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Herbal medicinal plants for the treatment of memory impairment: A futuristic approach for neurological Studies

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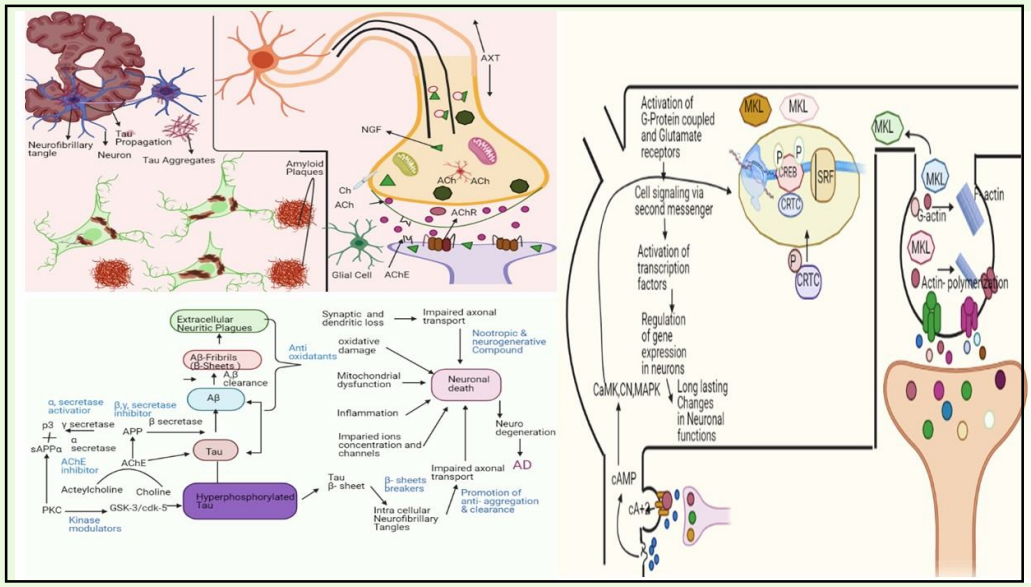
Abstract

Alzheimer's disease is affecting ~45.0 million individuals worldwide and is ranked as the fifth leading cause of death globally. The investigation of novel drug targets for treating cognitive impairments associated with neurological and psychiatric disorders remains a primary focus of study in central nervous system (CNS) research. Many promising new therapies are progressing through preclinical and clinical development, and offer the potential of improved treatment options for neurodegenerative diseases such as Alzheimer's disease (AD). Medicinal plants and herbal remedies are now gaining more interest as complementary and alternative interventions and are a valuable source for developing drug candidates for AD. Indeed, several scientific studies have described the use of various medicinal plants and their principal phytochemicals for the treatment of AD. This article reviews a subset of herbs for their anti-inflammatory, antioxidant, and cognitive-enhancing effects. This article systematically reviews recent studies that have investigated the role of neuroprotective herbs and their bioactive compounds for dementia associated with Alzheimer's disease and pre-Alzheimer's disease. PubMed Central, Scopus, and Google Scholar databases of articles were collected, and abstracts were reviewed for relevance to the subject matter. Medicinal plants have great potential as part of an overall program in the prevention and treatment of cognitive decline associated with AD. It is hoped that these medicinal plants can be used in drug discovery programs for identifying safe and efficacious small molecules for AD.



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1. Introduction

Dementia is a broad category of neurodegenerative pathologies, whose main symptom is a decline in cognitive ability severe enough to interfere with activities of daily living. Among them, Alzheimer disease (AD) is the most common type, accounting for 60% and up to 80%

of the total dementia cases (Calabro *et al.*, 2020). Alzheimer disease is affecting ~45.0 million individuals worldwide and is ranked as the fifth leading cause of death globally. In the United States alone, an estimated 5.8 million individuals live with AD dementia today, and this number is expected to grow to 13.8 million by 2050. Similarly, in Western Europe, dementia affects ~2.5% of people aged 65-69 years, escalating to about 40% of those aged 90-94 years (Wu *et al*., 2021), and by 2050, there will likely be up to 18.9 million patients with dementia in Europe and 36.5 million in East Asian countries (Hampel *et al*., 2021).

The morphological changes of the brain related to typical ageing differ from those that happen with AD. Amid the most remarkable is the aggregation of Aβ and tau hyperphosphorylation in Alzheimer's brain (Uddin *et al.,* 2018) Afterwards, several novel hypotheses emerged to explain the pathogenesis of AD, including the cellular senescence, infection-triggered AD hypothesis, as well as neuro immuno modulation hypothesis. Recently, dysfunction of the immune system has attracted great attention for its correlation with AD progression. Once produced, the Aβ peptide can form oligomers that inhibit long-term potentiation and mediate Aβ toxicity (Wu *et al.,* 2021).

These conditions may be treated with nootropics, which help to improve memory and learning abilities. Nootropic agents are known as "smart drugs" "brain boosters" or "memory-enhancing drugs" (Suliman *et al*., 2016) and are used to stabilize mood and behavior and also show a promising effect on other neurodegenerative diseases such as schizophrenia, attention deficit hyperactivity disorder, and Parkinson's disease. Synthetic drugs like piracetan, aniracetam, levetiracetam, fosracetam, oxiracetam, and oxiracetam-anticholine-sterases like donepezil are used as nootropic agents. However, sometimes these drugs show side effects. For this reason, these agents are conditioned to their uses, and the use of herbal supplements is approved as a safe nootropic agent (Vitthalrao, 2018).

Options for altering the progression and symptoms of Alzheimer's disease (AD) can be found in herbal medicine. Preparation of and marketing of drugs derived from medicinal plants appears to be gaining momentum in health-related areas, and their scientific and commercial significance is being recognized. The efficacy and safety of these plant-derived products for a specific application have been proven (Verma *et al*., 2013; Ghai *et al*., 2020). There are a number of ayurvedic medicines and surgical procedures that can be used to treat a wide range of ailments in ayurvedic medicine. Stress and its effects on the nervous system are extensively discussed in Ayurvedic texts. Vata vyadhi, the Sanskrit word for nervous system disorders, was thought to be caused by an imbalance of Vata, the biological air humour, the energy that flows through the brain and the nerves (the ancients considered nerve impulses to be a kind of wind or air traveling through the body) controlling both voluntary and involuntary functions. As a result, Vata imbalances are always characterized by some degree of nervous system weakness, disturbance, or hypersen-sitivity. Direct mentions of age-related memory loss, preventative care, and therapeutic interventions are included in these texts. It is only recently that mechanistic studies have been conducted on the role of these herbs in nervous system disorders and dementias, including Alzheimer's disease-related dementia, as these texts explain the use of a number of herbs (Ricciarelli and Fedeli, 2017). Flavonoids are employed in the treatment of first manifestations of Alzheimer's disease, such as cognitive decline and memory impairment, due to their ability to traverse the blood-brain barrier (BBB) as well as inhibit the formation of neurofibrillary tangles. Natural flavonoids mostly exhibit antioxidant along with neuroprotective properties, hence aiding in the partial restoration of impaired brain cells (Paramita Das *et al.,* 2021).

These drugs mainly contain extracts, claimed to enhance mental ability, from plants such as *Centella asiatica, Acorus calamus, Rhodiola rosea, and Bacopa monnieri*. In total, compounds isolated from these plants in previous studies include flavonoids, glycosides, saponins, terpenoids, terpenes, phenolic compounds, and alkaloids, which are responsible for therapeutic activities. Saponins, polyphenols, and flavonoids possess nootropic activity and may include other drug activities such as antioxidants and neuroprotectants, based on their facilitation of the retention of acquired learning in mice (Uddin *et al.,* 2018).

The herbal extracts and phytoconstituents such as flavonoids, phenolic compounds, glycosides, alkaloids, *etc*., despite their extraordinary potential antioxidant activity (*in vitro*) *via* enzyme inhibition, demonstrate less or no nootropic activity (*in vivo)* due to their poor lipid solubility and/or improper molecular size, resulting in poor absorption and bioavailability.

The bioavailability can be improved with the use of different novel delivery systems like phytosomes, liposomes, niosomes, *etc*., which could enhance the release rate as well as the ability to cross the lipoidal membranes. This phytosome technology is a revelation for significant bioavailability improvement, significant clinical benefit, tissue delivery, and nutrient safety without compromise. With the help of this technology, water-soluble phytoconstituents are turned into a molecular lipid-compatible complex that can get through the biomembrane and into the systemic circulation (Wu *et al.,* 2021).

2. Pathophysiology of memory impairment

The pathophysiology of memory impairment is multifactorial and can be understood better by several hypotheses, *viz*., the cholinergic hypothesis, the amyloid hypothesis, and the tau hypothesis, as described in Figure 1. In the present article, we have included the glutamate excitotoxicity.

2.1 Cholinergic hypothesis

The central cholinergic system is considered the most important neurotransmitter involved in the regulation of cognitive functions. Loss of cholinergic neurons in the nucleus basal is magnocellularis of the cortex due to this acetylcholine level deficit, and it is one of the major features of AD, in the first instance of memory loss. AChE is an enzyme which has very high catalytic activity and degrades thousands of ACh molecules per second, which leads to memory loss. Other neurodegenerative diseases, like Parkinson's disease, dementia with Lewy bodies, and, most recently, vascular dementia, have been linked to cholinergic disturbances, which correlate with the rate of memory loss (Suliman *et al*., 2016; Vitthalrao, 2018).

2.2 Amyloid hypothesis

Our hypothesis is that the main component of plaques is the amyloid protein (AP), the causing substance of dementia pathologies. These are derived from the amyloid precursor protein, which is cleaved by the beta secretase. The result is the direct consequence of this

deposition of the neurofibrillary encounters; the loss of the cell; vascular damage and dementia. This was the start of the amyloid cascade theory in 1992, when Hardy and Higgins (Calabro *et al.*, 2020) showed that the buildup of **Aβ** peptides in the brain parenchyma was the main cause of Alzheimer's disease (Suliman *et al.*, 2016; Verma *et al.*, 2013).

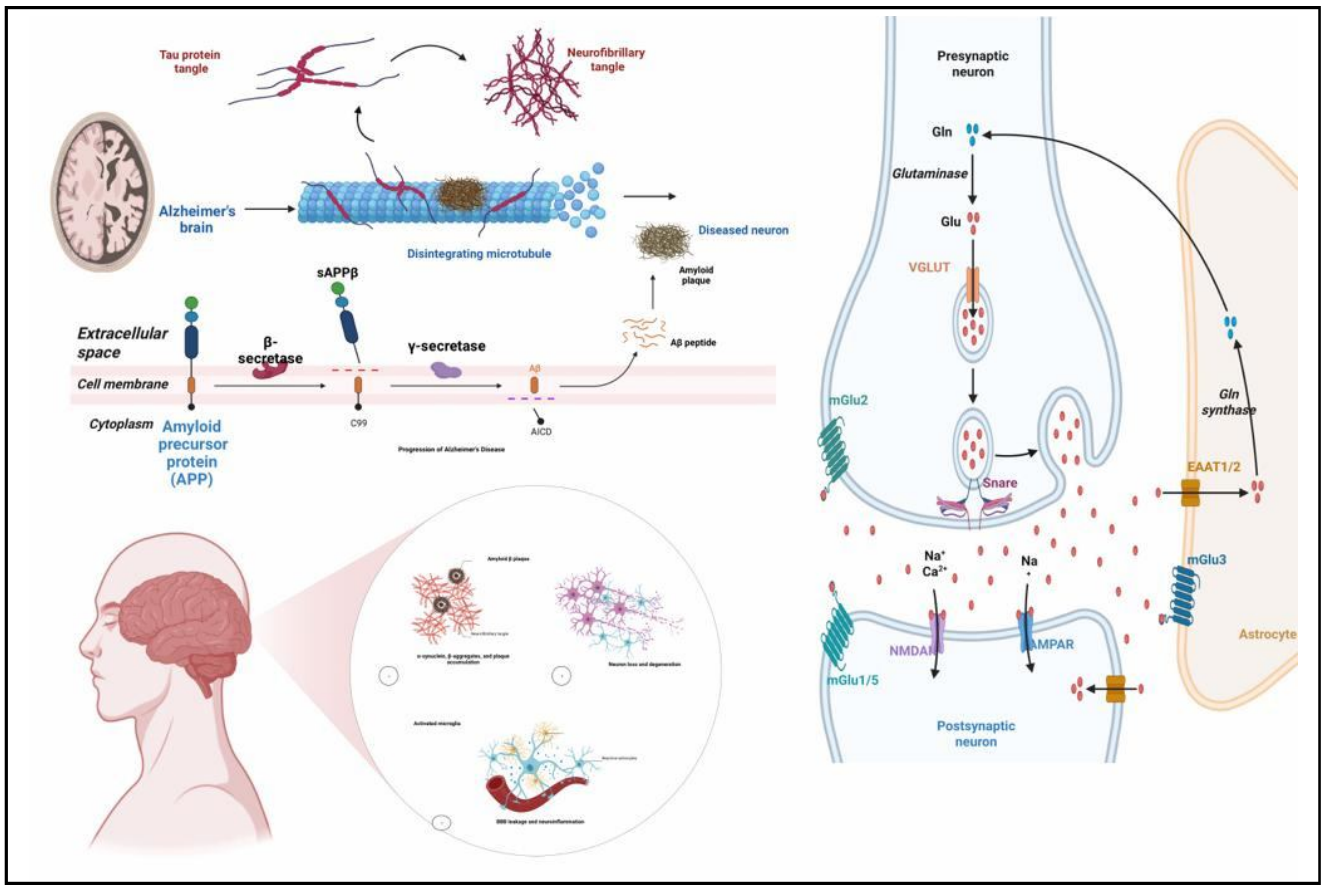

Figure 1: pathogenesis of Alzheimer disease.

2.3 Tau hypothesis

Patients with AD indicated the accumulation of tau in neurons deranges the cells' ability to solidify their communication with other neurons, preventing them from storing new memories. According to the tau hypothesis, normal adult tau changes into PHF-tau and NFTs when its phosphorylation is too much or too irregular. This is due to a natural chemical modification of tau called acetylation that is escalated in Alzheimer's disease, which results in tau moving from its normal location in the neurons to the synapses (Suliman *et al.*, 2016; Ghai *et al.*, 2020).

3. Current target therapies of cognitive enhancing agents

The pathogenesis of AD has been intensely examined, but the mechanisms of the disease still remain unclear. Genetically, AD can be classified into two types: 1. Based on early-onset familial AD and 2. Late-onset sporadic AD. Histopathologically, the disease is characterized by an accelerated accumulation of amyloid-β (Aβ) peptides in the form of extracellular senile plaques (SPs) and hyperphosphorylated and glycol-sylated microtubule-associated tau protein in the form of intracellular neurofibrillary tangle (NFT). A recent study of AD brain shown decreasing activity of acetylcholine-transferase (ChAT) and dysfunction of Ach containing neurons contributes substantially to the cognitive decline in AD. ChAT is responsible for the synthesis of Ach from acetyl-CoA. Additionally, overactivation of NMDA receptors proposes that neuronal cell death and abnormal rise in intracellular calcium is the cause of gradual cognitive loss in AD patient's condition results in the gradual death of neurons and finally causes loss of memory and cognitive functions. On the basis of available scientific reports, we have summarized the potential targets in Figure 1 for drug development and management of AD.

3.1 Mechanism of action of cognitive enhancing agents is described following

3.1.1 Malondialdehyde level

Malondialdehyde levels were substantially higher in cognitive disease patients regardless of genotype, apolipoprotein E, and μ4 all. The μ4 alone increases Alzheimer's risk 5,114 times and increases the risk of high malondialdehyde levels to 9,342,10. Cognitive enhancer drugs are targeted to reduce the level of malondialdehyde levels in the brain and increase the level of antioxidant molecules such as glutathione and superoxide dismutase (Rao *et al.*, 2021).

3.1.2 Acetylcholinesterase

Since cholinergic deficiency is congruent and early in AD, acetylcholinesterase (AChE) has been shown to be the most important diagnostic target in symptomatic Alzheimer's disease improvement (AD). Some drugs that improve thinking work by

reducing or blocking the acetylcholinesterase enzyme in the brain, which breaks down acetylcholine (Marucci *et al*., 2020).

3.1.3 Enhancement of acetylcholine level

Acetylcholine impairment is the most significant neurochemical deficiency in AD. Acetylcholine was the first neurotransmitter to be recognised and used in the central and peripheral nervous system by all cholinergic neurons. Some drugs are targeted to increase choline uptake, which facilitates ACh production and increases the affinity to bind their receptors (Singh *et al*., 2013).

3.1.4 CREBs pathway

The activation of NMDA receptors induces the release of calcium ions, which are responsible for the activation of various metabolic pathways such as calmodulin-dependent protein kinase (CaMK), extracellular signal-regulated kinase (ERK) and cAMP. This is responsible for the consequential activation of long-term potentiation and leads to the activation of numerous functional protein synthesis pathways, as depicted in Figure 2.

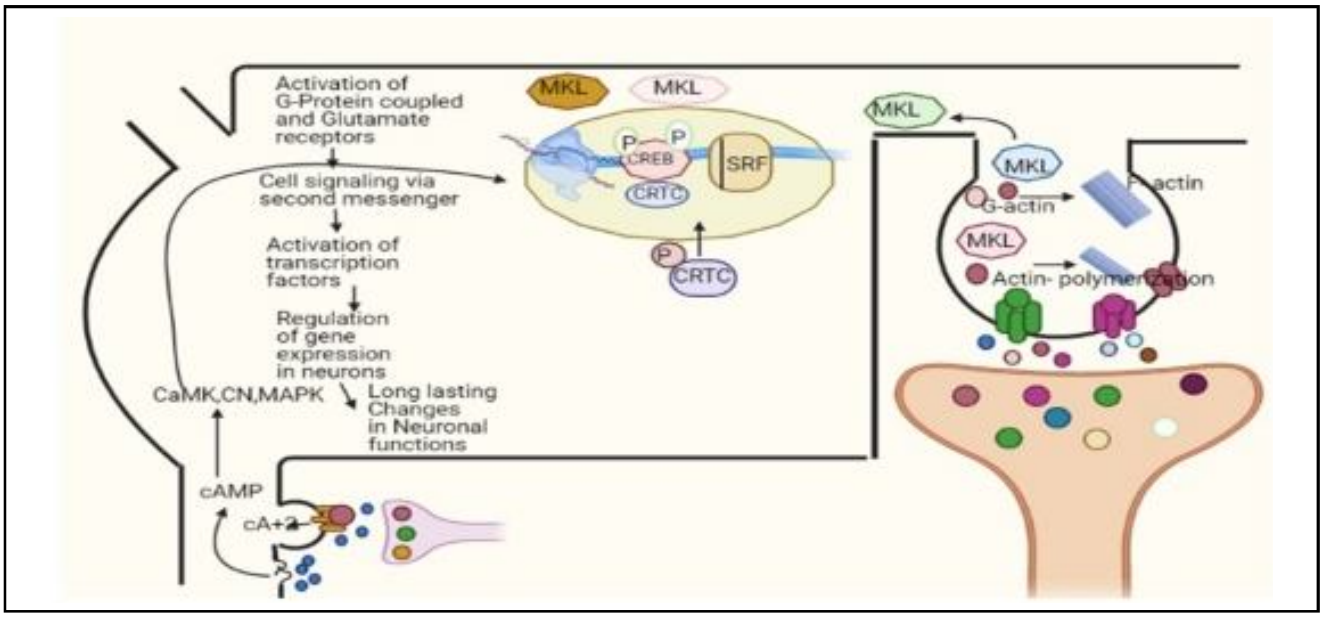

Figure 2: CREB pathway.

4. Approved drug for the treatment of cognitive disorder (Ghai *et al.*, 2020)

There are many drugs used for cognitive disorders. They may be synthetic, semi-synthetic, or natural supplements that can improve the mental status by reducing enzymes that degrade the neurotransmitters and promoting neurochemical production by improving the oxygen supply, enabling better transmission and rejuvenating neuronal growth. They contribute to stabilizing the nervous system. These are some synthetic drugs and the mode of action (Table 1) which is involved in cognitive disorder (Lopez-Riquelme *et al*., 2016).

Table 1: List of drugs and their mechanism of action which is used as a memory enhancer

Drugs	Mechanism of action	Uses
Rivastigmine	Non selective AChE inhibitors	Rivastigmine results in moderate cognitive function improvements and slows cognitive decay against placebo (Mehta *et al*., 2012).
Galantamine	Selective AChE inhibitors	Galantamine lowers **Aβ** peptide levels by modulating the cholinergic function (Stanciu *et al*., 2020).
Memantine	Non-competitive inhibitors of NMDA receptors	Memantine provided behavioural benefits in combination with an acetylcholinesterase inhibitor (AChEIs) (Mutahir *et al*., 2016).
Donepezil	Selective AChE inhibitors	Donepezil improves cognitive function, global function, global intensity, activities of daily life, and behaviour (Onor *et al*., 2007).
Piracetam	Selective AChE inhibitors	It enhances cognitive functions like comprehension, memory, focus, and perception without producing sedative or psychostimulant effects (Santos *et al*., 2020).

5. Proceeding clinical trial on cognitive drugs

The immunotherapies based on amyloid-plaque and gamma-secretase are presently being executed in clinical trials by different sponsors. Accordingly, inhibitors of **Aβ** and presenillin and many more treatments in human patients in clinical studies are being examined. One of the technological innovations was to stimulate clearance by active vaccination of A peptide from the AD patients' brains, *i.e.*, anti-antibodies are undertaken. A lot of monoclonal anti-A anticorps and other agents such as nutraceuticals are being studied in clinical studies (as shown in Table 2). Phosphodiesterases (PDEs) are a large group of eleven enzyme families responsible for cAMP (cyclic monophosphate adenosine) and cGMP removal (cyclic guanosine monophosphate). CAMP and cGMP are increased, and gene activation is increased by PDE inhibitors (Folch *et al*., 2018; Cummings *et al*., 2017; Van Dyck, 2018).

Table 2: List of some nutraceuticals, antibodies vaccines on which clinical trial going on (Folch *et al*., 2018)

Investigational drug/nutraceutical	Mechanism of action	Category	Sponsor	Clinical trial end date
Grape seed extract	Anti-oligomerization agent	Nutraceutical	Mount sinai alzheimer's disease Research center	2020, September (trial completed)
CNP520	Hinders APP's β-site split, reducing the production of amyloids	Amyloid vaccine	Axsome therapeutics	2024, July
Telmisartan	Enhance the working of the vasculum	Blocker of angiotensin receptor (ATR)	Sunnybrook health sciences centre	2021, March (trial completed)
Solanezumab	Remove the plaque of amyloid	Antibody based	Eli Lilly	2022, July
ABBV-8E12	Removes tau protein	Monoclonal antibody based	Abbvie	2021, June
Aducan+umab	Remove the plaque of amyloid	Antibody based	Biogen	2022, April
Crenezumab	Remove the plaques	Antibody based	Roche/Genentech	2021, July
Gantenerumab	Remove the plaques	Antibody based	Roche	November 2019 (trial completed)
Deferiprone	ROS reduction that can harm neurons	Iron chelator	Neuroscience trials, Australia	2021, December
Dronabinol	Improve aggression (AD symptoms of neuropsychiatric)	Endocannabinoid CB1 and CB2 partial agonist	John Hopkins University	2020, December (trial completed)
Icosapent ethyl (purified form of Omega 3 fatty acidEPA	Neuroprotective protects against pathological diseases	Derivative of omega 3 fatty acids (nutraceutical)	University of Wisconsin	2021, November

6. Polyherbal ayurvedic formulations available for cognitive enhancers

6.1 Various herbal cognitive enhancer drugs available in the market

Table 3: List of herbal formulations available in the market (Knott *et al*., 2017; Prathyusha *et al*., 2021)

Name of the formulation	Marketed brand name	Uses
Stresswin	Ashwagandha	Anxiety, depression, memory loss
Ashwagandharista	Ashwagandha	Depression, anxiety, calming nerves, improve memory
Churna	Saraswata Churna	Low intelligence, loss of memory, disorder of speech
Vati/Guggulu	Manasmitra Gutika	Psychiatric conditions, improve intelligence
Oil preparations	Balashwagandhalakshadi Tailam	Strengthens and tones muscles, improve nerve conduction
Bhasma/Rasaushadhi's	Mukta Pishti, Rajata Bhasma, Svarna Bhasma, Smritisagara Rasa	Inflammation, acidity, inhibition of microbes, depression, stress, hypertension, brain and nerves disorder
Avaleha	Chandravleha	Bronchitis, COPD, cough, improve memory
Arka	Shankhakeetadi, Nasya	Psychotic disorders
Ghrita preparations	Brahmi, Ghrita, Chetasa, Ghrita Kushmanda Ghrita, Siddharthaka Ghrita	Depression, memory enhancer, speech disorder
Asava/Arishta	Saraswatarishta	Loss of memory,anxiety, fatigue, insomnia
Smrutihills	Ashwagandha	Nervine disorder, memory enhancer
Golden Milk	Ashwagandha	Improving mood, Boosting immune system
Brahmi	*Bacopa monnieri*	Improves memory, decreases antidepressant effect

Plants are widely known for their ethnomedicinal use and their current use of derived drugs. This is especially good because 80 per cent of the world's 122 medicines made from plants can be traced back to their use in traditional medicine.

The plants in the brain are known as nootropic plants, and their isolated components are known as intelligent medicinal products (nootropic = mental effects). Smart medications can be supplements, nutraceuticals, and mental functional foods. Some cognitive herbal enhancer formulations (Table 3) are already accepted and marketed in this table (Knott *et al*., 2017) (Figure 3).

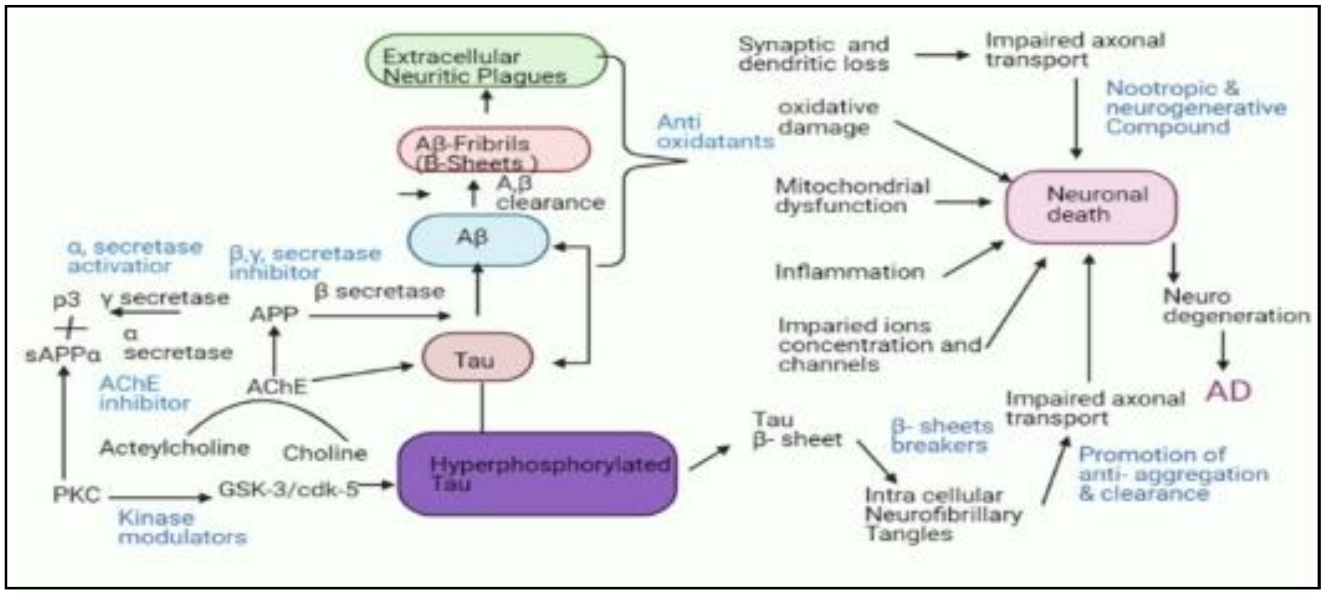

Figure 3: Pathways of memory impairment and their suggested ameliorative.

7. Ethnoherbal plants used as a memory enhancing agents

A large number of medicinal plants for their memory enhancing effects have been recently reported and are described in the following table. Different researchers have reported inhibitors of ache, neuroprotective agents, antioxidants, and reduced Aβ deposition. The available literature of plants tested to inhibit ache activity was thoroughly studied by one review and many phytoconstituent products such as flavonoids, alkaloids, phenolic compounds, and glycoside were reported (Table 4) (Knott *et al*., 2017). The medicinal plants those are having antioxidant properties help enhance the ability to remember and learn power because antioxidants have the ability to effectively stop these chain events by actively scavenging and neutralizing free radicals, impeding the progression of further oxidation processes (Akram and Nawaz, 2017). *Bacopa monneri* plays a crucial role in improving the condition of the brain works as an antidepressant, and anti-Parkinson effect (Xia *et al*., 2014).

Table 4: List of medicinal Plants with their phytoconstituent, extract, evaluation model, and likely action mechanism for memory enhancing activity

S. No.	plant name	Part used	Extract used in research model	Method used	Chemical constituents	Probable mode of action	Animals	References
1.	*Abelmochus moschatus*	Seeds	Ethanolic	EPM	Phenols, flavonoids antioxidant	Anti-cholinesterase,	Mice	Nandhini *et al*., 2014
2.	*Acorus calamus*	Rhizome	Methanolic	Ellman's method	b-asarone	AchE, Ach increases	Rats	Pattanik *et al*., 2013
3.	*Albizia adianthifolia*	Leaf	Aqueous	EPM, RAM	Flavonesapigenin	Antioxidant	Rats	Beppe *et al*., 2014
4.	*Alangiumsalvi folium*		Ethanolic	EPM, MWM	Flavonoids, Saponins, tannins	Antioxidant	Mice	Parameshwari *et al*., 2018
5.	*Albizzia lebbeck*	Leaf	Petroleum ether	EPM, PAT	Saponins	DA level, inhibition of GABAergic transmission 5-HT level increases	Mice	Chintawar *et al*., 2015
6.	*Alpinia oxyphylla*	Fruits	n-butanol	MWM, Y-Maze, AAT	Phenolic acid	NO inhibitory, neuroprotection	Mice	Shi *et al*., 2015
7.	*Bacopa monnieri*	Aerial part	Alcoholic	ORT	Bacopaside I	AchE, stimulation of Ach, antioxidant property	Mice	Thile *et al*., 2015

8.	*Bauhinia variegata*	Leaf	Flavanoid extract	EPM, RRA	Flavanoids	Protective effect, enhance cognitive aptitude	Rats	Jatav *et al*., 2014
9.	*Baccharis trimera*	Aerial part	Hydroalcoholic	BAIP	Phenolic compound	Antioxiant	Cell lines	Paiva *et al*., 2015
10.	*Blepharismad eraspa*	Seeds	Methanolic	MWM, EPM	Flavonoids	Inhibiting AchE activity, Ach con-centrationincreases	Rats	Lakshmi *et al*., 2015
11.	*Brassica oleracea*	Leaves	Chloroform	Y-maze, PAT, MWM	oxo-DHODE, THODE	Inhibition of AchE, antioxidant	Rats	Anantha and Satyavati, 2015
12.	*Cajanus cajan*	Leaves	Hydroalcoholic	EPM, Actoph-otometer	Quercetin	Inhibit whole brain AchE	Rats	Ahmad *et al*., 2018
13.	*Carica papaya*	Fruits	Ethylacetate	EPM, MWM, Y-Maze	Alkaloids, flavonoids, glycosides	Antioxidant	Mice	Kumar and Virender, 2013
14.	*Caralluma fimbriata*	Aerial part	Hydroalcoholic	ORT, MWM, LA	Alkaloids, flavonoids, glycosides	Nootropic and anxiolytic	Mice	Rajendran *et al*., 2014
15.	*Celastrus paniculatus*	Seeds	-	RAM, MWM,	Phenolic compound	Decrease AchE	Rats	Vishnu and Shan, 2017
16.	*Clitoria ternatae*	Aerial, part	Aqeous	PAT	-	Decreased AChE, increase Ach	Rats	Gollen B *et al*., 2018
17.	*Coccinia grandis*	Fruits	Ethanolic	EPM, MWM, HWM	Flavonoids, tannins and polyphenols	Decreased AChE, increase Ach	Rats	Yashashwini, 2018
18.	*Crataeva nurvala*	Bark	Ethanolic	EPM, Y-maze	Melatonin	Inhibit AchE	Rats	Bhattacharjee *et al*., 2015
19.	*Cressa cretica*	Whole plant	Petroleum ether, ethanolic, chloroform	EPM, PAP	Flavonoids	Antioxidant	Mice	Khare *et al*., 2014
20.	*Cucumis sativus*	Fruits	Paste	EPM	Agmatin, cucurbitacins	F2-isoprostane levels, Reduce Aβ deposition	Mice	Kumar *et al*., 2014
21.	*Cucurbita maxima*	Seeds	n- Hexane	EPM, MWM, PCT, SRT	Cucurbitacae	Decrease AChE	Rats	Jawaid *et al*., 2014
22.	*Cyperus rotundus*	Root	Ethanolic	MWM, PAT	flavonoids, phenolic compound	Antioxidant	Rats	Rabieia *et al*., 2018
23.	*Dalbergia sisso*	Leaf	Ethanolic	EPM, PAP	Flavonoids, tannins, alkaloids	AchE	Mice	Sau and Handral, 2015
24.	*Desmodium triquetrum*	Roots	Methanolic	EPM, MWM	Alkaloids, flavonoids	Cholinergic transmission	Mice	Joshi *et al*., 2018
25.	*Embelia ribes*	-	-	EPM, MWM	Embelin, pierre	Neuroprotective	Mice	Saini *et al*., 2019
26.	*Fructus akebiae*	Fruit	Ethanolic	MWM, ORT, TM	-	-	Rats	Wang *et al*., 2014
27.	*Fructus gardenia*	Whole plant	Methanolic	PAT	Geniposides	Acetylcholine enhancing	Mice	Nam and Lee, 2013

28.	*Gelsemium sempervirens*	Whole plant	Hydroalcoholic	EPM, Y-Maze, PAP	Alkaloids, iridoids, coumarin	Inhibition of both AchE, β- secretase, antioxidant activity	Mice	Palit *et al*., 2014
29.	*Glycyrrhyza glabra*	Roots, Rhizomes	Aqueous	PAP, EPM	-	Cholinergic transmission	Mice	Dhingra *et al*., 2013
30.	*Indigofera tinctoria*	Leaves	Aqueous	MWM, SMT, EPM	Flavonoids apigenin, quercetin, kaempferol	Facilitation of neurotransmitters (Acetylcholine), antioxidant potential	Mice	Chowdhury and Juvekar, 2014
31.	*Lagnaria siceraria*	Fruits	Aqueous	OFT, HDT, MWM, SRT, DBT	Choline level increases lipotropic factor	Facilitation of neuro-transmitters (Acetylcholine)	Rats	Aslam and Najam, 2013
32.	*Lawsoni ainer mis*	Leaves	-	Y-Maze	-	Enhancement of neurotransmission, inhibition	Mice	Venugopalan *et al*., 2017
33.	*Lycopodiellac ernua*	Aerial part	Methanolic	PAT, MWM	Alkaloids, huperziines A& B	Inhibited AchE	Mice	Chuong *et al*., 2014
34.	*Marsilea quadrifolia*	Whole plant	Ethanolic	Epm, MWM, Y-Maze	Thiaminase enzyme, steroids	Facilitation of choli-nergic transmission	Mice	Ashwini *et al*., 2012
35.	*Melissa officinalis*	Leaves	Methanolic	MWM	Rosamarinic acid	Activation of anti-oxidant enzymes	Rats	Soodi M *et al*., 2014
36.	*Mimosa pudica*	Whole plant	Ethanolic	RAM, MWM	Alkaloids, flavo-noids, steroids, tannins, phenolic	Protective effect on Alzheimer disease	Rats	Ittiyavirah and Pullochal, 2014
37.	*Mori fructus*	Mulberry	Ethanolic	ORT, PAT	Hesperetin, epica-techin, fiestin flavonoids	Ach level increases synthesization, increased the level of CERB and ERK	Mice	Kim and Oh, 2013
38.	*Murraya koenigii*	Leaves	Methanolic	EPM, PAP	Mahanimbine	Reduced choline-sterase activity	Mice	Mani *et al*., 2012
39.	*Myrstica fragrans*	Seeds	Methanolic	*In vitro* AChE	Lignans	Reduced AChE	-	Cuonga *et al*., 2014
40.	*Nelsonia canes cens*	Whole plant	Hexane, dich-loromethane, acetonitrile, ethylacetate, butanol	KI	Phenolic compound	Antioxidant, AchE inhibition	-	Ouattaral *et al*., 2013
41.	*Ocimum sanctum*	Leaves	Aqueous	T-maze, IAT	-	AChE inhibitor	Adult male Zebra Fish	Maddula *et al*., 2017
42.	*Passiflora incarnate*	Leaves	n-Butanol	EPM, ORT	Flavonoid, alkaloid, phenolic compound	Facilitation of brain cholinergic neurotransmission	-	Ingale and Kasture, 2012
43.	*Phylanthus acidus*	Leaves	Methanolic	EPM, ORT, MWM	-	Decrease AChE, Antioxidant	Rats	Uddin *et al*., 2016
44.	*Piper longum*	Fruit	Aqueous	Y-Maze	Piperlongumine, tannins, phenols	Decreases the memory loss	Rats	Kilari *et al*., 2015
45.	*Prunus amygdalus*	Shelled Almond	-	RAM, EPM	Phytosterols, flavonoids	Increased Brain 5-HT	Rats	Haider *et al*., 2012

46.	*Pterocarpus marsupium*	Wood	Methanolic	MWM, EPM	Saponins	Facilitation of cholinergic transmission	Mice	Chauhan and Chaudhary, 2012
47.	*Rhus verniciflua*	Bark	Ethylacetate	PAT	Flavonoids	Increase in CREB phosphorylation	Mice	Cho *et al*., 2013
48.	*Ribes nigrum*	-	Juice	Y-maze	Alkaloids	Inhibition of AChE	Mice	Stefanello *et al*., 2017
49.	*Rosmarinus officinalis*	Leaf	Aqueous	MLA, MMC, PAT, ORT	Rosmarinic acid	AChE inhibitory activities and butyr-ylcholinesterase inhibitory activities	Rats	Ozarowski *et al*., 2013
50.	*Saracaasoca flower*	Flower	Ethanolic	EPM, MWM	Flavonoids, glycosides	Facilitate cholinergic system	Mice	Parameshwari *et al*., 2018
51.	*Securinegaleu copyrus*	Fruits	Ethanolic	EPM	Flavonoids	Neuroprotective effect	-	Sheikh *et al*., 2014
52.	*Sida cordifolia*	Whole plant	Aqueous, hydroalcoholic	EPM, PAT	Alkaloids, flavonoids, Saponins	AChE inhibition, antioxidant	Mice	Khurana *et al*., 2017
53.	*Spinacia oleracea*	Leaves	aqueous	ERM, MWM	-	Inhibition of AChE	Mice	Reddy *et al*., 2019
54.	*Taverniera cuneifolia*	Roots	Methanolic and aqueous	EPM	Saponin	Ach level increases	Mice	Jamdhade and Surwase, 2013
55.	*Thymus vulgaris*	Whole plant	Ethanolic	PAT, MWM	Flavonoids	Increase Ach level	Rats	Rabiei *et al*., 2015
56.	*Tiliacorarace mosa*	Leaf	Methanolic, hexane, chloroform	Ellman's method	Saponin, triterpenoids	Antioxidant	Mice	Kumar *et al*., 2016
57.	*Tinospora cordifolia*	Stem	Ethanol, ethyl acetate, n-butanol	EPM, PAP, ORT	Saponins	Anticholinesterase	Mice	Une *et al*., 2014
58.	*Tridex procumbens*	Leaves	Aqueous	EPM, CPC	Flavonoids, saponin, alkaloids	Increased noradre-nergicactivity	Mice	Ramrao *et al*., 2018
59.	*Typha angustata*	Leaves	Methanolic, Aqueous	Y- maze	-	-	Mice	Kumar *et al*., 2014
60.	*Urnicarhynch ophylla*	Hooks	Ethyl acetate	MWM, PA T	Phenylpropan-oids, aromatic compounds, terpenes	Anticholinesterase	Rats	Chul and Ung, 2013
61.	*Vigna aconitifolia*	Seeds	Ethanolic, petroleum ether	EPM, PAT	Saponins	AchE inhibitory	Mice	Makrani *et al*., 2014
62.	*Vigna mungo*	Seeds	Ethanolic	CIH, LIH	Alkaloid, saponin, phenoliccom-pounds	Antagonize the serotonergic action	Rat	Ahmed *et al*., 2016
63.	*Vigna radiate*	Seeds	Petrolium ether, ethanolic, aqueous	RAM, MWM	Carbohydrates, flavonoids, alkaloids, terpenoids, tannins	-	Mice	Bhandurge *et al*., 2012
64.	*Vitis vinifera*	Fruits	Juice	MWM, ORT	Flavonoids, phenolic compound	AchE inhibitory	Mice	Aslam and Sultana, 2015
65.	*Vitex negundo*	Leaf	Hydroalcoholic	EPM, ORT	flavonoids, triter-penoids, phenolic acid, lignans	AchE inhibition, antioxidant effect, and/or increase in cholinergictrans mission.	Mice	Otari *et al*., 2012

8. Conclusion

Cognitive deficit is a major cause of memory loss in human beings and it is affecting the older generation recently. Consequently, it leads to delusions, inability to create new memories as well as inability to recognize common things. The pathophysiology behind dementia is not clearly understood, but one major cause is the formation of plaques of amyloids that elevate the AChE level of an enzyme responsible for degradation of Ach and hence memory loss. A variety of synthetic drugs are available which are helpful in the reduction of signs and symptoms of disease. The side and adverse effects restrict their acceptability as a successful therapy for long-lasting effects. Some herbal drugs have great potential for improving and maintaining cognitive behaviour by one or different mechanisms.

In the present review, the authors have described plants that have nootropic activity due to the presence of phytoconstituents, flavonoids, saponins, polyphenols, terpenoids, *etc*. The above-mentioned plants show their effects either by blocking the AChE enzyme and/or antioxidant property that leads to an increased level of Ach, which ultimately helps in improving the cognitive behaviour of the patient suffering from dementia. Various animal models, *viz*., Y-Maze, Elevated Plus Maze, T-maze, Radial Arm Maze, and Elman's method (*in vitro*) are also included in this review which would help the new researchers in finding new pathways. Herbal cognitive agents improve the quality of life by healing the mental disorders pertaining to their smart actions. These agents would be more helpful in improving cognitive impairment when followed by diet, exercise, and moral support.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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