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A Comprehensive Review of Traditional Indian Medicinal Plants For Therapeutic Implications In Alzheimer's Disease And Its Associated Symptoms

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ABSTRACT

Ayurvedic medicinal plants have been the single most productive source of leads for the development of drugs. In India, it is reported that traditional healers use nearly 2,500 plant species as regular sources of medicine for the treatment of various diseases. Alzheimer's disease is the age associated progressive neurological disorder that causes brain cells to degenerate and finally dies. It is the most common form of dementia in people of 65 years and older with a continuous decline in thinking, behavioral and social skills that disrupts their ability to function independently. These disruptions cause nerve cells in the brain to stop working, lose connections with other nerve cells and finally die. As the disease progresses, a person will develop severe memory impairment and lose the ability to carry out everyday tasks. This disease is named after Dr. Alois Alzheimer in 1906 noticed changes in the brain tissue of woman who had died of an unusual mental illness. Her symptoms include memory loss, unpredictable behaviour, dehydration, malnutrition, infection & death. After she died, he examined her brain and found many amyloid plaques and tangled bundles of fibres. There is no treatment that cures the disease process in the brain, but some herbs may help to improve brain function, reduce its symptoms & improve quality of life and help the patients to some extent. The objective is to provide a systematic review of the ongoing evidence pertaining to the use of medicinal herbs in the treatment of AD and its associated symptoms.

INTRODUCTION

In 1906 the credit of discovering a dementia condition, which was later known as Alzheimer's disease, goes to German physiatrist and neuropathologist Dr. Alois Alzheimer [1]. It was the eighth-leading cause of death. AD is such a progressive neurodegenerative disease seen in elderly population which was brought on by extracellular beta amyloid or senile plaque depositions and intracellular neurofibrillary tangles of hyperphosphorylated tau proteins build up in the hippocampal region of the brain [2], resulting in the gradual decline of a person's memory and ability to learn reason, make judgements, remembering words, forgetting names, misplacing things, communication, and carry out daily activities [3]. Seventy percent of Alzheimer's disease is caused due to genetic factor and twenty one percent is due to environmental factors. Most cases of Alzheimer's disease are late-onset which develops after an age of 60. [4] Age is the greatest non-genetic risk factor amongst all [5]. It causes functional as well as structural disturbance of brain's nerve cells. In early means of disease, it also causes synaptic dysfunction of nerve cells thereby affecting the communication within neural circuits which is important for memory and other cognitive function [6]. Patients with AD also frequently display aggression, irritation, and irritability. In severe situations, individuals lose all memory, sense of time and place, and become entirely incontinent. Patients eventually need all-encompassing care as they become completely dependent on others. The patient must be placed in a nursing home with 24-hour nursing care because of their complete reliance on others. AD thus poses a significant challenge for patient management [7].

Prevalence of the disease:

This disease is the most common form of dementing illness, affecting more than 5 million Americans, a number estimated to increase to 7.7 million by 2030. According to the World Health Organization (WHO) estimation, the overall projected prevalence in global population will quadruple in the next decades, reaching 114 million patients by 2050. 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 [7]. There are no effective options available at present for prevention and treatment of Alzheimer disease. 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. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented. The future of treatment of Alzheimer's disease lies in the targeting of neuritic plaques (NPs) and neurofibrillary tangles (NFTs), which have the potential to delay neurodegeneration. This review article will provide brief knowledge to Alzheimer's disease and its diagnosis, causes and some of the highlights and emerging trends in Alzheimer disease treatments [8].

Historical Background:

Alois Alzheimer, a German physician, reported the first case of Alzheimer's disease in 1906.[9] He first saw Auguste Deter, a 51-year-old woman, in 1901. Auguste's husband Karl brought her to a mental hospital after she began exhibiting unusual behaviour, including hiding items, threatening neighbours, and accusing her husband of adultery. She also lost the ability to do daily activities such as cooking and housework. Auguste came under Alzheimer's

care at a mental hospital in Frankfurt. Then he observed and recorded her behavioural patterns, she could speak but not write her own name, she could name objects such as a pencil but not the food she was eating, she was polite sometimes but loud and offensive at other times. He diagnosed Auguste with "presenile dementia" [10]. Upon her death in 1906, biopsy of her brain revealed diffuse cortical atrophy and "particular changes in cortical cell clusters" [11]. Alzheimer described plaques and tangles of nerve fibres which researchers would identify in the 1980's as beta amyloid plaques and neurofibrillary tangles of tau [12,13]. That year, Alzheimer gave a presentation on Auguste at a German psychiatry conference, asserting these cortical lesions to be the cause of her symptoms. He published a research paper the next year, and a psychiatry textbook in 1910.

Etiopathogenesis:

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 [14]. The brain has 100 billion nerve cells (neurons). Each nerve cell connects with many others to form communication networks. Groups of nerve cells have special jobs. Some are involved in thinking, learning, and remembering. Others help us see, hear, and smell. To do their work, brain cells operate like tiny factories. They receive supplies, generate energy, construct equipment, and get rid of waste. Cells also process and store information and communicate with other cells. Keeping everything running requires coordination as well as large amounts of fuel and oxygen [15].

AD is one such a neurodegenerative disorder of the brain which decline memory. The disease initially affects the outer layer of the brain which is responsible for learning and short-term memory, but moves progressively inwards to impact other functions such as language, reason and social behaviour, before moving to those parts important for body regulation. The hippocampus is a region in the brain that plays a significant role in memory and is heavily affected as the disease advances. It is understood that Alzheimer's disease causes a loss of connection between neurons over time. Etiology of disease is still not clear. The disease symptoms arise due to extracellular beta-amyloid plaques and intracellular neurofibrillary tangles. The following are various hypothesis for AD [16].

a) **Genetic factors:** Gene mutations are due to metabolic, lifestyle or environmental factors which may lead to disruption of innervation to primary motor and sensory cortices and cerebellum. This leads to disrupting neuronal communication [17].

b) **Amyloid hypothesis:** 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 due to mitochondrial dysfunction, increased metal levels, inflammation and ß-amyloid peptides. Oxidative stress participates in the development of AD by promoting amyloid -ß deposition, tau hyper phosphorylation and the successive loss of synapses and neurons [18]. 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 [19]. APP can be proteolyzed directly by α-secretase and then γ-secretase, a process that does not generate amyloid-ß, 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-ß [20].

c) **Tau hypothesis:** 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 [21]. 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 [22]. 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 [23].

d) Individuals with **Down's syndrome** (trisomy 21) have an increased risk of developing early-onset AD [17].

e) **Cholinergic hypothesis:** AD is caused due to reduced synthesis of acetylcholine. Acetylcholine was the first neurotransmitter to be found to be defective in AD (ACh). It was found that the short-term memory impairment in AD was largely caused by a cholinergic deficiency since cholinergic function is necessary for short-term memory function. In the cortex and hippocampus, regions of the brain important in cognition and memory, markers for cholinergic neurons such as choline acetyltransferase and acetylcholinesterase, enzymes responsible for the synthesis and breakdown of ACh, respectively, are diminished [24]. Cholinergic neurons are primarily impacted in the nucleus basalis and the entorhinal cortex, where the earliest loss of neurons occurs. Up to 90% of the cholinergic neurons in the nucleus basalis of Mynert may go as the disease worsens Loss of cholinergic activity in these regions has been shown to be linked to reductions in learning ability and memory [25,26].

Stages of Alzheimer's disease [28-30]:

The progression of disease is defined by seven clinical stages each with its own challenges and symptoms. These stages are also called as "Reisberg stages" after the doctor who created them, Barry Reisberg, MD. By identifying the current stage of the disease, physicians can predict what symptoms can be expected in the future and possible courses of treatment.

Table 1: Stages of Alzheimer's disease

Stage	Reisberg Stage	Common symptoms
No Dementia	I) No cognitive decline	• No complaints of memory problems • No evidence of cognitive deficits
Early stage	II) very mild cognitive decline	• Reports of memory problems, like misplacing objects
	III) Mild cognitive decline	• Impaired concentration • Difficulty with work tasks • Some denial and anxiety about the deficits
Middle stage	IV) Moderate cognitive decline	• Trouble remembering personal history • Trouble travelling or handling finances • Reduced expressions of emotions • Withdrawal from situations that are challenging
	V) Moderately severe cognitive decline	• Some assistance needed • Evidence of short-term memory loss • Lack of orientation to time, place or date • May need assistance with choosing what to wear

	VI)	Severe cognitive decline	• Lack of awareness of recent activities or surroundings • Activities of daily living may require assistance • Evidence of incontinence and or bowel issues • Sleep disturbances • Personality and behavior changes occur, including hallucinations, anxiety, agitation, and obsessive behavior
Late stage	VII)	Very severe cognitive decline	• Significant personality and behavior changes • Loss of speech and ability to hold a conversation • Difficulty moving, eating and swallowing • Loss of bladder and bowel control • Unable to do daily activities without assistance

Clinical manifestations [31]:

Common symptoms of the disease can be divided into

i) Symptoms related to cognitive impairment

a) Memory loss
b) Language impairment
c) Temporal and spatial disorientation
d) Impairment of executive functions and judgement

ii) Non cognitive symptoms:

a) Behavioural changes (Apathy, agitation, aggression, irritability)
b) Mood disorders (Depression, Anxiety)
c) Mutism (Inability to speak)
d) Hallucinations and paranoia
e) Hyposmia (a reduced ability to smell and to detect odors)
f) Insomnia (Inability to speak)
g) Myoclonus (spasmodic jerky contraction of groups of muscles)
h) Seizures
i) Urinary incontinence

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 [32].

- ✓ Age
- ✓ Family History
- ✓ Obesity
- ✓ Genetics
- ✓ Smoking
- ✓ Alcohol consumption
- ✓ Education
- ✓ Sex

Diagnosis:

It is very important to get an early and accurate diagnosis of Alzheimer's disease in order to effectively treat it as early as possible. Alzheimer's disease can be reliably diagnosed with a complete examination that includes the following tests:

• A complete medical and psychiatric history
• A neurological examination
• Laboratory tests to rule out anaemia, vitamin deficiencies, and other conditions
• A mental status examination to evaluate the person's thinking and memory
• Talking with family members or caregivers

- Diagnostic tests for Alzheimer's Disease: One of the key diagnostic tests for dementias such as Alzheimer's is the Mental Status Examination (MSE).
- The Mini-Cog test takes about three minutes to administer and is often used in Emergency Departments, for people who appear to have some type of dementia like Alzheimer's disease.
- Urinalysis Urine test: Routine analysis of urine is just one of the tests that your doctor will do if Alzheimer's disease or another type of dementia is suspected. Urinalysis (urine tests) screens for abnormalities. Urinalysis can detect a number of diseases or conditions where symptoms may be similar to dementias such as severe renal disease.
- Mild Cognitive Impairment (MCI) : People may sometimes fear the onset of dementia, whereas, they will be experiencing mild cognitive impairment.
- Visual Clues to Dementia Diagnosis There are a number of strong visual clues that can indicate that someone may be suffering from a dementia such as Alzheimer's disease. Appearance, dress, and personal hygiene may deteriorate. Visual clues are important, but provide only one aspect of human behaviour and presentation that may lead to diagnosis.
- Lumbar Puncture test : Although uncommon in tests of dementia the lumbar puncture can reveal rare diseases that can mimic the signs of dementia
- The Mini Mental State Examination (MMSE) is most commonly used to test for memory problems and contributes to a possible diagnosis of dementia [33].
- The electroencephalogram (EEG) is a useful tool in the diagnosis of Alzheimer's. Those with the disease have a diffuse and symmetrical slowing of the brain waves that register on the EEG [31].

Assessment of dementia involves a two-step process in most cases:

Firstly, it is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, delirium, and mild cognitive impairment as is observed in most cases, therefore these diseases need to be distinguished first. Secondly, once dementia syndrome is recognized, the diagnosis of a subtype is important because it may determine the kind of treatment possible.

Clock Test:

For cognitive screening in general practice, the clock test is popular because of its non-confrontational nature and because the normal drawing of a clock more or less excludes the presence of important cognitive impairment. How ever, the rules for scoring the tests can be quite complex and using a solitary cognitive test to screen for the presence of a dementia syndrome does not do justice to the wide variety of symptoms and indications that make up the clinical syndrome of dementia. Activities of daily living are assessed alongside cognition, but there is less consistency in the assessment instruments used [34].

Detection Methods:

Neuroimaging is a promising and widely expanding area of research for detecting Alzheimer's disease. There are multiple brain imaging procedures that can be used to identify abnormalities in the brain, including PET, MRI, and CT scans which are considered to be preliminary tests for the detection of disease. Each scan involves a unique technique and detects specific structures and abnormalities in the brain and associated parts. It has become increasingly clear that, if the disease is to be treated successfully, it must be detected as early as possible, perhaps even before symptoms are evident. Thus, there is a great need for reliable diagnostic methods so that treatment to slow or prevent the disease can begin as early as possible to treat the disease in proper way.

A characteristic, pathological sign of Alzheimer's disease is the formation of insoluble amyloid plaques that accumulate in the brain and neurons. The presence of these plaques can be measured in the brain using positron emission tomography (PET camera) to visualize radioactive tracer molecules that bind to the amyloid plaques. Amyloid levels can also be measured in spinal fluid. While amyloid accumulates in the brain in Alzheimer's disease.

PET (Positron emission tomography):- It uses radiation signals to create a three-dimensional colour image of the human body [36] . The patient is injected with a radiotracer, composed of a radioactive medicine bound to a naturally occurring chemical. For the study of the Alzheimer's disease chemical is usually glucose and is used widely. The radiotracer travels to the organs that use that specific molecule for energy. As the compound is metabolized, positrons are emitted. The energy from these positrons is detected by the PET scan, which converts the input to an image on the output screen. This image shows the function of the patient's body by showing how effectively the radio tracer is broken down. The amount of positron energy emitted creates a variety of colors and intensities, which reflects the extent of brain activity. A PET scan has the capacity to detect changes in metabolism, blood flow, and cellular communication processes in the brain and other activities taking place inside the brain [36]. A study published in the 1996 Journal of Clinical Psychiatry described the method of using a PET scan to detect the changes in glucose metabolism in the brain of an Alzheimer's disease patient. It is observed that in the parietal, temporal, and posterior cortices, an abnormally low metabolic rate of glucose is seen. The rate was further decreased in patients who had an advanced stage of the disease and affected more locations in the brain [37]. Small and his colleagues discovered that a PET scan could be used to detect the changes in glucose metabolism well before the clinical presentation of symptoms. In addition to diagnosis, a PET image could also be implemented in determining the effectiveness of Alzheimer's disease treatments [38].

CT (computed tomography): This scan takes a series of cross-sectional images of the body. With the help of a computer, the individual scans are integrated and incorporated into one detailed image [39]. The CT scan provides the physician with information about the density of tissues in the body and in various parts of the brain. For improved clarity, a contrast dye may be injected to provide a distinction between similar tissues [40].

MRI: Magnetic resonance imaging techniques, first used in 1977, create two or three- dimensional images of the body that can be used to diagnose injury and illness. The essential component of the MRI system is the super conducting magnet, which produces a large and stable magnetic field [41]. There are smaller gradient magnets that create weaker magnetic fields. These magnets allow for different parts of the body to be scanned. The human body is composed of billions of atoms. However, it is the hydrogen atoms that are altered by the magnetic field. Hydrogen atoms are each randomly spinning around an axis, but inside the magnetic field of the MRI, the molecules are lined up with the direction of the field. Half of the atoms point towards the patient's head, and half point toward the feet, cancelling each other out. A few atoms out of every million are not cancelled out. The machine then emits a radio frequency pulse specific to hydrogen, which causes these protons to spin in a different direction. When the spinning ceases, the protons release energy, which is interpreted by the system. Using a contrast dye, each type of tissue responds differently and appears as a unique shade of gray when the image is created [36]. Knowing how the system works, researchers are able to determine if an MRI can effectively detect the structural changes and cellular death seen in the brain of an Alzheimer's disease patient. Atrophy of the hippocampus is often seen in Alzheimer's disease, even before the appearance of clinical symptoms [35]. The Nun Study, conducted in 2002, collected post mortem MRI scans of 56 participants with varying degrees of cognitive impairment. The MRI was used to detect the hippocampal volume and determine its significance as an indicator of AD neuropathology [42]. The results indicated that the scans could be used to identify non-demented elderly with Alzheimer's disease neuropathology who have not yet presented with memory impairment. By identifying the risk for these patients to develop Alzheimer's disease well before the appearance of symptoms, physicians may be able to administer treatment to slow the progression of the disease. A more recent study conducted in 2009 by the Departments of Radiology and Neurology at the University of Pennsylvania investigated the use of sodium magnetic resonance imaging in the detection of Alzheimer's disease. This imaging technique uses the same principle as discussed above. However, instead of measuring the hydrogen atoms, this technique uses naturally abundant sodium, 23Na. This ion was chosen because of the ability of sodium in the brain to detect tumors and track cell death [43]. The participants included five healthy elderly adults and five who had a probable diagnosis of Alzheimer's disease. When neuronal death occurs, the intracellular space is decreased. Therefore, there is an increased concentration of sodium in the extracellular space, causing stronger signal intensity from the MRI for patients who have Alzheimer's disease. Though this technique is not yet perfected, studies are being conducted to determine if the increased signal intensity is caused by a change in ion concentration or a change in volume [38].

Control Measures in Alzheimer's to lower the Risk of Dementia: The prevention of AD is major public health face, but numerous promising therapies targeting B-amyloid have unsuccessful in late-stage clinical trials [44].

a) **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 nonsmokers and ex-smokers. Hence, it is strongly advised to quit this detrimental habit [45].
b) **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 [46].
c) **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 [47].
d) **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 [48].
e) **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 [49].

Screening methods for Alzheimer's activity [50]:

In-Vitro models:

1. Inhibition of acetylcholinesterase activity in rat striatum.
2. Inhibition of butyryl cholinesterase activity in human serum
3. Molecular forms of acetylcholinesterase from rat frontal cortex and striatum
4. Release of (H3) Ach and other transmitters from the rat brain slices
5. Ex-Vivo cholinesterase inhibition
6. Stimulation of phosphatidylinositol turnover in rat brain slices
7. Uncompetitive NMDA receptor antagonism.

In-Vivo models:

- ✓ **Passive avoidance:**

1. Step Down
2. Step through
3. Scopolamine induced amnesia in mice
4. Two compartment test
5. Up-hill avoidance

- ✓ **Active avoidance:**

1. Shuttle box avoidance
2. Jumping avoidance (one way shuttle box)
3. Runway

- ✓ **Discrimination learning:**

1. Open field test
2. Radial arm test
3. Y-Maze test
4. Morris water maze test

- ✓ **Conditioned response:**

1. Condition nictiating membrane response
2. Automated learning and memory model in mice

- ✓ **Genetic models**

1. Tau models
2. Alpha beta tau models
3. Secretase model
4. APOE models
5. Axonal transport models.

Drug Therapy or treatment:

There are two types of medication used to treat Alzheimer's disease. Both work in different ways

a) Acetylcholinesterase inhibitors
b) N-methyl D-aspartate antagonists.

a) Cholinesterase Inhibitors: There are lower levels of a chemical called acetylcholine in the brain of a person with Alzheimer's disease. Acetylcholine performs the function of sending messages between nerve cells. Cholinesterase inhibitors (CI) aim to increase acetylcholine availability in synaptic neurotransmission in order to treat memory disturbances. Currently, three CIs are being used as the first-line treatment in mild to moderate Alzheimer's disease: donepezil, rivastigmine and galantamine [51]. While donepezil and rivastigmine are both selective inhibitors, galantamine inhibits both ACh and butyrylcholinesterase. Side effects as a result of CIs are minimal and are usually limited to gastrointestinal symptoms such as diarrhoea, nausea and vomiting [52].

b) NMDA Receptor Antagonists: Memantine is a non-competitive NMDA receptor antagonist effective in the treatment of moderate-to-severe Alzheimer's disease. The modulation of NMDA receptors results in reduced glutamate-induced excito toxicity. The positive effect on cognitive function translates to behavioral improvements: patients were less agitated and required less assistance from caregivers [53].

Antidepressants and Antipsychotics: CIs and memantine help to control the symptoms to a certain extent, but as patients continue to deteriorate, control by these drugs becomes insufficient. Depression is very common, especially in the early and late courses of the disease.

Antidepressants: Selective serotonin reuptake inhibitors (SSRI: citalopram, fluoxetine, paroxetine, sertraline, trazodone), tricyclic agents and combined serotonergic and noradrenergic inhibitors may be used to counter this [54].

Antipsychotics: It includes Olanzapine, Quetiapine and Risperidone, which are used to treat psychosis and agitation [55].

Herbal therapeutics in AD:

Mankind has always searched for herbal remedies for a vast spectrum of needs such as enhanced nutritional values, physical and mental well-being and treatment for various diseases. Civilizations across the globe have sought herbs and plants of great therapeutic importance. The local literature of every civilization is a repository of such traditionally used medicinal plants. Almost 80% of the world's inhabitants rely mainly on traditional medicines for their primary health care. Plants based drugs have no severe side effects and are user friendly. 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 [56]. The pharmacological property of each compound differed in their active principles and many Indian medicinal plant composites are represented as neuroprotective and active compounds [57]. neuro-pharmacologically the herbs or their preparations (or both) are used to treat CNS disorders [58]. 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[59]. Modern research is exploring natural phytochemicals for their therapeutic properties against multiple factors implicated in AD, as they are repeatedly proved to be safe, economic and reliable.

TABLE 2: LIST OF TRADITIONAL PLANTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Plant name	Family	Parts used
Acorus calamus	Acoraceae	Roots and rhizomes
Aegle marmelos	Rutaceae	Leaf
Aframomummeleg ueta	Zingiberaceae	Root
Angelica archangelica	Apiaceae	Roots
Angelica sinensis	Apiaceae or Umbelliferae	Root
Asparagus racemosus Wild	Asparagaceae	Root
Azima tetracantha Lam.	Salvadoraceae	Leaves
Bacopa monniera	Scrophulariaceae	Whole plant
Bertholettia excelsa	Lecythidaceae	Nuts
Biota orientalis	Coniferae	Leaves
Camellia sinensis	Theaceae	Leaves
Centella asiatica	Umbelliferae	Leaf
Celastrus paniculatus	Celastraceae	Whole plant
Clitoria ternatea	Leguminosae	Roots, seeds, leaves
Codonopsis pilosula	Campanulaceae	Root
Collinsonia canadensis	Lamiaceae	Root
Commiphora weighitti	Burseraceae	Gum resin
Convolvulus pluricaulis	Convolvulaceae	Root
Coptis chinensis	Ranunculaceae	Rhizome
Coriandrum sativum	Apiaceae	Leaves
Crocus sativus	Iridaceae	Dried stigma
Curcuma longa	Zingiberaceae	Rhizomes
Evodia rutaecarpa	Rutaceae	Fruit
Galanthus nivalis	Amaryllidaceae	Bulbs
Garcinia indica	Clusiaceae	Fruit
Gastrodia elata	Orchidaceae	Root
Ginkgo biloba	Ginkgoaceae	Fruit and Seed
Glycyrrhiza glabra	Fabaceae	Roots
Huperzia serrata	Lycopodiaceae	Leaves
Nardostachys jatamansi	Valerianaceae	Roots and rhizomes
Lipidium Meyenii	Brassicaceae	Root
Limonia acidissima (L.)	Rutaceae	Pulp powder

Magnolia officinalis	Magnoliaceae	Bark
Matricaria recutita	Asteraceae	Flower heads
Metaplexis japonica	Apocynaceae	Whole plant
Melissa officinalis	Lamiaceae	Leaf
Morusalba (L.)	Moraceae	Leaf
Mucuna pruriens	Fabaceae	Seeds
Ocimum sanctum	Labiatae	Leaf
Panax Ginseng	Araliaceae	Root and Rhizome
Piper methysticum	Piperaceae	Seeds, fruit
Phyllanthus emblica (L.)	Phyllanthaceae	Fruit
Polygala tenuifolia	Polygalaceae	Root
Polygonum cuspidatum	Polygonaceae	Root
Pongamia pinnata	Fabaceae	Stem bark
Psidium guajava (L.)	Myrtaceae	Whole plant
Rosmarinus officinalis	Lamiaceae	Leaves
Salvia officinalis	Lamiaceae	Leaf and Rhizome
Salvia lavandulaefolia	Lamiaceae	Leaf and Rhizome
Salvia miltiorrhizia	Lamiaceae	Leaf and Rhizome
Syzygium Aromaticum	Myrtaceae	Flower buds
Terminalia chebula	Combretaceae	Air-dried Fruit
Tinospora cordifolia	Menispermaceae	Stem
Urtica dioica	Clusiaceae	Leaves
Withania somnifera	Solanaceae	Root

Conclusion:

In this review article, Alzheimer disease and its clinical features have been briefly discussed. There are four stages of Alzheimer disease in series i.e., predementia, mild, moderate and severe. Pneumonia is the most common cause of death in Alzheimer disease, followed by myocardial infarction and septicaemia. Various risks factors like age, genetics, education etc. are associated with Alzheimer disease. In addition, environmental factors, vascular factors and psychosocial factors also contribute to Alzheimer disease. Positron emission tomography, Computed tomography and Magnetic resonance imaging are the techniques available for detection of Alzheimer's disease in patients. The cause of Alzheimer disease can be explained on Amyloid hypothesis and Cholinergic hypothesis. Cholinesterase inhibitors and N-methyl D-Aspartate antagonists are the class of compounds used for treatment of Alzheimer disease. The delay in neurodegeneration by targeting neuritic plaques (NPs and Neurofibrillary (NFTs) is future potential mechanism for treatment of Alzheimer disease. The creation of AD treatment methods has advanced greatly. Anti-inflammatory, anti-amyloid, anti-oxidant, and pro-cholinergic medications are a few of these tactics. The creation of alternative therapy modalities for AD remains very important. Interests in the utilization of different herbal products increase day by day. As several studies show that utilization of synthetic drugs have side effects, so there is a need of alternative source of drugs which have low or negligible side effects. Recently, herbal medications have undergone extensive testing in human studies as well as in animal and cell models of AD. Herbal medications have fewer hazardous side effects, are easily absorbed via the BBB, and have a variety of synergistic effects, such as increased cognitive and cholinergic functioning. As a result, herbal medicines seem to be a potential complementary therapy for AD patients. However, more investigation into each herb's pathophysiology and phenotypic behaviour in carefully planned clinical trials is required in order to evaluate their negative effects in AD patients.

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