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HERBAL REMEDIES FOR NEURODEGENERATIVE DISORDER (ALZHEIMER'S DISEASE): A REVIEW

Parul Agarwal*, Shashi Alok, Amreen Fatima and Prem Prakash Singh

Institute of Pharmacy, Bundelkhand University, Jhansi- 284121, Uttar Pradesh, India

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Correspondence to Author:

Parul Agarwal

Institute of Pharmacy, Bundelkhand University, Jhansi- 284121, Uttar Pradesh, India

E-mail: agarwal.parul88@gmail.com

ABSTRACT: Alzheimer's disease, a neurodegenerative disorder is characterized by intense memory loss enough to interfere with social and occupational execution. It is the most general form of dementia, affecting more than 20 million people worldwide. The treatments of Alzheimer's disease are through cholinesterase inhibitors or NMDA-receptor antagonists, while doubts remain about the therapeutic efficacy of these drugs thus herbal medicine product have been used in the cure of Behavioral and Psychological Symptoms of Dementia. The genes play an important role in the development of Alzheimer's disease. The objective of this article was to show that the herbal medicine is useful in the treatment of cognitive disorders in the elderly. Although some Food and Drug Administration-approved drugs which are available for the treatment of Alzheimer's disease, the outcomes was not good enough, and there is a place for alternative medicine, that is, herbal medicine. Herbal remedies for Alzheimer's disease have become more and more popular in the recent years, some herbs that is Ginger, Turmeric, Liquorice, Ginseng, Sage, Rosemarry and etc mention below are useful for cognitive impairment of Alzheimer's disease. This paper reviews the clinical effects of a synthetic drugs and herbal medicines for the treatment of Alzheimer's disease.

INTRODUCTION: In the last few years, there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter [1]. Early humans recognized their dependence on nature for a healthy life and since that time humanity has depended on the diversity of plant resources for food, clothing, shelter, and medicine to cure myriads of ailments.

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Led by instinct, taste, and experience, primitive men and women treated illness by using plants, animal parts, and minerals that were not part of their usual diet [2]. The use of plant-based health products was also increased in other European countries [3]. Export–Import Bank reports reveal that the global trade of plant-derived and plant originated products is around US $60 billion (with growth of 7% per annum) where India holds stake of US $1 billion which is expected to reach 3 trillion US$ by the end of 2015 [4, 5].

Disease Profile: Alzheimer's disease (AD) is a progressive inexorable loss of cognitive function associated with the presence of senile plaques in the hippocampal area of the brain. The disease is the most common form of dementing illness among middle-aged and older adults, affecting more than 5 million Americans, a number estimated to increase to 7.7 million by 2030.

Symptoms typically appear after age 60, and some early-onset forms of the disease are linked to a specific genetic defect. Although the etiology is unknown, genetic factors clearly play a role in 10% to 15% of cases [6].

Alzheimer's disease is characterized as a progressive neurodegenerative disorder and considered as prominent cause of dementia in the elderly. The main characteristics of this disease are difficulties in household handling routine and cognitive and emotional disturbance in the elderly. Dementia is a loss of brain function that occurs with certain diseases. Alzheimer's disease is one form of dementia that gradually gets worse over time. It affects memory, thinking, and behavior [7]. So far, efforts to find a cure for AD have been disappointing, and the drugs currently available to treat the disease address only its symptoms and with limited effectiveness. The underlying pathogenesis is a loss of neurons in the hippocampus, cortex, and subcortical structures [8].

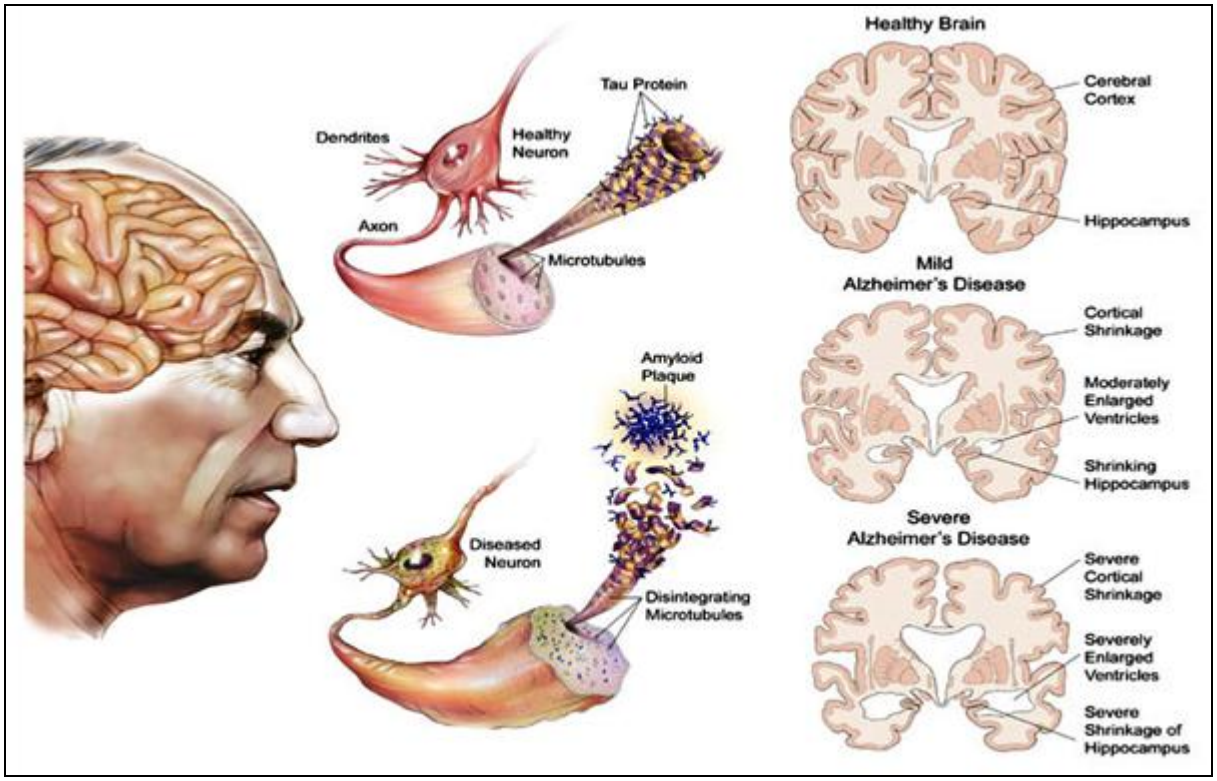

FIG. 1: NEUROLOGICAL DAMAGE LEADS TO THE DECREASE OF CORTICAL AND HIPPOCAMPAL SIZE. The hippocampus is involved in memory processing.

There are two types of AD:

1. **Early onset AD**: Symptoms appear before age 60. This type is much less common than late onset. However, it tends to get worse quickly. Early onset disease can run in families. Several genes have been identified.

2. **Late onset AD**: This is the most common type. It occurs in people age 60 and older. It may run in some families, but the role of genes is less clear [9].

Causes:

1. **Age-related changes in the brain:** One of the great mysteries of Alzheimer's disease is why it largely strikes older adults. Research on how the brain changes normally with age is shedding light on this question. For example, scientists are learning how age-related changes in the brain may harm neurons and contribute to Alzheimer's damage.

2. **Genetics:** The more researchers learn about Alzheimer's disease, the more they realize that genes play an important role in its development. Early-onset Alzheimer's is a rare form of the disease. It occurs in people age 30 to 60 and represents less than 5 percent of all people who have Alzheimer's disease. Most cases of early-onset Alzheimer's are familial Alzheimer's disease, caused by changes in one of three known genes inherited from a parent.

Most people with Alzheimer's disease have "late-onset" Alzheimer's, which usually develops after age, 60. Many studies have linked the APOE gene to late-onset Alzheimer's. This gene has several forms. One of them, APOE ε4, seems to increase a person's risk of getting the disease. However, carrying the APOE ε4 form of the gene does not necessarily mean that a person will develop Alzheimer's disease, and people carrying no APOE ε4 can also develop the disease.

3. **Environmental/lifestyle factors:** Research also suggests that a host of factors beyond basic genetics may play a role in the development and course of Alzheimer's disease. There is a great deal of interest, for example, in associations between cognitive decline and vascular and metabolic conditions such as heart disease, stroke, high blood pressure, diabetes, and obesity. Understanding these relationships and testing them in clinical trials will help us understand whether reducing risk factors for these conditions may help with Alzheimer's as well [10].

4. **Plaques:** These clumps of a protein called beta-amyloid may damage and destroy brain cells in several ways, including interfering with cell-to-cell communication. Although the ultimate cause of brain-cell death in Alzheimer's isn't known, the collection of beta-amyloid on the outside of brain cells is a prime suspect.

5. **Tangles:** Brain cells depend on an internal support and transport system to carry nutrients and other essential materials throughout their long extensions. This system requires the normal structure and functioning of a protein called tau. In Alzheimer's, threads of tau protein twist into abnormal tangles inside brain cells, leading to failure of the transport system. This failure is also strongly implicated in the decline and death of brain cells [11].

Prevention: At present, there is no definitive evidence to support that any particular measure is effective in preventing AD. Global studies of measures to prevent or delay the onset of AD have often produced inconsistent results. However, epidemiological studies have proposed relationships between certain modifiable factors, such as diet, cardiovascular risk, pharmaceutical products, or intellectual activities among others, and a population's likelihood of developing AD. Only further research, including clinical trials, will reveal whether these factors can help to prevent AD [12].

Although cardiovascular risk factors, such ashypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and course of AD, statins, which are cholesterol lowering drugs, have not been effective in preventing or improving the course of the disease [13]. The components of a Mediterranean diet, which include fruit and vegetables, bread, wheat and other cereals, olive oil, fish, and red wine, may all individually or together reduce the risk and course of Alzheimer's disease. There is limited evidence that light to moderate use of alcohol, particularly red wine, is associated with lower risk of AD [14].

Symptoms:

The early symptoms of AD can include:

a) Difficulty performing tasks that take some thought, but used to come easily, such as balancing a checkbook, playing complex games (such as bridge), and learning new information or routines.

b) Getting lost on familiar routes.

c) Language problems, such as trouble finding the name of familiar objects.

d) Losing interest in things previously enjoyed, flat mood.

e) Misplacing items [15].

As the AD becomes worse, symptoms are more obvious and interfere with your ability to take care of yourself. Symptoms can include:

a) Change in sleep patterns, often waking up at night.

b) Delusions, depression, agitation.

c) Difficulty doing basic tasks, such as preparing meals, choosing proper clothing, and driving.

d) Difficulty reading or writing.

e) Forgetting events in your own life history.

f) Hallucinations, arguments, striking out, and violent behavior.

g) Using the wrong word, mispronouncing words, speaking in confusing sentences.

h) Withdrawing from social contact.

People with severe AD can no longer:

a) Understand language.

b) Recognize family members.

c) Perform basic activities of daily living, such as eating, dressing, and bathing [15].

Diagnosis: Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions. Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically [16].

1. **Criteria:** The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984, extensively updated in 2007.

   These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD. A histopathologic confirmation including a microscopic examination of brain tissue is required for a definitive diagnosis. Eight cognitive domains are most commonly impaired in AD-memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities [17].

2. **Techniques:** Neuropsychological screening tests can help in the diagnosis of AD. In the tests, people are instructed to copy drawings similar to the one shown in the picture, remember words, read, and subtract serial numbers. Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia [18].

   Blood tests can identify other causes for dementia than AD—causes which may, in rare cases, be reversible. It is common to perform thyroid function tests, assess B12, rule out syphilis, rule out metabolic problems (including tests for kidney function, electrolyte levels and for diabetes), and assess levels of heavy metals (e.g. lead, mercury) and anaemia. Psychological tests for depression are employed, since depression can either be concurrent with AD (see Depression of Alzheimer disease), an early sign of cognitive impairment, or even the cause [19].

3. **Imaging:** When available as a diagnostic tool, single photon emission computed tomography (SPECT) and positron emission tomography (PET) neuroimaging are used to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination. In a person already having dementia, SPECT appears to be superior in differentiating Alzheimer's disease from other possible causes [20].

   Volumetric MRI can detect changes in the size of brain regions. Measuring those regions that atrophy during the progress of Alzheimer's disease is showing promise as a diagnostic indicator. It may prove less expensive than other imaging methods currently under study [21].

4. **Non-Imaging biomarkers:** Recent studies have shown that people with AD had decreased glutamate (Glu) as well as decreased Glu/creatine (Cr), Glu/myo-inositol (mI), Glu/N-acetylaspartate (NAA), and NAA/Cr ratios compared to normal people. Both decreased NAA/Cr and decreased hippocampal glutamate may be an early indicator of AD [22].

Stages:

1. **Stage 1:** No impairment (Normal function)

   The person does not experience any memory problems. An interview with a medical professional does not show any evidence of symptoms of dementia.

2. **Stage 2:** Very mild cognitive decline (may be normal age related changes or earliest signs of Alzheimer's disease).

   The person may feel as if he or she is having memory lapses, forgetting familiar words or location of everyday objects. But no symptoms of dementia can be detected during medical examination or by friends, family or co- workers.

3. **Stage 3:** Mild cognitive decline (early stage Alzheimer's can be diagnosed in some, but not all, individuals with these symptoms).

   Friends, family and co-workers begin to notice the difficulty. During a detailed medical interview, doctors may be able to detect problems in memory or concentration.

4. **Stage 4:** Moderate cognitive decline (Mild or early stage Alzheimer's disease).

At this point, a careful medical interview should be able to detect clear- cut systems in several areas:

a) Forgetfulness of recent events.
b) Forgetfulness about one's own personal history.
c) Greater difficulty performing complex tasks, such as planning dinner for guests, paying bills or managing finances.

5. **Stage 5:** Moderate severe cognitive decline (Moderate or mild stage Alzheimer's disease).

Gaps in memory and thinking are noticeable, and individuals begin to need help with day-to-day activities. At this stage, those with alzheimer's may:

a) Be unable to recall their own address or telephone number or the high school or college from which they graduated.
b) Become confused about where they are or what day it is
c) Have trouble with less challenging mental arithmetic; such as counting backward from 40 by subtracting 4s or from 20 by 2s
d) Need help choosing proper clothing for the season or the occasion.

6. **Stage 6:** Severe cognitive decline (Moderately severe or mild stage Alzheimer's disease).

Memory continues to worsen, personality changes may take place and individuals need extensive help with daily activities. At this stage, individuals may:

a) Lose awareness of recent experiences as well as of their surroundings.
b) Tend to wander or become lost.
c) Remember their own name but have difficulty with their personal history.
d) Have increasingly frequent trouble controlling their bladder or bowel.
e) Distinguish familiar and unfamiliar faces but have trouble remembering the name of a spouse.

7. **Stage 7:** Very severe cognitive decline (Severe or late-stage Alzheimer's disease).

In the final stage of this disease, individuals lose the ability to respond to their environment to carry on a conversation and, eventually, to control movement. They may still say words.

At this stage, individuals need help with much of their daily personal care, including eating or using the toilet. They may also lose the ability to smile, to sit without support and to hold their hands up [23].

Drug Treatment:

Medicines for AD include:

- Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne, formerly called Reminyl).
- Memantine (Namenda).

Other medicines may be needed to control aggressive, agitated, or dangerous behaviors. Examples include haloperidol, risperidone, and quetiapine. These are usually given in very low doses due to the risk of side effects including an increased risk of death.

It may be necessary to stop any medications that make confusion worse. Such medicines may include painkillers, cimetidine, central nervous system depressants, antihistamines, sleeping pills, and others. Never change or stop taking any medicines without first talking to your doctor [24].

TABLE 1: SYNTHETIC DRUGS USED IN ALZHEIMER'S DISEASE

S no.	Drug	Chemical name	Mode of action	Uses
1.	Donepezil	(±)-2, 3-dihydro-5, 6-dimethoxy2-[[1-(phenylmethyl)-4-piperidinyl] methyl]-1H-inden-1-one hydrochloride [25].	It is a reversible inhibitor of the enzyme acetylcholinesterase. Acetylcholinesterase is an enzyme, which breaks down the neurotransmitter acetylcholine [26].	It is used to treat confusion (dementia) related to Alzheimer's disease [27].
2.	Rivastigmine	3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate [28].	It binds reversibly with and inactivates chlolinesterase (acetylcholinesterase), preventing the hydrolysis of acetycholine, and thus leading to an increased concentration of acetylcholine at cholinergic synapses [29].	It is used to treatdementia related to Alzheimer's disease and Parkinson's disease. It may improve memory, awareness, and the ability to perform daily functions [30].
3.	Galantamine	(4aS,6R,8aS)- 5,6,9,10,11,12-hexahydro- 3-methoxy-11-methyl- 4aH-benzofuro[3a,3,2-ef] [31].	It reduces the action of AChE and therefore tends to increase the concentration of acetylcholine in the brain [32].	It is used for indicated for the treatment of mild to moderate vascular dementia and Alzheimer's [33].
4.	Memantine	1-amino-3,5-dimethyladamantane hydrochloride [34].	It acts as a non-competitive antagonist at different neuronal nicotinic acetylcholine receptors (nAChRs) at potencies possibly similar to the NMDA and 5-HT3 receptors [35].	It is used for managing Alzheimer's disease for people with moderate Alzheimer's disease who are intolerant of or have a contraindication to acetylcholinesterase inhibitors [36].
5.	Haloperidol	1-Butanone,4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-. 4-[4-(p-Chlorophenyl)-4-hydroxypiperidino] [37].	It is a typical butyrophenone type antipsychotic that exhibits high affinity dopamine D2 receptor antagonism and slow receptor dissociation kinetics [38].	It has found it to be an effective agent in treatment of schizophrenia, Alzheimer's disease, sclerosis, delirium, etc [39].
6.	Risperidone	3-[2-[4-(6-fluoro-1, 2-benzisoxazol-3-yl)- 1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one [40].	Blockade of dopaminergic D2 receptors in the limbic system alleviates positive symptoms of schizophrenia such as hallucinations, delusions, and erratic behavior and speech [41].	It is used in people with dementia, such as those suffering from Alzheimer's disease [42].
7.	Quetiapine	2-[2-(4-{2-thia-9-azatricyclo[9.4.0.0^{3,8}]pentadeca-1(11),3(8),4,6,9,12,14-heptaen-10-yl}piperazin-1-yl)ethoxy]ethan-1-ol [43].	Its activity is likely due to a combination of Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia [44].	It is used off-label for aggression, Alzheimer's disease, anger management, anxiety, dementia, depression, stress disorder, and sleeplessness [45].
8.	Cimetidine	*N*-cyano-*N*-methyl *N'*-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]-ethyl]-guanidine.	It binds to an H_2-receptor located on the basolateral membrane of the gastric parietal cell, blocking histamine effects [46].	It is effective in the treatment of common warts, herpes zoster, calcific tendinitis and Alzheimer's Disease [47].

TABLE 2: HERBAL DRUGS USED IN ALZHEIMER'S DISEASE

S no.	Herbal Drugs	Biological source/ Family	Chemical constituents	Mode of action	Uses
1.	Ginkgo	*Ginkgo biloba* / Ginkgoaceae	It contains terpene trilactones, ginkgolides A, B, C, J and bilobalide, biflavones, proanthocyanidins, alkylphenols, polyprenols [48].	It acts to varying degrees as scavengers for free radicals, which have been considered the mediators of the excessive lipid peroxidation, decline of membrane fluidity, and cell damage observed in Alzheimer's disease [49].	It is effective at treating mild to moderate dementia at the higher single dose of 240 mg daily, and is mainly used as memory boosting [50].
2.	Sage	*Salvia officinalis* / Lamiaceae	It contains cineole, borneol, thujone, tannic acid, oleic acid, ursolic acid, cornsole, fumaric acid, chlorogenic acid, caffeic acid, nicotinamide [51].	It possesses powerful antioxidant properties as well as Acetylcholinesterase-inhibiting compounds [52].	It is found to be effective in the management of mild to moderate Alzheimer's disease [53].
3.	Rosemarry	*Rosmarinus officinalis* / Lamiaceae	It contains carnosic acid, rosmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid, rosmaridiphenol and rosmanol [54].	It contain antioxidant compounds, carnosol and carnosic acid, which have been shown to be powerful inhibitors of lipid peroxidation [55].	In addition to improving memory, it would seem that it can protect the brain from strokes and conditions such as Alzheimer's Disease [56].
4.	Turmeric	*Curcuma longa* / Zingiberaceae	It contains essential oils, curcumin, and polyphenol. Curcumin is the active substance of turmeric [57].	It involves inhibition of articular NF-B, a transcription factor activated in vascular endothelium and synovial cells in RA joints [58].	It is used in diseases, such as cancer, Alzheimer's disease, arthritis, diabetes and other clinical disorders [59].
5.	German Chamomile	*Chamomilla recutita* / Asteraceae	It contains bisabolol oxide A, alpha-bisabolol, bisabolol oxide B, cis-enyne-bicycloether, bisabolon oxide A, chamazulene, spathulenol and (E)-beta-farnesene [60].	Extracts of plant might inhibit morphine dependence and withdrawal possibly by increasing cyclic adenosine monophosphate (c-AMP) levels [61].	It is used in stomach, irritable bowel syndrome, gentle sleep aid, mild laxative, anti-inflammatory, bactericidal and Alzheimer's disease [62].
6.	Ginseng	*Panax ginseng* / Araliaceae	It contains ginsenosides, or saponins, 20(S)-protopanaxadiol (PPD) and 20(S)-protopanaxatriol (PPT) [63].	It involves inhibition of generation or aggregation of amyloid beta (Aβ), enhancement of the removal of Aβ from the neurons, interruption of tau hyperphosphorylation [64].	It is used for neurological disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis [65].
7.	Liquorice	*Glycyrrhiza glabra* / Leguminoceae	It contains glycyrrhizin, glycyrrhizic, glycyrrhetinic acid and two molecules of glucuronic acid [66].	Inhibition of viral binding to cell membranes and replication, as well as interference with cellular signal transduction [67].	It is used in a flavoring agent, tobacco, candy industries, beverage industries, cancer therapy, alzheimers disease, antiviral activity [68].
8.	White willow bark	*Salix alba* / Salicaceae	It contains salicin, salicortin, populin, fragilin, tremulacin, Salicyl alcohol, saligenin, salidroside, vanillin, syringin, salicylic acid, caffeic and ferulic acids [69].	Salicin is a nonselective COX-1 and COX-2 inhibitor, effectively acting as an anti-inflammatory by blocking prostaglandin release [70].	It is used in pain, inflammation, fever, rheumatic ailments, headaches, toothache, gout, gastrointestinal disorders, diarrhea, and wound healing [71].
9.	Ginger	*Zingiber officinale* / Zingiberaceae	It contains zingerone, shogaols, gingerols, β-sesquiphellandrene, bisabolene, farnesene, β-	It also seems to inhibit the synthesis of prostaglandin-E2 (PGE2) and thromboxane B2	It is used in Alzheimer's Disease, Irritable Bowel Syndrome, motion sickness, morning sickness,

			phelladrene, cineol, and citral [72].	(TXB2), it inhibits thromboxane synthetase. It seems to act on serotonin receptors [73].	colic, dyspepsia, osteoarthritis, anorexia, and upper respiratory tract infections [74].
10.	Chinese knotweed	*Polygonum multiflorum* / polygonaceae	It contains Chrysophanol, Physcion, Emodin, Aloeemodin, Rhein, Noreugenin, Apigenin, Daucosterol, beta-Sitosterol, Stearic acid [75].	The study was designed to determine the effect of *Polygonum multiflorum* water extract on Abeta induced cognitive deficits and oxidative stress [76].	It is used in Alzheimer's disease, Cardiovascular and Cerebral, Memory and Learning, High Blood Pressure, Cancers [77].
11.	Stinging nettle	*Urtica dioica* / Urticaceae	It contains Acetylcholine, histamine, 5-hydroxy tryptamine, protein, fat, fiber, etc [78].	It enhances the cholinergic system in the brain may be useful in treating Alzheimer's disease [79].	It is used in Alzheimer's disease and certain types of cancers, asthma, bronchitis and sinusitis, etc [80].
12.	Maca	*Lepidium meyenii* / Brassicaceae	It contains acyclic keto, alkaloids, amino acids, arginine, histidine, phenylalanine, threonine, tyrosine, anthocyanines, glucotropaeolin [81].	It exerts its antioxidant and AChE inhibitory activities [82].	It is used to increase sex drive, improve fertility, Alzheimer's disease (AD), hypothyroidism, natural immunostimulant [83].
13.	Maritime pine bark	*Pinus pinaster* / Pinaceae	It contains catechin, taxifolin, procyanidins, catechin, epicatechin units, and phenolic acids [84].	Morphological pathology reveals that neuronal apoptosis is associated with senile plaques containing amyloid-beta peptide (Abeta) in AD brains [85].	It is used in anti-inflammatory, anti-mutagenic, antimetastatic, anticarcinogenic, and high antioxidant activities [86].
14.	Lemon balm	*Melissa officinalis* / Lamiaceae	It contains caffeic acid, luteolin-7-O-glucoside, isoquercitrin, rhamnocitrin, rosmarinic acid, ferulic acid, methyl carnosoate, hydroxycinnamic acid [87].	Patients who took a standardized extract of lemon balm orally daily for four months appeared to have reduced agitation and Alzheimer's symptoms [88].	It is used in anxiety, insomnia, dyspepsia, dysmenorrhea, cramps, headache, toothache, Alzheimer's disease [89].
15.	Huperzine A	*Huperzia serrata* / Huperziaceae	It contains lycoposerramine H, serratidine, obscurumine A, 11α-O-acetyllycopodine, huperzine A, huperzine B, huperzinine, lycodine [90].	The extract of *Huperzia serrata*, serves as a powerful inhibitor to an enzyme called acetylcholinesterase (AChEI), and studies have shown that Alzheimer's patients derive benefits from having this enzyme inhibited [91].	It is used in neurodegeneration, such as myasthenia gravis and Alzheimer's disease [92].
16.	Saffron	*Crocus sativus* / Iridaceae	It contains Gentisic, gallic acids, lycopene, picrocrocin, safranal, crocin, zeaxanthin, α- and β-carotenes [93].	Preliminary evidence of a possible therapeutic effect of saffron extract in the treatment of patients with mild-to-moderate Alzheimer's disease [94].	It is used in anticarcinogenic anti-mutagenic, immuno modulating, antioxidant-like properties, macular degeneration and retinitis pigmentosa [95].
17.	Harar	*Terminalia chebula* / Combretaceae	It contains arjunglucoside I, arjungenin, chebulosides I and II, chebulinic acid, gallic acid, ethyl gallate, punicalagin [96].	It exert acetylcholinesterase inhibitory and has suggested developing this herb as a potential in the treatment of AD [97].	It is used in homeostatic, antitussive, laxative, diuretic, and cardiotonic activities [98].
18.	Rheum	*Rheum glabricaule* / Polygonaceae	It contains n-hexacosnic acid, palmitic acid, daucosterol, chrysophanol-8-Me ether, citreorosein, chrysophanol 8-O-beta-D-glucopyranoside [99].	In in vitro experiments, rhapontigenin exerted a dose-dependent protective effect on mitochondrial functioning against amyloid beta (1-42) neurotoxicity [100].	It is used in Cancer, GI effects, Lipid-lowering effects, Renal effects, Alzheimer disease, Antimicrobial, Dental, Estrogen, Heptoprotective effects [101].

19.	Kava	*Piper methysticum* / Piperaceae	It contains 2, 5, 8-trimethyl-1-naphthol, 8,11-octadecadienoic acid-methyl ester, and 7-dimethoxyflavanone-5-hydroxy-4' [102].	Desmethoxyyangonin, one of the six major kavalactones, is a reversible MAO-B inhibitor and is able to increase dopamine levels in the nucleus accumbens [103].	It is used in muscle relaxant, anaesthetic, anticonvulsive and anxiolytic effects [104].
20.	Wuzhuyu	*Evodia rutaecarpa* / Rutaceae	It contains rutaecarpine, limonin, wuchuyuamide I, evocarpine, taraxerone, methyl coumarate, and caffeine [105].	It inhibits prostaglandin and/or COX-2 production, using one or more indolequinazoline alkaloids [106].	It is used in obesity, diabetes, Alzheimer's disease, cardiovascular, anti-atherosclerosis agents [107].
21.	Shankhpushpi	*Convolvulus pluricaulis* / Convolvulaceae	It contains convoline, convolidine, convolvine, confoline, convosine, kampferol and steroids phytosterol [108].	Hippocampal regions associated with the learning and memory functions showed a dose-dependent increase in acetylcholine esterase activity in the CA1 and CA3 area with plant treatment [109].	It is used in psychostimulant, tranquilizer, brain tonic, alterative, febrifuge, fever, nervous debility, loss of memory, also in syphilis, loss of memory, Alzheimer's disease [110].
22.	*Ashwagandha*	Withania somnifera / Solanaceae	It contains withanolides A to Y, dehydrowithanolide R, withasomniferin A, withasomidienone, withasomniferols A to C, withaferin A, and withanone [111].	withanamides has been shown to scavenge free radicals generated during the initiation and progression of AD. Neuronal cell death triggered by amyloid plaques was also blocked by withanamides [112].	It is used in antioxidant activity, free radical scavenging activity, and an ability to support a healthy immune system, central nervous system, Alzheimer's disease [113].
23.	*Guggulu*	*Commiphora mukul* / Burseraceae	It contains terpenes, sesquiterpenoids, cuminic aldehyde, eugenol, and the ketone steroids Z-and E-guggulsterone, and guggulsterols I, II, and III [114].	Decreased neuronal cholesterol levels, in turn, inhibit the beta-amyloid-forming amyloidogenic pathway, possibly by anti-acetylcholine esterase activity [115].	It is used in anti-dementia drug, cholesterol-lowering, antioxidant, Alzheimers disease [116].
24.	Brahmi	*Bacopa monniera* / Scrophulariaceae	It contains Bacoside A, Bacoside, Betulinic acid, D-Mannitol, Stigmastanol, b-Sitosterol, Stigmasterol [117].	It inhibited cholinergic degeneration and displayed a cognition-enhancing effect in a rat model of AD [118].	It is used in the treatment of memory loss, its potential benefit in the treatment of Alzheimer's disease [119].
25.	Biota	*Biota orientalis* / Cupressaceae	It contains 15-methoxypinusolidic acid, isopimarane diterpene, ent-isopimara-15-en-3 alpha, 8 alpha-diol diterpenes, lambertianic acid, 15-dien-18-oic acid [120].	It acts indirectly to inhibit phosphodiesterase which may be important in treatment of AD pathology [121].	It improve concentration, as well as combat restlessness, anxiety and agitation in patients with Alzheimer's disease and dementia [122].
26.	*Jyotishmati*	*Celastrus paniculatus* / Celastraceae	It contains triacylglycerol (TAG), free fatty acids (FFA), diacylglycerol (DAG), esterified sterols (STE) and mono acylglycerol (MAG) [123].	The aqueous extracts of CP seed have dose-dependent cholinergic activity, thereby improving memory performance [124].	It sharpening the memory and improving concentration, cognition-enhancing properties and antioxidant properties [125].
27.	Gotu Kola	*Centella asiatica* / Umbelliferae.	It contains asiatic acid and asiaticoside [126].	It inhibits beta-amyloid cell death *in vitro*, suggesting a possible role for *gotu kola* in the treatment and prevention of AD and beta-amyloid toxicity [127].	It is used in intelligence, longevity, and memory, Alzheimer's disease [128].

Ayurvedic Herbs: Some Ayurvedic herbs like Guduchi, Yashtimadhuk, Padma (*Nelumbo nucifera*), Vacha, *Convolvulus pluricaulis*, Shankhpushpi, Pancha-Tikta-Ghruta Gugguli, Amalaki, Musta Arjun, Amalaki, Ashwagandha, Galo Satva, Kutaj, and others are excellent herbs for slowing down the brain cell degeneration caused by Alzheimer's. They enhance the brain's ability to function, and therefore, provide stability when used consistently [129].

CONCLUSION: Generally, there is significant evidence supporting a role of the ACH in AD. As cholinergic function is essential for short-term memory, the cholinergic insufficiency in AD was also believed to be dependable for much of the short-term memory deficit. The management of AD remains a challenge in the modern medicine because of the pathogenesis of AD is a difficult process relating both genetic and environmental factors, therefore herbal medicines are regarded as new and promising sources of potential anti-AD drugs. Herbal medicines have prospective to treat AD because of their cognitive benefits and more significantly, their mechanisms of action with respect to the fundamental pathophysiology of the disease. Our review has acknowledged several herbal medicines with potential therapeutic effects for AD. However, no serious adverse events were reported. Moreover, the future direction should highlight the trial of new herbs that are potentially successful in treating the root of the disease.

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ABREBBIATION: Alzheimer Disease (AD), apolipoprotein E (APOE), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), glutamate (Glu), creatine (Cr), N-acetylaspartate (NAA), Acetylcholinesterase (AChE), nicotinic acetylcholine receptors (nAChRs), cyclic adenosine monophosphate (c-AMP), protopanaxadiol (PPD), 20(S)-protopanaxatriol (PPT), amyloid beta (Aβ), prostaglandin-E2 (PGE2), thromboxane B2 (TXB2), Amyloid beta protein (Abeta), triacylglycerol (TAG), free fatty acids (FFA), diacylglycerol (DAG), esterified sterols (STE), monoacylglycerol (MAG), *Convolvulus pluricaulis* (CP).

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