

Unlocking Nature's Potential Natural Compounds for Alzheimer's Disease Treatment.

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ABSTRACT

A high incidence of dementia (60–80%) and a high rate of memory loss are two of the most common symptoms of Alzheimer's disease (AD), which affects the elderly. Researchers have recommended that traditional Chinese medicine (TCM) and Indian medicines can be used to prevent and cure AD. Several studies have linked neuroinflammation linked to amyloid- β (A β) deposition in the brain to the pathophysiology of neurodegenerative disorders. As a result, more research is needed to determine the role of inflammation in neurodegeneration. Increased microglial activation, cytokine production, reactive oxygen species (ROS), and nuclear factor kappa B (NF- κ B) all play a role in the inflammatory process of AD. The significance of neuroinflammation in neuroprotection and the molecular mechanisms that various natural compounds, phytochemicals, and herbal formulations employ in various signalling pathways are the main topics of this review. Researchers are currently concentrating on naturally occurring substances that are pharmacologically active and have the ability to reduce neuroinflammation, which makes them a potential treatment option for AD. The researchers also looked into the limitations of earlier research on AD, TCM, and Indian Ayurveda. The effects of therapeutic whole-plant extracts on AD have been the subject of numerous investigations. Clinical studies have demonstrated the anti-inflammatory, anti-amyloidogenic, anticholinesterase, and antioxidant qualities of lignans, flavonoids, tannins, polyphenols, triterpenoids, sterols, and alkaloids. This review includes a list of additional sources as well as information about several medicinal plants and isolated substances that are used to treat AD.

I. INTRODUCTION

Alzheimer disease (AD) is a debilitating neurological condition that progressively deteriorates memory and cognitive abilities [1] It has become a major public health concern that impacts individuals,

families, and healthcare systems globally since Dr. Alois Alzheimer first brought it up in 1906. An outline of Alzheimer's disease's pathophysiology, epidemiology, and clinical manifestations. It is a complex neurological disorder characterized by progressive behavioral problems, cognitive decline, and memory impairment. The incidence increases with age, primarily impacting the elderly. As the world's population ages, the burden of AD is expected to rise sharply, posing major challenges to healthcare systems and society at large.[2] Approximately 44 million individuals globally suffer from the illness or dementia associated with it. Nevertheless, current estimates indicate that by 2050, this ratio would more than triple.[3] The diagnosis of Alzheimer's disease occurs every 66 seconds. [4] 44 million individuals globally suffer from the illness or its associated disorders. Though current estimates indicate that this ratio would more than triple by 2050, [5] This is not an inevitable outcome. AD manifests in three ways: memory loss, cognitive impairment, and ultimately the incapacity to take care of oneself. Because of this development [6] AD units are now the most prevalent kind of special care unit in nursing homes. Taking care of AD sufferers not only places a load on everyone involved in the process, including the family's finances. Because of this illness, public health and medical institutions face a major challenge in preventing and treating AD. Therefore, substantial funds should be set aside for fundamental studies on the illness.[7] Traditional Indian and Chinese medicine was initially used to prevent and treat neurodegenerative diseases more than 3000 years ago in China and other South Asian countries.[8] The idea of comprehensive treatment, which is central to the practice, is a basic tenet of TCM. It is currently largely employed in multitarget and multichannel treatment, which can be used to prevent and treat diseases that have multiple targets and are challenging to treat.[9] Ginkgo biloba extracts, including EGB761, have been shown by researchers to enhance neuropsychiatric symptoms,

cognitive function, and functional abilities in AD patients. When using herbal remedies, baicalein [10] Tanshinone [11] and huperzine A are monomers that have been shown to be effective in treating AD. The purpose of this review is to provide an overview of the various medicinal plants and isolated compounds that are used to treat AD.

PATHOPHYSIOLOGY

Two of the most popular theories, the tau protein hypothesis and the A β theory, both contend that AD is caused by A β plaques in the brain [12]. Of the three probable situations, the A β theory is the most widely accepted and utilized. According to the A β hypothesis, the tau protein hypothesis is the least frequently accepted theory in the scientific world,

whereas the A β hypothesis is the most widely accepted theory. After being broken down by the enzyme β -secretase, amyloid precursor proteins build up in the brain as amyloid β -plaques, which subsequently cause A β protein to build up. This type of cutting produces a number of unique compounds, each of which may contribute to the long-term development of AD.

Conversely, the most significant of the three components is the molecule A β . It accumulates and forms oligomers despite having a high propensity for improper folding. These oligomers eventually form plaques in the brain, impairing nervous system function. It is challenging to differentiate between the different kinds of oligomers that may be hazardous to human health using currently available techniques.

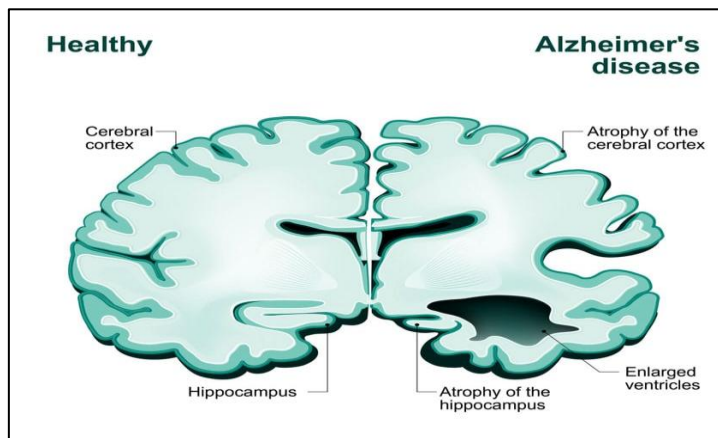


FIGURE 1 : Disintegrating Microtubules in Alzheimer's Disease

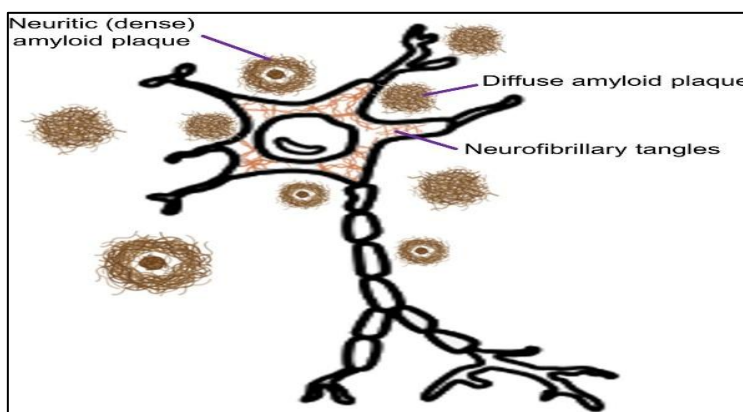


FIGURE 2 : Amyloid Plaques and Neurofibrillary Tangles in Alzheimer's Disease

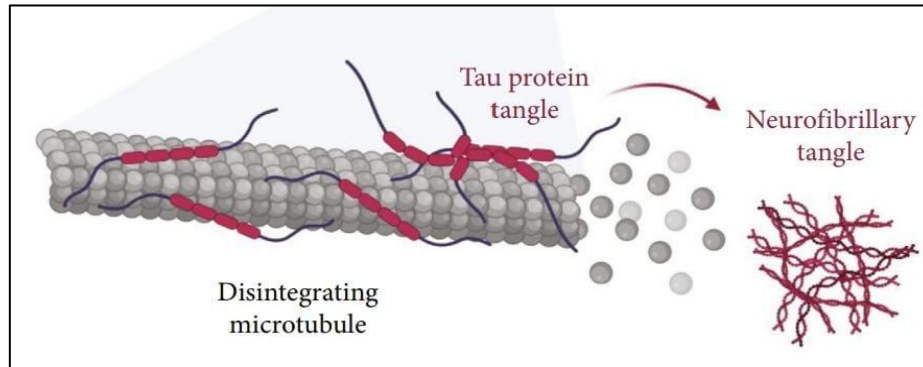


FIGURE 3 : Tau Protein Tangles and Microtubule Disintegration

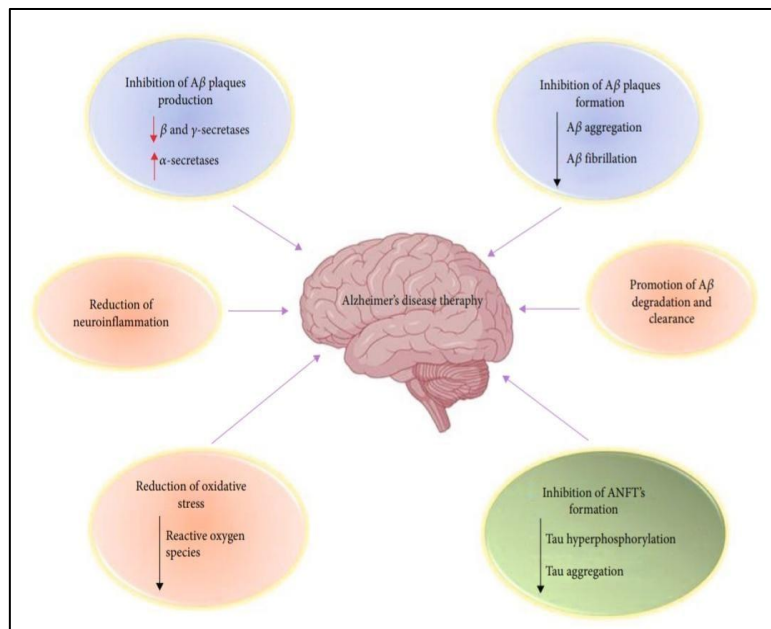


FIGURE 4 : The many pathways linked with Alzheimer's disease therapy are depicted schematically.

The development of neurotic plaques from extracellular A β is the hallmark of cerebral amyloid vascular disease (CAVD), sometimes referred to as cerebral amyloidosis. Early in the course of the illness, diffuse A β plaques were observed in the brain's frontal and parietal lobes, confirming the virus's existence. Although the precise course of the disease is currently unknown, it is anticipated that as it advances, diffuse plaques and neurogenic plaques will become more common throughout the larger neocortical region, spreading in the following directions: neocortex, hippocampus, brain stem, and cerebellum. According to a different view, the tau protein lessens the effect of A β on brain function. The brains of AD patients often have disordered and phosphorylated tau protein, which is also the case in healthy individuals, according to similar studies in

the general population. Tau protein is very dangerous because it is insoluble, clumps together, and takes on a variety of shapes and forms [13]. When the pathogenic tau protein interacts with surrounding healthy neurons, it can misfold and spread throughout the brain, causing AD and other neurodegenerative diseases like Parkinson's disease and vascular dementia. The scientific community refers to these proteins as prion-like proteins because they can cause homologous proteins to exhibit the same aberrant conformation [14], which makes them contagious. A self-amplification cascade starts at some point during the process because homologous proteins frequently produce the same aberrant conformation. Numerous research have indicated a causal relationship between A β and the production of p-tau [15, 16], and other studies have confirmed similar findings. The Src

kinase Fyn, which uses the neurotransmitter NMDA as a substrate, is postsynaptically targeted by the axonal protein tau and its phosphorylated version (p-tau). According to an animal study, tau has a dendritic effect on A β , causing postsynaptic toxicity of A β in transgenic mice that produce human amyloid precursor protein. The behavioral problems of these transgenic animals are improved when endogenous tau levels are reduced. Additionally, it was shown that oligomeric A β stimulated astrocytes to release glutamate, which was followed by synaptic NMDA receptors. Roberson and associates found that stimulation raised tau levels in brain neurons [16]. All of these studies provide credence to the theory that, as mentioned earlier, tau levels in the environment control A β toxicity. Particular concern is not the amount of A overexpressed or depleted in the body, but rather the amount of neurotoxicity existing in the body [17]. In several studies, a decrease in the total number of synaptic connections has been associated with an increase in p-tau expression, although this has not always been the case. A lack of microtubules causes the protein tau to develop improperly in glial and neuronal cells. This abnormal development is suspected to be the cause of several neurodegenerative disorders.

Neuroprotective potential of Medicinal plants against Alzheimer's disease

Since the beginning of human history, medicinal plants have been utilised to treat illnesses all across the world. Natural products have attracted a lot of attention and advanced humankind. Natural goods have attracted a lot of attention and helped create new medications. Neuronal novel medications may benefit from the use of medicinal plants. The brain's neuronal neurotransmitter systems may benefit from the use of medicinal herbs. Chemical messengers called neurotransmitters are used by the brain's neurotransmitter systems. Neurotransmitters are chemical messengers that carry data from one nerve cell to another. An imbalance in these neurotransmitters can cause a number of neurological and mental health conditions. Numerous therapeutic plants can treat a range of neurological and mental health conditions. The potential of a number of therapeutic herbs to affect neurotransmitter levels and function has been investigated [18]. Been investigated for their ability to affect neurotransmitter activity and levels. Plant extracts may be a more effective and innovative therapeutic option for AD since they can affect numerous targets at once, making them preferable to single medications. Alkaloids, once, which makes them a

more effective and cutting-edge AD treatment option. Among the crucial secondary metabolites of plants are alkaloids, flavonoids, and phenolic acids. It has been shown that flavonoids and phenolic acids are important in avoiding neurodegeneration in AD. Antioxidants are important in avoiding neurodegeneration in AD. Antioxidant-rich plants may help reduce the pathogenesis of neurological symptoms by minimising oxidative stress, which is known to be one factor that speeds up the advancement of AD. In fact, because of the substantial impact of medication, avoiding oxidative effects stress, which is believed to be one element that promotes AD progression, Antioxidants are important in mitigating AD-related neurodegeneration [19,20,21]. By minimising oxidative stress, which is known to be one factor that speeds up the course of AD, antioxidant-rich plants may help reduce the aetiology of neurological symptoms. In reality, medicinal plants have a considerable effect on avoiding oxidative stress, which is known to be one factor that accelerates the progression of AD, without causing any visible side. In fact, researchers are developing scientific interest in medicinal plants because of their enormous array of chemical diversity and their considerable effects, which have no discernible negative effects [22,23]. Only a small number of herbal medicines have been investigated in clinical testing, despite the fact that many of them have shown promising outcomes in experiments. Experimental results for the medicinal plants that have demonstrated efficacy in treating AD are encouraging. Panax ginseng (PG), Curcuma longa (CL), Centella asiatica (CA), Ginkgo biloba (GB), Glycyrrhiza glabra, Withania somnifera (WS), Bacopa monnieri (BM), Tinospora cordifolia (TC), and Convolvulus pluricaulis (CP) are among the medicinal plants that have demonstrated efficacy in treating AD. A review of a few plants with anti-AD and other pharmacological properties offers fresh perspectives on treating AD. This review offers fresh perspectives on how to treat AD [24].

1. Panax ginseng

PG is a widely used traditional Chinese medicine that is a member of the Araliaceae family. It is used to treat a variety of conditions, such as neurological illnesses, cancer, inflammation, and cardiovascular disease. Furthermore, a recent study on PG, a widely used traditional Chinese medicine that belongs to the Araliaceae-family, suggested that because of its neuroprotective qualities, it has the potential to cure liaceae and is used to treat a variety of illnesses, including cancer, inflammation, and several diseases related to the central nervous system, including AD.

Neurodegenerative and cardiovascular diseases are associated with ginseng [25]. Furthermore, in a recent study, phytochemicals such as sugars, carbohydrates, amino acids, phytosterol, and saponins [26,27]. However, the main components that prevent Alzheimer's are ginsenosides and gintonin [28].

2. Curcuma longa

Due to therapeutic properties, CL, a member of the Zingiberaceae family, has been used to treat medical conditions from ancient times [29]. Due to its ability to treat a wide range of illnesses, including liver blockage, jaundice, ulcers, colds, inflammation, and brain disorders, CL, often referred to as turmeric, has been utilized for a long time. Terpenoids, flavonoids, phenylpropene derivatives, alkaloids, and steroids are among the chemical components of CL that have therapeutic efficacy against the aforementioned illnesses [30–31]. The acetylcholinesterase activity in AD is inhibited by curcuminoids. Recent research indicates that curcumin may be therapeutically effective in the pathophysiology of AD, and investigations conducted in vitro have indicated that curcumin suppresses A β aggregation and A β -induced neuroinflammation [32]. Furthermore, curcumin has been demonstrated to alleviate behavioral impairment in AD animal models by reducing tau phosphorylation, A β deposition, and A β oligomerization in vivo [33–34]. The main neurotoxin in AD that results in oxidative stress and neuronal degeneration is amyloid-oligomers.

3. Ginkgo biloba

GB is a popular herbal plant with significant therapeutic significance that is a member of the Ginkgoaceae family [37]. Bioactive substances such as flavonoids, terpenoids, proanthocyanidins, phytosterols, and carotenoids are abundant in GB leaves [38,39]. The main components with therapeutic efficacy include flavonoids such as biflavones like bilobetin, ginkgetin, and isoginkgetin and flavonols like quercetin, kaempferol, myricetin, and isorhamnetin. Furthermore, there is significant pharmacological activity in the terpenoids (ginkgolides A, B, C, J, M, K, and L), sesquiterpene (bilobalide), phytosterols (stigmasterol, β -sitosterol), and carotenoids (α -carotene, γ -carotene, and lutein). Many disorders, including atherosclerosis, diabetes, asthma, cancer, and AD, are treated with the bioactive chemicals derived from the leaves, exocarp, and seeds of GB [40,41]. Nonetheless, the primary role of flavonoids with antioxidant activity is in the treatment of AD [42]. Through diverse neuro-pharmacological routes,

natural bioflavones have also been shown to have neuroprotective properties in a variety of neurodegenerative disease models. Additionally, the researchers proposed that GB inhibits A β -induced neuroinflammation and lowers neuroinflammation by stimulating microglial M2 polarization and blocking the activation of the NLRP3 inflammasome. GB thus provides protection against AD's clinical manifestations [43]. Ginkgetin, one of the bioflavones, recently demonstrated neuroprotective efficacy by blocking neuro-inflammatory and apoptotic pathways in a study by Tian et al. [44].

4. Centella asiatica

CA, sometimes called Mandukaparni, is a well-known medicinal plant in the Umbelliferae family that is used to cure a variety of illnesses because of its exceptional pharmacological qualities [45]. Carotenoids, terpenoids, phenols, sugars, and amino acids are abundant in the plant's leaves, according to a thorough investigation into the chemical composition of the plant. Additionally, tannins, sugars, resins, glycosides (brahminoside, centelloside, asiaticoside A, glycoside D, and Future Pharmacol. 2023, 3 887 asiaticoside B), and phenolic compounds (kaempferol, chlorogenic acid, quercitrin, and luteolin) are among the other phytoconstituents of CA. Centellosides, or pentacyclic triterpenoid saponins, are also found in CA and are thought to be one of the plant's primary bioactive substances. As a powerful medicinal plant with beneficial pharmacological properties, including as antifungal, antidiabetic, antioxidant, antiulcer, cardioprotective, immunostimulant, and hepatoprotective properties, CA has piqued interest. The plant has also long been used as a neuroprotective herb to treat a variety of CNS conditions, including anxiety, dementia, epilepsy, and AD. Among these, it has been demonstrated that the CA extract promisingly improves memory and learning in AD patients [46-47].

5. Glycyrrhiza glabra

Glycyrrhiza, a member of the Leguminosae family and one of the most popular herbs in the world, has six variations and 29 species [48]. The Chinese Pharmacopoeia lists three kinds of Glycyrrhiza plants as medicinal: Glycyrrhiza glabra (GB), Glycyrrhiza uralensis (GU), and Glycyrrhiza inflata (GI). Glycyrrhiza's diverse range of chemical components, which include flavonoids (liquiritin, liquiritigenin, chalcones isoliquiritin, and isoliquiritigenin), isoflavonoids (glabridin, galbrene, and shinpterocarpin), stilbenoids, coumarins, alkaloids,

polysaccharides, triterpenoid saponins, and proteins. The plant's dried roots and rhizomes have been used in medicine for millennia because of their antibacterial, expectorant, antiulcer, anxiolytic, and diuretic properties [49]. Additionally, GB has been shown to have neuroprotective, anti-inflammatory, and antioxidant properties in the treatment of dementia-related neurodegenerative illnesses [50-51]. It has been shown that Glycyrrhiza crude extract, active phytoconstituents, and their derivatives have excellent anti-AD potential by acting on many AD events, such as suppression of A β and pTau.

6. Bacopa monnieri

Often referred to as the miracle tree or the tree of life, BM, a member of the Plantaginaceae family, is used extensively as a functional food and nutritional supplement all over the world [52]. For ages, BM, also called Brahmi, has been utilized as a nootropic ayurvedic plant to treat a variety of neurological conditions. Antioxidant, antibacterial, antifungal, antidiabetic, antihypertensive, anticancer, hepatoprotective, antineoplastic, bronchodilatory, and immunostimulatory properties are just a few of the numerous pharmacological actions of this medicinal herb. Memory and cognitive abilities are greatly improved by a number of neuroprotective triterpenoidal saponins, including betulinic acid, bacoside-A, bacoside-B, and bacosaponins [53,54]. Interestingly, the results of the study indicate the use of an extract of BM for the treatment of AD because it has cholinergic effects similar to those of galantamine, rivastigmine, and donepezil [55].

7. Tinospora cordifolia

TC, also called Guduchi, is a perennial climbing herb found all over the world that is a member of the Menispermaceae family [56]. Immunomodulatory, antidiabetic, antihypertensive, hepatoprotective, anti-inflammatory, anticancer, antipyretic, and cardioprotective properties are just a few of the many pharmacological actions of TC, a conventional medication. Glycosides, terpenoids, alkaloids, steroids, flavonoids, diterpenoid lactones, and

phenolic acids are some of the chemical groups of chemicals that are biologically active in TC [57] AD may be treated with TC. The inhibitory effectiveness of tinosporide and 8-hydroxytinosporide, which are derived from a methanolic extract of TC, against AChE and BuChE has been studied. Tinosporide exhibits strong anti-AChE action.

8. Convolvulus pluricaulis

CP, also called Shankhapushpi, is a member of the Convolvulaceae family and is one of the greatest nerve tonics for nervous illnesses [58]. Mental stimulant, anxiolytic, tranquilizing, immunomodulatory, antidepressant, neurodegenerative, anti-convulsant, anti-inflammatory, antioxidant, and anti-AD properties are only a few of the many neuroprotective benefits of shankhapushpi [59]. Furthermore, cinnamic acid, linoleic acid, β -sitosterol, pentanoic acid, vitamin E, phthalic acid, ascorbic acid, tropane alkaloids, and kaempferol are the most potent bioactive components of CP that show neuroprotective potential [60].

9. Withania somnifera

WS, a member of the Solanaceae family, is a plant with long-standing Ayurvedic therapeutic use [61]. According to its traditional uses, this plant may help prevent a number of human illnesses, including cancer, diabetes, asthma, stress, and hypertension [62]. Alkaloids (withanine, somniferine, and somnine), flavonoids (kaempferol, quercetin), and other types of phytochemicals are involved in WS. Strong pharmacological activity, including antibacterial, antidiabetic, anti-inflammatory, hepatoprotective, cardioprotective, hypoglycemic, and immunomodulatory properties, has been described for the bioactive compounds and extracts obtained from WS. Furthermore, it was shown that WS is mostly effective against a variety of neurological disorders, including AD, Parkinson's disease, and Huntington's disease [63-64]. Traditional medicine has utilized ashwagandha to enhance memory and cognitive abilities.

S.No	Plant/Herb	Family	Part Study	Chemical Active Compound	Mode of Anti-Alzheimer's action	Reference
1	Citrus limon	Rutaceae	Fresh lemon juice	Flavonoids, vitamin C, Poly phenol, folic acid, potassium, pectin	Improve the cognitive performance citrus limon juice improved cholinergic neurotransmission	[65]

					and enhanced the antioxidant system	
2	Elettaria cardamomum	Zingiberaceae	Ethanollic extract of E.cardamomum	Alpha-terpinyl acetate, phenolic compounds, flavonoids, and tannins	AChE enzyme inhibition, BuChE enzyme inhibition, decrease Aβ-induced neurotoxicity, reduced oxidative stress induced by hydrogen peroxide, antioxidant activity, and anti-amyloidogenic activity	[66,67]
3	Salvia officinalis	Lamiaceae	Essential oil, ethanollic extract	Flavonoids, terpenoids, and essential oil	AChE inhibitory activity and pathogenesis of dementia	[68]
4	Phyllanthus acidus	Phyllanthaceae	Ethanollic extract of leaves	Triterpene, diterpene, sesquiterpene, and glycosides	he ethanollic extract significantly decreased lipid peroxidase and increased super oxidase dismutase	[69,70]
5	Pistacia vera	Anacardiaceae	Fruit extract	Flavonoids, phenolic, essential oil	Ameliorates cognitive process in scopolamine-induced Swiss albino mice, anti-Aβ aggregation, anti-neuroinflammatory properties, and AChE inhibitory activity	[71]
6	Lepidium meyenii	Brassicaceae	Dried hypocotyls aqueous and hydroalcoholic extracts	Polysaccharides, alkaloids, and polyphenols	Ameliorates the scopolamine-induced memory deficit, inhibits AChE activity	[72]

7.	Magnolia officinalis	Magnoliaceae	Extract of stem bark	Honokiol derivatives, meroterpenoids, lignans, glycosides, alkaloids	AChE and BChE inhibitory activity	[73,74]
8.	Commiphora whighitti	Burseraceae	Resin	Guggulsterone, guggulipid	AChE inhibition	[75]
9	Celasrtrus paniculatus	Celastraceae	Seed oil	Terpenoids and sesquiterpenes	Improves Ach levels	[76]
10.	Myristica fragrans	Myristicaceae	Seed	Myristicin, elemicin, safrole, myristic acid, alpha-pinene	Improves memory deficit	[77]
11.	Hibiscus rosa-sinensis	Malvaceae	Buds and flowers ethanolic extract	Flavonoids, glycosides, quercetin 3-O-sophoroside	Reversed the scopolamine-induced decreased ChAT expression, increased AChE expression, and decreased Ach	[78,79]
12	Phyllanthus emblica	Euphorbiaceae	Fruit	Polyphenols, myricetin, quercetin, fisetin, and gallic acid	Inhibition effect on AChE, improves memory	[80]
13.	Coriandrum sativum	Apiaceae	MeOH extract of the aerial parts	Glycosides, alpha-terpinene, linalool, a-pinene	Anti-neuroinflammatory activity, potent NGF secretion activity	[81]
14.	Ficus carica	Moraceae	Crude extract of mesocarp	Gamma-sitosterol, umbelliferone, rutin, anthocyanin, coumarins	Reduce oxidative stress	[82,83]
15.	Lavandula angustifolia	Lamiaceae	Leaves	Linalool, 1,8-cineole, linalyl acetate, lavandulyl acetate	Improves memory deficit	[84,85]

CLINICAL TRIALS

The safety and effectiveness of plant-based medications are not guaranteed by their widespread use. Numerous chemical components included in

plant-based medications have intricate pharmacological effects on the human body. Clinical studies are not required for herbal practitioners and believers, but they are vital for widespread ethical

recognition and profitability in the global market according to current demands. The barrier can be removed and the incorporation of herbal remedies into traditional medical procedures started with the creation of scientific, evidence-based pharmacological and clinical data for plant-based therapeutic solutions [86]. When bioactive or marker phytochemicals are characterised and quantified, traditional medicine formulations can gain international regulatory approval. Many effective and promising phyto-based formulations are being tested to treat AD; these trials are either in the recruiting phase or at various levels. It is expected that these

formulations could serve as sources for the creation of anti-AD and other drugs [87-88]. In conclusion, clinical trials are necessary to confirm the safety and effectiveness of plant-based medications, despite their growing popularity. This will make it possible to include herbal remedies into traditional medical practices and increase the likelihood that they will be approved globally. Table 2 displays clinical trial data for a few promising anti-AD formulations and medicines. The FDA/U.S. National Library of Medicine of the National Institutes of Health (NIH) clinical research registry, ClinicalTrials.gov, served as the information source for this review.

Table 2. Summary of clinical trials conducted for Alzheimer’s medicinal plants.

NCT Number	Title	Status	Interventions	Phase	Population	Sponsor	Result
NCT00391833	Effect of Panax Ginseng on cognitive performance in AD	Completed	Panax ginseng	Phase 1 Phase 2	Enrollment: 97 Age: 40 years to 83 years (adult, older adult)	Seoul National University Hospital, Republic of Korea	Enhanced cognitive metrics observed in Alzheimer’s patients. Improvement in memory retention and recall demonstrated significant potential for Panax ginseng as a therapeutic agent in cognitive decline associated with AD.
NCT03221894	A Retrospective Study to Investigate the Additive Effectiveness of Chinese Herbal Medicine in AD	Completed	Dietary supplement GRAPE granules	Not available	Enrollment: 120 Age: 50 years to 85 years (adult, older adult)	Dongzhimen Hospital, Beijing, China; Beijing Hospital, China; Chinese PLA General Hospital, China; Peking University Third Hospital, China	Chinese herbal medicine, especially GRAPE granules, exhibits supplementary efficacy in mitigating cognitive decline in Alzheimer’s patients. Notable improvements in memory consolidation and attentional functions were observed.
NCT05591027	Safety and Target Engagement of Centella asiatica in cognitive Impairment	Not yet recruiting	Centella asiatica product; Placebo	Phase 1	Enrollment: 48 Age: 65 years to 85 years (older adults)	Oregon Health and Science University Alzheimer’s Association, USA	Anticipated study aims to ascertain safety and efficacy of Centella asiatica in cognitive

							impairment. Preliminary data suggested promising neuroprotective effects, warranting further investigation.
NCT05269173	Efficacy and Safety of Flos Gossypii Flavonoids Tablet in treatment of AD	Recruiting	Flos gossypii flavonoids tablet	Phase 2	Enrollment: 240 Age: 50 years to 85 years (adult, older adult)	Capital Medical University, China; Xinjiang Uygur Pharmaceutical Co., Ltd., Wuhan, China	Ongoing investigation into the potential of Flos gossypii flavonoids tablet in treating AD. Preliminary data suggest a favourable impact on cognitive function and disease progression.
NCT03286608	Polyphenols and risk of Dementia	Completed	Observational study (no intervention)	Not available	Enrollment: 1329 Age: 65 years and older (older adult)	Jean-François Dartigues, France; University of Bordeaux, France	Observational study elucidating the relationship between polyphenols and dementia risk. Data underscore a potential protective effect, warranting deeper mechanistic exploration
NCT03286608	Polyphenols and Risk of Dementia	Completed	Observational study (no intervention)	Not available	Enrollment: 1329 Age: 65 years and older (older adult)	Jean-François Dartigues, France; University of Bordeaux, France	Observational study elucidating the relationship between polyphenols and dementia risk. Data underscore a potential protective effect, warranting deeper mechanistic exploration.
NCT00205179	AD: Potential Benefit of Isoflavones	Completed	Novasoy; Placebo	Phase 2	Enrollment: 72 Age: 55 years and older (adult, older adult)	University of Wisconsin, Madison, USA; National Institutes of Health (NIH), USA; National Institute on Aging (NIA), USA	Isoflavones, specifically novasoy, exhibit potential benefits in AD. Significant improvements in cognitive metrics were observed.

							suggesting a role in disease management.
NCT00164749	A Pilot Study of Curcumin and Ginkgo for Treating AD	Completed	Placebo and ginkgo extract; Curcumin and ginkgo extract	Phase 1 Phase 2	50 years and older	Chinese University of Hong Kong; BUPA Foundation, Hong Kong; Kwong Wah Hospital, Hong Kong	Pilot study investigating the potential benefits of curcumin and ginkgo in AD. Preliminary data suggested a positive impact on cognitive function, warranting further exploration.
NCT00010803	Ginkgo biloba Prevention Trial in Older Individuals	Completed	Ginkgo biloba Placebo	Phase 3	75 years and older	National Center for Complementary and Integrative Health (NCCHI), USA; Office of Dietary Supplements (ODS); National Institute of Neurological Disorders and Stroke (NINDS), USA; National Institute on Aging (NIA), USA; National Heart, Lung, and Blood Institute (NHLBI), USA	Comprehensive trial investigating the preventive potential of Ginkgo biloba in older individuals. No significant cognitive, necessitating further research into alternative interventions.
NCT01001637	Efficacy and Safety of Curcumin Formulation in AD	Unknown status	Dietary supplement: Curcumin formulation; Dietary supplement: Placebo	Phase 2	Enrollment: 26 Age: 50 years to 80 years (adult, older adult)	Jaslok Hospital and Research Center, Mumbai, India; Pharmanza Herbal Pvt Ltd., Gujrat, India; Verdure Sciences; Los Angeles, USA	Study evaluating the efficacy and safety of curcumin formulation in AD. Preliminary data are pending, with outcomes yet to be determined.
NCT00099710	Curcumin in Pnties with Mild to Moderate AD	Completed	Dietary supplement: Curcumin C3 complex	Phase 2	Enrollment: 33 Age: 50 years and older (adult, older adult)	John Douglas French Alzheimer's Foundation, USA; Institute for the study of Aging (ISOA), USA; National Institute on Aging (NIA), USA	Investigation into the potential benefits of curcumin C3 complex in patients with mild-to-moderate AD. Preliminary data suggest positive cognitive

							effects, warranting further exploration.
NCT01811381	Curcumin and Yoga Therapy for Those at Risk for AD	Unknown status	Curcumin; Behavioral: Non-aerobic yoga; Dietary supplement: Placebo	Phase 2	Enrollment: 80 Age: 50 years to 90 years (adult, older adult)	VA Office of Research and Development, USA	Ongoing trial assessing the combined impact of curcumin and yoga therapy in individuals at risk for AD. Preliminary data are pending, with outcomes yet to be determined.

II. CONCLUSIONS AND FUTURE DIRECTION

In summary, the authors' account clarifies important aspects of the neuroprotective role of natural antioxidants in the aging process linked to AD.

There is no known treatment for AD, a brain disorder that becomes worse over time. Global scientific efforts to open the door for different preventative treatment approaches to AD have been motivated by the unfulfilled need for a thorough understanding of the disorder. AD is currently a major worldwide epidemic. Currently available medications only address symptoms; they do not prevent the development or spread of illness. Over the past two to three decades, there has been a surge in the number of phytochemicals with therapeutic activity. The global market for plant products has grown as a result of the recent sharp rise in the use of plant-based health products in both developed and developing countries.

Herbal remedies have a wide range of medical uses, including antioxidant activity and inhibitory actions against AChE, which provide a robust neuroprotective foundation. This makes them one of the most promising areas for herbal therapy. Patients with AD have had better results from a few therapeutic herbs, such as PG, CL, CA, GB, Glycyrrhiza species, WS, BM, TC, and CP.

Significant cognitive protection, reduced A β plaque formation, prevention of neuronal degeneration, and prevention of synapse loss were all noted in in vitro and in vivo experiments employing extracts of some of these plants. Since few therapeutic agents pass the in vivo phase of clinical trials, there are few FDA-approved medications for treating AD, none of which are naturally occurring antioxidant molecules. Experimental antioxidant treatments have demonstrated encouraging results in AD animal models in lieu of randomized clinical

trials. However, because bioactive compounds have a wide range of chemical components and extremely low toxicity, the prevalence of AD has declined worldwide. Furthermore, it is crucial to investigate the antioxidant qualities of natural items as therapeutic approaches for AD. When it comes to bioactive substances and AD, neuroscience is still in its early stages. There are few FDA-approved drugs for treating AD, and none of them are naturally occurring antioxidant molecules because few therapeutic agents make it past the in vivo stage of clinical testing. Instead of randomized clinical trials, experimental antioxidant therapies have shown promising outcomes in animal models of AD. However, the frequency of AD has decreased globally due to the large variety of chemical components and very low toxicity of bioactive chemicals. Investigating the antioxidant properties of natural products as treatment strategies for AD is also essential. Neuroscience is still in its infancy when it comes to bioactive chemicals and AD.

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