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A Review: Pharmacological and herbal remedies in The Management of Neurodegenerative disorder (Alzheimer's)

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Abstract
Alzheimer's disease (AD) is a progressive, neurodegenerative disorder and has become a great health problem particularly among the elderly people, generally occurs after the age of 55 years and increase in incidence with advancing age, affecting nearly 25 million people worldwide. Alzheimer's disease (AD) was first identified by the German psychiatrist, Alois Alzheimer, in 1907. People with this disease may exhibit symptoms of short-term memory loss, diminished motor skills, inefficient coordination and impaired intellectual capabilities. The cause of AD is not exactly known, but is thought to include both genetic and environmental factors (multifactorial). There is no known cure for Alzheimer's disease, since it is not possible to reverse the death of brain cells but the symptoms can be managed by some pharmacological agents and herbal remedies. The herbal remedies are becoming more popular in the recent years and providing very promising benefits to the patients suffering from AD. Several clinical trials using herbal mixtures are also going on and will hopefully show positive results for treating AD in the future. This paper reviews the Pathophysiology of AD along with the synthetic drugs and herbal medicines which are used for the Management of AD.

Keywords: Alzheimer's, neurodegenerative disease, Herbal treatment, Pathophysiology, traditional medicine

1. Introduction
Alzheimer's disease (AD) is a progressive, Irresolvable Neuro disorder that is prevalent worldwide among the elderly population. It is nothing but a common type of dementia that is characterized by either short-term memory loss or long-term memory recall, impaired speech, diminished motor skills, inefficient coordination and impaired intellectual capabilities [1]. AD is multifactorial in nature with an unknown etiology that is characterized by several pathological manifestations, including abnormal beta-amyloid (Aβ) accumulation, death of cholinergic neurons, microtubule τ protein aggregation, metal dyshomeostasis of copper, iron and zinc, metal-induced oxidative stress and other aspects [2]. AD is Named after the german physician, Alois Alzheimer identified this in 1906 [3]. Worldwide, about 50 million people are suffering from dementia, including AD. Moreover, by 2050, this number is estimated to rise double [4].
Due to degeneration of cholinergic neurons the levels of the acetylcholine (ACh) neurotransmitter in the body gets low which leads to symptoms of AD. Inhibition of enzyme acetylcholinesterase (AChE) which breaks ACh to choline and acetate, concentration of ACh increases in synapse. Excessive stimulation of the NMDA receptor causes increase in entry of calcium ion on the receptor through ion channel results in neuronal injury or death [5].
AD management is believed to be complex since no particular treatment has been developed to control its symptoms. The majority of the treatments available for AD emphasize on treating neurological and behavioral problems that can deteriorate as the disease progresses. Limited efficacy, side effects, and poor patient compliance of contemporary system of medicine warrant the exploration of alternative therapeutic strategies of AD. Options from herbal and traditional remedies such as traditional Indian medicine (Ayurveda) and traditional Chinese medicine (TCM) are being researched because of the natural approach with insignificant side effects as compared to conventional allopathy methods.

These traditional systems have also contributed to the growing list of valuable medicinal herbs, compounds and unique management methods [6].

From an early 90's century herbal medicine is said to be the best treatment to cure any disease. But from last few years there is increase in growth of herbal treatment in India as well as in other countries. The increase in use of herbal medicine is due to its natural origin and it have less side effects as compared to all other treatment [7]. Treatment with herbal medicine can also be called as Neutraceuticals approach. The term neutraceuticals was given by Stephen Defelice MD and is derived from "nutrition" and "pharmaceutical". Herbal medicine which are used in treatment are derived from medicinal plants, minerals etc [8]. Numerous herbal medicine are used to treat neurodegenerative diseases such as Alzheimer's Disease (AD). Herbal plants have various activities such as antioxidant, anti-inflammatory, anticholinesterase, antiamyloid effect, β- and γ- secretase inhibitors and due to all these activities which are present in plants it helps to boost memory, manage behavioral as well as psychological symptoms associated with AD [9].

1.1 Etiology

The exact cause if AD is not known but it is believed that several environmental and genetic risk factors trigger the symptoms of AD. Some of the causing factors are given below:

- **Age-related changes in the brain:** Researchers have claimed that older adults have more risk of having AD. Scientists are still learning, how age-related changes in the brain may harm neurons and contribute to Alzheimer's damage.
- **Genetics**: It is known that genes play an important role in the development of AD. Early-onset Alzheimer's is very rare form, It occurs in between the age of 30 to 60. 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.
- **Environmental/lifestyle factors:** Conditions such as heart disease, stroke, high blood pressure, diabetes, and obesity are also linked as risk factors for AD [10].

1.2 Symptoms

The symptoms which are seen in mild, moderate and severe form of AD are difficulty in performing tasks, learning new things, playing complex games, flat mood and personality changes, hallucinations, delusions and paranoia, loss of bowel and bladder control, irregular sleep pattern and increase in sleep, difficulty in doing daily basic activities such as reading, writing, and working with numbers. As AD becomes worse, symptoms such as increased anxiety, depression, delusions are seen [11, 12].

1.3 Diagnosis

To diagnose Alzheimer's dementia, reviewing medication history, family history and symptoms is important. Some Laboratory tests are also performed for diagnosis of Alzheimer's dementia known as Brain imaging test which helps in Distinguish between different types of degenerative brain disease and Rule out other causes, such as hemorrhages, brain tumors or strokes. The brain-imaging technologies most often used are Positron Emission Tomography (PET), Magnetic resonance imaging (MRI) and Computerized tomography (CT) [11, 13].

2. Pathophysiology of AD

Neuronal loss in AD is particularly seen in amygdala, hippocampus, entorhinal cortex and cortical association areas of frontal, temporal and parietal cortices. It can also be seen in subcortical nuclei such as cholinergic basal nuclei. Brain imaging test of the patient in AD reveals the atrophy of brain such as enlarged ventricles. The formation of senile plaques and neurofibrillary tangles (NFTs) shows the presence of AD. Plaques are formed due to extracellular deposition of filamentous β-amyloid which is a cleavage product of amyloid precursor protein [14, 15]. In order to explain AD various causative factors have been put forward in terms of hypothesis such as cholinergic hypothesis, tau hypothesis, oxidative stress hypothesis and metal ion hypothesis [16]. Pathophysiology of AD is summarized in Fig.1.

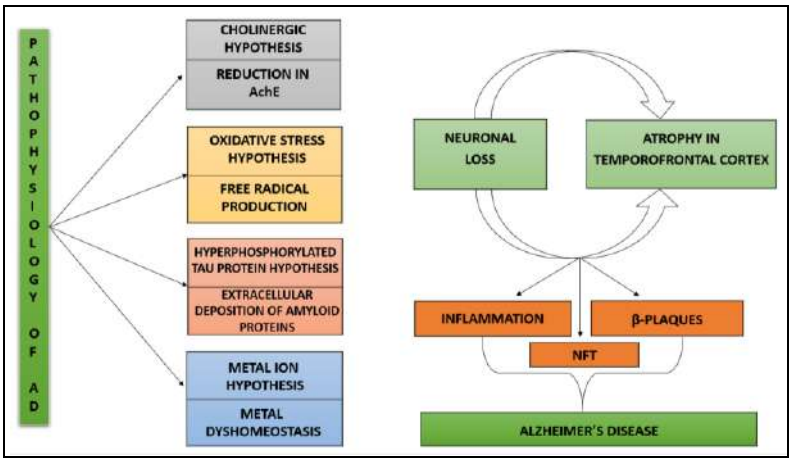

Fig 1: Hypothesis for Pathophysiology of Alzheimer's disease

2.1 Cholinergic Hypothesis

Acetylcholine (ACh) is the first neurotransmitter defect which was found in AD. Apo-lipo-protein E (APOE) is the most important genotype associated with AD. Choline acetyl- transferase and acetylcholinesterase is a major marker for cholinergic neurons which plays important role

in synthesis and degradation of ACh. Level of ACh is decreased in area of brain, cortex and hippocampus which are involved in cognition and memory. Mainly cholinergic neurons of nucleus basalis and the entorhinal cortex get affected [14, 15]. This recognition of acetylcholine role in memory and learning leads to cholinergic hypothesis and it therapeutically increases cholinergic activity [17]. The best approach used in AD is cholinesterase inhibition. Tacrine was the first drug which was approved for clinical use in AD. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®) are the three new cholinesterase inhibitors which are currently available [15].

2.2 Oxidative Stress Hypothesis

In generation of AD, oxidative stress plays major role in damaging CNS. There are several factors which causes oxidative damage to CNS this include high content of unsaturated lipid, high oxygen consumption. Damage by reactive oxygen species (ROS) and reactive nitrogen species kept in check by antioxidant defence cascade which consists of enzymatic and non-enzymatic compounds. There are various sources which plays vital role in production of ROS such as endogenous sources like mitochondria, cytochrome P 450 etc., antioxidant defenses like vitamins (A, C and E), glutathione peroxidase, catalase. Due to imbalance between ROS and cellular antioxidant defences there is failure of biological functions. Redox-active (Fe,Cu) and redox-inactive (Zn) metals are the major sources due to which free radicals are formed and causes oxidative stress in AD. Neuron contains large number of polyunsaturated fatty acid and when it reacts with ROS results in molecular apoptosis and lipid peroxidation reaction, also less glutathione in neuron causes oxidative stress injury [18, 19].

2.3 Amyloid Cascade and Tau Protein Hypothesis

Amyloid hypothesis states that there is formation of senile plaques (SP) which is formed due to amyloid beta (Aβ) deposition generated by proteolytic cleavage of amyloid precursor protein (APP) by the action of α-secretase, β-secretase and γ-secretase. Two steps are involved in generation of Aβ from APP which include β-secretase and γ-secretase. First step involves generation of membrane bound soluble C-terminal fragment by β-site APP cleaving enzyme (BACE1). There is further generation of $A\beta_{40}$ and $A\beta_{42}$ by γ-secretase, $A\beta_{42}$ is more neurotoxic. This pathway by which APP is cleaved is called amyloidogenic pathway [20].

The neurofibrillary tangles (NFTs) is another major feature in AD formed by hyperphosphorylated Tau protein. Tau protein is a highly soluble microtubule-associated protein (MAP), which mainly exists in axon. The main function of tau protein is to maintain stability of neurons. Normally the balance between the phosphorylation and dephosphorylation of Tau protein is maintained but when there is formation of double-helix fiber due to aggregation of hyperphosphorylation tau protein, it loses the function of connecting and stabilizing microtubules, which leads to death of neurons [21].

2.4 Metal ion Hypothesis

Metal ions play an important role in the maintenance of homeostasis [22]. The relationship between metal ions and neurodegenerative diseases has attracted much attention in recent years [23, 24]. The brain is rich in metals that act as essential cofactors in metalloproteins to participates in the process of metabolism, the concentration of metal ions in the brain is tightly regulated through the blood brain barrier, when the blood brain barrier of metal ion regulation system degradation, metal ion transport dysfunction, metal ions (iron, copper, manganese, aluminum, zinc, etc.) begin to affect the oxidative stress response of mitochondria and the wrong folding proteins, and ultimately lead to neurodegeneration [25, 26, 27, 28].

Studies have indicated that aluminum, zinc, copper and iron can lead to changes in the conformation of the Aβ protein. Aluminum can lead to the accumulation of Aβ and Tau protein, aluminum and copper are involved in the process of the development of nerve inflammation [29, 30, 31]. The increased levels of iron, aluminum and copper in the aged human brain may reflect the relationship between age and neurodegenerative diseases [32] Current Evidence indicates changes in the equilibrium of redox transition metal; mainly copper (cu), iron (Fe), and other trace metals. Their levels in the brain are found to be high in AD. In other neurodegenerative disorders, Cu, Magnese, aluminum, and Zinc are involved [33].

3. Management of AD

There are two types of treatments available to manage AD; conventional pharmacotherapy and other is use of medicinal herbs for the treatment of AD.

3.1 Conventional Pharmacotherapy

Conventional pharmacotherapy for AD which is approved by the Food and Drug Administration (FDA) are mainly of two types:

- **Acetylcholinesterase inhibitors** – Galantamine, Huperzine A, Tacrine, Donepezil, Rivastigmine
- **N-methyl-D-aspartate glutamate antagonist (NMDA antagonist)**- Memantine

3.1.1 Acetylcholinesterase inhibitors

The first drugs which were approved by FDA in treatment of AD is acetylcholinesterase inhibitors. It acts by restricting the breakdown of acetylcholine by cholinesterase enzyme and therefore there is increase in concentration of acetylcholine at sites of neurotransmission. In 1993, FDA approved the first drug Tacrine as acetylcholinesterase inhibitors in treatment of AD. But now a days Tacrine is rarely used due to its hepatotoxicity. USFDA also approved three more drugs for treatment of patients suffering from mild to moderate AD i.e. donepezil, rivastigmine, and galantamine. These three drugs does not shows hepatotoxicity as tacrine [34, 35, 36]. There are two drugs in cholinesterase inhibitors which are derived from natural product i.e. Galantamine and Huperzine A.

3.1.1.1 Galantamine

Galantamine is a tertiary alkaloid which was isolated from Galanthus species (snow drop) and also in other plants belonging to Amaryllidaceae plant family like Narcissus species (Narcissus spp). It is an extract of flowers and bulbs of daffodil and lilies. Galantamine is a reversible Ach inhibitor which can also be prepared synthetically by various methods. It prevents the cytotoxicity caused by aggregation of Aβ and thus improves cognitive dysfunction and affords neuronal protection. By allosteric modulation of pre- and post-synaptic nicotinic receptors it enhances central

neurotransmission. After oral administration galantamine get rapidly absorbed. It is used to treat mild to moderate AD. Galantamine was first formulated as immediate release preparation, since of half-life of drug is 7hours dose should be given twice a day [37, 38, 39].

3.1.1.2 Huperzine A

Huperzine A is an quinolizindine alkaloid which is extracted from a plant Huperzia serratum belonging to family Lycopodiaceae. It is reversible and effective inhibitor of AChE which crosses blood brain barrier (BBB) and provide protection against neuronal damage. It increases level of acetylcholine in brain by inhibiting acetylcholinesterase activity and therefore improve cognitive function in patient with AD. It shows longer duration of action when compared with galantamine, tacrine and donepezil. Huperzine A have other advantages such as higher oral bioavailability, fewer adverse reaction etc. [40, 41].

3.1.1.3 Tacrine

Tacrine was the first drug which was approved in the treatment of AD by FDA in 1993 as acetylcholinesterase inhibitor. Tacrine (tetrahydroaminoacridine, THA) marketed under the name Cognex®. It is non-competitive (reversible) inhibitor of AChE and BChE. It shows cholinergic toxicity due to its more specificity towards BChE as compared to AChE. Tacrine inhibits monoamine oxidases by interaction with muscarinic receptor. In the synthesis of bivalent THA more effordsare done to increase its specificity towards PAS site of AChE. The use of drug was reduced due to elevation of liver transaminases which consists of alanine aminotransferase (ALT) and aspartate aminotransferase, because of these the risk of liver injury was increased (hepatotoxicity). Therefore, tacrine was withdrawn from the market. Tacrine is absorbed from GIT and its peak plasma concentration increase with increase in oral dose, also if taken with food its concentration decreases upto 30% [42, 43, 44].

3.1.1.4 Donepezil

Donepezil is the another acetylcholinesterase inhibitor used in treatment of mild to moderate AD in 1997. Donepezil is the piperidine based derivative. It is non-covalent reversible inhibitor of acetylcholinesterase, it forms bond with enzyme and simultaneously interacts with the PAS. It shows less selectivity towards BChE. The resulting increase in acetylcholinen in the CNS for synaptic transmission, it is more selective towards cerebral cortex. Tacrine is widely absorbed after oral administration, half-life is upto 70hours also it is used in all the stages of AD. It shows few side effects such as nausea, diarrhea, anorexia [45, 46].

3.1.1.5 Rivastigmine

Rivastigmine is a carbamate derivative,it inhibits both AChE and BuChE. It is said to be pseudo-irreversibe inhibitor because it forms carbamoylated complex with the active-site serine. Rivastigmine was found to be the only drug in which cytochromeP450 isoenzymes is not involve in its metabolism and therefore it minimizes drug-drug interaction. It is marketed under the trade name Exelon. All the other drugs used in AChE are available in oral form while rivastigmine is available in the form of transdermal patch and approved for mild to moderate AD in several countries such as USA, Europe, Latin America and Aisa. During clinical trials it show side effect, affecting the gastrointestinal tract. Rivastigmine have half-life of about 3hour in patch and about 1hour in capsule [47, 48].

3.1.2 N-methyl-D-aspartate glutamate antagonist (NMDA antagonist)

NMDA receptor antagonist was approved by FDA in October2003, memantine is the only drug in NMDA which was approved by FDA in treatment of AD. Mitochondrial dysfunction and calcium overload was a result of Glutamate mediated excitotoxicity, increasing nitric oxide generation which forms high level of oxidants and neuronal apoptosis. This complete process is blocked by NMDA receptor antagonist [49].

3.1.2.1 Memantine

Memantine (1-amino-3, 5-dimethlyadamantane) is a member of the aminoadamantane class of organic molecules. In 2002, memantine was approved as a therapeutic drug in treatment of moderate to severe AD by the European Agency for the Evaluation of Medicinal Products (EMEA), followed by USA Food and Drug Administration (FDA) in 2003.Memantine is the only drug which is included in NMDA having low affinity, voltage dependent, non-competitive antagonist of NMDAR is prescribed in AD along with AChEI. At high concentration memantine can inhibit mechanisms of synaptic plasticity. It protects neurons by decreasing glycogen synthase kinase 3β (GSK- 3β) activity by attenuating tau phosphorylation. Depending upon Mini- Mental State Examination score < 20. While prescribing memantine to patient with renal failure or epilepsy caution should be taken. The half- life of drug is 60-100 hours, starting dose of memantine is 5 mg once daily, with a target dose of 20 mg/day [50, 51, 52].

3.2 Herbal Drugs used In the Management of AD

Several Herbal Medicines have been used since ancient times for treatment of neurological disorders because of their lesser side effects and greater efficacy. Such herbs are Ashwagandha (Withania somnifera), Turmeric (Curcuma longa), Shankhpushpi (Convolvulus pluricaulis), Ginkgo Biloba, Saffron (Crocus sativus), Brahmi (Bacopa monnieri), Gotu Kola (Centella asiatica), Triphala (emblica officinalis), Cat's claw (uncaria tomentosa) [53].

3.2.1 Ashwagandha (Withania somnifera)

Ashwagandha which also known as Indian ginseng or winter cherry, is one of the most prominent herbs prescribed as a brain rejuvenator for AD. Withania somnifera is a small woody shrub belonging to the family Solanaceae and is widely grown in India [54]. Its flowers are greenish or yellowish in color and about one centimeter long [55, 56]. The major phytoconstituents of W. somnifera are isopellertierine, anferine, withanolides, withaferins, sitoindoside VII and VIII and withanoloides. Other chemical compounds are withanine, somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropane, choline and cuscohygrine [57, 58, 59, 60]. Ashwagandha possess antioxidant activity, free radical scavenging activity, as well as an immune system booster [61]. The plant extract of Ashwagandha is used in treatment and prevention of various diseases such as Arthritis, impotence, amnesia, cancer and neurodegenerative disorders. The mechanism of action of

Ashwagandha in humans is not clear but It improves cognitive behavior in rats subjected to oxidative damage that occurs in AD and can reverse accumulation of β-Amyloid peptides (Aβ) implicated in the disease. Animal studies have shown that the Sitoindosides VII-X and Withaferina A (glycowithanolides) are the active phytophenols, responsible for the mechanism of increased cortical Muscarnic acetylcholine capacity, with a modulation of cholinergic neurotransmission. Molecular modeling studies showed that Withanamides-A, C Uniquely bind to active moiety of beta-amyloid and prevent fibril formation. Aqueous extract increases the cholinergic activity, whereas Methanol extract causes neuritis outgrowth in dose and time dependent manner in human neuroblastoma cells [62]. A prospective, placebo controlled study reported that treatment with ashwagandha-root extract improved immediate and general memory functions and enhanced executive function, attention and information processing speed in adults with a mild cognitive impairment. There is limited data available on the clinical use of Withania for cognitive impairment. [63] By the studies conducted till now, it was observed that the preparations and extracts of W. somnifera root did not cause any toxicity even on chronic treatment [64].

3.2.2 Turmeric (Curcuma longa)

It is a perennial herbaceous plant commonly known as turmeric belonging to the family Zingiberaceae. It is used in Asia for thousands of years in Ayurveda, Siddha, Unani, traditional Chinese medicine. India is the world's largest producer, consumer and exporter of turmeric. Turmeric is obtained from the rhizome of the plant, and is commonly used in India as a food flavoring and coloring agent [65]. The turmeric powder contains 60-70% carbohydrates, 6-13% water, 6-8% proteins, 3-7% essential oils, 2-7% dietary fiber, 1-6% curcuminoids. The bright yellow colour that rhizome is mainly due to the polyphenolic compounds called curcuminoids. The active constituents of turmeric are turmerone oil, curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclocurcumin Turmeric is anti-inflammatory, antiseptic, and antibacterial and has long been used to treat a wide variety of conditions including liver detoxification, to prevent infection and inflammation, to balance cholesterol levels, to treat allergies, to stimulate digestion, and to boost immunity [66, 67, 68]. It has been proven that curcumin usage is useful in the treatment of AD and dementia it also has the ability to decrease the formation of Amyloid plaques and delays degradation of neurons Curcuminoids are proven to have strong antioxidant action demonstrated by the inhibition of the formation and propagation of free radicals [66]. Curcumin is the principal curcuminoid whose anti-inflammatory property is associated with reduced risk of AD [69]. Several studies conducted on animals having AD, have reported improvement in cognitive function in the curcumin-treated group. Researchers attribute the improvement to curcumin's ability to lower Aβ plaque levels as well as to its anti-inflammatory and antioxidant properties [70, 71, 72]. Curcumin also reverses cognitive impairments in various animal models of AD. Higher doses of curcumin are more effective compared to the lower doses. When curcumin was given in combination with piperine, improvements in cognition were greater especially against chronic diseases [73]. Curcumin forms strong complexes with metals such as copper, zinc, or iron and blocks metal-triggered Aβ aggregation, toxicity, and inflammation as these metals are concentrated in the AD brain and trigger amyloid aggregation or oxidative neurotoxicity [74, 75, 76, 77].

3.2.3 Shankhpushpi (Convolvulus pluricaulis)

Shankhpushpi is a common plant found in Northern India, it has various species such as Convolvulus pluricaulis (CP), Convolvulus microphyllus, Evolvulus alsinoides, and Clitoria ternatea (CT), it belongs to family Convulvulaceae. The whole plant of shankhpushpi is used as nervine tonic to improve memory and cognitive function. Leaves are elliptical in shape, the branches are 30cm long and plant consists of blue flower [78, 79]. Plant contains various phytochemicals such as alkaloids (shankhpushpine and convolamne), glycosides, flavonoids, coumarines also there are some other constituents which are present in plant are Sitosterol, Hydroxy cinnamic acid, Octacosanol. Hippocampus is a main region of brain which is responsible for learning and memory function shows dose dependent increase in acetyl cholinesterase activity. Cholinergic and glutamatergic signaling is increased by group of neutraceuticals known as racetams. An ethanolic extract of Convolvulus pluricaulis when tested in-vitro shows antioxidant activity [80, 81]. It is used in the treatment of dementia, OCD, phobias, Insomnia. It calms the nerves by regulating stress hormones, Adrenaline and cortisol. Ethanolic extract, ethyl extract of it and aqueous fraction significantly improved learning and memory in rats [65].

3.2.4 Ginkgo Biloba

It is commonly called as ginkgo, it has several uses in traditional medicines and as a source of food. This plant is native to china and south Japan. Extracts of ginkgo leaves contain different types of phytochemicals include phenolic acid, proanthocyanidins, flavonoid glycosides (Myricetin, kaempferol, isohamnetin, quercerin), Terpens, ginkolides, biobalides, ginkgo biflavones and alkylphenols. Ginkgo biloba (Gb) has been in the spotlight primarily for its potential role in treating AD. The flavonoids and Terpens in the extract significantly inhibit acetylcholinesterase activity in brain. Ginkolides is a potent anti-oxidant with cholinergic and neuroprotective activities hence it protects against Aβ-Protein induced oxidative damage [53]. Gb is used as an initial treatment for early-stage AD and vascular dementia. Treatment with Gb extract enhanced memory retention in young and old rats also short-term memory in mice is improved. Several studies indicate that ginkgo delays the progression of AD and is as effective as the cholinesterase inhibitors for treating AD. Gb extract also improves ADLs among AD individuals and is preferred over other AD medications because of its negligible adverse effects [82, 83, 84, 85].

3.2.5 Saffron (Crocus sativus)

Saffron (Crocus sativus) is a small perennial plant belonging to the family of Iridaceas and it is a crimson colored spice. The plant is widely cultivated in Iran, Afghanistan, Turkey and Spain [86]. Saffron is a perennial stemless herb, comprises of the dark red stigma to reddish brown and style is yellowish brown to yellowish orange. Size of stigma and style are about 25 and 10mm long. Microscopic study reveals that when drug is soaked and observed under microscope stigmas are found either separate or united in

three to the apex of yellowish styles, each stigma has the shape of slender funnel [87]. Chemical constituents found in saffron are crocin - (responsible for the color), picrocrocin- (responsible for the bitter taste), and safranal- (responsible for odor and aroma). Stigmas of plant contains arotenoids, α-crocetin and glycoside crocin (responsible for saffron yellow color) and picrocrocin. The plant shows various medicinal activities such as antihypertensive, anticonvulsant, antitussive, antigenototoxic and cytotoxic effects, anxiolytic aphrodisiac, antioxidant, antidepressant, antinociceptive, anti-inflammatory, and relaxant activity [87, 88]. It increases blood flow in retina and choroid. The aqueous- ethanolic extract of *C. sativus* stigmas has good antioxidant properties [89]. 30mg/day dose of saffron was found to be effective in treatment of mild to moderate AD. Saffron inhibits the aggregation and deposition of beta-amyloid plaques, therefore help to treat AD. Saffron is safer in comparison to conventional treatment as it is natural and have less adverse effects. Crocin is the most important component in saffron which is responsible in improvement of learning and memory. In hippocampal neurons, crocin antagonizes the inhibitory effect of ethanol on NMDA receptor. Thus crocin is new pharmacological drug for studying the mechanism of ethanol inhibition of NMDA receptor activities. From the above statement it can be concluded that crocin plays a important role in treating neurodegenerative damage induced by oxidative stress [90].

3.2.6 Brahmi (Bacopa monnieri)

Bacopa monnieri (B. monniera), is a small, perennial creeping herb with numerous branches, small oblong leaves and light purple or white flowers belonging to the Scrophulariaceae [91]. It is Traditionally used for anxiety relief, as a tonic for the brain to enhance learning and memory development, and prevention of epilepsy [92]. The main chemical compounds of B. monniera are triterpenoid saponins known as bacosides. The bioactive phytochemicals present in this plant include saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A, B, C, D, E, and F, alkaloids, sterols, betulic acid, polyphenols, and sulfhydryl compounds, which may be responsible for the neuroprotective roles of the plant [93, 94, 95, 96]. The bacosides also enhances kinase activity, neuronal synthesis, and restore synaptic activity. Bacopa monnieri possesses various biological activities such as anticonvulsant, antidepressant, anxiolytic, analgesic, anti-inflammatory, antioxidant, antimicrobial, antiulcerogenic, anti-Helicobacter pylori, adaptogenic, antineoplastic, bronchodilatory, hepatoprotective and immunostimulatory [97]. During the studies, Bhrami extracts shows protection of neurons from beta- Amyloid induced cell death by suppressing cellular acetyl cholinesterase activity. It has also reversed actions such as depletion of acetyl choline, reduction in Choline acetyl Transferases, decrease in Muscarnic cholinergic receptor binding in frontal cortex and hippocampus. [92] During the studies, Individuls above 55 years of age with memory impairment, standardized Bacopa extract 125 mg was given twice daily for 12 weeks in a double blind, placebo-controlled manner. There was a significant improvement in mental control, logical memory and paired associated learning [98].

3.2.7 Gotu Kola (Centella asiatica)

Centella asiatica (C. asiatica), a small, annual herb found throughout India and commonly known as mandukparni or jalbrahmi. It belongs to the family Apiceae**.** It has small fan-shaped green leaves with white or light purple-to-pink or white flowers and it bears small oval fruit. It is used as a memory enhancer, delay ageing, prevent memory related disorders and when it is given with milk, It enhances memory [99, 100, 101]. The main chemical constituents of C. asiatica are asiaticosides, asiatic acid, madecassoside, madasiatic acid, brahmoside, brahminoside, isothankuniside, thankuniside and centelloside. This plant is essential for brain and nerve cells and it's capable of enhancing intellect and logetivity. It has various activities such as anti-inflammatory, antioxidative stress, antiapoptotic effects, neuroprotective effects, wound healing, antipsoriatic, antiulcer, hepatoprotective, antidepressant activity, nootropic activity, anticonvulsant, sedative, immunostimulant, cardioprotective, antidiabetic, cytotoxic and antitumor, antiviral, antibacterial, insecticidal and antifungal [99]. The study shows that when Aqueous extract of C. asiatica is given in 100, 200 and 300 mg/kg doses orally for 14 days, it improves cognitive functions in normal rats. Similarly, aqueous leaf extract showed improvement in learning and memory in rats, and modulated dopamine, 5 hydroxytryptamine (5-HT) and noradrenaline systems in the rat brain in-vivo. Thus the clinical and experimental studies shows positive results for C. asiatica as it enhances memory However, its use for treatment of AD remains to be evaluated [100].

3.2.8 Triphala (Emblica officinalis)

Triphala the name itself indicates that it cconsists of three fruits (tri= three and phala=fruits) namely Amalaki (Emblica officinalis; Phyllanthus emblica), Bibhitaki (Terminalia bellerica), and Haritaki (Terminalia chebula), usually present in equal proportion [102]. Amalaki it belongs to the family Euphorbiaceae, it is found all over India can be planted in gardens. Fruits of amalaki is rich in Vitamin C, seeds contains fixed oil, essential oil and phosphatides also fruits, leaves and barks are rich in tannins. It is used to treat anemia, hyperacidity, peptic ulcer, dyspepsia, diarrhoea, eye inflammation etc. Fruit of the plant is most useful and used for supplementing Vitamin C. Fresh juice of fruit is given as tonic, diuretic, laxative remedy. Bibhitaki belongs to the family of Combretaceae, it is grown in deciduous forest of India and Burma. Its seeds contains greenish yellow oil and fruit contains 17% tannin and gallo-tannic acid (colouring matter) and resin. The fruit is digestible, laxative and in disease of eye, nose, heart and urinary bladder. The bark of plant is used in asthma and for hairs, oil is good. Haritaki, it also belongs to the family Combretaceae and it is found in Maharashtra, M.P, W. Bengal, Karnataka, Ceylon. Fruit of the plant contains chebulic acid, tannin 30% and gallic acid. The unripe fruit is astringent and used in dysentery and diarrhoea. It is also useful in sore throat, bleeding piles, constipation, heart and bladder disease etc. The ripe fruits strengthens the brain, eyes and gums [103]. Triphala loweres serum total cholesterol, triglycerides, and LDL- cholesterol and increased levels of HDL cholesterol. Control trial of 62 obese subjects, subjects were randomly assigned to take five grams of either triphala (n = 31) for 12 weeks, 2 times a day, no adverse effects were observed. When compared with placebo group, triphala shows significant decrease in body weight, mean fasting blood sugar. [104, 105]. In patients

with AD multiple pathogens have been identified in oral cavities and brain such as oral bacteria, fungi, herpes viruses which triggers the immune response. Therefore triphala reduce the chronic activation of the innate immune system in AD [106].

3.2.9 Cat's claw (Uncaria tomentosa)

Cat's claw is a popular herbal supplement derived from a tropical vine,belongs to the family Rubiaceae. It grows very rapidly in the Amazon rainforest and in other tropical areas of South and Central America. Two prevalent species of cat's claw are Uncaria tomentosa and Uncaria guianensis, both are for their anti-inflammatory properties in South America [107]. Plant of leaves contain high amount of oxindole alkaloid content as compared to stem, bark and branches. U. toemntosa contains newly identified polyphenolic compound namely proanthocyanidins that possess both plaque and tangle with reducing and inhibitory effect. Proanthocyanidin B2 diminish the brain plaqueand enhances short term memory, it is stronger inhibitor of brain inflammation. After treating 8-month-old mice with the CC extract for 14 days, reduction in the Aβ load (by 59%) and plaque number (by 78%) in the hippocampus and cortex was observed, it also shows reduction in astrocytosis and microgliosis and improve hippocampus dependent memory. Some components of extract also crosses the BBB and enter brain parenchyma. It is considered as potential plant in treatment of AD as it is strong eliminator of Aβ plaques [108, 109].

3.3 Other Medicinal Plants for AD

There are several other medicinal plants that have a role in the prevention or treatment of AD but several studies shows that their role in AD is very limited. These plants include vacha (Acorus calamus), guduchi (Tinospora cordifolia), guggul (Commiphora wightii), jatamansi (Nardostachys jatamansi), jyotismati (Celastrus paniculatus), rosemary (Rosmarinus officinalis), Green tea (Camellia sinensis), St john's wort (Hypericum perforatum), sage (Salvia spp), Rhodiola rosea, Moringa oleifera, shilajit, and lemon balm. Further studies are still going on for the efficacy of these drugs.

4. Conclusion

Since, the etiology of the neurodegenerative diseases is not exactly known, the pharmaceutical industry is facing various challenges in the drug discovery process. There are small number of pharmacological agents available to manage the symptoms of AD including ayurvedic system. The ayurvedic system of medicine has gained more popularity in recent years as they have very lesser side effects. It is now hoped that various treatment options which are currently under Development process and undergoing Research and clinical trials will be available soon to manage neurodegenerative disorders with positive results.

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