes[63]. Understanding these pathways is required for the development of targeted therapies for tau-associated neurodegenerative disorders [64]

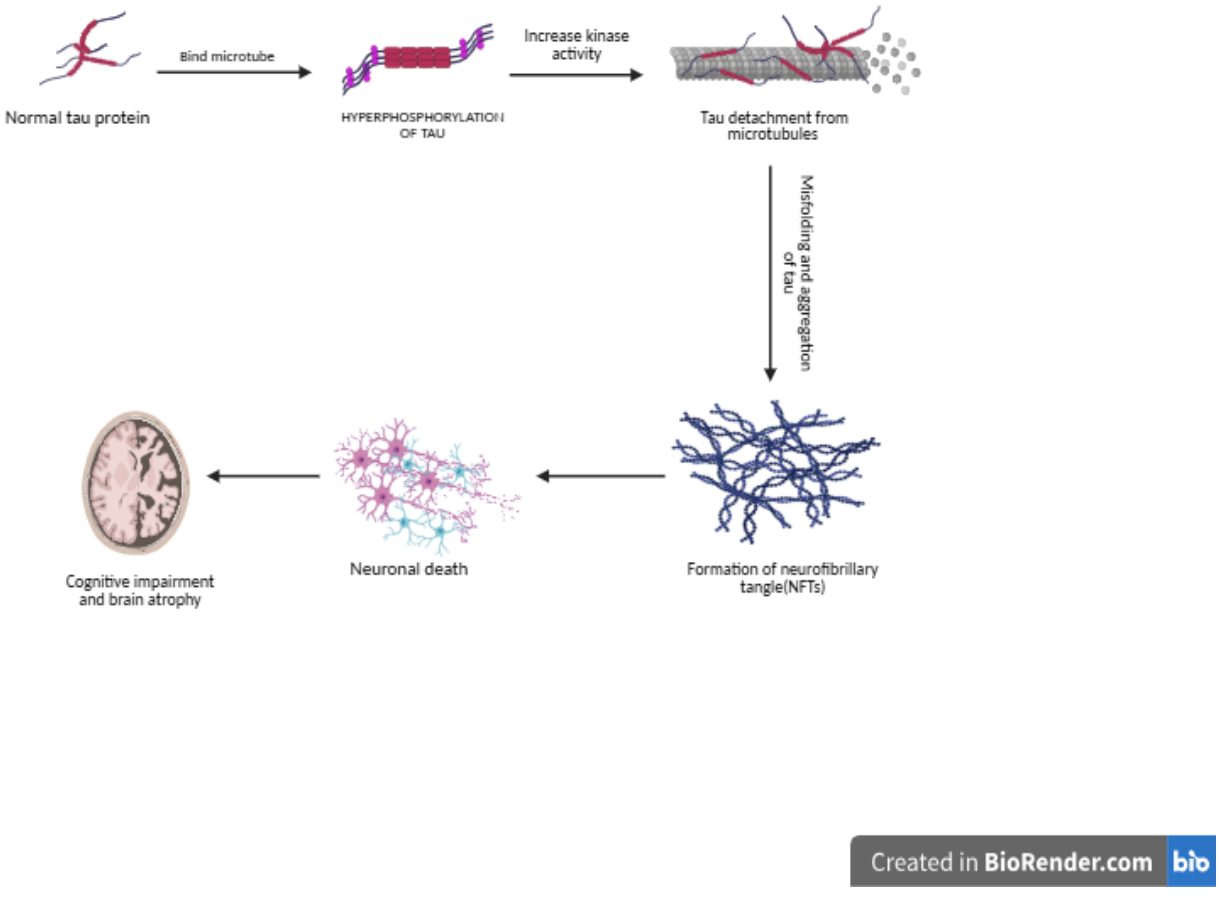

Fig. (2) Shows the Neurofibrillary tangles (NFTs) hypothesis

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2.3 Mitochondria dysfunction and oxidative hypothesis-

This is one of the long-standing hypotheses concerning the pathogenesis of early AD, namely the role of mitochondrial dysfunction and oxidative stress. [65] Mitochondria are especially susceptible because they are the main energy producers in the brain, and their impairment caused by the development of AD results in the failure of bioenergetics and the induction of oxidative stress[66]. It is one of the clear and early signs of AD, even in the absence of Aβ plaques and tau tangles. Multiple mitochondrial processes are known to be disturbed in AD, [67] and in the brains of AD patients, the addition of full-length APP and truncated proteins may be deposited within the protein import channels of the mitochondrial APP, blocking protein import of the mitochondrial machinery and causing mitochondrial dysfunction[68]. Mitochondrial defects exhibited in AD include poor dynamics (fission/fusion), motility, and calcium buffering capacity, which cause overproduction of reactive oxygen species (ROS)[69]. Oxidative stress is an age-related disease, such as AD. Oxidative stress precedes the conditions in AD and is thought to be a major cause of NFT formation in AD[70,71]. Oxidative stress contributes significantly to different neurodegenerative diseases, such as AD. Oxidative stress primarily occurs because of the inconsistency of reactive nitrogen species (ROS/RNS) such as H2O2, OH, O2 radicals, nitrogen dioxide radical (NO2), etc. [71,72. These results suggest that mitochondrial-directed therapies have favorable potential, where ATP synthesis improvement, inhibition of ROS, and membrane potential stabilization are the subjects of current strategies. [73]

3. THERAPEUTIC STRATEGIES.

Unfortunately, the treatment of AD is ineffective, and the primary clinical concern is to reduce the development of the disease. To date, AD or other symptom-alleviating drugs that are available and approved by the Food and Drug Administration for treatment include galantamine, donepezil, tacrine, rivastigmine, and memantine.[13] The existing classes of drugs currently used to treat AD are cholinesterase inhibitors donepezil and galantamine, the antibiotic rifampicin, the NMDARs antagonist memantine, and combinations of memantine and donepezil. Investigational treatments are aimed at Aβ pathology, tau pathology, and cholinesterase inhibitor use. These are γ-secretase inhibitors, β-secretase inhibitors, α-secretase modulators, aggregation inhibitors, metal-disrupting drugs, drugs that improve Aβ clearance, inhibitors of tau hyperphosphorylation, inhibitors of tau aggregation, and drugs that promote tau clearance.[74,75]] Currently, a global pattern of common cerebral disorders such as those entrenched in AD can be observed in some regions of the globe, and [76–78] the study of natural products as possible remedies is difficult because of their abundant chemical composition, extensive use in traditional medicine, and the ability of such proven sources to target numerous pathological processes characteristic of AD. Natural products also present a highly complex mode of action (e.g., antioxidant, anti-inflammatory, neuroprotective properties), which fits well with the complexities of AD causation that includes amyloid plaque formation, tau tangles, neuroinflammation, or oxidative stress [79–81] More so, relative to conventional drugs that may induce undesirable adverse effects such as gastric upset or neuropsychiatric disorders, natural products are typically safer and have reduced adverse effects[82]. The future of AD diagnosis and management lies in new biological treatment techniques such as gene therapy, immunotherapy, stem cell therapy, microRNA therapy, multi-omics, and probiotic therapy. These methods are slowly becoming the most promising new treatment in the future. [83]

3.1 Plant based therapy-

Neurodegenerative diseases such as Alzheimer's disease may have therapeutic value that is enhanced through natural products that exhibit anti-inflammatory, antioxidative, neuroprotective, and neuroreparative qualities. Figure (3) These features may be specifically aimed at the hyperphosphorylation of tau protein, oxidative stress, accumulation of amyloid-beta, and neuroinflammation, which can all contribute to the etiology of Alzheimer's disease[7,84]. With more information on AD processes, there is an increasing need to find bioactive compounds of natural origin that may supplement or complement the existing treatment modalities[7,84,85]. Since the number of potential natural chemicals is too large, research on these molecules promises the possibility of new, cheap, and effective treatments of the Alzheimer disease[86]. The most common herbal and plant therapies are chemical agents that exhibit diverse beneficial pharmacological and biochemical activities [87,88](Figure 4). Phytochemicals have been proven as based on scientific facts and shown as effective in the prevention and treatment of Alzheimer as well as affordable and safe. Several plants (their family, dose administration, its effect, animal models, and phytoconstituents) are shown in Table (1)

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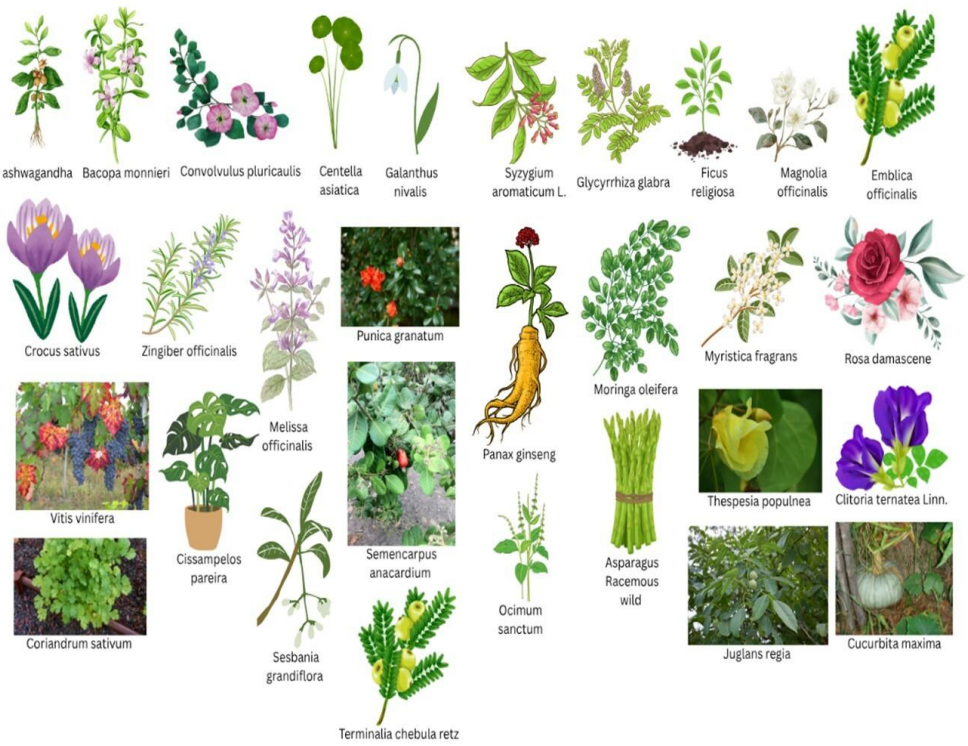

Fig. (3) Plants that exhibit anti-inflammatory, antioxidative, neuroprotective qualities which help in the treatment of AD

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TABLE- 1 Herbs that are used in the Treatment of Ad

S. N	Plant name /common name	Family	Part used	Extraction/ fraction	Active constituents	Drug Administration	Induction model	Treatment duration	Produced effects	Citation
1	Withania somnifera (ashwagandha)	Solanaceae	Root	Aqueous extract	Withanone Withaferin Withanolides Withanolides C	Oral administration (100/200 mg/kg)	3-NP-induced HD	14 days	Anti – inflammatory properties Anti –oxidant effects Rejuvenating effects Improved long-term memory and learning ability ↓AChE activity ↑Ach receptor expression ↑cholinergic markers like Ach and ChAT	74,89
2	Curcuma longa (Turmeric)	Zingiberaceae	Rhizome	Hydrophobic extract	Curcumin and polyphenol	Oral administration (10,20 and 50 mg/kg)	SDAT induction	21days	Anti – inflammatory Anti-oxidants	90,91
3	Bacopa monnieri (Brahmi)	Scrophulariaceae	Aerial part	Alcoholic extract	Bacopasaponin A, B, C, D pseudojujubogenin, brohmine, herpestine, monnierin	Oral administration (20,40 and 80 mg/kg)	Ethylcholine aziridium ion (AF64A)	2 weeks	Anti-inflammatory inhibitors properties Anti – oxidants	92

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									Aβ-aggregation inhibitors properties	
4	Convolvulus pluricaulis (Shankhpushpi)	Convolvulaceae	Root	Aqueous, extract	Steroids, anthocyanin's, flavanol, glycosides and triterpenoids	Oral administration (100,150 and 250 mg/kg)	Scopolamine-induced cognitive impairments in wistar rats	7 days	Memory enhancing properties ↓Glutathione reductases, ↓AChE Anti-oxidants Neuroprotective effects	93
5	Centella asiatica (Mandookaparni)	Apiaceae	Whole plant	Aqueous extract	Flavonoids, terpenoids, essential oil, alkaloids, carbohydrate, amino acid	Oral administration (200,500,700 and 1000 mg/kg body weight)	-	15 days	↑ intelligence and improve cognitive function ↑ working memory and improve self-mood AChE inhibitor	94
6	Celastrus paniculants (Jyotishmati)	Celastraceae	Seed	Aqueous extract	Alkaloids, sesquiterpenes, paniculatine B, triterpenoids, sterol	Oral administration (500 and 1500 mg/kg)	Sodium- nitrite induced amnesia rodent model	15 days	Improve memory performance ↓Anticholinesterase enzyme ↑ Ach level	95
7	Nardostachys jatamansi (Jatamansi)	Valerianaceae	Rhizome	Methanolic extract	Carbohydrate ,alkaloids,glycosides, saponins,proteins,amino acid	Oral administration (200 and 400 mg/kg)	Sleep –Deprived amnesic model	14 days	Anti-oxidants ↓Acetyl cholinesterase activity enhance memory by increasing cholinergic level	96

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8	Galanthus nivalis (Common snowdrop)	Amaryllidaceae	Bulbs	-	Galantamines, nivalidine, narwedine, and lycorine	Oral administration 10,30 or 50 mg/kg	Scopolamine induced model	-	Antioxidants and anti-amyloid activities	97
9	Syzygium aromaticum L. (Clove)	Myrtaceae	Flower	Ethanolic extract	eugenol (70–85%), eugenyl acetate (15%) and β-caryophyllene (5–12%).	I.V administration (2 and 10 µg/ml)	$A\beta_{25-35}$ induced neurotoxic cells	-	Acts as a scavenger of superoxide radicals Elevate the antioxidants enzyme (SOD, Cat, GSH)	98
10	Glycyrrhiza glabra (Mulethi)	Leguminosae	Roots	Acetone	Glabridin	Oral administration (1,2 and 4 mg/kg P.O)	Scopolamine – induced impairment	3 days	Neuroprotective agents Anti-inflammatory properties Anti –oxidants ↑Ach level in brain AChE inhibitor	99
11	Ficus religiosa (peepal)	Moraceae	Leaves bark	Methanolic extract	Compestrol, stigmasterol,28-isofucosterol, α-amyrin, β-amyrin, lupeol, tyrosine, asparagines, alanine, threonine	(10,50 and 100 mg/kg I.P)	Scopolamine-induced anterograde and retrograde amnesia in mice	2 days	possesses anti-amnesia effect via modulating brain serotonin levels ↑Ach level memory enhancing effect	100
12	Magnolia officinalis (houpu magnolia)	Magnoliaceae	Stem	Ethanol extract	Honokiol, obovatal, magnolol,4-o-methyl honokiol	Oral administration (10mg/kg)	Transgenic mouse model	3 months	inhibit memory impairment and aβ deposition in the brain tg2576 mice ↓BACE activity	101

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									anti-stress activity	
13	Lepidium meyenii (Maca)	Brassicaceae	Root	Aqueous and hydroalcoholic extract Pentane extract	Macaridine, lepidin A, lepidin B, tetrahydro-β-carbolines, glucotropaeolin, glucoalyssin, benzylisothiocyante, brassicasterol, macamide, macaenes	I.V administration (aqueous-0.50 and2.00g/kg) (hydroalcoholic-0.25 and 1.00 g/kg) (pentane-3,10 mg/kg)	Scopolamine induced memory impairment in mice	35 days	Acts as a neuroprotectant Improve memory deficits inhibitor effect on AChE activity	[102]
14	Emblica officinalis (Amla)	Phyllanthaceae	Fruit	Hydroalcoholic extract	Phenolic compounds, tannoids, tannins, vitamin C, flavonoids, phyllembelic acid, gallic acid, ellagic	Intraperitoneal administration (150,300,450 and 600 mg/kg)	Scopolamine induced amnesia in mice	7 days	Anti-inflammatory agents Memory enhancing properties Ache inhibitors Anti-oxidants	[103]
15	Tinospora cordifolia (Giloy)	Menispermaceae	Leaf	Alcoholic extract	alkaloids, glycosides, lactones, steroids, polysaccharides and aliphatic compounds	Oral administration (140 and 280 mg/kg)	Alprazolam induced amnesia in albino mice	-	Cholinesterase inhibitors Anti-inflammatory effects ↓AChE properties	[104]
16	Crocus sativus (kesar)	Iridaceae	Stigma	Aqueous extract	Carotenoids, crocins, safranal, picrocrocin, quercetin, kaempferol	I.P administration (15 and 30 mg/kg)	Streptozotocin – induced cognitive deficits in rats	3 weeks	Anti –oxidants Anti-inflammatory Acetylcholinesterase inhibitors Aβ-aggregation inhibitors	[105]

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17	Zingiber officinalis (Adhrak)	Zingiberaceae	Rhizome	Ethanolic extract	Essential oil, 6-shogaol, 6-gingerol, 8-shogaol and methoxy-[6]-gingerol	Oral administration (50 and 100 mg/kg, p.o.)	Beta –amyloid induced model in mice	8 days	Nootropic effect rejuvenator ↑acetyl cholinesterase inhibitory activity antioxidant	[106]
18	Panax ginseng (Ginseng)	Araliaceae	Whole part	-	Ginsenosides	Oral administration (100 and 200 mg/kg/d)	Aged senescence-accelerated mouse prone 8 (SAMP8) mice	12 weeks	Neuroprotective effects Improve cognitive and memory performance	[107]
19	Punica granatum (Anar)	Lythraceae	Peel, seed	Water/ ethanol	Punicalin, Punicalagin, quercetin, rutin, catechin, flavan-3-ol	Oral administration (500 mg/kg)	Scopolamine induced cognitive deficit in rats	5 days	Aβ-aggregation inhibitors Cognitive and memory improvement properties	[108]
20	Evolvulus alsinoides (Vishnukranti)	Convolvulaceae	Aerial part	Ethanol extract	Betaine, evolvine stearic acid, oleic acid, linoleic acid	Oral administration (100 and 200 mg/kg)	Scopolamine induced amnesia in rate	30 days	Improve the acquisition and retention of memory Nootropic effect Adaptogenic	[109]
21	Melissa officinalis (lemon Balm)	Lamiaceae	Leaves	Hydro-alcoholic extract	Phenolic compound (rosmarinic acid, caffeic acid, metrillic acid) Flavonoids (Luteolin, apigenin) β-caryophyllene, germacrene, oleanolic acid, uroslic acid	Oral administration (50,100,200,400 mg/kg P.O)	Amyloid β-rat model	30 days	Modulate mood &memory performance ↓STL (step-through latency) Acetylcholinesterase inhibitor Improve cognitive impairment Antioxidant	[110]

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									Nicotinic receptor stimulation	
22	Salvia officinalis (common sage)	Lamiaceae	leaf	Aqueous extract	7α-methoxyrosmonal, diterpenes, rosmarinic acid, carnosic acid, quercetin and isorosmanol	Interperitoneally administration (300 mg/kg)	-	7 days	Shows antioxidants properties Have cognitive-enhancing properties Helps in preventing age-related problems	[111]
23	Ficus racemosa (Goolar Fig)	Racemosa	Bark	Aqueous extract	B-sitosterol, stigmasterol, lupenol, lupeol, gluanol acetate, racemosic acid, kaempferol, bergenin, behenate	Oral administration (250-500 mg/kg)	Exteroceptive behavioral model	4 weeks	Enhanced Ach level in hippocampi Reduction in TL (transfer Latency) Acetylcholinesterase inhibitor memory enhancing activity antioxidant property	[112]
24	Moringa oleifera (Drumstick tree)	Moringaceae	Leaves	50% hydroalcoholic	β-carotene, tannins, phenolic, saponins vitamin C	0ral administration (100,200 and 300 mg/kg)	Age-related dementia	7 days	Improve spatial memory ↓ MDA level ↑SOD, CAT and AChE activity	[113]
25	Prunus Amygdalus (Badaam)	Rosaceae	Seed	Ethanolic extract	Flavonoids, phenolics and anthocyanins	Oral administration (250 and 500 mg/kg)	Scopolamine induced- amnesia	21 days	↑The level of lipid peroxidation antioxidant action	[114]

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26	Myristica fragrans (Nutmeg)	Myristicaceae	Seed	n-hexane extract	Myristicin and myristic acid, eugenol pinene, elemicin, isoelemicin	Oral administration (5,10 and 20 mg/kg P.O)	1.Scopolamine induced amnesia 2.aging-induced amnesia	3 days	Antioxidants Enhanced learning and retention property Acetylcholinesterase inhibitor	[115]
27	Rosa damascene (Gulab)	Rosaceae	Flower	Methanolic extract	Flavonoids (quercetin, kaempferol, myricetin, gallic acid) Glycoside derivatives	I.P administration (300,600 and 1200 mg/kg)	Amyloid-β-induced rat model	21 days	Anti –oxidants Nootropic effects Anti-inflammatory	[116]
28	Vitis vinifera (Angoor)	Vitaceae	Fruit	Hydro-alcoholic extract	Gallic acid, catechin epicatechin, flavone, flavanols quercetin catechin	Oral administration (400mg/kg P.O)	Aluminum-induced oxidative stress in rat brain	45 days	Antioxidant Anti-amyloidogenic Memory enhancer Neuroprotectant	[117]
29	Lavandula angustifolia (Lavender)	Lamiaceae	Leaves Flower	Aqueous extract	Linalool, Linalyl acetate, Flavonoids	Interperitoneally administration (50,100 and 200 mg/kg)	Aβ-induced rat model	20 days	Anti –oxidants Ability to clear Aβ plaques from AD hippocampus Memory and cognitive enhancer	[118,119]
30	Murraya koenigii (Meethi neem)	Rutaceae	Leaves	Ethanolic extract	Phenolic compound, vitamins Carbazole alkaloids, Terpenoids	Oral administration (300-500 mg/kg)	Scopolamine induced aged mice	15 days	Nootropic effect Anticholinesterase property	[120]
31	Ficus carica	Moraceae	Fruit	Ethanolic extract	Flavonoids, glycosides, tannins, maslinic acid, protocatechuic, bergapten, uroslic acid	Oral administration (100 and 200 mg/kg P.O)	Scopolamine induced impairment animal model	27 days	Anti –inflammatory effects Neuroprotective effective Anti-amyloid activity	[121]

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									Cognitive enhancer	
32	Coriandrum sativum (Coriander)	Apiaceae	Leaves	-	Volatile oil, proteins, flavonoid (Quercetin, isoqurectin), caffenic acid, carotene and carbohydrate	Oral administration (5,10 and 15 % w/w)	Diazepam, scopolamine induced amnesia in mice	45 days	↓ oxidative stress in rat hippocampus which improve memory impairment Neuroprotective effects ↓AChE activity	[122]
33	Cissampelos pareira	Menispermaceae	Root	Hydroalcoholic extract	Alkaloids (Pelosine, bebeerine, hyatine, hyatinine, cissampareine, curine)	Oral administration (100,200 and 400 mg/kg P.O.)	Exteroceptive behavioral models	7 days	Significant improve memory and learning properties Anti – inflammatory Anti –oxidants	[123]
34	Rhodiola rosea	Crassulaceae	Root and leaf	Aqueous extract	Phenols, flavonoids, alkaloids	I.V administration (400 mg/kg)	3xTg-AD mice	3 months	neuroprotective, antiapoptotic	[124]
35	Clitoria ternatea Linn. (Shankhpushpi)	Fabaceae	Leaf	Ethanolic extract	Tannins, glycosides, flavonoids	Oral administration (150 and 300 mg/kg)	Stress – induced amnesia in rat	-	↑Acetylcholinesterase activity and Ach content in rat brain improve memory activity Neuroprotective, antioxidant, anticholinergic activity	[125,126]
			Root and aerial part	Alcoholic extract		Oral administration (300 and 500 mg/kg)	Electroshock – induced amnesia in rat	7 days		
36	Sesbania grandiflora	Fabaceae	Seed, fruit	Ethanolic extract	Steroids, saponin, flavonoids, tannins,	Oral administration (200 and 400 mg/kg P.O)	Celecoxib induced amnesia	14 days	↓ AChE and MDA activity	[127]

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					and phenolic compounds				improve memory improve cognitive dysfunction Neuroprotective, Antioxidant, antidementia activity	
37	Areca catechu Linn. (Arecanut)	Palmae	-	Methanolic extract	Polysaccharides, polyphenols (flavonoids, tannins), fibers, proteins, alkaloids (Arecoline, arecoline, guvacine, guvacoline, isoguvacoline, arecoline)	Oral administration (500 m/kg)	-	21 days	Anticholinesterase activity ↓BChE activity Anti –amnesic activity	[128]
38	Acorus calamus. L	Acoraceae	Rhizome	Ethyl acetate, ethanolic and aqueous extract	Quinone, flavonoids, phenols	Oral administration (200, 400, and 600 mg/kg)	Lipopolysaccharide -induced neuroinflammation in rat	NA	Possesses memory enhancing property ↓AChE properties	[129]
39	Thespesia populnea	Malvaceae	Bark	Ethanolic extract	Thespesone, mansonone-D, mansonone-H, thespone	Oral administration (100,200 and 400 mg/kg)	Exteroceptive behavioral models	7 days	memory improving property cholesterol lowering property anticholinesterase anti-inflammatory activity	[130]

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40	Semencarpus anacardium	Anacardiaceae	Seed	Milk extract	Alkaloids, unsaturated lipid, terpenoids, steroids flavonoids, glycosides	Oral administration (100 mg/kg BW)	NH_4Cl- induced hyperammonemia rats	8 days	Nootropic effect Memory enhancing properties ↓AChE anti-inflammatory property	[131]
41	Asparagus Racemous wild (Satmuli)	Asparagaceae	Root	Methanolic extract	Steroidal saponins, isoflavones, asparagine, essential oil, flavonoids, resin, tannin, arginine, tyrosine	Oral administration (100 mg/kg)	Scopolamine induced amnesia mouse model	One week	↓Monoamine oxidase A Neuroprotective effects Anti-oxidants	[132]
42	Sida cordifolia L.	Malvaceae	-	Aqueous and hydro-ethanolic extract	Ephedrine, pseudoephedrine, quinazolines, cryptoleptins, fumaric acid, sterculic flavonoids, saponins, n-methyl tryptophan	Oral administration (50,100 and 250 mg/kg)	Reserpine induced model	7days	Neuroprotective effects Anti-oxidants Anti-amnesic properties AChE inhibitors	[133]
43	Ocimum sanctum (Tulsi)	Labiatae	Hole plants	Hydroalcoholic extract	Alkaloids, glycosides, saponins, tannins, vitamin C, maleic acid, citric acid, tartaric acid	Oral administration (300 and 500 mg/kg P.O)	H2O2 induced neuronal cell		Antioxidant activity ↓lactate dehydrogenase leakage ↓lipid peroxidation DNA damage ↓ ROS generation	[134]

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44	Cucurbita maxima (Pumpkin)	Cucurbitaceae	seeds	NA	Ferulic acids, caffeic acid, and coumaric acid	Oral administration (100 and 200 mg/kg)	Scopolamine induced- amnesia	5 days	Antioxidants properties and helps in relieving stress Anti-amnesic effect ↓TNF expression in hippocampus ↓Acetylcholinesterase ↑Glutathione levels	[135]
45	Juglans regia (Walnut)	Juglandaceae	kernel	Ethyl acetate extract	α-tocopherol, ellagic acid, and juglone	Oral administration (2 or 4 µg)	Amyloid-beta peptide-induced cell	-	↓Oxidative stress Shows anti-amyloidogenic activity	[136]
46	Terminalia chebula retz	Combretaceae	Fruit	ethanolic extract	7- methyl gallic acid chebulic acid, terchebin, gallic acid, punicalagin	I.V administration (20-100 µg/ml)	Aβ induced toxicity	-	Memory enhancer Anti-inflammatory Anti-aging Anti –oxidants ↓AChE and BChE	[137]
47	Enclipta prostrata L.	Asteraceae	-	Ethanolic extract	Alkaloids, glycosides, coumarins, flavonoids, sterols	Oral administration (25,50,100 and 200 mg/kg P.O)	Scopolamine induced in mice	One week	↑level of superoxide dismutase ↓Glutathione-S-transferase ↓MDA in brain Nootropic effect	[138]

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									Enhance memory and learning activity	
48	Cuminum cyminum Linn. (Cumin)	Apiaceae	seeds	Aqueous extract	Monoterpenes β-pinene, P-cymene, Cinnamaldehyde and menthadien carboxaldehydes	Oral administration (100,200 and 300 mg/kg/day)	Scopolamine – induced amnesia	-	Acts as a scavenger of free radicals Protects the CNS against any injury Act as a memory impairment Anxiolytic effect Neuroprotective effects	[139]
49	Pistacia vera L. (pistachio)	Anacardiaceae	Seeds	Hydroalcoholic extract	Vitamin E family, carotenoids, phenolics, flavonoids	Oral administration (10,50, or 100 mg/kg)	-	14 days	Possesses antioxidant and anti-amyloid activities Improve learning and memory	[140]
50	Uncaria rhynchophylla (Gouteng)	Rubiaceae	Stem	Aqueous extract	Rhynchophylline, isorhynchophylline, and hirsuteine	Oral administration (10,20 and 30 mg/kg)	Scopolamine induced model	-	Free radical scavenging activity Protection against kainic acid- induced neuronal damage	[141]

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51	Cicer arietinum L. (Chickpea)	Fabaceae	Entire plant	-	Carbohydrates, proteins, amino acids, fixed oil, alkaloids, phenolic compounds	Oral administration (10 mg/kg)	$AlCl_3$- induced model	6 weeks	Neuroprotective effects	[142]
52	Ptychopetalum olacoides (Marapuama)	Oleaceae	Roots	Ethanolic extract	Ptychonal, muirapuamine, and theobromine	I.P. administration (50,100 and 800 mg/kg)	Memory deficits aging mice	2.5 months	Possesses antianemic, anticholinesterase, and neuroprotective properties	[143]
53	Scutellaria baicalensis Georgi) (skullcap)	Labiatae	Root	70% ethanolic extract	Flavonoids, wagonin, baicalin, oroxylin A	Oral administration (10,30 and 100 mg/kg)	Ibotenic acid induced model rats	1 week	Promotes the recovery of memory loss	[144]
54	Thymus vulgaris (Thyme)	Lamiaceae	-	Hydro – alcoholic extract	Thymol, carvacrol, 8-terpinene, p-cymene and α-pinene	Oral administration (50 and 100 mg/kg/BW)	Scopolamine-induced amnesic rat	15 days	↓subcortex MDA level Increase Ach level in brain	[145]

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55	Olea europaea (Olive)	Oleaceae	Fruit, oil, leaves	Methanol-ethanol extract	Oleuropein, tyrosol, hydroxytyrosol, caffeic acid, verbascoside, and rutin	Oral administration (360,600 or 1000 mg/kg W/W)	-	3 months	Possesses antioxidant, anti-inflammatory, and antiamyloid properties	[146]
56	Allium sativum (Garlic)	Amaryllidaceae	Bulb	Ethanol extract	2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)	Oral administration (5,10 and 20 mg/kg)	Aβ- induced model	3 weeks	Neuroprotective Anti-inflammatory activities ↓intracellular reactive oxygen species (ROS)	[147]
57	Mentha piperita L. (Peppermint)	Lamiaceae.	Leaves and aerial part	n-hexane	menthol, menthone, neomenthol, methyl acetate, isomenthone, 1,8-cineole, linalool, α-pinene, β-pinene, limonene, carvone, and pulegone	Oral administration (50 and 100 mg/kg)	Scopolamine-induced amnesia	19 days	Nootropic effects Anti-amnesic effects	[148]
58	Coptis chinensis Franch.	Ranunculaceae	Entire plant	-	Berberine	Oral administration (25 or 100 mg/kg/day)	Transgenic AD mice	4 months	Anti-oxidants Neuroprotective effects Memory enhancer AChE inhibitors	[149]

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59	Foeniculum vulgare (Fennel)	Apiaceae	seeds	Methanolic extract	Estragole, limonene, fenchone, and β-myrcene	Oral administration (200 mg/kg P.O)	Scopolamine – induced amnesia modeling mice	8 days	↓effect against AChE and BChE ↑ROS production ↑Lipid peroxidation Neuroprotective effects	[150]
60	Spinacia oleracea (spinach)	Amaranthaceae	Leaves	-	Ferulic acid, coumaric acid, quercetin, spinacetin, and myricetin	Oral administration (400 mg/kg BW)	-	14 days	↓Neuronal death and production of ROS ↓Locomotor activity ↑serotonin level ↑pentobarbitone induced sleeping time	[151]
61	Phoenix dactylifera L. (Date palm)	Aceraceae	Fruit	NA	Cinnamic acid, caffeic acid, protocatechuic, gallic acid, dactylifiric acid, and epicatechin	Intracerebroventricularly administration (2% and 4%)	Transgenic mouse model	4 months	Antioxidants properties Helps in enhancing memory ↑Learning and memory impairment ↓astrocyte and microglial activation ↓amyloidogenic APP metabolism by modulating β- secretase	[152]

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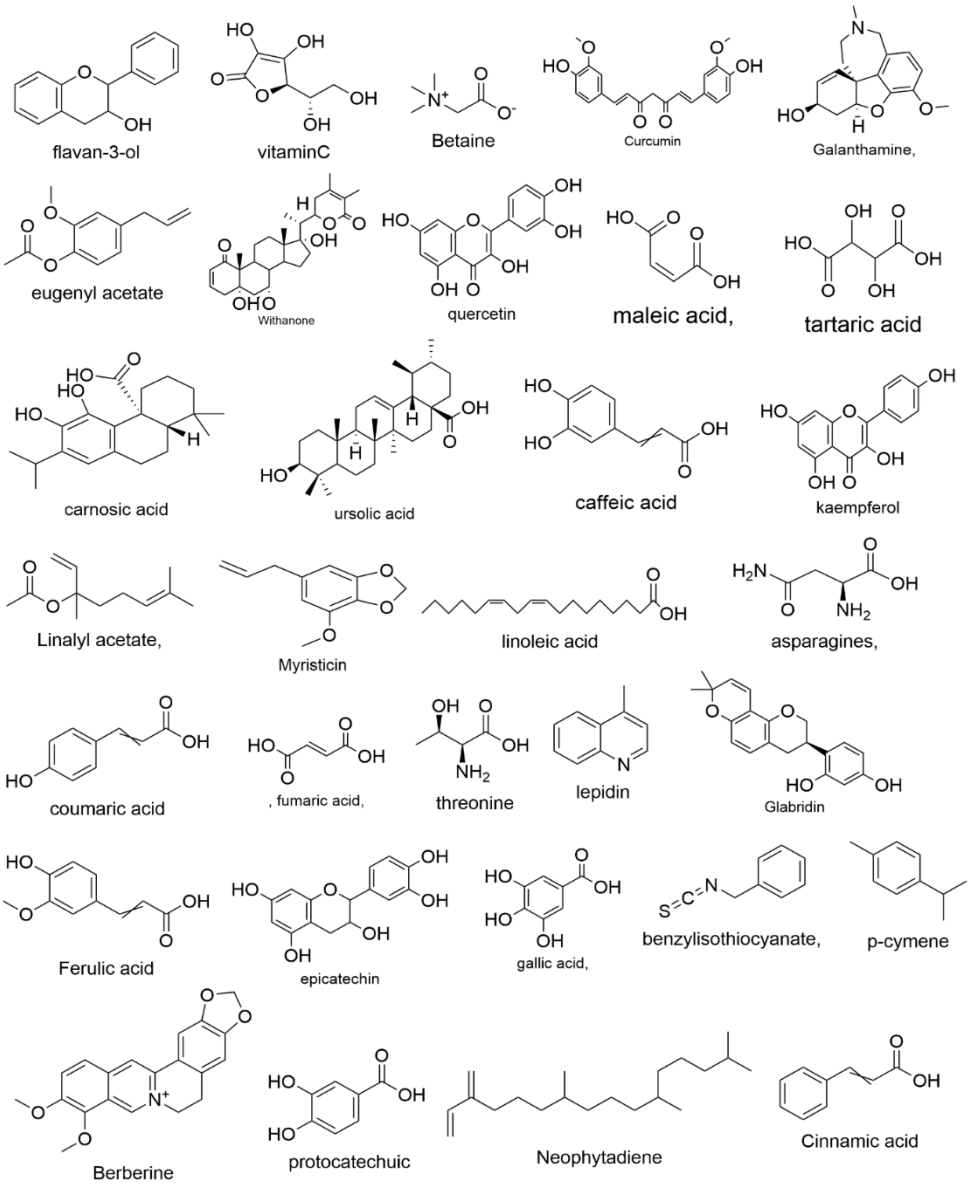

Fig. (4) Example of plant-derived phytochemical for AD

3.2 Chemical based therapy –

In order To slow the course of the behavioral, psychological, and cognitive symptoms of Alzheimer's disease, the current drug treatment approach is sympatholytic rather than curative. The FDA-approved medications shown in Table (2) Figure (5) [153,154] are administered orally and transdermally and are members of the NMDA antagonist receptor and anticholinesterase inhibitor (AChEI) families. [155,156] Memantine is used for moderate to severe Alzheimer's disease, while galantamine, rivastigmine, and donepezil are used for mild to moderate Alzheimer's. NMDA receptor antagonists and cholinesterase inhibitors (cholinesterase inhibitors) are two types of medications used in chemical-based therapy. [157]

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TABLE- 2 FDA- Approved Drugs that are used in the treatment of AD

S.NO	DRUG	BRAND NAME	CATEGORY	TARGET	STATUS	ADMINISTRATION
1	Brexpiprazole	Rexulti	Atypical antipsychotic	Novel D2dopamine andserotonin1A partial agonist	FDA approved in 2023	Orally administrated
2	Donepezil	Aricept	AChEIs	Reversible acetylcholinesterase inhibition Increase synaptic acetylcholine	FDA approved in 1996	Orally administrated
3	Rivastigmine	Exelon	AChEIs	Inhibits both BChE and AChE	FDA approved in 2000	Administered through Orally or via transdermal patch
4	Galantamine	Razadyne	Parasympathomimetic	Competitive inhibitor of AChE	FDA approved in 2001	Orally administrated
5	Memantine	Namenda	NMDA antagonist	NMDA receptor antagonist	FDA approved in 2013	Orally administrated
6	Tacrine	Cognex	parasympathomimetic	reversible cholinesterase inhibitor	FDA approved in 1993	Orally administration
7	Aducanumab	Aduhelm	Anti-Aβ Immunotherapies	Targeting Aβ plaques	FDA approved in 2021	IV administration
8	Lecanemab	Leqembi	Anti-Aβ Immunotherapies	Targeting Aβ	FDA approved in 2023	IV administration
9	Semorinemab	-	Tau-targeting therapies	Anti-tau monoclonal antibodies	Phase II/III	IV administration
10	Tideglusib	-	tau-targeting therapies	GSK-3β inhibitor Decrease Tau hyperphosphorylation	Phase II	IV administration

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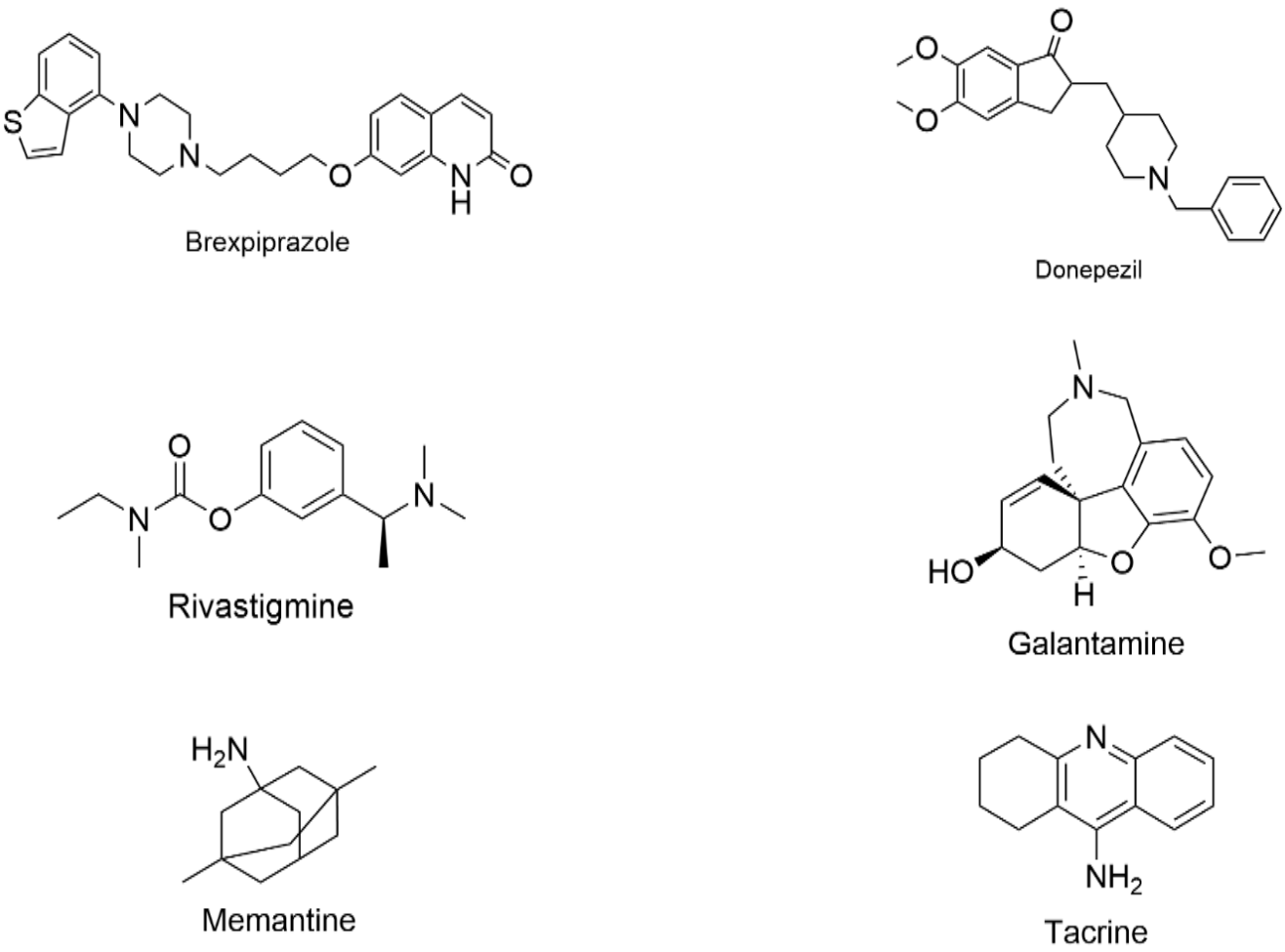

Fig. (5) Structure of FDA approved drugs for the management of AD

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3.3 Alternative interventions-

Neurodegenerative diseases can be treated pharmacologically, and non-pharmacological therapies can be used instead of drugs. [156]. In addition to adopting an improved lifestyle, some researchers are keen to involve the use of alternative methods as preventative intercessory measures for AD[158]. The Alzheimer Prevention Foundation International (APFI) has guidelines for the prevention of AD, which are presented in Figure (6).

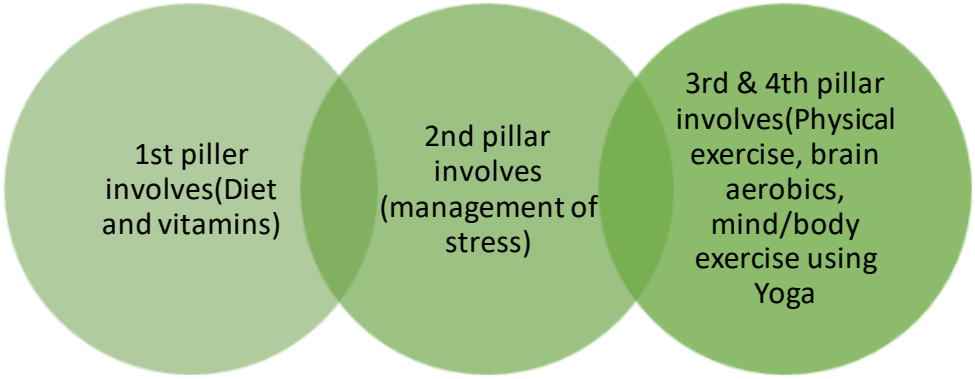

Fig (6). Shown four pillars for prevention of AD

Other alternative approaches may include music therapy, Diet therapy, & physical therapy

3.3.1 Music therapy-

The patient's quality of life and confidence can be greatly enhanced by MT, an exciting nonpharmacological approach for treating Alzheimer's disease[159]. These neurogenesis processes caused by music can be beneficial to Alzheimer patients since it enhances mood and mentality state of the disease-affected-people due to the prevention of the anterior hippocampus atrophy build-up and possible restoration of the hippocampus integrity, other possible effect shown in figure (7) [160,161]Other patients have found that it enhances AD pathology, agitation and anxiety, depression, aggressive behavior, and episodic memory and decelerates the rate of cognitive deterioration, especially in autobiographical, amyloid depositing, and glucose metabolic terms[162]. Consequently, music is a unique stimulus that effectively engages patients due of its memorizing ability. Therefore, it may be used as a possible strategy to treat Alzheimer's disease symptoms, thereby improving the cognitive state and general well-being of patients[160]. The application of MT appears to be safer than Hormonal Replacement Therapy (HRT), and patients are not at risk of adverse side effects. It is important to remember that no unwanted results from the music existed[163]. The ability of MT to enhance sleep levels by acting as a melatonin agonist may benefit sleep without posing a risk of hormone treatment. In addition, MT is easy to administer and is safe, effective, and compliant form of treatment. [164]

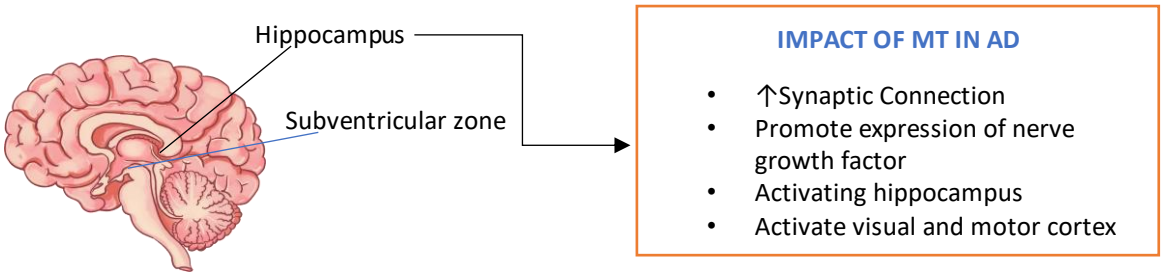

Fig. (7) shows the mechanism of music therapy in Alzheimer disease

3.3.2 Diet therapy-

Diet, in combination with physiological needs, considerably impacts the nature and composition of the microbial population in the gastrointestinal tract. The incorrect development of intestinal microecologies due to incorrect dietary preferences may activate a chain reaction of inflammatory processes. The etiology of Alzheimer's disease may be significantly influenced by this imbalance. The presence of a large variety of mechanisms through which dietary interventions may enhance the functionality of the brain, including

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regulation of the composition of gut flora[165]. Probiotics are the most commonly consumed nutritional supplement. According to a study on the effects of probiotics on cognitive functioning, there are several ways through which probiotics can be used to enhance mental performance. The 12-week intervention targeted people between the ages of 60 and 90 and comprised a regular (usual) diet and incorporation of 200 mL of probiotic milk daily.

The results of the study indicated that probiotic supplementation therapy prevents neuron-neuroexcitation and neuroinflammation, as the supplemented group in the experiments had superior cognitive performance[166]. The ketogenic diet, also known as the modified Atkins diet, has low levels of proteins, sugars, and high amounts of fat[167]. A low-glycemic diet has proven to be beneficial in Alzheimer's disease treatment because of the high metabolic histopathological issues that predominate before brain development[168]. Of the 26 randomly assigned to a randomized, double-blind trials, 21 (81%) successfully completed the entire research process. This is an experiment in which patients with early-stage Alzheimer's disease were questioned about changes in their brain functions after following a ketogenic diet. Although the findings demonstrated a significant increase in cognitive ability in the ketogenic diet group compared to the regular diet group, there was a statistical insignificance in its relation to the variation in the ketogenic diet group's cognitive capacity. In addition, a significant improvement in the quality of life and functional performance was observed in the ketogenic diet group[169]**.** The MIND diet has gained popularity because it can be used to delay the onset of Alzheimer's disease and has neuroprotective effects[170]. Dietary Approaches to Control Hypertension (DASH) and Mediterranean diet are incorporated into the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND diet), and compared[171] to the improvement of anti-inflammatory and antioxidant potential of the brain based on the pathways of the gut flora and gut-brain axis, the MIND diet includes amino acids such as it also contains micronutrients such as vitamin D and B vitamins that help brain function and are coordinated in reducing the advancement of Alzheimer's disease. [171]

4. Conclusion-

Alzheimer's disease has a complex pathology, which can be successfully treated with the multimodal treatment package, which involves evidence-based non-pharmacologic alternative modalities, synthetic pharmacologic, and phytoconstituent based methods. Whereas bioactive compounds found in plants and integrative ways of healing provide neuroprotective, anti-inflammatory, and resilient synapses, conventional medicines can influence amyloid and tau pathology. Advanced delivery technology, including nanocarriers and personalized drug conjugates, could increase the precision and bioavailability of treatment in the brain. Individualized regimens consisting of lifestyle management regimens, multi-target medications, and molecular diagnostics based on the leadership of AI are secrets of the future. The goals of these regimens include the restoration of cognitive integrity and functional independence in patients as well as decreasing neurodegeneration.

Submission Declaration:

This manuscript has not been published previously and is not under consideration for publication elsewhere. The authors confirm that the work is original and have read and approved the final manuscript for submission.

Conflict Of Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Declaration Of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Ethics Statement:

This review paper, "**Holistic and Conventional Approaches in Alzheimer's Therapy: Exploring Herbal, Synthetic, and Alternative Interventions",** involves no experimental research, human subjects, or animal studies that need ethical approval; instead, it is based entirely on publicly available literature. For academic openness and integrity, all acknowledged sources were appropriately referenced. I have done all in my power to provide an objective, accurate, and thorough literature review free from any conflicts of interest that could affect how the data are interpreted. The development of this study did not involve any instances of scientific misconduct, data manipulation, or plagiarism. Let me know if you need refinement.

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