Review Article

A Review on Medicinal Plants Against Various forms of Dementia

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ABSTRACT

Dementia includes a wide range of neurodegenerative diseases which leads to various complications of the brain functioning. It is a clinical syndrome wherein gradual decline of mental and cognitive abilities occurs and this in a way renders an individual insufficient to function on his own due to severe memory loss. Various types of dementia are Parkinson's disease with dementia (PDD), Lewy body dementia (LBD), Vascular dementia (VaD), Huntington's Disease with dementia (HD), Frontotemporal dementia (FTD), Creutzfeldt-jakob dementia (CJD) and Alzheimer's disease with dementia (ADD). Medicinal plants used in dementia show varied mechanisms including effects on β-Amyloid plaque formation, Acetylcholinesterase (AChE), α and β-secretase, NMDA receptors, glutathione levels and cerebral blood flow. There have been a lot of medicinal plants used for trials against dementia and most of them have shown to have promising results in-vitro. This review article is about different medicinal plants which can potentially treat dementia.

Keywords: Parkinson's disease with dementia, Lewy body dementia, Vascular dementia, Huntington's disease with dementia, Frontotemporal dementia, Alzheimer's disease with dementia, Medicinal plants.

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INTRODUCTION

The International Classification of Diseases (ICD 10, WHO, 1992) defines dementia as a 'syndrome due to disease of the brain, usually of a chronic or progressive nature, due to which there is obstruction of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement'. Dementia includes a wide range of neurodegenerative diseases which results in various complications of the brain functioning. Dementia is related to various other conditions like deficits in cerebral blood flow, mitochondrial dysfunction and oxidative damage. It is a clinical syndrome wherein gradual decline of mental and cognitive abilities occurs and this in a way renders an individual insufficient to function on his own due to severe memory loss. Metabolic disorders, which participate in dysregulation of energy management, AIDS which causes indirect damage to the brain via immune-activated macrophages or systemic infections often result in dementia. Some environmental factors like toxins present in the abuse substances or air pollution can also lead to neuronal damage and thereby to dementia. Dementia is also connected with various gene polymorphisms and genetic mutations.[1] Dementia is primarily of following types:

Parkinson's disease with dementia (PD)

Cortical tissue size reduction has been observed to be one of the main causes of PD along with presence of subcortical lesions.[2] This is a type of dementia which occurs at a later stage proceeding a Parkinson's disease. This dementia is characterized by a progressive dysexecutive syndrome, forgetfulness, slowing of thought processes and impaired ability to manipulate acquired knowledge with added complications in cognition and other psychotic symptoms. Hallucinations usually of the visual type including clear, colorful and rarely fragmented figures of family and friends were observed. Treatment of dementia included synthetic drugs which improved cognition and hallucination symptoms like Donepezil, thereby only providing symptomatic relief and not treating the root cause of the disease. Rivastigmine which is a dual cholinesterase inhibitor namely butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) was also used. The extrapyramidal symptoms were found to be effectively controlled by Rivastigmine.[3]

Lewy body dementia (LBD)

Lewy bodies were found to be bodies of varying shapes like round, triangular and irregular. They were found to be present beside the nucleus in truncated forms.[4] They have a dense inner core and an outer portion consisting of abnormally condensed and phosphorylated neurofilament proteins like ubiquitin, α-synuclein and associated enzymes. Visual hallucinations, olfactory and auditory disturbances were commonly observed in patients with LBD. These hallucinations resulted in varying emotional states like fear, amusement, anger etc. Hypophonic speech, stooped posture and gait were also found to be

prevalent in patients.[5] Treatment therapy consisted of synthetic agents namely antipsychotics like Clozapine, Chlormethiazole and lorazepam. Neuroleptics like Thioridazine and Sulpiride were also used.[6]

Vascular dementia (VaD)

It is one of the most common types of dementia which involves cognitive impairment which precipitates because of an existing vascular disorder like a cardiac stroke, atherosclerosis or cardiac arrest which leads to multiple cerebral tissue lesions like Hemorrhage infarction, Hippocampal sclerosis and white matter lesions. These changes then in a way lead to dementia.[7] The symptoms associated with this disease are motor delay, depressive mood, low motivational energy, anxiety, abnormal thoughts and somatic irregularities. Cerebrovascular injury can also lead to corticospinal and extrapyramidal side effects like weakness and slowed muscular movements that in a way contribute to delaying of the behavioural patterns and decision-making abilities.[8] Treatment was done using Donepezil which improved cognition in patients, but it was shown to have a variety of side-effects. Rivastigmine showed considerable progress in executive functioning, verbal fluency as well as the behavioural patterns. Memantine showed a mild effect on improving cognition but had less side-effects in patients.[9]

Huntington's disease with dementia (HD)

Huntington's disease is a type of genetic disease with abnormalities in the Huntington gene which can then precipitate into dementia. Symptoms associated with the disease is a combination of three types of impairments namely:

1. Movement disorders: These consist of voluntary and involuntary disorders. These consist of continuous and irregular jerky movements. Unnatural eye movements, dysphagia, muscular rigidity and posture disturbances.
2. Cognitive disorders: Aphasia, agnosia, shortcomings in cognitive speed and flexibility are common. Retrieving memories and past events is a major problem observed in patients. Also, visuospatial activity and judgemental defects were known to develop.
3. Psychotic disorders: Depression, irritation and apathy are the most commonly observed. Prominent symptoms include feelings of worthlessness, self-blame, changes in sleep patterns, changes in appetite, anxiety, loss of energy and hopelessness.[10]

Treatment included synthetic drugs like Amantadine, Levetiracetam and Tetrabenazine. Also, some neuroprotective in clinical trials included Coenzyme-Q10, Creatine and Minocycline.[11] Several selective serotonin reuptake inhibitors were also used and were believed to benefit HD patients. Mood stabilizers like carbamazepine and valproate were thought to help with emotional stability and impulsivity. Antipsychotics were thought to benefit psychosis-related symptoms. Donepezil, Rivastigmine and Memantine were found to show questionable benefits in clinical trials.[12]

Frontotemporal Dementia (FTD)

It is a differential type of dementia with its locus in the frontal and/or temporal lobes involving progressive atrophy. It is also called Pick's disease after a Physician Arnold Pick. The three major pathogenic proteins implicated for the development of FTD are phosphorylated tau protein, trans active response DNA- binding protein- 43 (TDP-43) and fused in sarcoma (FUS) protein.[13]

Two vivid types of FTD exist:

1. Behavioral variant FTD: It includes personality changes, disinhibition and apathy. Reduced inhibition often results in poor financial decision making that can lead to financial ruins. Patients show loss of sympathy and empathy towards family and friends. A decrease in social responsiveness to emotional and other needs of people. Binge-eating, increased consumption of sweets or alcohol and weight gain are different aspects of this type.
2. Progressive Aphasia: Defects in language prediction, object naming, syntax or word comprehension are apparent during conversation.

Motor symptoms include hyperreflexia, spasticity, weakness, muscle atrophy and dysphagia are observed.[14] A lot of synthetic drugs were used. Commonly, selective serotonin reuptake inhibitors like Fluoxetine, Fluvoxamine, Sertraline or Paroxetine showed improvement in neuropsychiatric disorders. Antipsychotics like Olanzapine, Risperidone and Aripiprazole showed improvements in cognitive abilities, delusions, agitation, neuropsychiatric symptoms and overall behaviour. Cholinergic drugs like Rivastigmine, Donepezil and Selegiline showed improved behaviour and cognition.[15] But these synthetic drugs could only alleviate the symptoms rather than treating the root cause.

Creutzfeldt-Jakob dementia (CJD)

It is one of the rarest forms of dementia which can be a familial, sporadic or iatrogenic type. The basic event which happens is the formation of abnormal prion protein. It is hypothesized to occur in a pathway where abnormal prion protein acts as a template for host prion protein to fold abnormally into a pathogenic conformation which causes this type of dementia. This process is autocatalytic.[16] The synthetic drugs which were tried in trials included Quinacrine which reduced cyclic amplification of prion proteins and their cyclization yet did not show efficacy.[17] Flupirtine was found to act as a neuroprotective by upregulation of proto-oncogene bcl-2 and normalization of glutathione levels. There was a significant improvement in cognition among CJD patients.[18] Pentosan polysulfate was observed to have completely removed the abnormal prion protein strain in the mice population, but was yet to be tested for efficacy in humans.[19] These synthetic drugs

however could only provide symptomatic relief and there remains no cure for this form of dementia.[17]

Alzheimer's disease (AD)

AD is characterized by loss of presynaptic cholinergic neurons which later proceeds to cortical cholinergic deficit and thus into dementia.[20] The hallmark of this type of dementia is deposition of amyloid ß-protein (Aβ complex) in the extracellular cortical plaques and formation of neurofibrillary tangles composed of phosphorylated tau-protein. These events in the hippocampus, cortex and nucleus basalis lead to cholinergic, serotonergic and noradrenergic deficits.[21] Symptoms of this type include disorientation, agitation, confusion, hallucinations, aggressiveness, paranoia, sleep disturbances, apathy, aphasia, depression and urinary incontinence. Rigidity, tremor, tardive dyskinesia, snout and grasp reflex, Babinski reflexes were the extrapyramidal symptoms observed.[22] Many synthetic drugs were used to treat AD. Cholinesterase inhibitors like tacrine, donepezil and rivastigmine were primarily used. Xanomeline and Milameline were the muscarinic cholinergic agonists which were also tested for their efficacy on providing symptomatic relief. Most of these drugs were only able to treat the cognitive deficits which was observed during the testing studies.[20]

FDA approved drugs for most forms of dementia include Rivastigmine, Donepezil, Memantine and Galantamine.[1] Other synthetic drugs only provide symptomatic relief to demented patients, hence there is a dire need to look for more drugs which could potentially treat dementia. Medicinal plants can help in this regard. Medicinal plants have a wide range of phytoconstituents which show wide varieties of activity. Such plants offer a manifold benefit against the progression as well as against the symptoms associated with various forms of dementia. Medicinal plants used in dementia show different mechanisms including effects on modulation of β-Amyloid plaque formation, acetylcholinesterase, α and β-secretase, NMDA receptors, glutathione levels and cerebral blood flow. There have been a wide range of medicinal plants used for trials against dementia and most of them have shown to have promising biological activities.

Flowchart depicting various types of dementia and medicinal plants which can potentially treat dementia are mentioned in Figure 1.

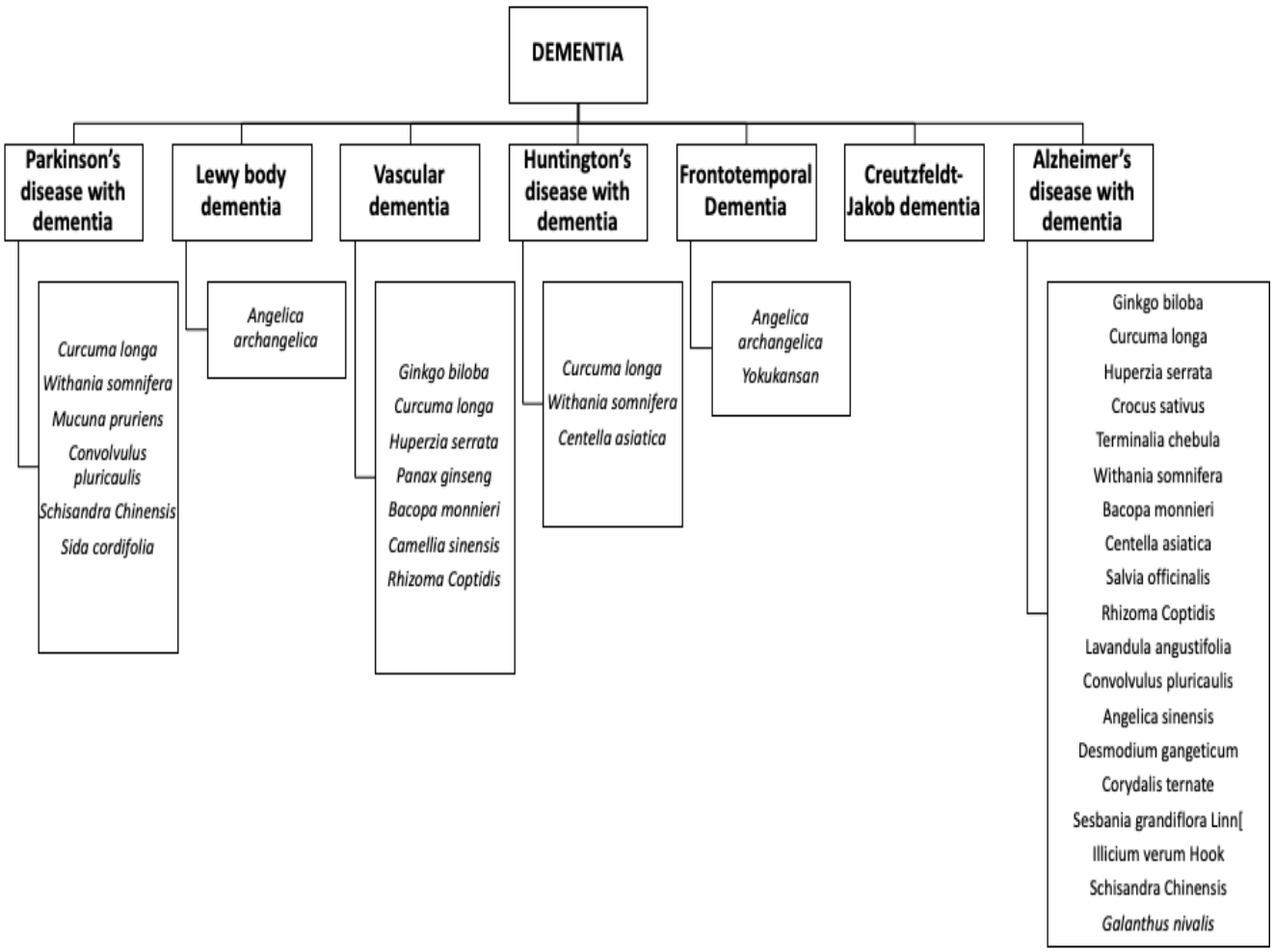


Figure 1: Flowchart representing types of dementia and the medicinal plants tried for treatment

These medicinal plants as well as their phytoconstituents responsible for activity have been listed in table 1.

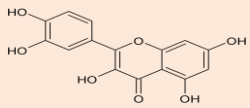
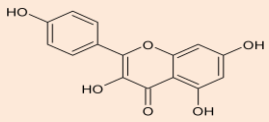
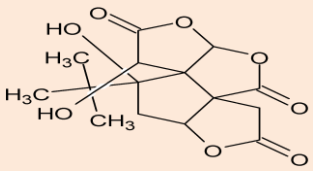
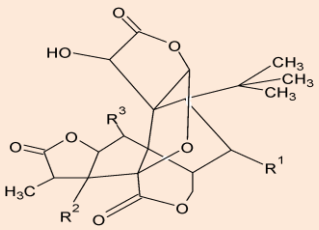
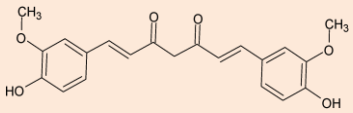
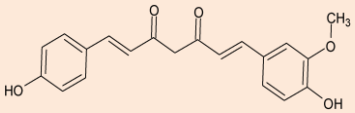
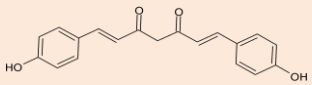
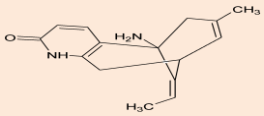
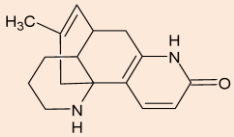
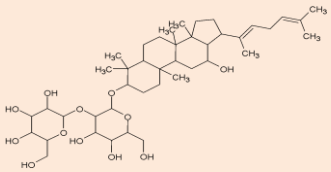
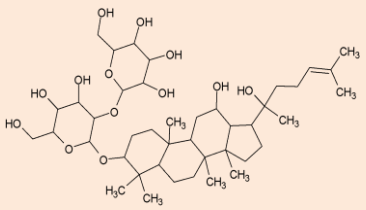
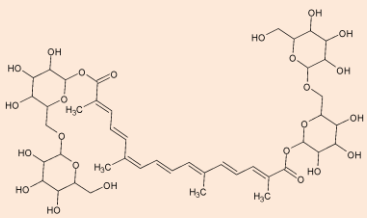
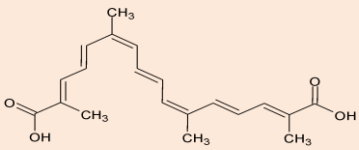
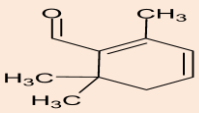
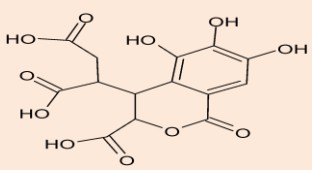
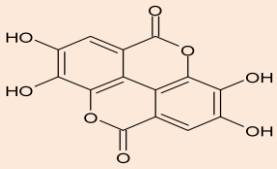
Table 1: Medicinal plants, their active constituents, part of plant used and mechanism of action

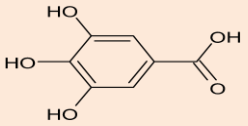
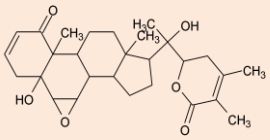
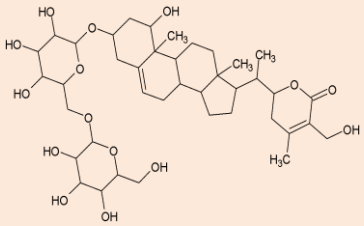
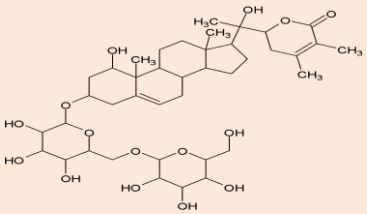
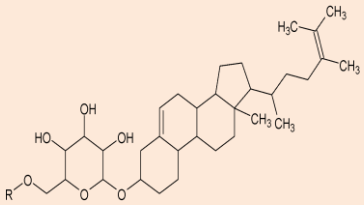
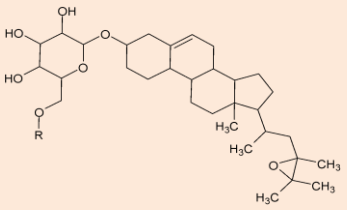
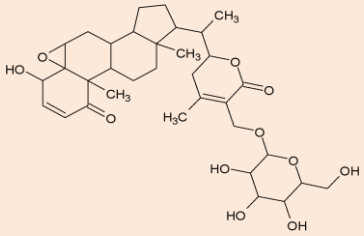
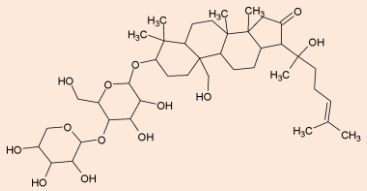
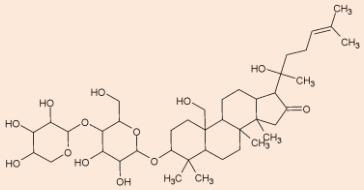
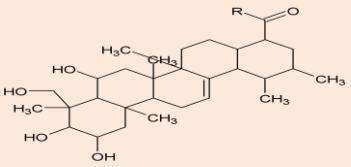
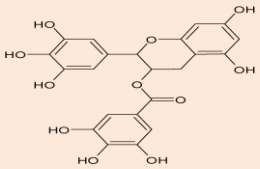
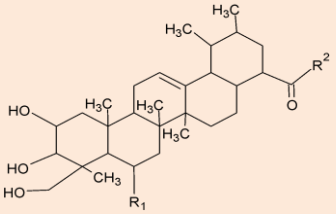
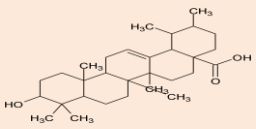
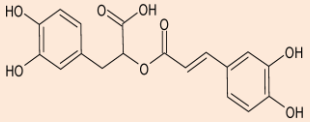
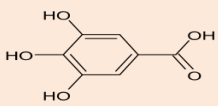
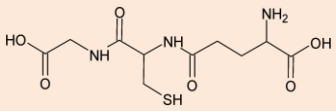
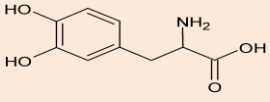
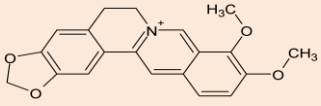
Common name Botanical name and Family	Chemical constituents	Form/ fraction of the plant	Used against type of dementia	Mechanism of action
Maidenhair tree, Kew tree [23,24,25] *Ginkgo biloba Ginkgoaceae*	Quercetin, kaempferol, ginkgolides	Leaves	VaD, AD	Enhances memory by increasing the availability of oxygen and help to eliminate free radicals from the system
Turmeric *Curcuma longa* [24,26,27,28] Zingiberaceae	Curcumin, curcuminoids	Roots and rhizomes	AD, HD, PD, VaD	Decrease in the formation of amyloid plaques and delay in degradation of neurons.
Toothed clubmoss *Huperzia serrata* [29,30,31,32,35] Lycopodiaceae	Huperzine A, huperzine B	Moss	VaD, AD	Inhibition of AChE, anti- β-amyloid peptide fragmentation, inhibition of oxygen- glucose deprivation, and NMDA receptor antagonism
Asian ginseng, Chinese ginseng *Panax ginseng* [24,30,33] Araliaceae	Ginsenoside Rg5, ginsenoside Rg3	Whole plant	VaD	Promotes β-amyloid peptide degradation and inhibition of AChE
Saffron *Crocus sativus* [30,34] Iridaceae	Crocin, safranal, crocetin	Flower	AD	Inhibition of oxidation induced formation of toxic amyloid fibrils
Gall nut *Terminalia chebula* [35,36] Combretaceae	Chebulic acid, gallic acid, ellagic acid	Fruit	AD	Inhibition of AChE and BuChE levels
Ashwagandha *Withania somnifera* Solanaceae [35,37,38,45]	Withanolide A, withanolide Ⅳ, withanolide Ⅵ, sitoindosides Ⅶ - Ⅹ	Roots	PD, AD, HD	Inhibition of AChE and decrease in level of β-amyloid peptide and glutathione level
Water hyssop, Brahmi *Bacopa monnieri* [24,39,40,41,42] Scrophulariaceae	Bacoside A, bacoside B	Rhizome	AD, VaD	Decrease in AChE, prevents β-amyloid deposits and formation of fibril
Tea plant, Tea shrub *Camellia sinensis* [24] Theaceae	Epigallocatechin-3-gallate	Leaves	VaD	Elevation of α-secretase activity and inhibition of β-secretase activity
Gotu kola *Centella asiatica* [30,43,44,45] Apiaceae	Asiaticoside, centelloside, brahmoside	Flowers	AD, HD	Inhibition of AChE inhibitor activity, decrease in level of β- amyloid and oxidative stress
Sage *Salvia officinalis* [26,44,57] Lamiaceae	Urosolic acid, Rosamarinic acid	Leaves	AD	Reduction in AChE and BuChE levels
Velvet bean *Mucuna pruriens* [46] Fabaceae	Gallic acid, glutathione, levodopa	Seeds	PD	Reduction in oxidative stress, mitochondrial and synaptic function
Huang lian *Rhizoma Coptidis* [47,51] Ranunculaceae	Berberine, palmatine, coptisine, protopine, epiberberine, jatrorrhizine,	Rhizomes	AD, VaD	Reduction in β-amyloid aggregation, oxidative stress and inhibition of cholinesterase activity
Lavender *Lavandula angustifolia* [48,49,50,51] Lamiaceae	Linalool, linalyl acetate, lavandulol, geraniol	Flowers	AD	Inhibition of β-amyloid plaque formation

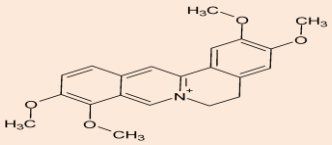
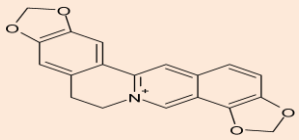
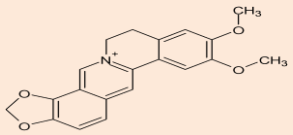
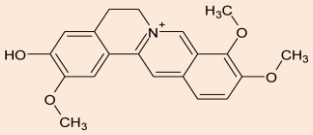
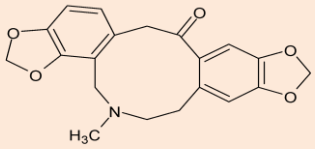
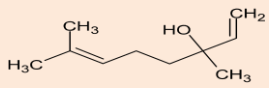
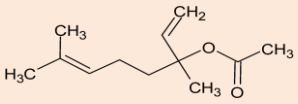
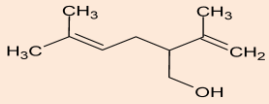
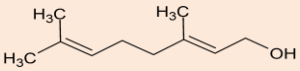
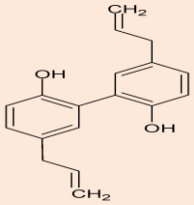
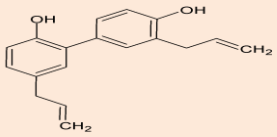
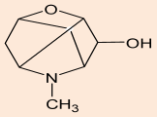
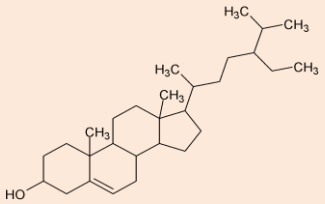
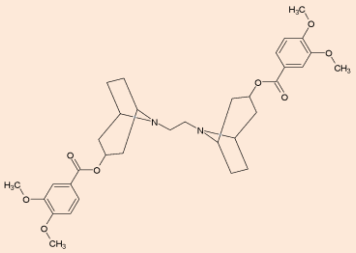
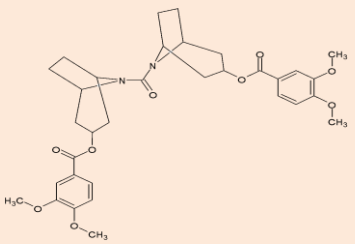
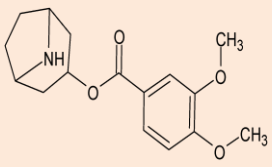
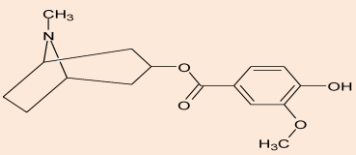
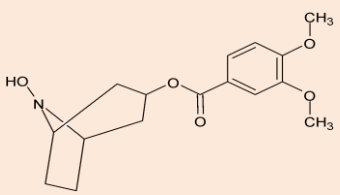
Houpa magnolia *Magnolia officinalis* [27,51,52] Magnoliaceae	Magnolol, honokiol	root and stem bark	AD	Inhibition of AChE activity and prevention of β-amyloid accumulation
Shankhpushpi *Convolvulus pluricaulis* [53,54] Convolvulaceae	Scopoline, ß-Sitosterol, convolvidine, subhirsine, convolvine, phyllabine, convoline, confoline	Whole plant	AD, PD	Inhibition of AChE level and β-amyloid plaque formation
Dong quai, female ginseng *Angelica sinensis* [55,56] Umbelliferae	Z-ligustilide, 11-angeloylsenkyunolide F, coniferyl ferulate, ferulic acid.	Roots	AD	Lowers hippocampal levels of Aβ and β-site amyloid precursor protein-cleaving enzyme
Feru-guard *Angelica archangelica* [51,57] Apiaceae	Ferulic acid	Whole plant	LBD, FTD	Inhibition of AChE activity and increase acetylcholine in the synapse
Salparni *Desmodium gangeticum*[41,58] Fabaceae	Gangetin, gangetinin, desmocarpine, desmodin	Whole plant	AD	Decrease in AChE level
Three-leaf corydalis *Corydalis ternata* [35,59] Papaveraceae	Protropine, coptisine, berberine	Tuber	AD	Inhibition of AChE activity
Agati, hummingbird tree *Sesbania grandiflora Linn* [39,60] Fabaceae	Oleanolic acid, glucuronic acid	Leaves and Flowers	AD	Decrease in AChE level
Star anise *Illicium verum Hook* [51] Illiciaceae	Anethole	Fruits	AD	Inhibition of AChE and BuChE
Five-flavor berry *Schisandra Chinensis* [30,61] Schisandraceae	Schizandrin	Fruits	PD	Reduction of oxidative stress, dopamine and tyrosine hydroxylase levels
Flannel weed, country mallow *Sida cordifolia* [62] Malvaceae	B- phenethylamine, tryptamines, vasicine, vasicinol	Roots	PD	Reduction of dopamine and oxidative stress levels
Yi-gan san Yokukansan [63,64] *Atractylodis lanceae rhizoma* (Asteraceae), *Poria* (Polyporaceae), *Cnidii rhizoma* (Umbelliferae), *Uncariae uncis cum ramulus* (Rubiaceae), *Angelicae radix* (Apiaceae), *Bupleuri radix* (Apiaceae), *and Glycyrrhizae radix* (Fabaceae)	18 β-glycyrrhetinic acid, geissoschizine methyl ether, hirsutene.	Roots, fungus, hooks	FTD	Decrease in brain glutamate level and modulation of serotonin function
Snowdrop *Galanthus* nivalis [65,66,67] Amaryllidaceae	Galantamine	Bulb	AD	Inhibition of AChE and enhancement of cholinergic function, reduction in oxidative stress

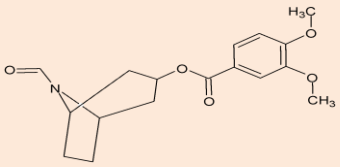
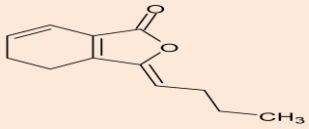
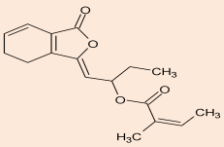
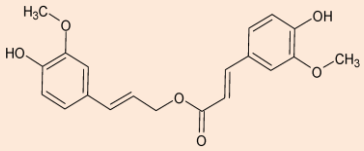
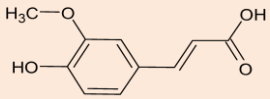
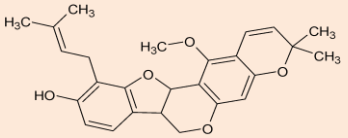
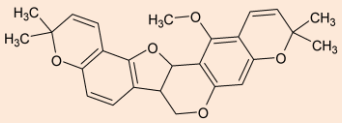
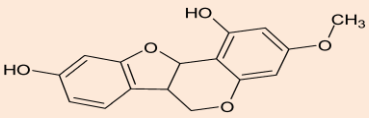
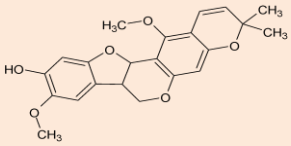
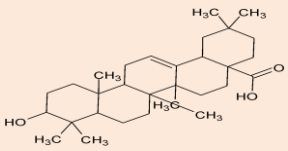
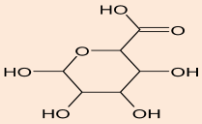
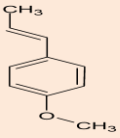
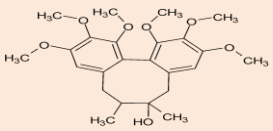
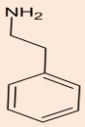
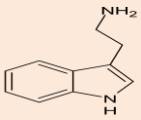
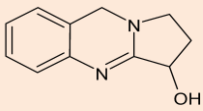
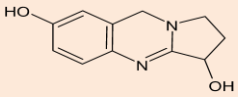
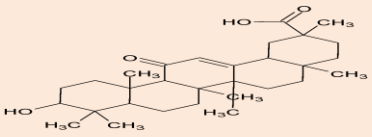
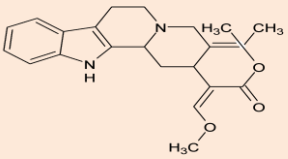
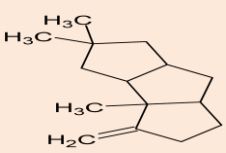
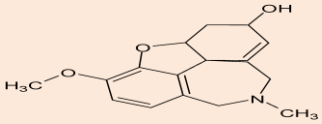
The chemical structures for the above-mentioned chemical constituents as per the order stated as above are given in Table 2.

Table 2: Chemical constituents and their structure

Chemical constituent	Structure	Chemical constituent	Structure
Quercetin		Kaempferol	
Bilobalide		Ginkgolides Ginkgolide A R1= H R2= OH R3= H Ginkgolide B R1= H R2= OH R3= OH Ginkgolide C R1= OH R2= OH R3= OH Ginkgolide J R1= OH R2= OH R3= H Ginkgolide M R1= OH R2= H R3= OH	
Curcumin		Demethoxycurcumin	
Bisdemethoxycurcumin		Huperzine A	
Huperzine B		Ginsenoside Rg5	
Ginsenoside Rg3		Crocin	
Crocetin		Safranal	
Chebulic acid		Ellagic acid	

Gallic acid		Withanolide A	
Withanoside Ⅳ		Withanoside Ⅵ	
Sitoindoside Ⅶ R= palmitoyl		Sitoindoside Ⅷ	
Sitoindoside Ⅸ		Bacoside A	
Bacoside B		Brahmoside R= Glu-Glu-Rha	
Epigallocatechin-3-gallate		Asiaticoside R_1= H R_2 = Glu-Glu-Rha Centelloside R_1=H R_2= Fru-Fru-Rha	
Ursolic acid		Rosmarinic acid	
Gallic acid		Glutathione	
Levodopa		Berberine	

Palmatine		Coptisine	
Epiberberine		Jatrorrhizine	
Protopine		Linalool	
Linalyl acetate		Lavandulol	
Geraniol		Magnolol	
Honokiol		Scopoline	
β- sitosterol		Convolvidine	
Subhirsine		Convolvine	
Phyllalbine		Convoline	

Confoline		Z-ligustilide	
11-angeloylsenkyunolide F		Coniferyl ferulate	
Ferulic acid		Gangetin	
Gangetinin		Desmocarpin	
Desmodin		Oleanolic acid	
glucuronic acid		anethole	
Schizandrin		β- phenethylamine	
Tryptamine		Vasicine	
Vasicinol		18 β-glycyrrhetinic acid	
Geissoschizine methyl ether		Hirsutene	
Galantamine			

CONCLUSION

In recent years, herbal drugs have shown tremendous potential in treating dementia. Studies have been done on animals to prove their efficacy against dementia. Some of them have shown promising results in animal studies. From this review, it is clear that medicinal plants play a vital role against various types of dementia. These medicinal plants have phytoconstituents which improve cognitive function and act as neuroprotective. We therefore conclude that these plants have a great potential in the treatment of dementia and can be used as a monotherapy or even as adjunct therapy in combination with other drugs.

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