

FULL PAPER

Natural products for attenuating Alzheimer's disease: A narrative review

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Alzheimer's disease (AD) is one of the most common neurodegenerative conditions and a major contributor to dementia in the elderly and its prevalence is rising quickly. There are currently 50 million AD sufferers globally, according to the epidemiological data. The most noticeable signs of AD are nearly nonexistent, and they typically include forgetting of recent events. The development of extracellular Amyloid-beta 42 plaques, intracellular hyperphosphorylated Tau tangles, oxidative overload because of mitochondrial malfunction, and genetic abnormalities are just a few of the mechanisms that contribute to AD. Through temporary palliative therapy, which reduces the rate of cognitive damage linked to AD, the current treatment primarily addresses symptoms. In numerous studies, medicinal plants have been linked to potential anti-AD effects. This review aims to explain the underlying pathways of action of various plant-mediated extracts, plant-secondary metabolites, and herbal remedies preparations tested against AD as published in various preclinical and clinical research studies.

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Introduction

Alzheimer's disease (AD) is an irreversible (may be fatal) neurological ailment that affects an increasing number of elderly people. According to research, AD is the most frequent cause of dementia in older people who gradually lose their capacity to remember things, think clearly, and eventually do the most basic tasks, leading to dementia, cognitive impairment, and physical or mental dysfunction [1]. Alois Alzheimer, a medical psychologist, presented the first AD patient, Auguste D., in November 1906 at the 37th south-west Germany Conference of south-west mental health professionals in Tübingen. Since then, AD research has spanned more than a century [2].

The primary cellular feature of AD is the accumulation of amyloid plaques, which are

primarily made up of beta amyloid peptides, and neurofibrillary tangles, which are collections of hyper-phosphorylated tau protein. Amyloid precursor protein is a protein found in the membranes of neuronal bodies and synapses. Amyloid beta (A β) is formed from amyloid precursor protein through amyloido-genesis, which is triggered by two enzymes, b- and g-secretase [3]. In different parts of the brain, cholinergic maladjustment coexists with amyloid plaque reserves. A significant decline in acetylcholine (ACh) thresholds is associated with the loss of cholinergic neurons in the brains of individuals with cognitive deficits as a consequence of reduced activity of enzymes necessary for ACh output [4]. Furthermore, it is thought that damaging free-radical overload caused by mitochondrial dysfunction, neuro-inflammation,

glutamatergic excitotoxicity, and a lack of hippocampus neurogenesis contribute to AD. As a result, it appears that AD is a complicated disease characterized by numerous detrimental brain states, including amyloid plaque deposition, oxidative stress, cholinergic system malfunctions, and brain inflammation (neuro-inflammation), in addition to decreased neurogenesis in the hippocampus (hippocampal neuronal loss) [5].

Currently, a number of drugs are being studied and applied in clinical settings to

slow the progression of AD, including donepezil, rivastigmine, galantamine, and memantine (The chemical structures of the abovementioned drugs are illustrated in Figure 1. These FDA-approved medications might help to keep thinking sharp over the long-term, slow memory loss, boost communication, and deal with some behavioral issues. However, it appears that all of these medications produced the same outcomes, with few, if any, effects and significant adverse effects [6].

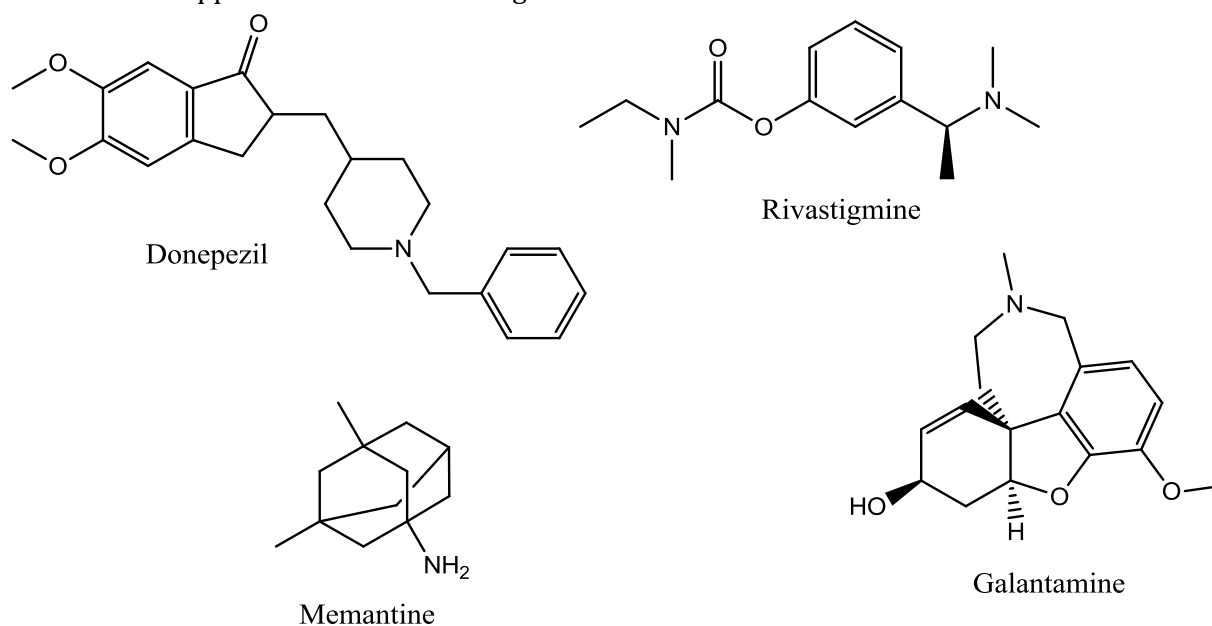


FIGURE 1 Chemical structures of the currently available drugs used in AD management

Even with the great invention and data collection in modern medicine, there is still no viable treatment for the most troublesome diseases in the world, like AD. Numerous bioactive chemicals with complex structures and unique pharmacological effects are produced in large quantities by natural sources, such as animals, microorganisms, plants, and marine-related organisms. Many of these bioactive substances have proved pharmacological effect in various diseases [7].

Different natural compounds are being investigated in a range of animal model types

in an effort to determine whether they can cure AD or the other neurodegenerative illnesses. Some of these medications are presently undergoing clinical studies with encouraging outcomes due to their neuroprotective, anti-inflammatory, antioxidant, anti-amyloidogenic, and anticholinesterase properties in addition to their affordability [3].

A flavonoid called luteolin, with the chemical structure depicted in Figure 2, is found in green pepper seeds and leaves, celery, chamomile tea, and a number of the other medicinal plants. The anti-

inflammatory, antioxidant, and anti-apoptotic properties of luteolin have been clearly demonstrated. In animal and cellular models of dementia, several studies have demonstrated that luteolin has neuroprotective properties [8]. In a 2014 study, Sawmiller *et al.* investigated whether luteolin could abolish the damaging effects resulting from overproduction of pro-inflammatory cytokines and phospho-tau, A β deposition, and glycogen synthase-3 activation. This research has demonstrated for the first time that luteolin could minimize AD-like features in an A β depositing mouse model [9].

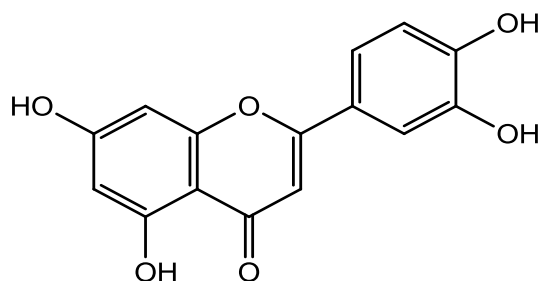


FIGURE 2 Chemical structure of luteolin

Catechin, is a polyphenol, with the chemical structure displayed in Figure 3, afforded its name from *Acacia catechu L.* Tea, cacao, apples, persimmons, berries, and grapes are just a few of the foods and herbs that contain catechins [10]. An investigation has conducted in 2016 by Suganthy *et al.* to evaluate the impact of catechin, derived from *Rhizophora mucronata*, on the *in vitro* fibrillation of A β . Results showed that catechin, significantly suppresses A β fibrillogenesis and it destabilizes mature fibrils that have already formed. Based on the findings of this study, there is new evidence that catechin may serve as a multi-potent bioactive compound in the treatment of AD [10].

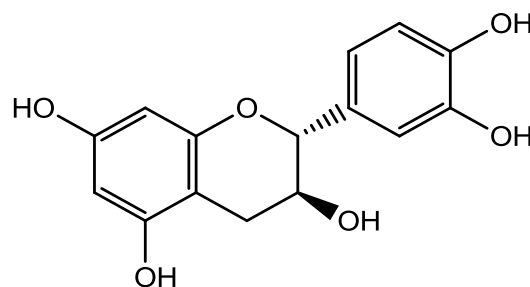


FIGURE 3 Chemical structure of catechin

In a study conducted in 2016 to evaluate the possible beneficial effects of marine plants in AD, Hielscher-Michael *et al.* have isolated many sulfolipids from algae. These sulfolipids have been tested for their ability to inhibit glutamyl cyclase, an enzyme believed to play a role in the progression of numerous illnesses, including arthritis, osteoporosis, and AD. The scientists have identified that sulfolipids attain inhibitory effect against this enzyme, and thus have a potential role in the management of AD. [11]

Apigenin, a flavonoid with the chemical structure demonstrated in Figure 4, is widely distributed in many plant-mediated sources, as illustrated in Figure 4. Fruits, especially those belonging to the citrus family, many vegetables (cabbage, celery, and bell pepper), and medicinal plants, and medicinal plants (*Carduus crispus* and *Elsholtzia rugulosa*) are only some of these natural resources. Apigenin has showed protective effects against A β -induced toxicity in rat cerebral microvascular endothelial cells in a research done in 2011 by Zhao *et al.* The same scientists have studied in 2013 the therapeutic value of apigenin in mouse model with AD. The findings showed that oral apigenin may reduce the load of A β , suppress the amyloidogenic process, and reduce oxidative stress in the studied mice, which may help to alleviate the learning and memory impairment associated with AD [12].



FIGURE 4 Chemical structure of apigenin and its natural resources

The effect of apigenin on the transgenic *Drosophila* template of AD, which communicates A-42 in the nerve cells, is the focus of research by Siddique *et al.* The AD flies were given access to the apigenin eating plan for a total of 30 days. Treatment of AD flies with apigenin caused a dose-dependent, marked decline in oxidative stress and a postponement of the lost opportunity of climbing competency. Apigenin also inhibits acetylcholinesterase (AChE) activity. Apigenin prevents A-42 accumulation, according to the research findings on immunoreactivity and molecular modeling [13].

Another natural substance which is expected to act on A β is berberine. The isoquinoline alkaloid, berberine, is the characteristic component of stems and roots of various *Berberis* species (*Berberis petiolaris*, *Berberis aristata*, and *Berberis vulgaris*) and also found in *Coptidis Rhizoma* [14]. A research performed by Chen *et al.* in 2020 has evaluated the medicinal potential of Berberine in AD. The results imply that

berberine could slow cognitive deterioration in AD mice by concurrently inhibiting tau hyperphosphorylation and tau autophagic clearance. These findings strongly suggest berberine as a possible treatment option for AD [14].

Curcumin is a polyphenol extracted from turmeric (*Curcuma longa*), as illustrated in Figure 5, which being used for centuries to cure various ailments, including cancer, liver diseases, diabetes, anorexia, coughs, and rheumatism. Huang *et al.* have studied in 2014 the impact of this naturally occurring polyphenol on A β -induced tau hyperphosphorylation. The research findings have shown that curcumin inhibits tau hyperphosphorylation, which was induced by A β . Similarly, Thaba *et al.*'s 2015 study on curcumin discovered that curcumin reduces A β -induced toxicity presumably through a non-specific pathway while exerting its neuroprotective effect against A β -induced toxicity by shifting the A β aggregation pathway towards the formation of harmless aggregates [15].



FIGURE 5 Chemical structure of curcumin and the physical appearance of its natural source

Myricetin is a well-known plant-derived flavonoid, and an important ingredient in different foods. This natural substance demonstrates a broad spectrum of activities, including potent antioxidant, anticancer, antidiabetic, anti-inflammatory, and neuroprotective effects. In 2016, Ramezani *et al.* have tested the potential effects of myricetin on hippocampal pyramidal neurons and cognitive and memory deficits in a Wistar rat model of AD produced by intracerebroventricular injection of streptozotocin. According to the study, myricetin substantially slowed cognitive decline. In addition, it may prolong the existence of pyramidal neurons in the hippocampus. The current research provides more proof that myricetin can be used to treat AD [16].

Targeted inhibition of beta-amyloid cleaving enzyme-1 (BACE1) has been demonstrated in some studies to regulate amyloid-beta production and deposition. Therefore, the BACE1 inhibition leads to a lessening of the burden of amyloid-beta, a

marker of AD genesis [5]. Tannic acid (TA) is a naturally produced polyphenol that is present in a wide variety of plants, such as legumes, cereals, beans, bananas, raspberries, wines, coffee, and a wide range of teas. Tannic acid, in addition to its powerful anti-inflammatory and antioxidant properties, appears to be a natural blocker of BACE1 activity [16].

In a study performed in 2011 by Mori *et al.*, tannic acid was administered orally to a transgenic mouse model to examine its effects against A β cascade and improve neuro-inflammation. The results have showed that dietary supplementation with tannic acid may be used prophylactically for AD by inhibiting the activity of A β -secretase and neuro-inflammation and consequently alleviating AD pathology. In another study conducted in 2013, Yao *et al.* have examined the possible inhibitory effect of tannic acid and its monomer, gallic acid, versus tau peptide through affording a molecular framework. The results concluded that tannic acid inhibits tau peptide, furthermore, tannic

acid, but not gallic acid, has recognized tau protein R3 through forming a hairpin structure, as demonstrated in Figure 6. This

structure is a crucial component needed to prevent tau polymerization [17].

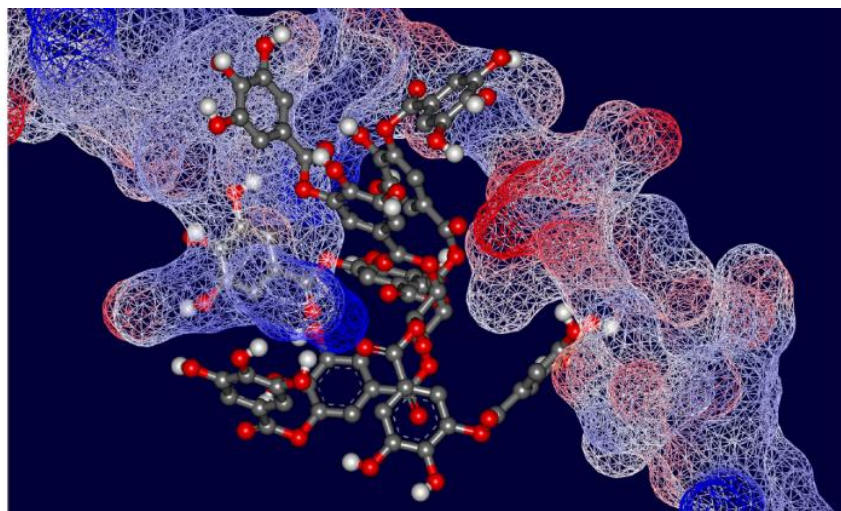


FIGURE 6 The binding of tannic acid and R3 protein through hairpin structure as suggested by Yao *et al.*

Cinnamon is a common spice obtained from the inner brown bark of several evergreen trees and shrubs, and it involves in the Lauraceae family. The three famous varieties are *Cinnamomum zeylanicum*, *Cinnamomum camphora*, and *Cinnamomum cassia* [18]. In 2020, Tepe and Ozalsan have examined the effectiveness of *Cinnamomum zeylanicum* essential oil against AD among the other bioactivities. They investigated the inhibitory effect of cinnamon oil versus the accumulation of A β peptide in the brain in addition to its possible blocking action versus monoamine oxidase (MAO) and AchE enzymes. The researchers have discovered that cinnamon oil greatly prevented the toxicity caused by A β in various neuronal cells besides inhibiting the enzymes; AchE and MAO. This study has showed that cinnamon oil may exhibit promising potential in relieving AD symptoms owing to its numerous activities [18].

Mangosteen, also known as *Garcinia mangostana* Linn, as demonstrated in Figure 7, is a common tropical fruit tree from the family of Guttiferae. Mangosteen contains various xanthenes that exhibit different

biological effects such as anti-inflammatory, antioxidant, anti-tumor, anti-bacterial, and neuroprotective properties. A study has performed in 2016 by Wang *et al.* to evaluate the therapeutic effect of various xanthenes isolated from mangosteen versus AD. The scientists have found that the mangosteen xanthenes demonstrated strong inhibition of A β aggregation, in addition to show potent DPPH radical scavenging and metal chelating action. These results imply that natural xanthenes have many anti-AD functions and may represent interesting therapeutic agents for its therapy [19].



FIGURE 7 The physical appearance of *Garcinia mangostana* Linn.

Huperzine-A, a sesquiterpene alkaloid, with the chemical structure indicated in Figure 8, isolated from club moss *Huperzia serrata*. Wang *et al.* have identified this alkaloid as a powerful, reversible, and specific AChE inhibitor in the 1980s. Besides, Huperzine-A act as a strong neuroprotective to the brain cells. In China, huperzine-A has been used for generations to treat blood problems, fevers, and edema [20].

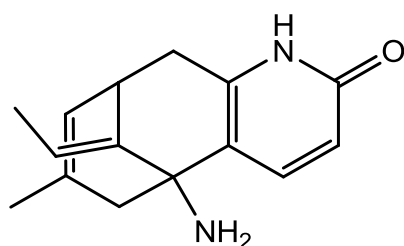


FIGURE 8 Chemical structure of Huperzine-A.

Huang *et al.* have studied in 2013 the mechanism of neuroprotection conferred by huperzine-A. The researchers have demonstrated that Huperzine A's unprecedented action on the regulation of brain iron was the source of the neuroprotective effect. Treatment with Huperzine A in this study decreased levels of aggregated A β peptide, improved the formation of amyloid plaques, and hyperphosphorylated tau in the cortex and hippocampus. The results of the current investigation have a number of significant implications. Firstly, it validates Huperzine A's position as an efficient medicine to treat the disease by confirming its positive effect in interfering with the pathologic process of AD. Secondly, the findings confirm the idea that iron plays a crucial role in the pathogenesis of neurodegenerative illnesses like AD and that altering the amount of iron in the brain could be a successful treatment for these conditions [21].

Withania somnifera, a tiny woody shrub from the plant kingdom's Solanaceae family. Due to its outstanding pharmacological characteristics, *withania somnifera* is utilized

as one of the main medications in Indian medicine [22]. Withanone, with the chemical structure illustrated in Figure 9, a substance extracted from the root of *Withania somnifera*. This bioactive substance was studied by Pandey *et al.* in 2018 to evaluate its therapeutic efficacy in AD. It was administered orally once daily to Wistar rats for a period of twenty-one days. The studies have revealed a significant improvement in cognitive function in the rats studied due to withanone's exceptional ability to reduce elevated levels of pro-inflammatory cytokines, such as TNF alpha, interleukin, nitric oxide, and lipid peroxidation, as well as inhibiting A β -42 aggregation [22].

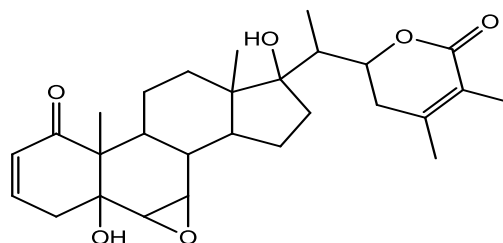


FIGURE 9 Chemical structure of withanone

Panax Ginseng, as depicted in Figure 10, is an herbaceous plant from the Araliaceae family. This plant has been utilized as a therapy for centuries throughout Asia, particularly in Korea, China, and Japan. Ginseng has recently gained popularity around the world. Its roots have traditionally been used to rejuvenate the physical and mental health, prevent aging, and boost energy. Ginsenosides, the triterpenoid derivatives, are the primary active pharmacological components in *Panax Ginseng*. A newly discovered ginseng ingredient that incorporates lysophosphatidic acids and reduces the severity of AD-related brain neuropathies is gintonin [23]. In 2019, an investigation was performed by Shin *et al.* to explore the effect of ginseng in AD mouse model. The outcomes of this study have shown that ginseng dramatically improves A β -induced mitochondrial pathologies.

Furthermore, this substance significantly improved many of AD-related pathologies such as $A\beta$ deposition, gliosis, and neurodegeneration, as well as abnormalities in hippocampal neurogenesis in AD brains. These findings imply that ginseng extract could serve as a mitochondria-targeting therapy for the management of AD [23].



FIGURE 10 The physical appearance of *Panax Ginseng*

In 2019, scientists have quantified some phenolic bioactivities in the peel and pulp of pomegranate using HPLC methodology in addition to investigate the scavenging activity and the reducing power against peroxy- and DPPH-radicals. According to the studies, AChE may be inhibited by extracts from the peel since they have considerably higher antioxidant qualities and phenolic contents than extracts from the pulp. Pomegranate peel inhibited AChE based on their phenolic

concentration. As a result, the industry may propose exploiting pomegranate peel in the production of nutraceuticals [24].

In an *in vitro-in vivo* AD rodent model, resveratrol, with chemical structure illustrated in Figure 11, has demonstrated its effectiveness as an antioxidant agent. This polyphenol inhibits amyloid accumulation, inhibits mitochondrial dysfunction, and activates the transcription of genes associated with long life [25]. In a mouse model of AD, Wang *et al.* proposed that a combination of three constituents, including grape juice, plant polyphenol resveratrol, and grape seed extract, minimizes cognitive impairment and $A\beta$ -mediated neuropathology [25].

In a mouse model of AD, treatment with rosmarinic acid, a phenolic acid molecule with the chemical structure presented in Figure 11, suppressed $A\beta$ buildup via monoaminergic signaling, reducing cognition deficits, enhancing synaptic control, and potentiating adult hippocampal neurogenesis. Furthermore, rosmarinic acid may have reduced $A\beta$ oligomerization in a rat AD modality test in which A4 was administered IV directly into the bilateral lateral ventricles, demonstrating that one month of oral Rosemary tea intake improves memory function in mice as measured by passive avoidance, elevated plus maze, and forced swimming tests [26].

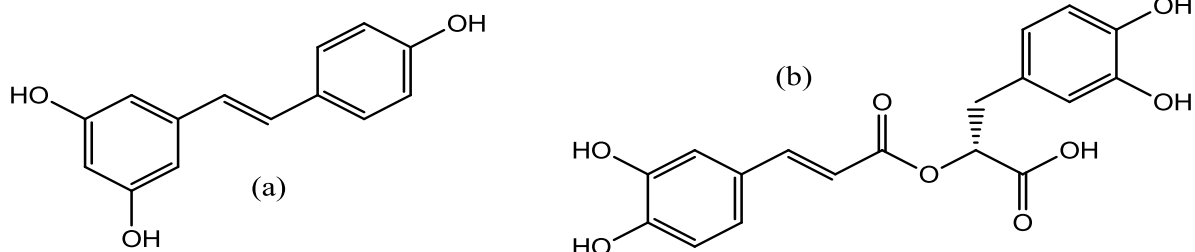


FIGURE 11 The chemical structures of resveratrol (a) and rosmarinic acid (b)

Safflower (*Carthamus tinctorius*) is valuable for both cooking and medicine, and its flavonoids and the other active ingredients have been employed extensively in clinical

settings. In numerous *in vitro* and *in vivo* models, it has been demonstrated that *Carthamus tinctorius* has positive effects on the pathology of AD. The active components

of *Carthamus tinctorius* can handle AD through a number of different methods. These anti-AD qualities include lowering tau protein hyperphosphorylation, preventing A β -aggregation, preventing apoptosis, reducing AChE activity and oxidative overload, enhancing synaptic plasticity, and reducing inflammation [27].

The naturally derived product named manniferin (MGF) is extracted from various plants, including *Mangifera indica L.* MGF has a variety of potent properties, ranging from damaging free-radical quenching to the reduction of mitochondrial malfunction, neuroinflammation, and cellular apoptosis. Its structure is composed of a C-glycosyl and a phenolic moiety. MGF, in particular, can pass through the blood brain barrier to protect neurons. Several studies suggest that MGF has the ability to shield the CNS from oxidative overload, neuroinflammation, mitochondrial dysfunction, and apoptosis in an *in vitro-in vivo* modality [28]. GK and co-workers isolated a triterpenoid product with a chemical structure illustrated in Figure 12 from the rhizome of *Curculigo orchioides Gaertn.* Spectroscopical techniques including HPLC, LC-MS, FTIR, ^{13}C -NMR, and ^1H -NMR, as well as molecular docking studies, were used to analyze the isolated compound. The organic substance offers novel potential treatments for AD. The isolated substance has excellent antioxidative properties, inhibits AChE, and provides neuroprotection against A β . Future research may employ *in vivo* tests to confirm the effectiveness of the isolated compound in the treatment of AD [29].

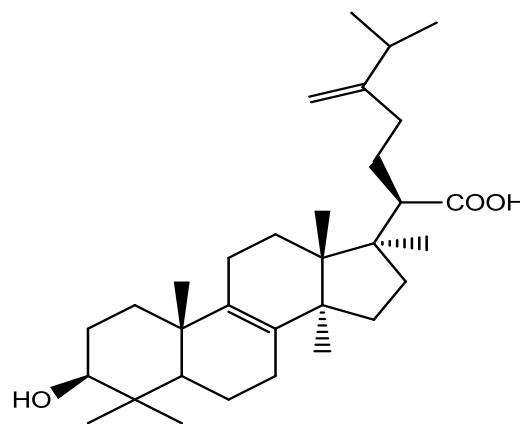


FIGURE 12 The chemical structure of the naturally derived triterpenoid from *Curculigo orchioides Gaertn*

One of the flavonoids obtained from the root of *Astragalus membranaceus* is a natural product called calycosin with the chemical structure illustrated in Figure 13. A wide variety of pharmacological activities are displayed by this substance. A potential diabetes medication called calycosin reduces hypertriglyceridemia, insulin resistance, and glucose intolerance. The cognitive deficits associated with diabetes are also prevented, lessened, and treated with calycosin. According to Song *et al.*, calycosin reduced inflammation and oxidative stress in the hippocampus of a mouse modality for AD [30].

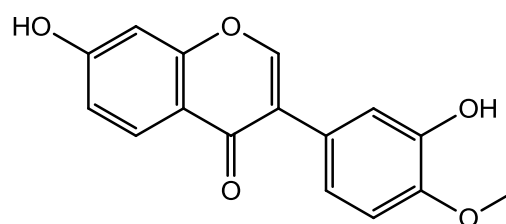


FIGURE 13 Chemical structure of calycosin

Another study looks into the neuroprotective potential of various extracts acquired from the plant named *Holothuria scabra*, particularly those rich in triterpene glycosides found in the butanol and ethyl acetate fractions, versus proteotoxicity and A β aggregation in the *in vivo* modality of AD.

The extracts mitigated the deficits in physiological behaviors caused by A β -related damaging effects by reducing the aggregation of A β and preventing the formation of toxic A β oligomeric forms. The lifespan of AD worms could also be increased, and free-radical levels could be lowered by these extracts. The results of this study suggested that *Holothuria scabra* extracts could be applied to treat or prevent AD [31].

A research in 2022 studied the phytochemicals from *Bacopa floribunda* were found to have higher levels of antioxidants *in vivo* to prevent the buildup of oxidative stress, which is a byproduct of the toxicity of the A β . Similarly, it prevented microglial activation to counteract A β 1-42-induced neuroinflammation. With higher doses of saponins (100-200 mg/kg) and flavonoid (100 mg/kg), crude saponins and flavonoids from *Bacopa floribunda* were found to be more effective at suppressing neuroinflammation, free-radical overload, and microgliosis induced by A β 1-42 [32].

Elmorsy and collaborators examined the neuroprotection of the methanolic *Indian Catechu* extract in a rat model of AD. The outcomes showed that this organic extract may have a positive impact on the progression of AD because of its significant free-radical trapping and anti-AChE effect, which was mirrored in the living creatures' behavioral functions and epitome clinical manifestations [33].

An ethanol extract of *Physalis minima L.* fruit was found to be a protective preparation against AD in an *in vivo* rat model in another study. The study's AChE inhibitory activity is a likely mechanism of action. The results also showed that the preventive impact of this ethanolic extract was more hopeful and afforded consequences compared with the standard [34].

The *Satureja cuneifolia* plant has potential in terms of both diabetes and AD, according to a study performed in 2020. *In vitro* experiments were used to determine the

hypoglycemic and anti-AD potentials of the aqueous and methanolic extracts. The same extracts' antioxidant capacity was evaluated using the free-radical trapping methodology and reducing power investigation. In addition, the plant's total flavonoids and phenolics were determined [35].

In vitro AD models both show promising neuroprotective properties for oxyphylla A, a novel compound derived from *Alpinia oxyphylla* of the chemical structure illustrated in Figure 14. According to a data supplied by Bian *et al.*, oxyphylla A reduces A β expression and improves cognitive deficits. Further investigation revealed that oxyphylla A has an antioxidative effect [36].

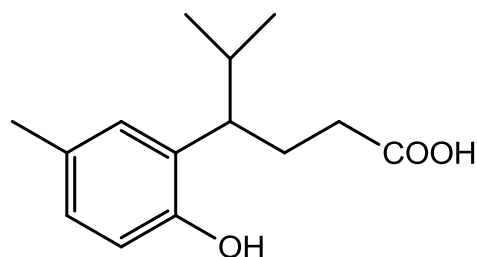


FIGURE 14 The chemical structure of oxyphylla A.

According to research, the main flavonoids in *Ulmus pumila L.*'s ethanolic extract, particularly astragalins with the chemical structure illustrated in Figure 15, present novel treatment possibilities for neurodegenerative disorders, particularly AD. This ethanol extract's therapeutic potential may be mediated by altering cholinergic and monoamine neurotransmission, anti-inflammatory pathways, and oxidative stress [37].

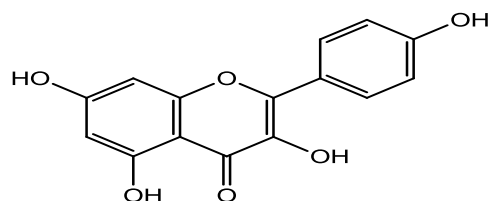


FIGURE 15 The chemical structure of Astragalins

The disease-modifying effects on AD were investigated using the *Elettaria cardamomum* extract and its principal bioactive phytoconstituent alphaterpinyl acetate. The study by Chowdhury and Kumar was a great success in proving alpha-terpinyl acetate's therapeutic potential because it binds to multiple drug targets and inhibits hydrogen peroxide-induced oxidative stress, amyloidogenic property, antioxidant capacity, AChE, and A β -induced neurotoxicity [38].

A nutraceutical formula based on date seed aqueous extract, nigella, and virgin olive oil could prevent and treat AD in rats. The formula was found to significantly enhance learning capacity, ameliorate neuronal damage, and regenerate the affected hippocampus tissue. It reduced brain nitrogen-based free radicals, α -TNF, A β -

amyloid, and tau protein levels in the hippocampus while also inhibiting AChE activity and expression in the brain and hippocampus [39].

Finally, another research studied unsaturated fatty acid amide hydroxy-sanshool (HAS) of the chemical structure illustrated in Figure 16, which is derived from *Zanthoxylum bungeanum*. In this research HAS significantly reduced the histopathological injuries, cognitive deficits, and deficits in spontaneous locomotion in AD mouse model. HAS obviously mitigated the damage brought on by oxidative stress through lowering the expression of malondialdehyde, enhancing the protective activity of the antioxidant enzymes, and slowing down the process of neurodegeneration [40].

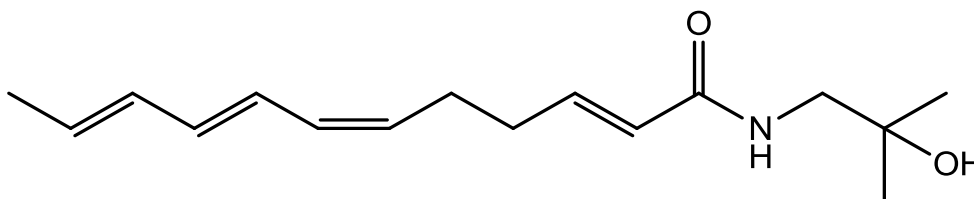


FIGURE 16 The chemical structure of HAS

Conclusion

This review gave a thorough account of the most recent developments in the study of plant products' anti-AD properties, as well as their potential applications and AD-fighting mechanisms. Numerous herbal extracts, fractions, phytochemicals, and herbal formulations are said to have anti-AD properties, according to the literature that was retrieved and analyzed from common sources. It is clear from the studies mentioned in this review that bioactive phytoconstituents and medicinal plants have a great deal of potential to treat diseases with complicated pathogenesis like AD. Furthermore, the synergy displayed by the bioactive contents found in plant products has been linked to the health benefits of those products. The complex and multifactorial

pathogenesis of AD may have an explanation in the potential synergy of the phytoconstituents found in extracts, fractions, and formulations. The complementary and alternative therapies have been studied in a number of preclinical and clinical trials because conventional anti-AD treatments only provide symptomatic relief. Unexpectedly, many of these anti-AD plants and biomolecules have also been shown to be effective against the other neurological conditions, pointing to a potential shared neuroprotective mechanism.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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