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ALZHEIMER'S DISEASE: A CHALLENGE IN MANAGING WITH CERTAIN MEDICINAL PLANTS - A REVIEW

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ABSTRACT: It is well known that some plants have medicinal properties and their knowledge has been accumulated in the course of many centuries, based on different medicinal systems such as Ayurveda, Unani and Siddha. In India, it is reported that traditional healers use nearly 2,500 plant species and 100 plant species serve as regular sources of medicine for the treatment of various diseases. Alzheimer's disease is globally recognized as the most common form of dementia and it disrupts critical metabolic processes which keep neurons healthy. These disruptions cause nerve cells in the brain to stop working, lose connections with other nerve cells and finally die. The destruction and death of nerve cell causes the memory failure, personality changes and problems in carrying out daily activities. The Alzheimer's disease has an abundance of two abnormal structures- amyloid plaques and neurofibrillary tangle. The Alzheimer's disease is caused by a mixture of genetic, environmental, and life style factors. The current review methodically summarizes the Alzheimer's disease and the effects of phyto-chemicals of medicinal plants in various models of Alzheimer's disease.

INTRODUCTION: Alzheimer's disease (AD) was the eighth-leading cause of death in 2001. It was discovered in 1906 by Alois Alzheimer, a German neurologist and psychiatrist. However, there was no cure and no effective treatment for it [1]. AD is a progressive neurodegenerative disease resulting in the gradual decline of a person's memory and ability to learn reason, make judgements, communicate, and carry out daily activities [2]. AD is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks.

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It is a progressive dementia disorder in an elderly population. The pathology includes accumulation of amyloid *β*-peptide (A*β*), neuro-inflammation and oxidative damage in the brain [3]. The nervous system is a complex network of nerve cells, which regulates body's voluntary and involuntary actions and transmits nerve impulses between different parts of the body.

Research in Alzheimer's disease has provided the intellectual framework for therapeutic intervention. It proposes that the deposition of β-amyloid is the initial pathological event in AD leading to the formation of senile plaques and then to neurofibrillary tangles, neuronal cell death, and ultimately causes dementia [4]. Alzheimer's disease is globally recognized as the most common form of dementia, with multiple studies projecting that by the year 2050, approximately 115 million people will be affected worldwide [5]. The effect of cholesterol in the development of AD apart from

mutations in the proteins involved in amyloid-*β* generation (ßAPP- ß- Amyloid precursor protein, presenilins), the strongest known risk factor influencing the incidence of sporadic AD is the genotype for apolipoprotein E (ApoE), the major carrier of cholesterol in the Central Nervous System (CNS). Individuals carrying one or two copies of the ApoE-e4 allele have a higher risk of developing the disease, compared to those carrying the e3 (the most common) or e2 (which appears to be protective) forms [6].

Methodology: Well-known scientific search engines namely, Google Scholar, PubMed, EMBASE, Mendeley, Science Direct, standard books, Springer Link were used to retrieve online literature. The results are cross-referenced to generate a total number of 95 references cited in this review, during the time span of 1993 - 2016. The current review methodically summarizes the Alzheimer's disease, effects of phytochemicals of medicinal plants in various models. **Table 2** represents the plants, parts used, active compound, mode of extraction and their mode of action in AD therapy. The pictures represent the stages of Alzheimer's disease and aging of brain (**Fig. 1**) and the difference between normal brain and Alzheimer's disease brain (**Fig. 2** and **3**).The difference between normal neuron and Alzheimer's disease-infected neuron, also accumulation of beta amyloid precursor protein in neurons is shown in **Fig. 4**.

Factors Affecting Alzheimer's disease: While scientists know that Alzheimer's disease involves the failure of nerve cells, the reason behind this is unknown. However, they have identified certain risk factors that increase the likelihood of developing AD.

Age: The greatest known risk factor for Alzheimer's disease is increasing age. Most individuals with the illness are 65 years and older. One in nine people in this age group and nearly one-third of the people who are 85 years and older have Alzheimer's.

Family History: Another risk factor is family history. Research has shown that those who have a parent, brother or a sister with Alzheimer's are more likely to develop the disease than individuals who do not. The risk increases if more than one family member has the illness [7].

Obesity: It was observed that the obesity at midlife may increase the risk of dementia and AD later in life. Further, the association was weakened by adjustment for other vascular risk factors and diseases, indicating that the effect of obesity on dementia might be partly mediated through these vascular factors. Nevertheless, midlife obesity, high systolic blood pressure and high total cholesterol level were all significant risk factors for dementia, each of them increasing the risk around twice [8].

Researchers have noted a clustering of cardiovascular risk factors, termed syndrome X or the metabolic cardiovascular syndrome. Factors commonly included in this syndrome are hypertension, obesity, dyslipidemia and glucose intolerance. Development of these risk factors is thought to reflect a common underlying pathology. The syndrome leads to an increased risk of diabetes and cardiovascular disease. Both these clinical conditions have been linked to an increased risk of vascular dementia (VaD) and AD [9].

Genetics:

The Alzheimer's disease can be Caused Due to Mutations in the APP Gene: The apolipoprotein E locus (APOE) on chromosome 19 APOE-e2, APOE-e3 and APOE-e4 is observed. A total of 80% of familial and 64 % of sporadic AD late onset cases have at least one APOE-e4 compared to 31 % of control subjects [10]. Autosomal dominant forms of Alzheimer's disease represented only 5 % of all Alzheimer's disease cases. Most AD patients have the sporadic form of the disease but for these Alzheimer's disease cases, genetic susceptibility factors could also increase or decrease the risk of developing the disease [11].

Sex: The overall incidence of Alzheimer's disease was similar in men and women. Over the age of 90 years the incidence of Alzheimer's disease was higher for women than men. The risk of vascular dementia was higher for men than women across all age groups. Both studies found that the incidence of dementia and Alzheimer's disease continued to increase with age up to 85 - 90 years, after which rates increased in women but not in men [12]. The prominent rise in incidence rates of dementia in the very old appear due to Alzheimer's disease, while rates for vascular dementia remains moderately constant. These inclinations are

particularly marked for minimal dementia, but emphasize the importance of Alzheimer's disease in the community as an origin of cognitive decline of all degrees [13].

Smoking: Smoking had a substantial relationship for increased risk of Alzheimer's disease. Smoking increases cardiovascular risk and nicotine may alter reaction time, learning and memory. Cardio vascular risk factors have been linked to augmented risk of dementia. A previous study found that the fresh smokers were found to be at higher risk of subsequent dementia, Alzheimer's disease, vascular dementia and cognitive decline [14].

Alcohol Consumption: Some studies have shown that heavy alcohol consumption might be associated with an increased risk of dementia in patients with mild cognitive impairment or in men carrying the APOE-e4allele [15]. Given the link between VaD, vascular function, and the increasing body of evidence suggesting that AD may be influenced by vascular factors, it may be concluded that this cardiovascular protection decreases incident dementia/cognitive decline. Counter to this are the effects of heavy alcohol consumption and alcoholism as detrimental to memory function [16].

Education: Poor education was cited as a risk factor for Alzheimer's disease, especially in males. Better education may reveal greater cognitive capacity and reserve, thus postponing the onset of the illness. Similar arguments apply to the size of the head and dementia risk. It is not clear whether it is the learning obtained in childhood or the life-time procurement of knowledge that is protective. Supposing the latter, a trial of cognitive training in individuals at risk of dementia is currently running in the USA [17].

Tau Protein: Tau is one of the microtubules associated with protein that are thought to have a role in the stabilization of neuronal microtubules these in turn provide the track for intracellular transport [18].The molecular mechanisms governing tau aggregation are mainly represented by several post-translational modifications that modify its structure and conformational state.

Hence, abnormal phosphorylation and truncation of tau protein have gained attention as crucial mechanisms that become tau protein in a pathological unit [19]. After neuronal damage, tau is released into extracellular space and may be increased in the cerebrospinal fluid (CSF). Elevated CSF levels of tau occur in parenchymal diseases, including neurodegenerative as well as vascular or inflammatory diseases [20].

Oxidative Stress and β-amyloid: Oxidative stress plays a substantial role in the pathogenesis of AD, a damaging disease of the elderly. The brain is more vulnerable than other organs to oxidative stress, and most of the components of neurons (lipids, proteins, and nucleic acids) can be oxidized in AD due to mitochondrial dysfunction, increased metal levels, inflammation and β-amyloid peptides. Oxidative stress participates in the development of AD by promoting amyloid -β deposition, tau hyper-phosphorylation and the successive loss of synapses and neurons [21].

The amyloid precursor protein observed in Alzheimer's disease pathology, suggests a time-course of plaque development beginning with neuronal amyloid precursor protein accumulation, then deposition into the extracellular space, subsequent processing by astrocytes or microglia, and resulting in beta-amyloid peptide accumulation in plaques [22].

APP can be proteolyzed directly by α-secretase and then γ-secretase, a process that does not generate amyloid-β, or reinternalized in clathrin -coated pits into another endosomal compartment containing the proteases BACE1 and γ-secretase. The latter results in the production of amyloid-β [23].

Phases of Alzheimer's disease: Alzheimer's disease typically progresses slowly in three general stages early, middle, later. Since Alzheimer's disease affects different way, each person may experience symptoms or progress through the different way [24].

Preclinical Stage: This mild stage, which usually lasts 2 to 4 years, is often when the disease is first diagnosed. In this stage, family and friends may begin to realize that there has been a deterioration in the patient's cognitive ability. Common symptoms at this stage were included [7]. Difficulty holding new information, difficulty with problem solving or decision making. Patients may start to have trouble managing finances or other instrumental activities of daily living which show

personality changes. The person may begin to withdraw socially or show lack of motivation and difficulty in conveying thoughts. Further, mislaying belongings or getting lost. The patient may have trouble navigating in familiar surroundings [25].

TABLE 1: DIFFERENT STAGES OF ALZHEIMER'S [26]

Moderate cognitive decline (Mild or early-stage Alzheimer's disease)	Moderately severe cognitive decline (Moderate or mid-stage Alzheimer's disease)	Very severe cognitive decline (Severe or late-stage Alzheimer's disease) Dementia
At this stage Diminished knowledge of recent events Reduced ability to perform challenging mental arithmetic Decreased capacity to perform complex tasks, such as marketing, planning dinner for guests, or paying bills and managing finances .	Major gaps in memory and deficits in cognitive function develop. Some assistance with day-to-day activities becomes necessary. At this stage, individuals may: Become confused about where they are or about the date, day of the week or season.	This is the ultimate stage of the disease when individuals lose the ability to respond to their environment, then the ability to sit without support, the ability to smile, and the ability to hold their head up. Reflexes become abnormal and muscles grow stiff [27].

Clinical criteria for Mild Cognitive Impairment (MCI): Subjective cognitive complaint, preferably collaborated by an informant objective memory and/or other cognitive impairments that a) are abnormal for the individual's age and education, as documented using neuropsychological testing b) represent a decline from previous levels of functioning, decline in the normal ability to perform activities of daily living but absence of dementia [28].

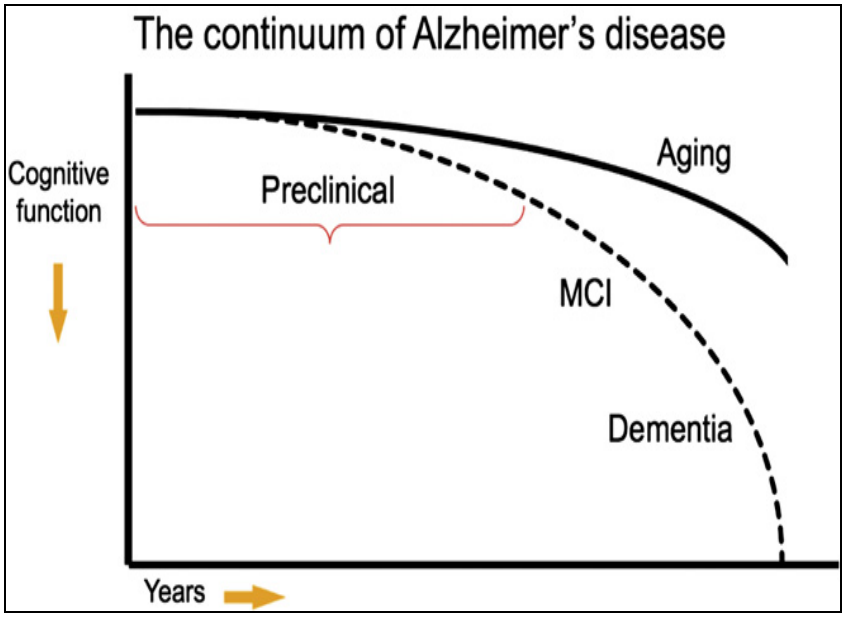


FIG. 1: THE STAGES OF ALZHEIMER'S DISEASE AND AGING OF BRAIN

Model of the clinical trajectory of AD. The stage of preclinical AD precedes mild cognitive impairment (MCI) and encompasses the spectrum of pre-symptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progress into MCI due to AD and AD dementia, as well as biomarker-positive individuals who have demonstrated subtle decline from their own baseline that exceeds the expected in typical aging, but would not yet meet criteria for MCI. Note that this diagram represents a hypothetical model for the pathological-clinical continuum of AD but does not imply that all individuals with biomarker evidence of AD-pathophysiological process will progress to the clinical phases of the illness [29].

The Alzheimer's disease is a progressive neuro-degenerative brain disorder it causes a major trouble of normal brain structure and function [31].

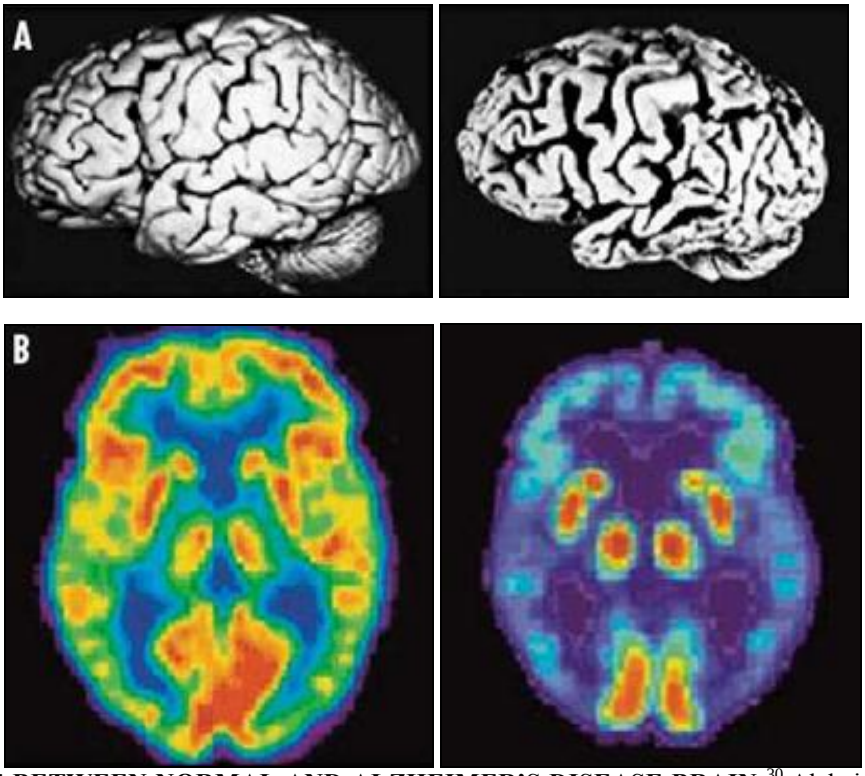


FIG. 2: DIFFERENCE BETWEEN NORMAL AND ALZHEIMER'S DISEASE BRAIN [30] Alzheimer's disease results in shrinkage of brain regions involved in learning and memory which is correlated with major reductions in cellular energy metabolism in living patients. **A)** Compared with the brain of a healthy person, the brain of an Alzheimer's disease patients exhibits marked shrinkage of gyri in the temporal lobe (lower part of the brain) and frontal lobes (left part of the brain). **B)** Positron emission tomography (PET) images showing glucose uptake (red and yellow indicates high levels of glucose uptake) in a living healthy person and a normal conrol subjects. The Alzheimer's patients exhibits large decrease in energy metabolism in the frontal cortex (top of brain) and temporal lobes (sides of the brain)

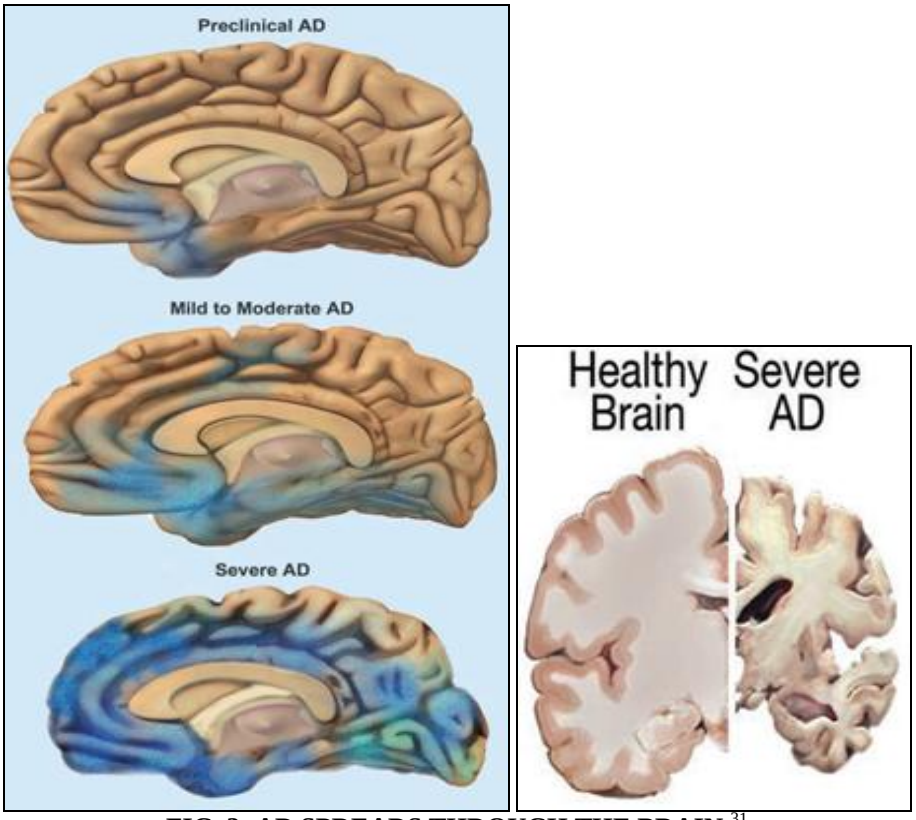


FIG. 3: AD SPREADS THROUGH THE BRAIN [31]

Control Measures in Alzheimer's to lower the Risk of Dementia: [32] The prevention of AD is major public health face, but numerous promising therapies targeting β-amyloid have unsuccessful in late stage clinical trials.

Quit Smoking: Smoking causes a great damage to the body, including the brain. According to studies, daily smokers are at a 45 % higher risk of developing Alzheimer's in comparison to non-smokers and ex-smokers. Hence, it is strongly advised to quit this detrimental habit [33].

Vitamin B: B Vitamins reduce the levels of a molecule known as homocysteine (HC), which harms the vascular system. When in elevated levels, it increases the risk of strokes, heart diseases, and other vascular problems. Having a higher intake and blood level of Vitamin B12 and folic acid, is associated with a part of the risk of developing Alzheimer's. Vitamin B6, B12 and folic acid, especially in combination, lower the blood levels of homocysteine, which is a key predictor of risk [34].

Vitamin D: Researchers have found a link between the reduced levels of Vitamin D and cognitive decline, causing dementia symptoms. Therefore, the use of Vitamin D supplements, prevents processes that contribute to dementia and Alzheimer's [35].

Control of Alcohol Intake: The excessive alcohol use raises the risk of dementia, so it has to be controlled in order to prevent various health issues, including dementia [33]. Staying cognitively active throughout life *via* social engagement or intellectual stimulation is associated with a lower risk of Alzheimer's disease [36].

Diet: A number of studies suggest that eating certain foods may help keep the brain healthy and that others can be detrimental to cognitive health. A diet that includes lot of fruits, vegetables and whole grains and is low in fat and added sugar can reduce the risk of many chronic diseases, including heart disease and type 2 diabetes. Researchers are looking at whether a healthy diet also can help preserve cognitive function or reduce the risk of Alzheimer's [35].

Neuroprotection: Neuroprotection is a broad term to cover any therapeutic strategy to prevent nerve cells called neurons from dying and it usually involves an intervention, either a drug or treatment [36]. Neuroprotection is commonly used to refer to any type of therapeutic strategy, usually pharmacological, that can prevent, delay or even reverse neuronal damage, whether it be neuronal death, axonal degeneration or any other form of neuronal injury. Neuroprotective strategies presently being evaluated including acetylcholinesterase inhibitor, glutamate antagonists, calcium channel blockers, nitric oxide synthase inhibitors and so on [37].

Herbal Neuroprotection: Several parts of the herbal plants such as roots, leaves, stems, barks, flowers and fruits are commonly rich in phenolic compounds and other secondary metabolites [5]. The pharmacological property of each compound differed in their active principles and many Indian medicinal plant composites are represented as neuroprotective and neuro-pharmacologically active compounds [38].

The herbs or their preparations (or both)are used to treat CNS disorders [39]. A few specific herbs and their active ingredients have been identified in particularly Alzheimer's neuroprotection (**Table 2**). Antioxidants are not the only active compounds that may stimulate or sedate the nervous system and those that reduce inflammation also help [40].

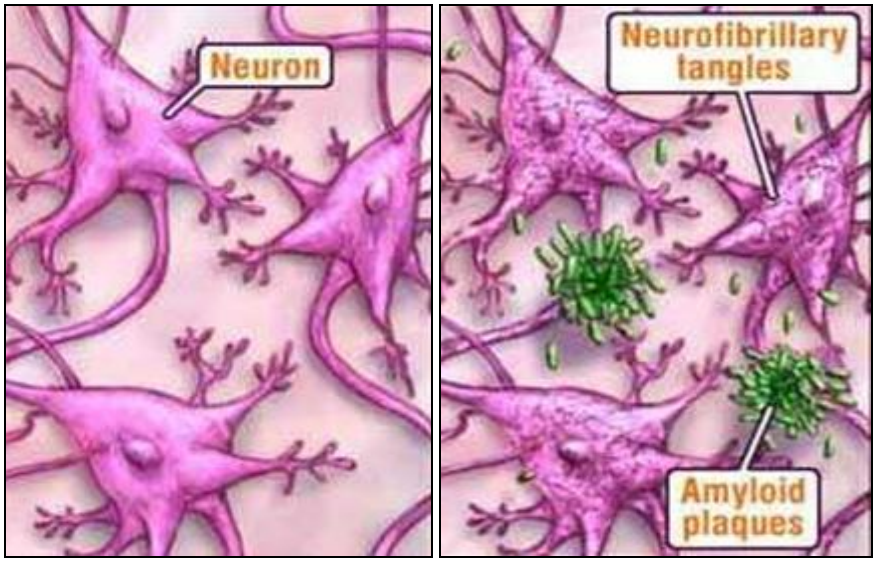
TABLE 2: PLANTS AND THEIR PHYTOCHEMICALS FOR TREATING ALZHEIMER'S DISEASE

Name	Family	Parts used	Biological active compound	Biological effect
*Acorus calamus (*Linn.)	Acoraceae	Roots and rhizomes	A and B-Asarone	The plant extract shows the neuroprotective effect against stroke and chemically induced neuro regeneration in rat [41]
Asparagus racemosus Wild	Asparagaceae	Root	Methanolic extract	It prevents ageing, increase longevity, improve mental function and it also used in nervous disorders [41]
Azima tetracantha Lam.	Salvadoraceae	Leaves	Methanolic extract	The preventive action against neurological disorders [42]

Acorus calamus (Linn.)	Acoraceae	Rhizomes	Methanolic and acetone extracts	The Neuroprotective effect of ethanol water (1:1) extract of rhizomes of *Acoruscalamus* against cerebral ischemia [43]
Angelica archangelica (L.)	Apiaceae	Root	Ethanolic extract	It helps inhibited ache activity *in-vitro* condition [44]
Aframomummelegueta	Zingiberaceae	Root	Extract of Aframomum, Pmi-006	Neuroprotective effectsin a rat model of traumatic brain injury [45]
Aegle marmelos	Rutaceae	Leaf	Methanolic Extract	The oxidative stress pathway contributes to Alzheimer's pathology. As a result, EAF has the potential to be an effective and safe treatment for AD [46]
Angelica sinensis	Apiaceae or Umbelliferae	Root	Z-Ligustilide, 11-Angeloylsenkyunolide F, Coniferyl Ferulate and Ferulic acid	Their ability to inhibit Ab1-40 toxicity On Dpc-12 cells, showed that they were potent anti-Alzheimer compounds[47]
Asparagus racemosus (L.)	Liliaceae	Root	Methanolic extract	The plant extract shows the neuroprotection in rats [48]
Bacopamonniera (L.)	Plantaginaceae	Whole plant	Bacosides	Considered as a possible remedy to counteract associated neurological disorders [49]
Convolvulus pluricaulis attenuates	Convolvulaceae	Root	Aqueous extract	Scopolamine administration was found to significantly increase the cerebral cortex and load as compared with the control [50]
Camellia sinensis	Theaceae	Levees	Epicatechin and Epigallocatechin Gallate	These results show the neuroprotective effects of Cs and its catechins [51]
Celastrus paniculatus Wild	Celastraceae	Whole Plant	Aqueous extract	The plant extract used to treat physical weakness, mental confusion, alleviate asthma symptoms, reduce headaches, pre-treatment of neuronal cells with Cp seed oil significantly attenuated glutamate-induced neuronal death [41]
Curcuma longa (L.)	Zingiberaceae	Rhizomes	Aqueous extract	Antidepressant activity is of significant importance in the management of AD [44]
Curcuma longa (L.)	Zingiberaceae	Rhizome Curcuma oil	Petroleum ether	The Curcuma oil ameliorated the ischemia induced neurological functional deficits and the infarct and edema volumes measured after 5 and 24 hrs of ischemia [52]
Coriandrum sativum (L.)	Apiaceae	Leaves	Leaf extract	Antioxidant activity [53]
Convolvulus pluricaulis Choisy	Convolulaceae	Whole plant	Ethanolic Extracts	Inhibits amyloid-B (Aβ) and increased amyloid precursor protein (Aβpp) level in rat [43]
Celastrus paniculatus	Apiaceae	Seed	Aqueous seed extract	Therapeutic potential has been established for use in AD patients [54]
Centella asiatica (L.)	Apiaceae	Leaf	Aqueous extract	The plant extract has been reported to have a comprehensive neuroprotection by different modes of action such as enzyme inhibition and its prevention of amyloid plaque formation in Alzheimer's disease [55]
Glycyrrhiza glabra	Leguminosae/ Fabaceae	Roots	Powder	The study shows consumption improves the general intelligence rather than STM (short term memory) [56]
Garcinia indica,	Clusiaceae	Fruit	Methanolic Extract	Exhibited significant neuroprotective potential against 6-ohda, indicating its anti-Parkinson's activity in rats [57]
Gastrodia elata	Orchidaceae	Root	Gastrodin	Gastrodinhas protective effects in experimental PD models [58]
Ginkgo biloba	Ginkgoaceae	Fruit and Seed	Ginkgolide *B*	Pathophysiology of Alzheimer's Disease The mechanism of action of Ginkgo is believed neuroprotective agent, an

				antioxidant, a freeradical scavenger, and it help to inhibition beta-amyloid deposition explains its benefit in Alzheimer's [59]
Limonia acidissima (L.)	Rutaceae	Pulp powder	Soxhlet-extract with methanol	They may prove as neuroprotective against ischemia-reperfusion induced brain injury [60]
Metaplexis japonica	Apocynaceae	Whole plant	Ethanol and Extract	The plant crude extract which indicate that the neuroprotective agent of MJC [61]
Morusalba (L.)	Moraceae	Leaf	Leaf extract	Mulberry leaf extract provides a viable treatment for Alzheimer's disease through the inhibition of amyloid beta-peptide (1e42) fibril formation and attenuation of amyloid beta-peptide (1e42)-induced neurotoxicity [62]
Mucuna pruriens	Fabaceae	Seeds	Ethanolic extract	The study shows that Mp treatment provides nigrostriatal dopaminergic neuroprotection against pq induced Parkinsonism by the modulation of oxidative stress and apoptotic machinery possibly accounting for the behavioral effects [63]
Melissa officinalis **(**Lemon Balm)	Lamiaceae	Leaf	Leaf extract	Improves cognitive function and reduces agitation in patients with mild to moderate Alzheimer's disease [54]
Ocimum sanctum	Labiatae	Leaf	Alcoholic extract	Can be employed in the treatment of cognitive disorders such as dementia and Alzheimer's disease [64]
Piper nigrum (L.)	Piperaceae	Seeds, fruit	Alcoholic and methanolic extracts	Neurodegenerative activity anxiolytic and antidepressant activity in Alzheimer rat model [43]
Panaxginseng	Araliaceae	Root and Rhizome	Ginsenoside Rg1	GinsenosideRg1 was observed to have a neuroprotective effect on dopaminergic neurons through the insulin-like growth factor-I receptor signaling pathway [58]
Panax notoginseng	Araliaceae	Root and Rhizome	Ginsenoside *Rg1*	Neuro protection against the oxidative stress [58]
Polygonum cuspidatum	Polygonaceae	root	Resveratrol	Diminish superoxide anion; inhibit ROS generation up-regulate the antioxidant status [65]
Pongamia pinnata	Fabaceae	Stem, bark	Ethanolic extract	The ethanol extract of stem bark of *Pongamia Pinnata* possesses Significant neuroprotective activity in albino rats [66]
Phyllanthus emblica (L.)		Fruit	Ethanolic extracts	The present study shows that the fruit possesses an excellent source for natural cognitive enhancer which could be developed in the treatment of AD and other neurodegenerative diseases [67]
Psidiumguajava (L.)	Myrtaceae	Whole plant and	Ethanolic extracts	To treat inflammation, diabetes and central nervous system depressant activity [68]
Syzygium Aromaticum	Myrtaceae	Flower buds	Aqueous extract	The study showed that clove offers neuroprotection against Alcl3-induced neurotoxicity [69]
Salvia miltiorrhizia bung	Lamiaceae	Leaf and Rhizome	Aqueous and ethanolic extract	Ithelps in protection against cerebral ischemia induced memory impairment in mice model. Extract improved cognitive dysfunction in rats [70]
Terminalia chebularetzius	Combretaceae	Air-dried Fruit	Water, methanol, and 95% ethanol extracts	The methanol and water extracts exhibit neuroprotective activities against H2o2-induced toxicity toward Pc12 cells and are potential candidates for the treatment of H_2O_2- induced

				neurodegenerative disease [71]
Withania coagulans	Solanaceae	Root	Alcoholic root extract	The potential neuroprotective activity of WCE was shown by reducing histological changes and MDA level in hippocampus [72]
Withania Somnifera (L.) *Dunal.*	Solanaceae	Root	The purified extract of the root	The plant mediated inhibition of nitric oxide production, which is known to mediate neurodegeneration during stress[73]
Zingibe rofficinalis	Zingiberaceae	Rhizome	Curcumin	Increasesneurotrophic factors release in the concentration- and time-dependent manners inhibit NFKbtranslocation and AP-1 activation [74]



NORMAL **ALZHEIMER'S**

FIG. 4: THE DIFFERENCE BETWEEN NORMAL NEURON AND ALZHEIMER'S DISEASE INFECTED NEURON[59]

Synthetic drugs for Neuroprotection: Neuronal cells are extremely vulnerable and have a limited capacity for self-repair in response to injury. For those reasons, there is obvious interest in limiting neuronal damage. Mechanisms and strategies used in order to protect against neuronal injury, apoptosis, dysfunction, and degeneration in the central nervous system are recognized as neuroprotection. The neuro-protection could be achieved through several classes of natural and synthetic neuroprotective agents (**Table 3**).

However, considering the side effects of synthetic neuroprotective agents, the search for natural neuroprotective agents has received a great attention [75].

The neurobiological bases of these benefits include the exercise-induced increase in levels of brain-derived neurotrophic factor (BDNF) [76] and other growth factors, stimulation of neuro-genesis, increase in resistance to brain insult [77] and improvement in learning and mental performance [78].

TABLE 3: SYNTHETIC DRUGS OR SUPPLEMENTS USED FOR NEUROPROTECTION

Name of the drug	Mode of action of drugs
Acetyl-L-carnitine	It is hypothesized that the "acetyl" component helps reduce oxidative damage and brain lactate levels [79]
Acetylcholineesterase inhibitors	This class of drugs functions by inhibiting the neurotransmitter acetyl choline, which can improve brain performance [80]
L-Theanine	It blocks NMDR receptor when stimulated excessively [81]
β-Lactam antibiotics	When administered to animals, the β-lactam ceftriaxone increased both brain expression of GLT1 and its biochemical and functional activity. Glutamate transporters are important in preventing glutamate neurotoxicity [82]
Modafinil	Central nervous system stimulants used for attention deficit disorder, narcolepsy or excessive sleepiness which includes methylphenidate, atomoxetine, modafinil, armodafinil and the amphetamines [83]

Clomethiazole (GABA agonists)	Neuroprotective agents inhibit reactions in the brain ischemic injury cascade which lead to neuronal death. Gamma-aminobutyric acid (GABA) is a naturally occurring inhibitory neurotransmitter that increases chloride influx into the neuron and counteracts the toxic effects of glutamate[81]
Galantamine hydrobromide	It is a reversible, competitive inhibitor of acetylcholinesterase (AChE), and is the only drug actively marketed for the treatment of AD with proven activity as an allosteric modulator of nicotinic acetylcholine receptors(nAChRs)[82]
NMDA receptor antagonists	Continuous activation of NMDA receptors [84]
Donepezil,	anti-dementia drugs [85]
Protein-polymer composite fibers	Peripheral nerve regeneration [86]
Omega-3 fatty acids	Plays a critical role in the development and function of the central nervous system [87]
R-flurbiprofen (Flurizan),	reduces beta-amyloid [88]
Anti-aggregant (NC-758 or Alzhemed)	To prevent the individual fragments from sticking together [87]
Aß antibody Fab PEG	Alzheimer's disease [89]
Gantenerumab (amyloid beta-protein inhibitors)	Early-stage Alzheimer's disease Phase III [90]
CSP-1103 (amyloid beta-protein inhibitor)	mild cognitive impairment in patients Phase II [91]
Propentofylline	In humans it improved cognitive functions as well as global of propen to fylline suggest it may be a promising neuroprotective drug for patients [92]
Antidepressant-Induced Neurogenesis	New neurons are generated in the adult hippocampus of many species includingrodents, monkeys, and humans [93]
Interleukin-1 Antagonists	Interleukin-1 (IL-1) is induced immediately after insults to the brain, and elevated levels of IL-1 have been strongly implicated in the neurodegeneration that accompanies stroke, Alzheimer's disease [94]
Olesoxime	Olesoxime (Trophos SA's TRO19622) is a cholesterol-like small molecule withremarkable neuroprotective properties *in-vitro*, as well as *in- vivo*. It has demonstratedactivity in four animal models, preventing neurodegeneration and acceleratingneuro-regeneration following neuro-trauma [94]
Donazepi	Alzheimer's disease [95]

DISCUSSION: The plants used in Indian medicine system are mentioned above in the **Table 2**. All these plants are used against anti-alzheimer's, anti-parkinsonism, anti-neuroglia, neuroprotective with memory enhancing property. Some of the phyto-chemical components of these plants are azimine, caepinealkaloids, flavonoids, phenolic compounds, bacosides and nicotine. In recent years, there is a great demand for plant based products because of the broad biological activity. The change in the modern life style and unhealthy food habit have resulted in obesity, diabetes, hyper tension, neurological disorders in a large population. During these conditions, people fully depend on synthetic medicines. However, the long term use of these drugs results in many side effects but natural based products and plant based drugs have no side effects or less side effects.

CONCLUSION: Alzheimer's disease is the most common cause of dementia, which is becoming more and more frequent in conjunction with growing population. In addition to this, individuals suffering from Alzheimer's disease is a socio-economic burden in India and other countries which is beyond comparison with any other diseases. Drugs to treat Alzheimer's disease are very expensive and have side effects. The middle-class family cannot afford to purchase these drugs. But the plant based products are less expensive and without side effects. These drugs may be helpful in enhancing memory in patients. Thus, the knowledge of the medicinal plants helps to develop drugs in modern medicine system.

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