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REVIEW ARTICLE

The Potential of Herbal Plants and Bioactive β Sitosterol in Circumventing Alzheimer's Disease – A Review

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Abstract

Alzheimer's Disease (AD), a neurological ailment, mostly affects the older population all around the world. Rational therapies show limited efficacy, adverse effects, and poor patient compliance therefore herbal drugs are considered as a suitable supplementation to the drug therapy for the treatment of AD. According to research, herbal drugs reduce symptoms of AD and also improve brain functioning by the inhibition of β amyloid, γ-secretase, and acetylcholine along with the regulation of antioxidants and the activation of α-secretase. Various herbal plants like *Salvia officinalis, Bertholletia excelsa, Withania somnifera* and *Urtica dioica* help in slowing down the progression of AD by scavenging the free radicals, inhibiting of lipid peroxidation, β amyloid, and tau phosphorylation. β sitosterol, a phytosterol found abundantly in plants has the ability to cross the Blood Brain Barrier and thus acts as a bioactive constituent in circumventing various neurological disorders. Numerous *in vitro* and *in vivo* investigations indicate that β sitosterol shows immunomodulatory, lipid-lowering as well as antioxidant properties. The plant sterol, β sitosterol has the capacity to decrease β amyloid platelet synthesis, indicating that it might be helpful in the treatment of prevention of AD. Treatment with β sitosterol can lessen plaque burden and also enhance spatial learning and recognition ability in patients suffering from AD.

Keywords: Acetylcholinesterase, Antioxidants, β Amyloid, Free Radicals, Herbal Plants, Lipid Peroxidation, Neurodegeneration, β Sitosterol, γ Secretase

1. Introduction

The process of neurodegeneration entails the gradual damage of neural units and the function accompanying it[1]. Alzheimer's Disease (AD), is a prevalent neurodegenerative malady that causes cognitive impairments, behavioral instability along with a progressive loss of memory[2]. With an estimated 46.8 million cases worldwide and a projected increase to 131.5 million cases by 2050, Alzheimer's Disease is the most prevailing cause of dementia[3]. Aging is the most prevalent non-genetic cause of AD[4]. AD usually accelerates with age, especially beyond the age of sixty[5]. Age is therefore the main cause of the emergence of AD[6]. With the increase in age, memory impairment along with the decrease in antioxidant defense mechanism takes places[7,8]. Patients who suffer from AD beyond 65 years of age are referred to as "sporadic", whereas patients who suffer from AD before 65 years of age are said to be "familial"[9].

Some of the pathophysiological alterations that underlie AD include extracellular amyloid plaque deposition[10], tau protein phosphorylation, lack of acetylcholine, and loss of neurons driven on by free radicals[11]. In AD, there is also a loss in brain weight and brain volume[12]. Evidence depicts that mostly the synapses, dendrites, and the channels

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through which the neurons in the brain send and receive signals are mostly vulnerable to AD[13].

Alzheimer's disease is the most common kind of dementia[14]. It occurs due to the abnormal formation of β amyloid (Aβ) and increased phosphorylation of tau protein. Aβ is a protein made up of 37-43 amino acids and is the critical initiator of AD. Aβ is formed from APP (Amyloid Precursor Protein) in the presence of γ secretase[15]. Tau protein is a microtubule-associated protein that when increases in amount results in AD. The hyperphosphorylation of tau protein results in the formation of Neurofibrillary tangles (NFTs) which surrounds the amyloid plaques[16,17]. Lipid peroxidation is also induced by β amyloid[18]. Lipids are altered by free radicals and the presence of lipid peroxides, antioxidant enzymes, amyloid plaques, and NFTs all exhibit substantial correlations in Alzheimer[19]. In AD, the buildup of this peptide causes synaptic malfunction, inflammatory stress, neuronal death, and cognitive impairments[20].

Oxidative stress also plays an important role in the etiology of Alzheimer[21]. It happens due to an imbalance between radical detoxifying enzymes[22]. The end products like glycation end products, nitration[23,24], lipid peroxidation[25,26], as well as free carbonyls[27], hydroxylation, and carbonyl-modified neurofilament protein[28] are examples of the oxidative damage that is observed in AD[29]. Due to oxidative stress, the cytoskeleton of the neurons is altered which serves as the primary cause of AD induced by free radicals which leads to neuronal death[30].

2. Materials and Methods

This review article offers a critical analysis of published literature on the various herbal plants used in the treatment of Alzheimer's Disease. The sources of information used in the present article include the Indian system of Medicine, traditional Chinese herbal medicine reports on the use of herbal drugs, research articles, and scientific databases like PubMed, Google Scholar, and Web of Science. It includes the usage of various herbal plants and their bioactive constituents along with the benefits of β sitosterol in the treatment of AD.

3. Neuro Protective Role of Herbal Plants in AD

The conventional allopathic treatments for AD possess a number of side effects including raised blood pressure, constipation, dizziness, diarrhea and many more thus an alternative approach, such as the use of herbal plants, may be beneficial due to their relatively few side effects[31]. Around 200 years ago, herbal medicines dominated the major pharmacopeias, and many modern synthetic pharmaceuticals have their origins in the plant kingdom. However, there is ongoing interest in herbal treatment for many illnesses, including psychiatric and neurological conditions[32]. Numerous research and documentation suggest that herbal remedies have a unique participation in AD therapy[33]. Neuroprotection, which applies to both acute and progressive neurodegenerative diseases, is the ability of a system to safeguard the CNS against neuronal damage. The herbal plants contain a variety of bioactive constituents that can be used to treat a wide range of disorders, including neurological disorders such as AD. Nature's gift of medicinal plants has not yet been fully appreciated. The active ingredient found in herbal medicine can be used to synthesize new medications[34]. Plants are capable of synthesizing chemical substances that are used to treat or prevent various diseases, including age-related ailments and cognitive problems.

There are various bioactive substances that help in preventing AD by inhibiting the development of β amyloid, acetylcholinesterase, tau phosphorylation, and ROS. These substances help in the treatment therapies of AD. Numerous bioflavonoids are already identified as effective free radical scavengers, monoamine oxidase, acetylcholinesterase, and butyrylcholinesterase enzyme inhibitors. In light of this, herbal plants are prospective lead ingredients for producing compelling medications for the prevention of Alzheimer[9]. The bioactive substances present in plants may affect the activity of other components of the same plant or of other plants[35-37].

3.1 *Melissa officinalis* L. and *Salvia officinalis* L. (Lamiaceae)

In an individual with Alzheimer, *Melissa officinalis* has been shown to enhance cognitive performance and reduce agitation. It is widely known that *M. officinalis* which contains 4-O-methyl honokiol and has both nicotinic and muscarinic binding abilities at the ACh receptors in the central nervous system[33]. It inhibits the formation of beta-amyloid and the death of nerve cells. It also inhibits the production of free radicals. *Salvia officinalis* contains rosmarinic acid as its active constituent which inhibits the formation of various reactive oxygen species induced by β amyloid, peroxidation of lipids, activation of

caspase 3, phosphorylation of tau protein along with the fragmentation of DNA[9].

3.2 *Ginkgo biloba* L. (Ginkgoaceae)

Ginko biloba is used as a Chinese herbal remedy for hundreds of years to cure a variety of disorders. It contains rutin as a bioactive constituent. Numerous reports depict that the extract of *Ginkgo biloba* has the ability to diminish AD symptoms and therefore retard the disease's progression. During the early stages of AD, *Ginko biloba* extract GBE is most effective. In the hippocampal region of the brain, GBE has been demonstrated to have the capacity to restore normal ACh receptor function. It can also boost cholinergic activity and relieve several disease-related symptoms[33]. It shows an antioxidant effect and inhibits aggregation of β amyloid along with anti-platelet activating factor in AD patient[38-40]. *Ginkgo biloba* can reduce hypertension and also prevent platelet accumulation. If administered in the beginning stage of AD, it has the potential to boost cognition[41].

3.3 *Acorus calamus* L. (Acoraceae)

Acorus calamus L. also recognized as "Acori Calami Rhizoma" are used to enhance memory. It contains eugenol and β asarone which acts as an acetylcholinesterase inhibitor and is also used in Ayurvedic medicine. Additionally, β asarone has been demonstrated to enhance memory and exhibit antioxidant characteristics in the CNS. Alpha asarone's cholinergic and antioxidant properties help in the treatment of memory impairment. Asarones sometimes show genotoxic and hepatocarcinogenic effects therefore it has been advised to use very low concentration of asarone in herbal preparations[42].

3.4 *Huperzia serrata* (Lycopodiaceae)

Huperzine A, a prominent quinolizidine-related alkaloid, has the potential to cure the symptoms of AD as it acts as an acetylcholinesterase inhibitor and may also have a positive impact on other neurotransmitter systems to enhance memory. It is neuroprotective against beta-amyloid, oxygen-free radicals, and glutamate.

Huperzine A is more specific for AChE than butylcholinesterase thus greatly enhances cognition and behaviour in AD patients[32]. It has the ability to improve memory, concentration, and learning. It significantly lowers excessively elevated free radicals in the blood and brains of Alzheimer's patients and elderly animals. Huperzine A can restore scopolamine-induced amnesia, raising the possibility that it could help patients suffering from AD or further cognitive disorders[41].

3.5 *Panax ginseng* (Araliaceae)

Triterpene saponins also comprehended as ginsenosides, are the chief constituent of *P. ginseng*. Ginsenosides exhibit a variety of biological activities that are mechanistically related to the pathology of AD, including antioxidant activity, inhibition of glutamate, beta amyloid-induced cytotoxicity, and beta amyloid-induced tau phosphorylation. They also exhibit neuroprotective activity, antagonize NMDA receptors, and modulate ACh release[42].

3.6 *Rosmarinus officinalis* (Lamiaceae)

Rosmarinus officinalis (Satapatrika) contains constituents like carnosic acid, apigenin, ursolic acid, carvacrol, oleanolic acid, thymol, and eugenol. It has the ability to naturally inhibit COX-2 and also comprises about 20 antioxidants and additional 12 anti-inflammatory substances out of which carnosic acid and ferulic acid are the two most dominant antioxidants which help in slowing down the progression of AD[20].

3.7 *Convolvulus pluricaulis* (Convolvulaceae)

It shows nerve regeneration and improved cognition[43,44]. The bioactive constituents present in *Convolvulus pluricaulis* are convolamine and scopoletin. In scopolamine-treated rats, *Convolvulus pluricaulis* (Shankhapushpi) extract decreased tau protein and mRNA levels as well as APP levels. The extract had neuroprotective benefits since it prevented the neurotoxicity of scopolamine under the microscope. Scopolamine's neurotoxic effects were diminished by CP treatment, demonstrating its neuroprotective properties[45]. Pretreatment with *C. pluricaulis* reduce free radicals and inhibits the depolarization of mitochondrial membrane while restoring various free radical scavengers and apoptotic markers[46].

3.8 *Curcuma longa* L. (Zingiberaceae)

The benefits and constraints of using *Curcuma longa* in brain carcinoma and other CNS-related disorders are revealed by curcumin pharmacology. The active constituent of turmeric is curcuminoids[47]. Curcuminoids

include curcumin[48] and the effects of curcumin include effects on tau protein and anti-amyloidogenicity. Curcumin can both prevent and treat neurodegenerative brain conditions. Oral administration of curcumin reduces plaque load in AD patient[49,50] and when injected it blocks the formation of plaque[51]. In order to create an injectable depot for the continuous local release of curcumin to treat neuroinflammation, curcumin, a TNF blocker in many cell types and tissues, underwent chemical optimization. Curcumin binds to and prevents the accumulation of amyloid sheet conformations that are common to many neurodegenerative diseases. It scavenges free radicals, balances inflammatory systems, and increases thermal impact systems for better clearing of fatal aggregates[21]. Curcumin forms a complex with metals like zinc, copper, and iron[52] and blocks metal-induced amyloid plaque formation[53], inflammation, and oxidative neurotoxicity[54,55].

3.9 *Matricaria recutita* L. (Asteraceae)

German chamomile can boost memory, relieve fatigue, soothe the nerves, prevent sleeplessness, improve digestion, use in cold and cough, and support the defense mechanism of the body. It reduces unconsciousness and elevates drowsiness when taken in larger doses[41].

Due to the presence of chamazulene, it shows antioxidant properties therefore it acts against free radicals and also acts as an acetylcholinesterase inhibitor due to which it is considered a potent herbal drug in the prevention of amyloid plaque formation thus helping in slowing the progression of AD.

3.10 *Glycyrrhiza glabra* (Fabaceae)

The main factor responsible for the development of AD is the presence of β-amyloid plaques, which are characterized by neuronal death. *Glycyrrhiza glabra* contains glycyrrhizin/glycyrrhizic acid and isoliquiritin which protects against the apoptotic neuronal cell death brought on by fragments. Licorice root extract is said to alleviate or even stop the death of brain cells in conditions like Alzheimer's and the symptoms that are associated with it[41].

3.11 *Galanthus nivalis* L. (Amaryllidaceae)

Galanthamine is the main component of the plant *Galanthus nivalis*. Recently approved as a viable therapy option for AD are acetylcholinesterase (AChE) inhibitors, often known as "anticholinesterase medicines"[41]. It is an isoquinoline alkaloid that can cross the blood-brain barrier which inhibits the acetylcholinesterase enzyme and increases the cholinergic neurotransmission which thereby helps in the treatment of AD.

3.12 *Commiphora wighitti* (Burseraceae)

The main component of guggulipid, guggulsterone, can be found in the plant resin *Commiphora wighitti* (Guggulu). Guggulipid is seen to strengthen memory[56]. *Commiphora wighitti* affects choline acetyltransferase levels of the brain and impairs cognition. *Commiphora wighitti* exhibits the greatest effects on memory capabilities and dementia disorder risk. It acts on the hippocampus region of the brain by lowering the choline acetyltransferase levels[41].

3.13 *Lipidium Meyenii Walp* (Brassicaceae)

Lipidium Meyenii, or Maca, exhibits positive memory and learning development. It shows antioxidant activity and also acts as an acetylcholinesterase inhibitor. Literature reveals that black maca improves memory and cognition in ovariectomized mice as it has the capacity to lower down lipid peroxidation along with acetylcholinesterase[41].

3.14 *Angelica archangelica* L. (Dudhachoraa)

Numerous compounds found in the plant *Angelica archangelica* of the family Umbelliferae, show similar effects to those seen in Alzheimer's disease medications[41]. *Angelica archangelica* has the same phytochemicals that help improve blood flow in the brain. It shows inhibitory effect on AChE[57].

3.15 *Tinospora cordifolia* L. (Menispermaceae)

Tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, 8-hydroxytinosporide and tinosporidine are some of the main phytochemicals found in *Tinospora cordifolia*. When given to animals with memory issues, *Tinospora cordifolia* has the ability to improve their memory. The production of acetylcholine and immunostimulation are the mechanisms through which *Tinospora cordifolia* enhances memory[58]. Its treatment improves cognitive function in AD patients[59]. It prevents oxidative stress and acts as an antioxidant. It

also increases the regulation of cytokines and lowers the breakdown of amines, therefore, preventing AD.

3.16 *Magnolia officinalis* L. (Magnoliaceae)

Magnolia officinalis has been proven to release acetylcholine from the hippocampus as well as to increase the effects of choline acetyltransferase and block acetylcholine cleavage. It contains 4-O-methyl honokiol which inhibits β-secretase thus inhibiting the formation of Aβ from APP. It shows antioxidant properties *in vivo*. It also contains magnolol which exhibits neuroprotective effects *in vitro*. Additionally, the substance seems to have an anti-inflammatory and antioxidant activity which is crucial in AD and other neurodegenerative problems[59].

3.17 *Collinsonia Canadensis* L. (Lamiaceae)

Collinsonia canadensis is also known as Horsebalm. Its main chemical components, carvacrol, and thymol, are used to treat AD. It has been suggested that horsebalm can stop acetylcholine from degrading. Normally, the blood-brain barrier in our bodies works to keep potentially hazardous substances from entering the brain tissues. It may, however, also stop beneficial medications from getting to the brain. Horsebalm chemicals appear to bridge that wide gap and thus can cross the BBB[59]. It acts by inhibiting the acetylcholinesterase enzyme thereby preventing the breakdown of acetylcholine in AD.

3.18 *Bertholettia excelsa* L. (Lecythidaceae)

Lecithin is present in significant concentrations in *Bertholettia exelsa* along with selenium[60]. Lecithin, which contains choline, is present in large quantities in it. Acetylcholine can be produced from choline. Acetylcholine levels in AD patients are raised by these building blocks. Therefore, an increased amount of acetylcholine prevents the progression of AD. Lecithin, which contains choline, is present in large quantities in it. Acetylcholine can be produced from choline. Acetylcholine levels in AD patients are raised by this building blocks[59].

3.19 *Urtica dioica* L. (Clusiaceae)

It is also known as Common nettle or stinging nettle and is found in the roots, stems, and leaves of *Urtica dioica* belonging to the family Urticaceae. Urtica dioica consists of boron, which elevates the body's estrogen which is good for recognition. Therefore, it is demonstrated to improve certain Alzheimer's sufferers' moods[61]. It contains ursolic acid and quercetin which acts as an antioxidant thereby lowering the oxidative stress in an AD patient.

3.20 *Withania somnifera* L. (Solanaceae)

Withania somnifera (Ashawgandha) also known as Indian ginseng is the most eminent herbal plant in Alzheimer's as it acts as a nerve tonic[62]. It contains active withanolides, withasomniferins, withasomniferols, withanone, withaferin[63] which indicates a strong antioxidant activity and a free radical scavenging activity[64] by boosting the activities of catalase, glutathione peroxidase, and superoxide dismutase. Additionally, ashwagandha is said to be a nerve tonic that revitalizes cells and increases energy[65]. A colorimetric approach based on Ellman's reaction, in previous research shows the amount of cholinesterase inhibition by *Withania somnifera*[59].

3.21 *Nepeta obtusicrena* (Lamiaceae)

The bioactive constituents present in *Nepeta obtusicrena* in oleanolic acid and ursolic acid. It shows antioxidant properties and also inhibits lipid peroxidation. It contains diterpene and triterpenes which inhibits the AChE and BChE enzymes present in the brain therefore it is also used in the treatment of Alzheimer's Disease[66].

3.22 *Thespesia populnea* (Malvaceae)

It contains Kaempferol, β sitosterol, gossypetin, and Quercetin. The plant shows the presence of tannins, alkaloids, phenols, flavonoids, saponins terpenes, lupenone, and Quercetin. It shows antioxidant properties therefore it increases the amount of Glutathione Peroxidase, Glutathione-s-transferase and decreases the amount of lipid peroxidation. It shows memory-enhancing properties and thus is used in lowering the progression of AD[67].

3.23 *Lawsonia inermis* (Lythraceae)

Lawsonia inermis shows acetylcholinesterase and selective butyrylcholinesterase inhibition. It acts as an antioxidant by scavenging the free radicals. It contains β-sitosterol along with 3-O-β-acetyloleanolic acid and oleanolic acid which are the most potent inhibitor of butyrylcholinesterase. Other constituents present in *Lawsonia inermis* are

3-O-(Z)-coumaroyl, oleanolic acid and betulinic acid. Its metal-chelating ability and antioxidant property helps in slowing down the progression of AD[68].

3.24 *Crataegus oxyacantha* (Rosaceae)

It is proven that *Crataegus oxyacantha* has anticholinesterase activity. It is also very well known for its antioxidant property in the treatment of AD. The constituents present in *C. oxyacantha* are β-sitosterol-3-O-β-D-Glucopyranoside, lupeol, β-sitosterol, betulin, betulinic acid, oleanolic acid, and chrysin. The combination of the antioxidant and cholinesterase inhibition activity of this herbal plant is considered the major target in the treatment of AD[69].

3.25 *Ficus carica* L. (Moraceae)

It is useful for the improvement of cognitive and behavioral deficits in Alzheimer's disease. Parts of *Ficus carica* L. like fruit contain coumarin, anthocyanin, and hydrocarbon which show antioxidant property thus act by scavenging the free radicals. The leaves and latex contain sterol and triterpenoids like β-sitosterol and 6-O-Linoleyl-β-D-glucosyl-β-sitosterol which helps in the treatment of AD[70].

3.26 *Aquilegia pubiflora* Wall. (Ranunculaceae)

Aquilegia pubiflora Wall. contains flavonoids, terpenoids, and phenols which shows anti-Alzheimer property and acts as antioxidants. The free radical scavenging activity of the plant helps in the treatment of AD. The *in vitro* studies also prove that the leaf extract of *Aquilegia pubiflora* Wall. shows acetylcholinesterase and butyrylcholinesterase inhibition[71].

3.27 *Polygonum hydropiper* L. (Polygonaceae)

The *in vitro* studies show the presence of β sitosterol in *Polygonum hydropiper* L. β sitosterol exhibited strong anticholinesterase properties and also corrects the behavioral deficits. It can cross the blood-brain barrier and accumulate in the brain, therefore, inhibiting acetylcholinesterase and attenuating the deficit in memory and behavior. *Polygonum hydropiper* L. also shows the presence of antioxidants which act by scavenging the free radicals in the brain and decelerating the progression of AD[72].

3.28 *Crocus sativus* L. (Iridaceae)

Crocus sativus L. commonly known as saffron. The stigma of saffron contains safranal, flavonoids, crocin, crocetin, picrocrocin and kaempferol. The antioxidant property of *Crocus sativus* L. is due to the presence of bioactive constituents like safranal, crocin, and picrocrocin. Crocetin helps in the inhibition of lipid peroxidation and lowing A42 in monocytes in AD patients. It can also prevent the accumulation of β amyloid in the brain[73]. Table 1 includes the bioactive substances present in various plants along with their mechanism of action.

4. β Sitosterol as Neuroprotective

β sitosterol, a plant sterol, is a substance with a structure like that of cholesterol found in vegetables, fruits, nuts etc[82]. Medical research on β sitosterol has been intensively investigated[83] and it is found that it shows antioxidant activity[84]. Its chemical structure is similar to that of cholesterol[85]. In the context of this, natural chemicals, particularly flavonoids, are prospective lead ingredients for creating powerful medications to fight AD[13]. Through the BBB, dietary phytosterols can aggregate in the brain tissue and may have an impact on cognitive performance[86]. The shear pattern of APP is altered by β sitosterol, suggesting that it may be used as an AD treatment[87] as it also inhibits high cholesterol-induced platelet β amyloid release[88]. Phytosterols are extensively found in plants, fungi, and animals. β sitosterol also has dietary benefits and has a number of positive effects on health and disease prevention[89].

Some significant plant sources of this compound are mentioned below. There are numerous plant families from which β sitosterol and its components are derived, and the plants given below describe some well-known sources[90].

β sitosterol is found in *Salvia officinalis*[91]. *Ginkgo biloba* L. leaves contain potential compounds called polyphenols that are isolated from lipids (GBL). By using petroleum ether extraction, saponification, and molecular distillation, ginkgo lipids are purified and determined by Nuclear Magnetic Resonance. β sitosterol is also isolated from *Acorus calamus*[92]. The presence of stigmasterol and β sitosterol is also encountered in the *Panax ginseng* roots which are measured using improved analytical technique[93]. HPTLC, a densiometric approach is used to measure phenolic compounds and terpenoids like β sitosterol in *Convolvulus pluricaulis*[94]. When the flowers of *Matricaria recutita* L. (Asteraceae) are hydrodistilled,

Table 1. Potential bioactive substances used in the treatment of alzheimer[9,44]

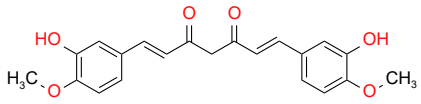
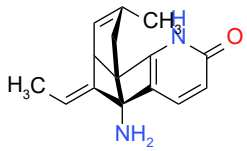
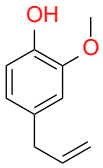
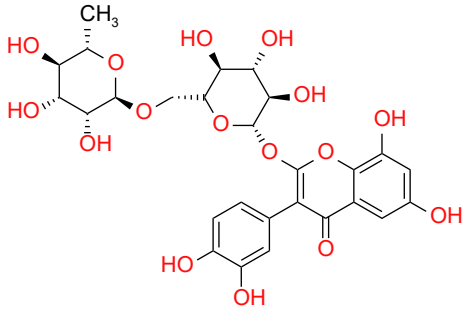
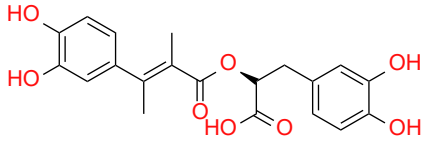
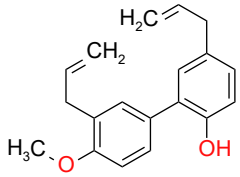
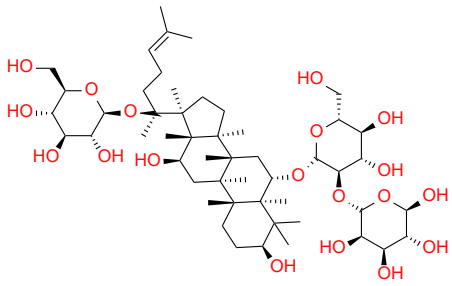
Plant/Botanical Name	Structure	Bioactive Substance	M.O.A.
Curcuma longa (Turmeric)		Curcumin	Inhibits beta-amyloid, phosphorylation of tau protein, α-secretase.
Huperzia serrata		Huperzine A	Inhibits the formation of beta-amyloid from amyloid precursor protein.
Acorus calamus		Eugenol	Inhibits Aβ-induced Ca^{2+} intake
Ginkgo biloba		Rutin	Attenuates Aβ25–35 induced apoptosis. Inhibits Aβ42 fibrillization and attenuates Aβ42-induced cytotoxicity dose-dependently
Salvia officinalis		Rosmarinic acid	Inhibits phosphorylation of tau, peroxidation of lipids, and production of free radicals along with activation of caspase 3.
Melissa officinalis		4-O-methylhonokiol	Inhibits the formation of beta-amyloid and the death of nerve cells. Inhibits the production of free radicals.
Panax ginseng		Ginsenoside Re	Reduce β amyloid-induced cell death

Table 1 to be continued...

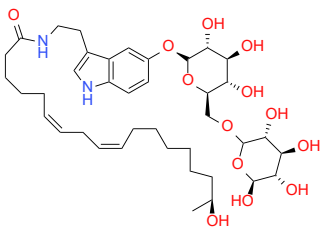
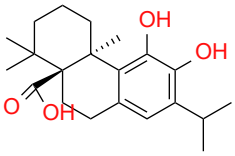
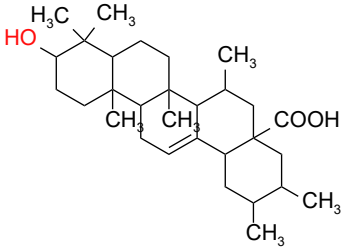
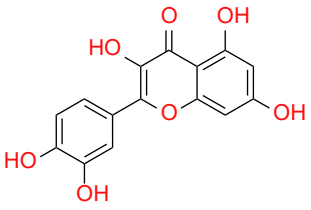
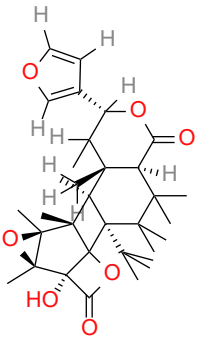
Plant/Botanical Name	Structure	Bioactive Substance	M.O.A.
Withania somnifera		Withanamide	Inhibits reactive oxygen species
Rosmarinus officinalis		Carnosic acid	Increase cognition by maintaining healthy nerve cells of the brain.
Urtica dioica	 	Ursolic acid Quercetin	Improves free radical scavenging activity. Inhibits peroxidation of lipid along with reactive nitrogen species. Increase the amount of dopamine. Restore GSH and reduce cytokines.
Tinospora cordifolia (Guduchi)		Tinosporide 8-hydroxytinosporide	Increase the amount of dopamine and decrease iron. Reduce the level of free radicals.

Table 1 to be continued...

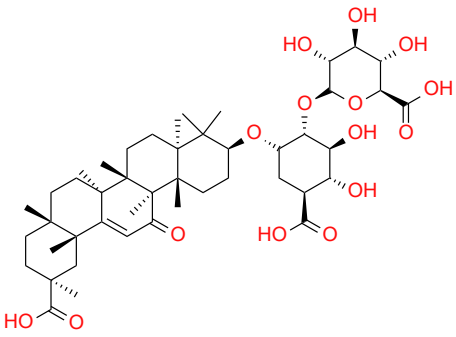
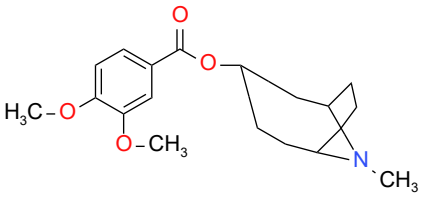
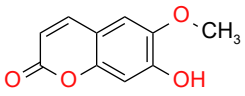
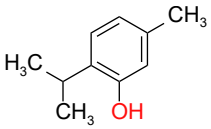
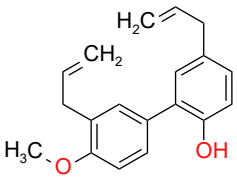
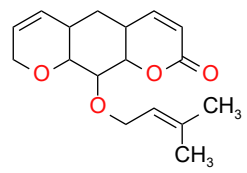
Plant/Botanical Name	Structure	Bioactive Substance	M.O.A.
Glycrhiza glabra (Yasti madhu)		Glycyrrhizin/ Glycyrrhizic acid Isoliquiritin	Suppress microglia activation and proinflammatory cytokine production (MCAO).
Convolvulus pluricaulis (Shankhapushpi)	 Convolamine  Scopoletin	Convolamine Scopoletin	Restore antioxidant and various apoptotic indicators. Inhibits generation of ROS. Alteration in the membrane of mitochondria by depolarizing it.
Bertholletia excelsa	Se	Selenium	Shows high antioxidant activity Inhibits lipid peroxidation and scavenged DPPH radicals *in vitro*[74].
Collinsonia canadensis L. Root extract		Thymol	Prevent the breakdown of acetylcholine via inhibition of acetylcholinesterase[75].
Magnolia officinalis		4-O-methylhonokiol	Inhibit β-secretase thus inhibiting the formation of Aβ from APP[76].
Angelica archangelica		Imperatorin (8-isopentenyloxypsoralen)	Inhibitory effect on AChE[77].

Table 1 to be continued...

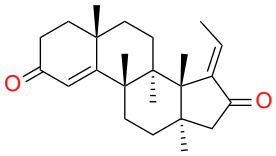
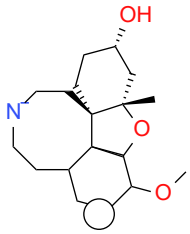
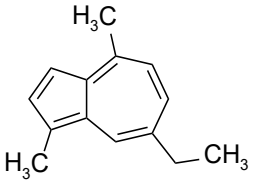
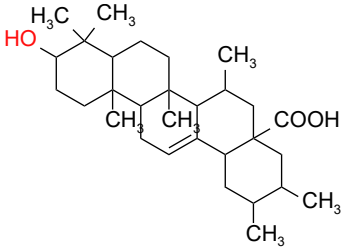
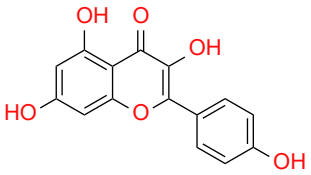
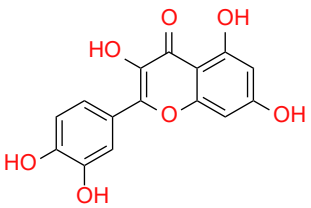
Plant/Botanical Name	Structure	Bioactive Substance	M.O.A.
Commiphora whighitti (Burseraceae)		Guggulsterone[78]	Reduce acetylcholinesterase contents in the hippocampus[79].
Galanthus nivalis (the snowdrop)[80]		Galanthamine	Shows acetylcholinesterase activity. Penetrates the blood-brain barrier readily and inhibits central cholinesterase[81].
Matricaria recutita		Chamazulene	Acts against free radicals[57].
Nepeta obtusicrena		Ursolic acid	Shows antioxidant property thereby acts as a free radical scavenger Inhibits lipid peroxidation. Inhibits AChE and BChE enzymes.
Thespesia populnea	 Kaempferol  Quercetin	Kaempferol Quercetin	Shows antioxidant properties. Increases the amount of Glutathione Peroxidase, Glutathione-s-transferase. Inhibits lipid peroxidation.

Table 1 to be continued...

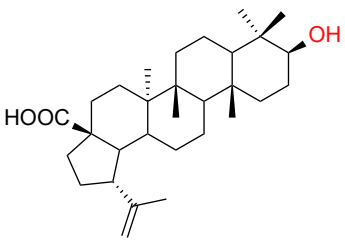
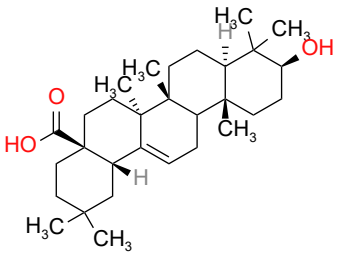
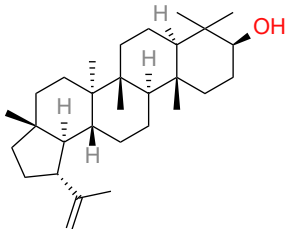
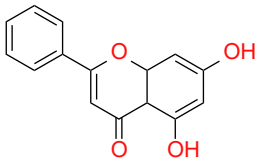
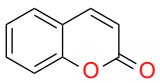
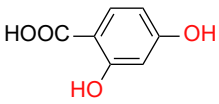
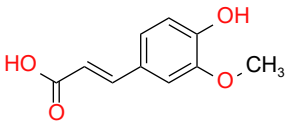
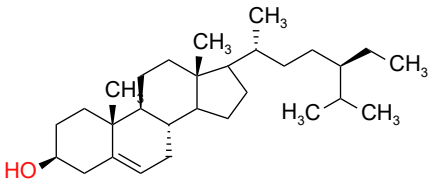
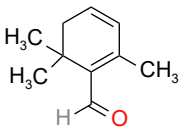
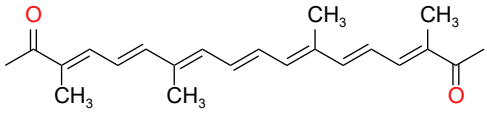
Plant/Botanical Name	Structure	Bioactive Substance	M.O.A.
Lawsonia inermis	 Betulinic acid  Oleanolic acid	Betulinic acid Oleanolic acid	Acts as acetylcholinesterase and selective butyrylcholinesterase inhibitor. It acts as an antioxidant by scavenging the free radicals.
Crataegus oxyacantha	 Lupeol  Chrysin	Lupeol Chrysin Betulinic acid Oleanolic acid	Shows anticholinesterase activity. Acts as an antioxidant.
Ficus carica L.	 Coumarin	Coumarin, anthocyanin, and hydrocarbon β-sitosterol and 6-O-Linoleyl-β-D-glucosyl-β-sitosterol	Acts as a free radical scavenger.

Table 1 to be continued...

Plant/Botanical Name	Structure	Bioactive Substance	M.O.A.
Aquilegia pubiflora Wall.	 Resorcylic acid  Ferulic acid	Resorcylic acid Ferulic acid	Shows antioxidant property and thus acts as a free radical scavenger. Inhibits acetylcholinesterase and butyrylcholinesterase.
Polygonum hydropiper L.		β sitosterol	Exhibits strong anticholinesterase properties. Correct behavioral deficits. Inhibits acetylcholinesterase and acts as an antioxidant.
Crocus sativus L.	 Safranal  Crocetin	Safranal Crocetin	Shows antioxidant property Inhibits lipid peroxidation. Lowers A42 in monocytes. Prevent the accumulation of β amyloid in the brain.

an essential oil is produced. Organic solvent extraction results in the production of a β sitosterol[95]. *Glycyrrhiza glabra* also depicts the existence of β sitosterol which is present in its roots[96]. β sitosterol was found to be the main steroid in *Lipidium meyenii* Walp[97]. *T. cordifolia* also contains β sitosterol which is best shown in its petroleum ether extract[98]. The Brazil nut has intriguing antioxidant and anti-cholesterol characteristics as it shows elevated amounts of unsaturated fatty acids, alpha-tocopherol and beta-sitosterol[99]. The chromatographic findings showed that caffeic acid, chlorogenic acid, β sitosterol, and stigmasterol were present in *Urtica dioica*[100]. From the roots of *Withania somnifera*, β sitosterol along with other phytosterols are isolated[101].

Oxyphytosterols can be produced as a result of their susceptibility to oxidation by reactive oxygen species like ozone[102]. β sitosterol is also used as pharmaceutical product and is regarded as reliable and a possible nutritional supplement with no harmful side effects[89]. Different neuroprotective and antioxidant effects of β sitosterol were found in several investigations. Following β sitosterol therapy, the amount of total glutathione shows that it may be a potent free radical scavenger. Additionally, when β sitosterol is fused into the cell membranes it helps in lowering the free radicals and also decreases the peroxidation of lipids caused due to the presence of glucose oxidase, which has beneficial effects on neurodegenerative diseases like AD[13].

According to research, β sitosterol has the ability to cross the BBB and aggregates in the cerebrum thus altering cognizance. This allows it to prevent esterase from degrading ACh, which lessens the memory and behavior deficit. The capacity of β sitosterol to scavenge free radicals in addition to inhibiting cholinesterase helps in AD therapy and other neurological illnesses. β sitosterol corrects behavioral anomalies in a variety of memory tests and also enhances motor coordination.

AD is characterized by the presence of amyloid plaque, NFTs along with the death of nerve cells. In the hippocampus of AD mice, there is increased beta-amyloid plaque formation and impaired neuronal function, which is associated with memory loss. β sitosterol has the ability to cross the BBB[103,104] and suppress the synthesis of β amyloid due to which the progression of AD decelerates[105].

Numerous studies indicate that sitosterol shows immunomodulatory, lipid-lowering as well as antioxidant properties along with antinociceptive, anxiolytic, and sedative effects[106].

β sitosterol is biosynthesized in a variety of ways by different organisms, although it typically follows the mevalonate pathway. Dimethylallyldiphosphate and isopentenyl diphosphate combine to create farnesyl diphosphate, according to the biosynthesis mechanism of sitosterol that was examined using the 13C-labeling method. Squalene, a triterpene, is then created by the fusion of two farnesyl diphosphate molecules. Cycloartenol, produced by the enzyme cycloartenol synthase from squalene, is a key precursor for the biosynthesis of sterols. After that, methylation transforms cycloartenol into 24-methylene cycloartenol. Then, it undergoes a number of enzymatic processes to become 24-methylenelophenol. It is converted from 24-methylenelophenol to 24-ethylenelophenol and then to fucosterol and subsequently β sitosterol[89].

β sitosterol shows potent anticholinesterase activity both *in vitro* and *in vivo*. It also improves behavioral impairments, with results that were on par with those of conventional medication. According to the potential positive effects provided by β sitosterol, it can inhibit the breakdown of acetylcholine and lessen the deficiency in behavior and memory[107]. β sitosterol increases ROS scavengers catalytically and non-catalytically[80]. It decreases the level of free radicals and peroxidation of lipids, demonstrating the compound's beneficial effects on neurological diseases[107].

According to reports, a number of substances derived from natural sources have high antioxidant properties and can be utilized as secure free radical scavengers. β sitosterol shows antioxidant properties by scavenging ROS. Further evidence for the anticholinesterase effect of β sitosterol comes from in silico studies where β sitosterol inhibited AChE and BChE activity by binding to their site of action. It scavenges free radicals and inhibits cholinesterase and in addition to reducing behavioral deviations in a variety of memory tests and it also enhances balance and motor performance in AD patients[107].

β sitosterol acts on the cholinergic receptors due to which they are stimulated and the level of ACh is sustained in the synaptic cleft for a longer period of time. An increased sitosterol's cholinergic transmission is anticipated to have beneficial effects on AD memory recovery and on the prevention of free radical-induced neurotoxicity in aged brains[108].

5. Conclusion

Herbal drugs have the ability to combat Alzheimer which has offered hope for new medication sources. They act by inhibiting acetylcholinesterase, escalating free radical scavengers, inhibiting the production of beta-amyloid from amyloid precursor protein along with activating other inhibitory pathways to combat Alzheimer's. To improve cognition and slow down the progression of Alzheimer, a number of natural compounds are utilized either alone or in conjunction with additional neuroprotective medicines. Phytochemical-based therapies for cognitive deficiency may show promise in human clinical trials as they show fewer side effects than other chemical-based drugs. In Alzheimer's and variant neurodegenerative diseases, herbs may indicate the potential. They are less toxic than pharmaceutical agents, which is one of their main advantages. The potential efficacy of β sitosterol against several AD pathogenic targets was evaluated in the current article. It is found that β sitosterol shows powerful anti-cholinesterase and antioxidant properties. It helps people with cognitive impairments, short-term memory problems, and locomotor limitations. Studies conducted in living organisms showed that beta-sitosterol effectively reaches the brain, inhibits cholinesterase metabolism-related enzymes, and acts as a free radical scavenger.

6. Acknowledgment

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