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Potential role of herbal plants and β sitosterol as a bioactive constituent in circumventing Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD), a neurological ailment, mostly affects the older population all around the world. The rational therapies show limited efficacy, adverse effects, and poor patient compliance; therefore, herbal drugs are considered a suitable supplement to the drug therapy for the treatment of AD. According to research, herbal drugs reduce symptoms of AD and also improve brain functioning through 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* L., *Bertholletia excelsa* L., *Withania somnifera* L., and *Urtica dioica* L. help slow down the progression of AD by scavenging free radicals, inhibiting lipid peroxidation, β amyloid and tau phosphorylation. B 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 and prevention of AD. Treatment with β-sitosterol can lessen plaque burden and also enhance spatial learning and recognition abilities in patients suffering from AD.

Keywords

neurodegeneration; herbal drugs; β amyloid; antioxidants; sitosterol; neuroprotection

Introduction

Alois Alzheimer, a German physician, inspired the name Alzheimer's Disease. In 1906, he documented the signs and symptoms of a patient referred to as "Auguste D." The term "Alzheimer's disease" was first used in a 1910 medical publication by Dr. Alzheimer's colleague, psychiatrist Emil Kraepelin. In AD, there is a process of neurodegeneration, which entails the gradual damage of neural units and the functions accompanying them (1). AD is a prevalent neurodegenerative malady that causes cognitive impairments, behavioural instability and 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, AD is the most prevalent cause of dementia (3). Ageing 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 for the emergence of AD (6). With the increase in age, memory impairment along with a decrease in antioxidant defence mechanisms take place (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". Fig. 1 illustrates

PREVALENCE OF ALZHEIMER'S DISEASE WORLDWIDE

	2015 (In million)	2030 (In million)	2050 (In million)
AMERICAS	9.4	15.8	29.9
AFRICA	4.0	7.0	15.8
EUROPE	10.5	13.4	18.6
ASIA	22.9	38.5	67.2
WORLD	46.8	74.7	131.5

Fig. 1: Prevalence of Alzheimer's Disease worldwide

the prevalence and frequency of AD worldwide.

The early symptoms of AD include memory impairment. Language and other cognitive abilities become increasingly impaired as the disease worsens. There are issues with identifying, word-finding, and subsequently comprehension and expression in both spoken and written language. Logical and reasoning skills are also affected in AD. Delusions, hallucinations, impatience, agitation, verbal or physical aggressiveness, roaming, and disinhibition are a few examples of behavioural alterations. In addition to incontinence and motor dysfunction, loss of self-hygiene, eating, dressing, and ambulatory capacities is also seen in patients with AD. Fig. 2 illustrates the symptoms of AD.

Some of the pathophysiological alterations that underlie AD include extracellular amyloid plaque deposition, tau protein phosphorylation, a lack of acetylcholine, and the loss of neurons driven on by free radicals (9). In AD, there is also a loss in brain weight and brain volume (10). Evidence depicts that mostly the synapses, dendrites, and channels through which the neurons in the brain send and receive signals are vulnerable to AD (11).

AD is the most common kind of dementia. 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 (12). Tau protein is a microtubule-associated protein that when increased in its amount results in AD. The hyperphosphorylation of tau protein results in the formation of neurofibrillary tangles (NFT's) (13) that surround the amyloid plaques (14). β amyloid oligomers are created due to a disproportion between the production and clearance of beta-amyloid, which leads to the development of amyloid plaques in the brain (13). Lipid peroxidation is also induced by β-amyloid. Lipids are altered by free radicals, and the presence of lipid peroxides, antioxidant enzymes, amyloid plaques, and NFTs all exhibit substantial correlations in AD. In AD, the accumulation of this peptide causes synaptic malfunction, inflammatory stress, neuronal death, and cognitive impairments (15). Fig. 3 illustrates the pathophysiology of

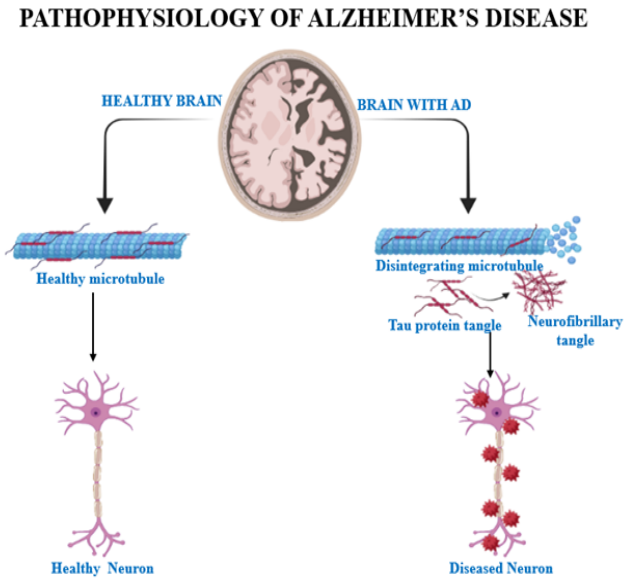


Fig. 3: Pathophysiology of Alzheimer's Disease

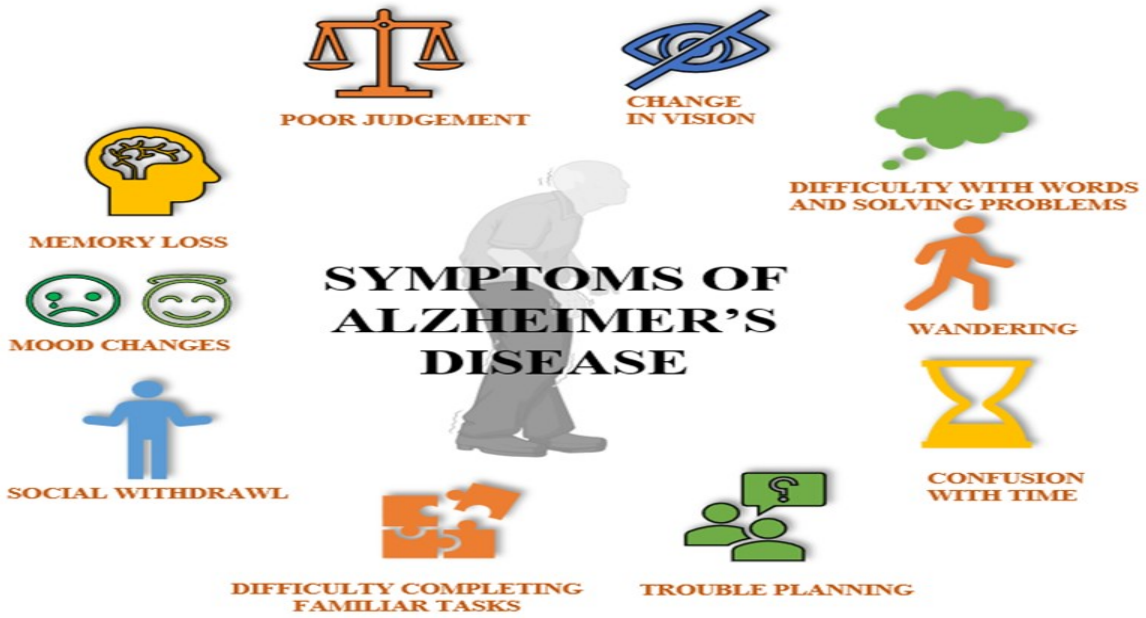


Fig. 2: Symptoms of Alzheimer's Disease

AD.

Oxidative stress also plays an important role in the pathophysiology of AD. It happens due to an imbalance between radical detoxifying enzymes. End products like glycation end products, nitration, and lipid peroxidation, as well as free carbonyls, hydroxylation, and carbonyl-modified neurofilament protein are examples of the oxidative damage that is observed in AD. Due to oxidative stress, the cytoskeleton of the neurons is altered, which is the primary cause of AD induced by free radicals, which leads to neuronal death. Fig. 4 illustrates some of the ways

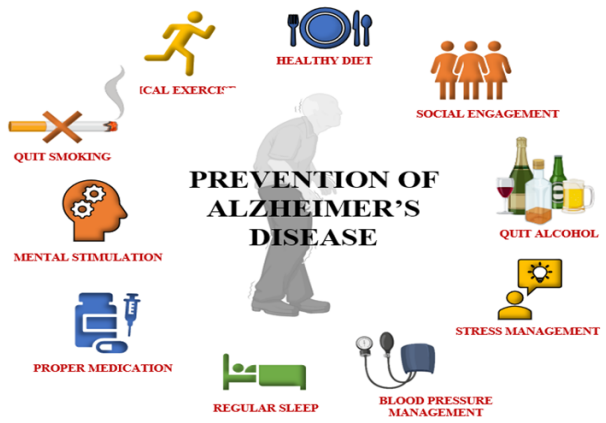


Fig. 4: Prevention of Alzheimer's Disease

to prevent AD.

Materials and Method

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, Chinese traditional 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.

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, diarrhoea, and many more; thus, an alternative approach, such as the use of herbal plants, may be beneficial due to their relatively few side effects (16). Around 200 years ago, herbal medicines dominated the major pharmacopoeias, 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 (17). Numerous studies and documents suggest that herbal remedies have a unique role in AD therapy (18). 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 (9). 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 reactive oxygen species. These substances help in the treatment 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 AD. The bioactive substances present in plants may affect the activity of other components of the same plant or of other plants (20-22). Table 1 includes the bioactive constituents, and part of plants used, along with the structures of bioactive constituents and the mechanisms of action of various plants used in the treatment of AD (29).

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

In individuals with AD, *Melissa officinalis* has been shown to enhance cognitive performance and reduce agitation. It is widely known that *M. officinalis* contains 4-O-methylhonokiol and has both nicotinic and muscarinic binding abilities at the ACh receptors in the central nervous system (18). 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, and fragmentation of DNA.

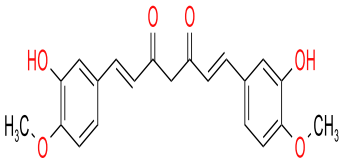
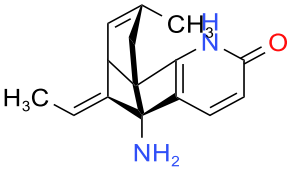
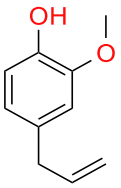
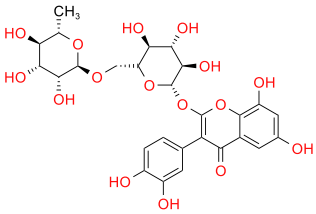
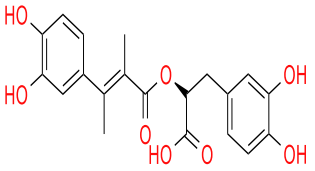
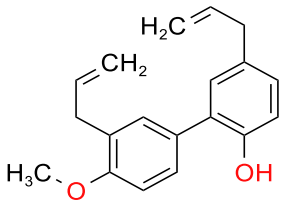
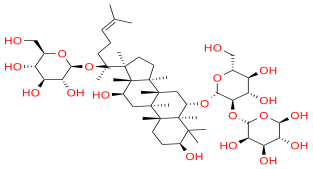
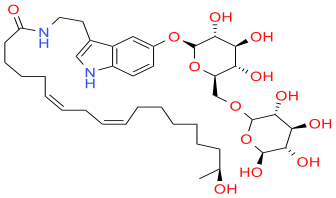
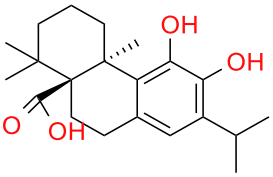
Ginkgo biloba L. (Ginkgoaceae)

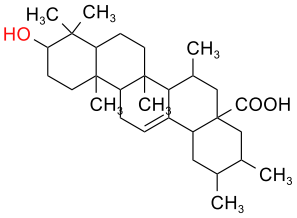
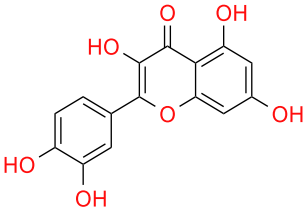
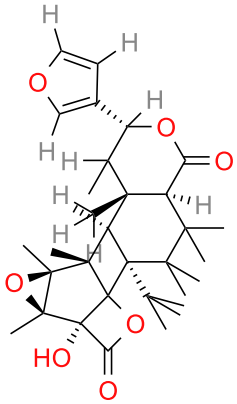
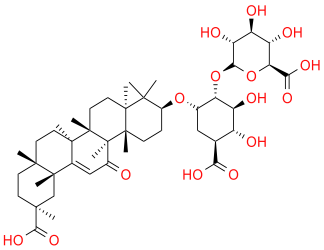
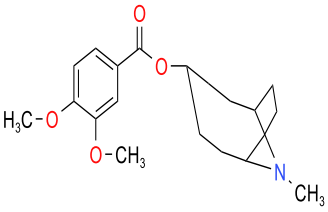
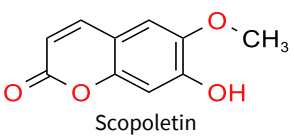
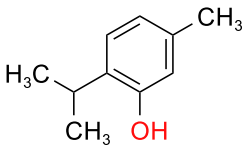
Ginko biloba has been used as a Chinese herbal remedy for hundreds of years to cure a variety of disorders. It contains rutin as a bioactive constituent. Numerous reports depict that the extract of *G. biloba* has the ability to diminish AD symptoms and therefore retard the disease's progression. During the early stages of AD, *G. biloba* extract is the 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 (18). It shows an antioxidant effect and inhibits aggregation of β-amyloid along with anti-platelet activating factor in AD patients (23-25). *G. biloba* can reduce hypertension and also prevent platelet accumulation. If administered in the beginning stages of AD, it has the potential to boost cognition (26).

Acorus calamus L. (Acoraceae)

Acorus calamus L., also known as "Acori Calami Rhizoma", is 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

Table 1: Potential Bioactive Substances used in the treatment of Alzheimer's Disease (9,10)

PLANT/BOTANICAL NAME/	PART OF PLANT USED	STRUCTURE	BIOACTIVE SUBSTANCE	MECHANISM OF ACTION
Curcuma longa L. (Turmeric)	Rhizomes		Curcumin	Inhibits β amyloid, phosphorylation of tau protein, α-secretase.
Huperzia serrata Thunb.	Leaves		Huperzine A	Inhibits the formation of β amyloid from amyloid precursor protein.
Acorus calamus L.	Rhizome and leaves		Eugenol	Inhibits Aβ-induced Ca2+ intake.
Ginkgo biloba L.	Dried leaves		Rutin	Attenuates Aβ25–35 induced apoptosis. Inhibits Aβ42 fibrillization and attenuates Aβ42-induced cytotoxicity dose dependently.
Salvia officinalis L.	Leaves		Rosmarinic acid	Inhibits tau phosphorylation, peroxidation of lipid and production of free radicals along with activation of caspase 3.
Melissa officinalis L.	Leaves		4-O-methylhonokiol	Inhibits the formation of β amyloid and the death of nerve cells. Inhibits production of free radicals.
Panax ginseng C.A. Meyer	Root		Ginsenoside Re	Reduce β amyloid induced cell death.
Withania somnifera L.	Root		Withanamide	Inhibits Reactive Oxygen Species.
Rosmarinus officinalis L.	Leaves and oil		Carnosic acid	Increase cognition by maintaining healthy nerve cells of the brain.

Urtica dioica L.	Roots		Ursolic acid	Improves free radical scavenging activity. Inhibits lipid peroxidation along with reactive nitrogen species. Increase the amount of dopamine. Restore GSH and reduce cytokines.
			Quercetin	
Tinospora cordifolia L. (Guduchi)	Root		Tinosporide 8-hydroxytino-sporide	Increase the amount of dopamine and decrease iron in the brain. Reduce the level of free radicals.
Glycrhiza glabra L. (Yasti madhu)	Root		Glycyrrhizin/ Glycyrrhizic acid Isoliquiritin	Suppress microglia activation and proinflammatory cytokine production (MCAO).
Convolvulus pluricaulis Choisy (Shankhapushpi)	Root	 Convolamine	Convolamine Scopoletin	Restore antioxidant and various apoptotic indicators. Inhibits generation of ROS. Alteration in membrane of mitochondria by depolarizing it.
		 Scopoletin		
Bertholletia excelsa L.	Kernel	Se	Selenium Lecithin	Shows high antioxidant activity. Inhibits lipid peroxidation and scavenge DPPH radicals *in vitro* (46).
Collinsonia canadensis L.	Root extract		Thymol	Prevent the breakdown of acetylcholine via inhibition of acetylcholinesterase (47).

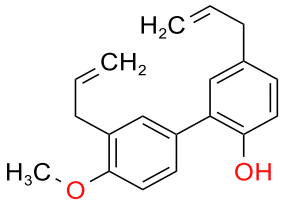
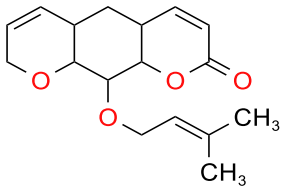
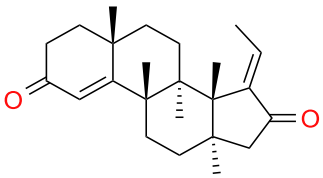
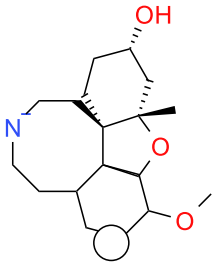
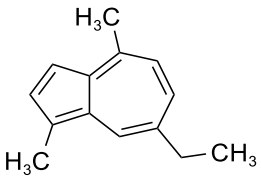
Magnolia officinalis L.	Bark		4-O-methylhonokiol	Inhibit β-secretase thus inhibiting formation of Aβ from APP (48).
Angelica archangelica L.	Seeds and root		Imperatorin (8-isopentenyloxypsoralen)	Inhibitory effect on acetylcholinesterase (49).
Commiphora wightti Arn. (Burseraceae)	Stem		Guggulsterone	Reduce acetylcholinesterase contents in the hippocampus (50,51)
Galanthus nivalis L. (the snowdrop)	Leaves		Galanthamine	Shows acetylcholinesterase activity. Penetrates the blood brain barrier readily and inhibits central cholinesterase (52,53).
Matricaria recutita L.	Root and flower		Chamazulene	Acts against free radicals (42).

exhibit antioxidant characteristics in the CNS. Alpha-asarone's cholinergic and antioxidant properties help in the treatment of memory impairment. Asarone's sometimes show genotoxic and hepatocarcinogenic effects; therefore, it has been advised to use very low concentrations of asarone in herbal preparations (27).

Huperzia serrata Thunb. (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 enhancing cognition and behaviour in AD patients (17). It has the ability to improve memory, concentration, and learning. It significantly lowers excessively elevated free radicals in the blood and brains of AD 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 (26).

Panax ginseng C.A. Meyer (Araliaceae)

Triterpene saponins, also known as ginsenosides, are the chief constituents 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, antagonise NMDA receptors, and modulate ACh release (27).

Rosmarinus officinalis L. (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 is also composed of about 20 antioxidants and 12 additional anti-inflammatory substances, of which carnosic acid and ferulic acid are the two most dominant antioxidants, which help slow down the progression of AD (15).

Convolvulus pluricaulis Choisy (Convolvulaceae)

It shows nerve regeneration and improved cognition (28,29). The bioactive constituents present in *Convolvulus pluricaulis* are convolamine and scopoletin. In scopolamine-treated rats, *C. 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 its treatment, demonstrating its neuroprotective properties (30). Pretreatment with C. *pluricaulis* reduces free radicals and inhibits the depolarization of the mitochondrial membrane while restoring various free radical scavengers and apoptotic markers.

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 (31). Curcuminoids include curcumin (32), 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 patients (33,34), and when injected, it blocks the formation of plaque (35). 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 the 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. Curcumin forms complexes with metals like zinc, copper, and iron (36) and blocks metal-induced amyloid plaque formation (37), inflammation, and oxidative neurotoxicity (38).

Matricaria recutita L. (Asteraceae)

German chamomile can boost memory, relieve fatigue, soothe the nerves, prevent sleeplessness, improve digestion, be used in cold and cough, support the defence mechanisms of the body. It reduces unconsciousness and elevates drowsiness when taken in larger doses (26).

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 and thus helps in slowing the progression of AD.

Glycyrrhiza glabra L. (Fabaceae)

The main factor responsible for the development of AD is the presence of β-amyloid plaques, which are characterised by neuronal death. *Glycyrrhiza glabra* contains glycyrrhizin/glycyrrhizic acid and isoliquiritin, which protect 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 AD and the symptoms that are associated with it (26).

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". It is an isoquinoline alkaloid that can cross the blood-brain barrier inhibiting the acetylcholinesterase enzyme and increases the cholinergic neurotransmission, which thereby helps in the treatment of AD (26).

Commiphora wightti Arn. (Burseraceae)

The main component of guggulipid, guggulsterone, can be found in the plant resin *Commiphora wightti* (Guggulu). Guggulipid is seen to strengthen memory (39). *C. wightti* affects choline acetyl transferase levels in the brain and impairs cognition. *C. wightti* exhibits the greatest effects on memory capabilities and dementia disorder risk (26). It acts on the hippocampus region of the brain by lowering the choline acetyl transferase levels.

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 lipid peroxidation along with acetylcholinesterase (26).

Angelica archangelica L. (Umbelliferae)

Numerous compounds found in the plant *Angelica archangelica* of the family Umbelliferae show similar effects to those seen in AD medications (26). *A. archangelica* has the same phytochemicals that help improve blood flow in the brain. It contains Imperatorin (8-isopentenyloxypsoralen), which shows an inhibitory effect on acetylcholinesterase (AChE) (40).

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, *T. cordifolia* has the ability to improve their memory. The production of acetylcholine and immunostimulation are the mechanisms through which *Tinospora cordifolia* enhances memory (41). Its treatment improves cognitive function in AD patients (42). 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.

Magnolia officinalis L. *(Magnoliaceae)*

Magnolia officinalis has been proven to release acetylcholine from the hippocampus, increase the effects of choline acetyltransferase, and block acetylcholine cleavage. It contains 4-O-methylhonokiol, which inhibits the 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 (42).

Collinsonia canadensis L. (Lamiaceae)

*Collinsonia canadensis*is is also known as Horsebalm. Its main chemical components, carvacol 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 (42). It acts by inhibiting the acetylcholinesterase enzyme, thereby preventing the breakdown of acetylcholine in AD.

Bertholettia excelsa L. (Lecythidaceae)

Lecithin is present in significant concentrations in *Bertholettia exelsa*, along with selenium. Lecithin, which contains choline, is present in large quantities. Acetylcholine can be produced from choline. Acetylcholine levels in AD patients are raised by these building blocks (42). Therefore, an increased amount of acetylcholine prevents the progression of AD.

Urtica dioica L. (Urticaceae)

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. *U. dioica*, which consists of boron, elevates body's oestrogen which is good for recognition. Therefore, it has been demonstrated to improve certain AD sufferers' moods. It contains ursolic acid and quercetin, which act as antioxidants, thereby lowering oxidative stress in an AD patient.

Withania somnifera L. (Solanaceae)

Withania somnifera (Ashawgandha), also known as Indian ginseng, is the most eminent herbal plant in AD as it acts as a nerve tonic. It contains active withanolides, withasomniferins, withasomniferols, withanone, and withaferin (43), which indicate strong antioxidant activity and free radical scavenging activity (44) 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 (45). A colorimetric approach based on Ellman's reaction in previous research shows the amount of cholinesterase inhibition by *W. somnifera* (42).

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. (54). Medical research on β-sitosterol has been intensively investigated (55) and it has been found that it shows antioxidant activity (56). Its chemical structure is similar to that of cholesterol (57). In context of this, natural chemicals, particularly flavonoids, are prospective lead ingredients for creating powerful medications to fight AD (11). Through the BBB, dietary phytosterols can aggregate in the brain tissue and may have an impact on cognitive performance (58). The shear pattern of APP is altered by β sitosterol, suggesting that it may be used as an AD treatment (59) as it also inhibits high cholesterol induced platelet β amyloid release. 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.

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 (60).

β-sitosterol is found in *Salvia officinalis* (61). *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* (62). The presence of stigmasterol and β-sitosterol is also encountered in the *Panax ginseng* roots, which are measured using improved analytical techniques. HPTLC, a densiometric approach, is used to measure phenolic compounds and terpenoids like β-sitosterol in *Convolvulus pluricaulis* (63). When the flowers of *Matricaria recutita* L. (Asteraceae) are hydrodistilled, an essential oil is produced. Organic solvent extraction results in the production of a β-sitosterol (64). *Glycyrrhiza glabra* also depicts the existence of β-sitosterol which is present in its roots (65). β-sitosterol was found to be the main steroid in *Lipidium meyenii* Walp (66). T. *cordifolia* also contains β-sitosterol which is best shown in its petroleum ether extract (67). The Brazil nut has intriguing antioxidant and anti-cholesterol characteristics as it shows an elevated amount of unsaturated fatty acids, alpha-tocopherol and beta-sitosterol (68). The chromatographic findings showed that caffeic acid, chlorogenic acid, β-sitosterol, and stigmasterol were present in *Urtica dioica* (69). From the roots of *Withania somnifera*, β-sitosterol along with other phytosterols, are isolated (70).

Oxyphytosterols can be produced as a result of their susceptibility to oxidation by reactive oxygen species like ozone (71). β-sitosterol is also used in pharmaceutical products and is regarded as a reliable and possible nutritional supplement with no harmful side effects. 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 down the free radicals and also decreases the peroxidation of lipids caused by the presence of glucose oxidase, which has beneficial effects on neurodegenerative diseases like AD (11).

According to research, β-sitosterol has the ability to cross the BBB and aggregate in the cerebrum, thus altering cognizance. This allows it to prevent esterase from degrading ACh, which lessens the memory and behaviour 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 behavioural anomalies in a variety of memory tests and also enhances motor coordination.

AD is characterised by the presence of amyloid

plaque, NFTs, and 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 and suppress the synthesis of β-amyloid due to which the progression of AD decelerates (72-74).

Numerous studies indicate that sitosterol shows immunomodulatory, lipid-lowering, and antioxidant properties, along with antinociceptive, anxiolytic, and sedative effects (75). β-sitosterol is biosynthesized in a variety of ways by different organisms, although it typically follows the mevalonate pathway. Dimethylallyldiphosphate and isopentenyldiphosphate combine to create farnesyldiphosphate, 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 farnesyldiphosphate 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 cycloartanol. 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 to β-sitosterol.

β-sitosterol shows potent anticholinesterase activity both *in vitro* and *in vivo*. It also improves behavioural impairments, with results that were on par with those of the conventional medication. According to the potential positive effects provided by β-sitosterol, it can inhibit the breakdown of acetylcholine and lessen the deficiency in behaviour and memory (76). β-sitosterol increases ROS scavengers catalytically and non-catalytically (52). It decreases the level of free radicals and peroxidation of lipids, demonstrating the compound's beneficial effects on neurological diseases (76).

According to reports, a number of substances derived from natural sources have high antioxidant properties and can be used 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 sites of action. It scavenges free radicals and inhibits cholinesterase, in addition to reducing behavioural deviations in a variety of memory tests, and it also enhances balance and motor performance in AD patients (76).

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 (77).

Conclusion

Herbal drugs have the ability to combat AD, which has offered hope for new medication sources. They act by inhibiting acetylcholinesterase, escalating free radical scavengers, inhibiting the production of beta-amyloid from the amyloid precursor protein, and activating other inhibitory pathways to combat AD. To improve cognition and slow down the progression of AD, 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. A clinical trial on the effects of resveratrol for AD treatment was conducted in 2012, which included 119 patients and was quadruple blinded. It depicted the presence of antioxidants in resveratrol, which helped slow down the progression of AD. In AD and variant neurodegenerative diseases, herbs may indicate their 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 has been 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.

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Authors' contributions

In this review article, AM did all the literature survey and analysed the data related to disease and treatment approaches with bioactive compounds and was the most important contributor in making the manuscript. SD and SK performed the systematic evaluation and elaboration of the conclusion. All authors read and approved the final manuscript.

Compliance with ethical standards

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