STM JOURNALS

International Journal of
Tropical Medicines

https://journals.stmjournals.com/ijtm

ISSN: 3048-6262
Volume 2, Issue 1, 2025
January—June
DOI (Journal): 10.37591/IJTM

Research IJTM

Comprehensive Approaches to Understanding and Managing Alzheimer's Disease

Chandrika Kadam*

Abstract

Alzheimer's disease is an advanced neurodegenerative disorder described by intense memory loss. It strictly affects the patient's quality of life. The popularity of AD has been increasing in recent years. It is the most common form of mental disorder affecting more than 20 million people in the world. The Alzheimer's disease is treated with cholinesterase inhibitors or NMDA-receptor (N-methyl D-aspartate) antagonists but here the question is about the therapeutic effect of these drugs and accordingly herbal medicine products have been used as a remedy of behavioral and psychological symptoms of dementia. Genes play a major part in the progress of Alzheimer's disease. In this article, we provided an overview of how herbal medicines are useful to cure psychological disorder in elder patients. Even though there are some drugs approved by Food and Drug Administration (FDA) convenient for the treatment of AD, but the outcome was not sufficient and thus the herbal medicines are the alternatives. In recent years the herbal medicines are becoming more popular, some of the herbs that is Ginseng, Ashwagandha, Brahmi, Emblica officinalis, Salvia officinalis, Uncariarhynchophylla, etc. are mentioned below. This article reviews the clinical evaluation, neuroprotective effects, anti-inflammatory effects, active constituent, mechanism of action, sedative, anxiolytic, antileprotic, antidepressant properties and health benefits of herbal medicines for the treatment of Alzheimer's disease.

Keywords: Neurodegenerative disorder, illness, psychology, phytomedicine, Alzheimer's disease

INTRODUCTION

Alzheimer's disease is a progressive and irreversible neurodegenerative disorder characterized by dementia, memory loss, and a decline in cognitive abilities. It primarily affects older adults, typically starting after the age of 60 (Figure 1). The disease is associated with a shortage of acetylcholine (ACh), a crucial neurotransmitter for short-term memory, leading to significant memory deficits. Projections indicate that by 2050, the number of individuals with Alzheimer's worldwide may surpass one billion. In response, there has been a notable increase in the use of herbal medicines, which are gaining acceptance in both advanced and developing countries. Traditional systems like Ayurveda refer to nervous system disorders as 'VataVyadhi,' attributing them to imbalances in Vata, the vital force governing brain and nerve functions. Research into herbal remedies reveals that compounds, such as alkaloids, flavonoids, and tannins can offer various benefits, including anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, hypolipidemic, and antioxidant effects. These compounds may help manage cognitive impairments associated with Alzheimer's. The global market for plant-based products is significant, valued at approximately US $60 billion with a 7% annual growth rate. India's share in this market is about US $1 billion, with expectations to reach US $3 trillion by the end of 2015 [1–3].

***Author for Correspondence**
Chandrika Kadam
E-mail: Chandrika13k@gmail.com

Student, Department of Pharmaceutics, Trinity College of Pharmacy, Pune, Maharashtra, India

Received Date: August 09, 2024
Accepted Date: August 17, 2024
Published Date: August 22, 2024

Citation: Chandrika Kadam. Comprehensive Approaches to Understanding and Managing Alzheimer's Disease. International Journal of Tropical Medicines. 2025; 2(1): 1–9p.

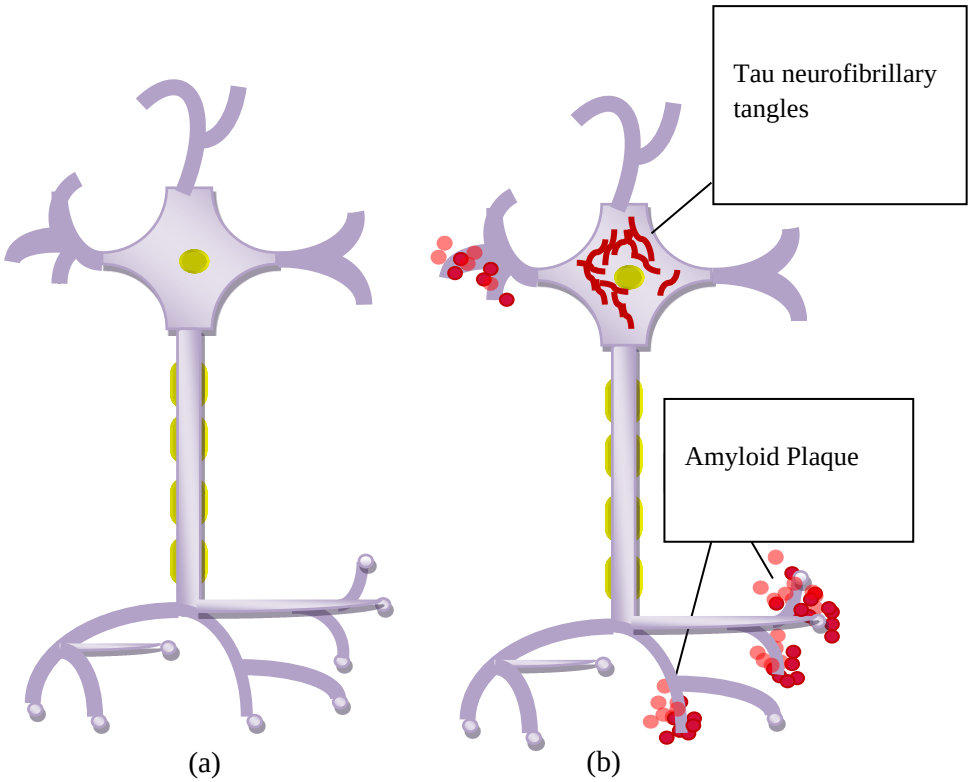

Figure 1. This represents (a) Healthy neuron and (b) Alzheimer's disease: Amyloid plaque deposited on dendrites and axon terminals.

TYPES OF ALZHEIMER'S DISEASE

- *Early-onset Alzheimer's disease:* It shows symptoms before the age of 60. It is much less common than the late onset. Although it gets terrible. This disease can run in families. Various genes have been recognized.
- *Late-onset AD:* This is the ordinary type. When symptoms begin after age 65. This disease runs in some families, but the role of genes remains unclear [4, 5].

CAUSES

- *Age-related changes in the brain:* One of the great mysteries of Alzheimer's disease is why it largely strikes older adults. Research on how the brain changes normally with age is shedding light on this question. For example, scientists are learning how age-related changes in the brain may harm neurons and contribute to Alzheimer's damage.
- *Genetics:* The more researchers learn about Alzheimer's disease, the more they realize that genes play an important role in its development. Early-onset Alzheimer's is a rare form of the disease. It occurs in people aged 30 to 60 and represents less than 5 percent of all people who have Alzheimer's disease. Most cases of early-onset Alzheimer's are familial Alzheimer's disease, caused by changes in one of three known genes inherited from a parent. Most people with Alzheimer's disease have late-onset Alzheimer's, which usually develops after age 60. Many studies have linked the APOE gene to late-onset Alzheimer's. This gene has several forms. One of them, APOE ε4, seems to increase a person's risk of getting the disease. However, carrying the APOE ε4 form of the gene does not necessarily mean that a person will develop Alzheimer's disease, and people carrying no APOE ε4 can also develop the disease.
- *Environmental factors:* Research says genetics factors may lead to the development and course of Alzheimer's disease. For example: a connection between vascular and metabolic conditions, such as heart disease, stroke, obesity, high blood pressure, and diabetes. Understanding these

relationships and examining them in clinical trials will help us to find out if reducing the risk factors for these circumstances may help with Alzheimer's.

- *Plaques:* These clumps of a protein called beta amyloid may damage and destroy brain cells in several ways, including interfering with cell to-cell communication. Although the ultimate cause of brain-cell death in Alzheimer's is not known, the collection of beta-amyloid on the outside of brain cells is a prime suspect.
- *Tangles:* Internal support and transport system is required to transfer nutrients and other important substances throughout the long extensions in brain cells. This system requires Tauopathies (tau) i.e., the microtubule-associated protein, forms insoluble filaments that accumulate as neurofibrillary tangles in AD. In Alzheimer's, the irregular tangles inside brain cells in threads of tau protein led to the failure of the transport system. And this failure is involved in the death of brain cells. Overview of Alzheimer's disease (Figure 2) [5, 6].

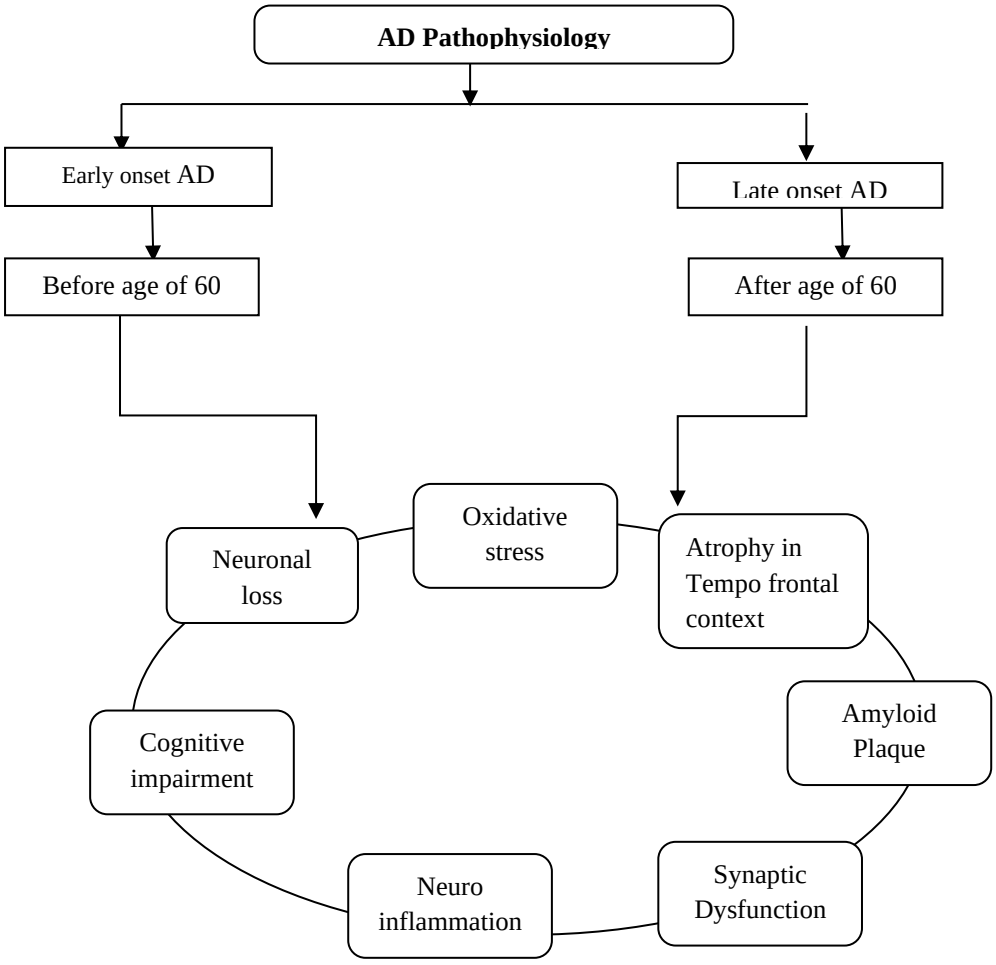

Figure 2. Pathophysiology of Alzheimer's disease.

PHYTOMEDICINE

- *Ginseng:* Panax ginseng family Araliaceae. The effect of Ginseng powder is essential for enhancing the learning abilities in animals. Ginseng has shown the main constituents of (*Triterpenoid saponin*) is identified as Ginsenoside to improve the brain cholinergic function and restoring the damaged neural networks, psychomotor and cognitive abilities. Panax saponin is used which is the main ingredient of Panax ginseng. Clinical Evaluation study for 12 weeks of Korean white Ginseng powder (4.5 g/day) or Korean red ginseng powder (9 g/day) on dementia shows significant improvement in patients classified into two groups. The small mental state test and AD disease scale and compared with a control group.

- *Ashwagandha (Withaniasomnifera):* Ashwagandha belongs to the family nightshade (Solanaceae) and its roots used widely for medicinal purpose. It has several properties like nervine tonic, aphrodisiac, and helps the body adapt to stress. It is widely used in Ayurveda which is categorized as Rasayana (rejuvenative). It also possesses antioxidant properties and increases immune response. Ashwagandha has a calming effect and may help to treat the people with AD. Several studies on it show that Ashwagandha root exhibited a calming effect on the central nervous system (CNS) in several mammalian species. It has minimum adverse effect.

POLYGALA TENUIFOLIA (*P. TENUIFOLIA*)

It belongs to the family Milkworts or Polygalaceae. Neuroprotective effects of *P. tenuifolia* are as follows:

1. *Anti β-amyloid(Aβ):* Senile plaque, abnormal aggregation of Aβ is a vital pathological feature of AD, and its foremost origin during the event of Neurocytotoxicity. The formation and clearance of Aβ within the brain of healthy people are in equilibrium; this balance was broken in the AD patient's brain because of excessive Aβ. Aβ has two kinds of existence, dissolution, and deposition. Aβ within the dissolved state promotes the expansion of neuritis and therefore, the survival of neurons causes axonal degeneration and neuronal degeneration on the opposite hand. *P. tenuifolia* extract and several other components derived from *P. tenuifolia* have exhibited anti-Aβ effect. For instance, *tenuifolia* was separated from crude extract of *P. tenuifolia* inhibits Aβ secretion without changing the ratio of Aβ1-40 and Aβ1-42 in African green monkey COS-7 cells which transfected with either APP695 cDNA or, therefore, Swedish mutation effect could also be associated with inhibition of the β-site AAP cleaving enzyme.
2. *Anti-inflammatory effects: P. tenuifolia's* root through inhibition of nuclear factor-kappaB (NF-kB) activation in lipopolysaccharide-induces BV2 microglial cells. Under pathological conditions (such as during the response to brain injury and the resulting exposure to lipopolysaccharide (LPS), activated microglia release neurotoxic and pro-inflammatory mediators, including gas (NO), prostaglandin E2 (PGE2), reactive oxygen species (ROS), and pro-inflammatory cytokines. Overproduction of those inflammatory mediators can cause different types of severe neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, cerebral ischemia, disseminated sclerosis, and trauma. As a traditional oriental medicine, Polygala (Korean name, Wonji; Chinese name Yuanzhi or Japnese name Onji), as traditional oriental medicine, has been used in Korea to treat various inflammatory diseases of brain from thousands of years. Recent studies indicate that *P. tenuifolia* root extract reduces cognitive dysfunction in several animals' models of memory and behavioral impairment and prevents ethanol induced cytotoxicity in hepatocytes in vitro inhibiting apoptosis. Additionally, extract of *P. tenuifolia* has been suggested to exhibit neuroprotection against neurotoxicity, which is induced by factors, such as LPS, substance P, glutamate. Active micro-adherence cells play an important role in neuroinflammation. Aβ can induce micro-adherence cells to bind to receptors on the plasma membrane of micro-adherence cells and release inflammatory cytokines. Water extracts of *P. tenuifolia* root (2,4 and 8 μg/mL) inhibit protein expression of nitric oxide (NO), nitric oxide synthase (iNOS), prostaglandin E2 (PGE2) and proinflammatory cytokines, such as interleukin (IL)-1β, and tumor necrosis factor (TNF)-α. We treated BV2 microglia (TNFα) and cyclooxygenase 2 (COX2) with lipopolysaccharide (LPS). In addition, water extract of *P. tenuifolia* root blocked the translocation and transcriptional activity of NFκB by inhibiting the degradation of IκBα and suppressing the expression of TLR4 and MyD88. In addition, water extract of *P. tenuifolia* root blocked the translocation and transcriptional activity of NFκB by inhibiting the degradation of IκBα and sTenuigenin suppresses MAPK/NFkB, activates the Nrf2/HO1 signaling pathway, suppresses LPS-induced PGE2 and NO production, and reduces iNOS and COX2 gene expression in RAW 264.7 macrophages.
3. *Enhancing central cholinergic system:* Acetylcholinesterase (AChE) is an essential nerve conduction enzyme that catalyzes the hydrolysis of the neurotransmitter acetylcholine (ACh) to stop signal transmission. AChE is also involved in cell development and maturation and promotes

the development and regeneration of neurons (49). AChE has become an important biomarker to diagnose Alzheimer's disease because it reduces AChE activity in the brains of patients with AD (50). Decreasing acetylcholinesterase while increasing the availability of ACh in central cholinergic synapses could be beneficial to alleviate the symptoms of AD. Therefore, AChE inhibitors show the most successful result for the treatment of AD. BT11 (*Pinus thunbergii* dried root extract) inhibited Aβ1-42-induced AChE activity of Sprague Dawley (SD) rats in a dose-dependent and non-competitive manner (IC50 value: 263.7 μg/ml). The results of the Y-maze task showed that Tenuigenin can improve the learning and memory capacity of the model group mice and, at the same time, can reduce AChE activity, reduce the level of malondialdehyde and increase SOD activity by the same time (54). Polymetallic acid is a hydrolysate of triterpenoid saponin that regulates cholinergic activity. It can dramatically increase the expression of ACh and ChAT, decrease AChE activity in the Hippocampus and prefrontal cortex [7–14].

CENTELLAASIATICA

It is a very important medicinal herb used in Alzheimer disease (56). Commonly known as Mandookparni or Indian pennywort. It had been used as a medicine in the Ayurvedic tradition of India for thousands of years and listed of the historic 'Sushruta Samhita'. *Centella asiatica* belongs to family Apiaceae, it is used as brain tonic due to its wide beneficial neuroprotective activity, also called as Gotu kola. Gotu kola should not be confused with kola as it does not contain any caffeine and has not been shown to have stimulant properties. It is a conflict; perennial herbaceous Creeper is found throughout Indian growing in moist places up to an altitude of 1800 m. It is tasteless, Odorless plant that thrives in and around water. It has small fan-shaped green leaves with white or light purple to pink or white flower and it bears small oval fruit. *Centella asiatica* results in the treatment of leprosy [15–17].

ACTIVE CONSTITUENTS

The primary active constituent of *Centella asiatica* are saponins (also called Triterpenoids), which include asiaticosides, in which a trisaccharide moiety is linked to the aglycone asiatic acid madecassoside and madasiatic acid. These triterpene saponin and their sapogenins are mainly responsible for the wound healing and vascular effects by inhibiting the production of collagen at the wound site. The total extract contains plant sterols, flavonoids, and other components with no known pharmacological activity, namely abundant tannins (20–25%), essential acid (0.1% with beta-chariophylen), Phytosterols.

MECHANISM OF ACTION BASED ON PRECLINICAL STUDIES

Centella asiatica, traditionally recognized in Indian medicine, has been associated with various effects on the central nervous system (CNS). It has been used as a stimulant, nervine tonic, rejuvenator, sedative, tranquilizer, and cognitive enhancer. The effects of *Centella asiatica* on the CNS are primarily attributed to its bioactive compounds, particularly brahmoside and brahminoside. These compounds are believed to contribute to their anxiolytic properties by interacting with cholecystokinin B (CCKB) receptors. These receptors are G protein-coupled receptors that play a role in regulating anxiety, pain, memory, and appetite. Preclinical studies have shown that the total triterpenes from *Centella asiatica* exhibit antidepressant properties. For instance, the administration of these triterpenes has been linked to a reduction in immobility time in experimental models, which is indicative of antidepressant activity. Additionally, biochemical analyses have revealed that these triterpenes can influence the levels of monoamine neurotransmitters and their metabolites in the brain. A significant reduction in corticosterone levels, along with an increase in serotonin (5-HT), norepinephrine (NE), dopamine (DA), and their metabolites, has been observed, suggesting that *Centella asiatica* may modulate the hypothalamic-pituitary-adrenal (HPA) axis and enhance neurotransmitter activity, thereby exerting its antidepressant effects. Moreover, *Centella asiatica* has been shown to increase levels of gamma-aminobutyric acid (GABA) in the brain, supporting its traditional use as an anxiolytic and anticonvulsant. Its neuroprotective and cognitive-enhancing potential has also been demonstrated, with findings indicating that *Centella asiatica* can mitigate cognitive deficits and reduce oxidative stress, further supporting its role in promoting mental well-being.

HEALTH BENEFITS

Centella asiatica, also known as gotu kola, is known for its potential to enhance cognitive functions by supporting brain and nervous system health, improving memory, and offering protection against age-related cognitive decline. The terpenoids present in gotu kola are believed to boost collagen production, which may help reduce the appearance of stretch marks. Additionally, this herb has been traditionally used in poultices and ointments to aid in wound and burn healing, reflecting its long-standing use in herbal medicine for skin repair and regeneration.

HUPERZIA SERRATA

Huperzine A (HupA), isolated originally from a traditional Chinese medicine Qiang Ceng Ta, whole plant of *Huperzia serrata*. Huperzine A is a plant-derived compound known for its ability to inhibit acetylcholinesterase, an enzyme responsible for breaking down acetylcholine, a crucial neurotransmitter in the brain involved in cognition and memory. By slowing the breakdown of acetylcholine, Huperzine A enhances the strength and duration of nerve impulses, which is particularly beneficial for individuals with Alzheimer's disease and dementia, where acetylcholine levels are significantly reduced. Unlike other acetylcholinesterase inhibitors like galantamine, donepezil, and rivastigmine, Huperzine A is both a competitive and reversible inhibitor, exhibiting higher potency and selectivity in both in vitro and in vivo studies. Beyond its effects on the cholinergic system, Huperzine A has demonstrated additional benefits that extend beyond acetylcholinesterase inhibition. Mitochondrial dysfunction, a critical factor in the pathogenesis of Alzheimer's disease, is one of the targets of Huperzine A. The compound has been shown to improve mitochondrial function, particularly under conditions of amyloid-beta (Aβ) exposure, which is known to contribute to Alzheimer's-related cellular damage. Huperzine A helps mitigate mitochondrial dysfunction by reducing the production of reactive oxygen species (ROS) and enhancing the activity of key enzymes involved in the respiratory chain and the tricarboxylic acid (TCA) cycle. Furthermore, Huperzine A decreases the penetration of amyloid-beta into mitochondria, thereby protecting against TCA cycle disruption. The compound also shows anti-oxidative stress and anti-apoptotic effects, as demonstrated in both in vitro and in vivo models, highlighting its potential as a therapeutic agent for Alzheimer's disease by targeting mitochondrial health and reducing cellular stress [18–20].

BRAHMI (BACOPAMONNIERI)

Brahmi is the oldest traditional ayurvedic medicines in India. Brahmi is known for enhancing memory, cognition, mood and other mental disorders. Brahmi has its own unique strong herbal taste and a bitter aftertaste. It is also used in treatment of epilepsy, insomnia, asthma, and rheumatism. Saponins and triterpenoidbacosaponins that include bacopasides III to V, bacosides A and B, and bacosaponins A, B, and C are active constituents of Bacopamonnie, Bacopamonnier extract shows neuropharmacological effects and their nootropic actions.

EMBLICA OFFICINALIS

Emblica officinalis family Euphorbiaceae. Evidence-based studies showed significant recovery in memory retention, especially in young rats and old rats. It alters diazepam and scopolamine induced amnesia. Thus, *Emblica officinalis* plays a vital role in the treatment of dementia and AD. To examine the efficacy of *Emblica officinalis*. The purpose of the examination is to check the memory-enhancing effect on experimenting animals like a rat for six weeks. The rats were administered with *Emblica officinalis* and Curcuma longa with Aluminium Chloride 100 mg/kg against aluminum-induced cognitive dysfunction and oxidative damage. Dose should be given to rats according to their body weights and significant route of administration like (PO: oral administration, IP: Intraperitoneal) *Emblica officinalis* (100 mg/kg, PO), curcumin (100 mg/kg, PO) and piracetam (200 mg/kg, IP).

MALKANGANI (CELASTRUSPANICULATUS)

It belongs to the family Celastraceae and known as 'Jyotishmati' or 'tree of life'. It is used in Ayurveda for centuries to improve learning and memory. It is also used in the treatment of rheumatism, gout, leprosy, leukoderma, paralysis, and asthma. Its different parts are used in the treatment of different diseases, e.g. roots against malaria, wood for tuberculosis, stems for urinary disorders, fruits as antiflatulent, and leaves in dysentery. Seeds of Malkangani protected neurons against H_2O_2-induced and glutamate-induced toxicity by their free radical scavenging properties. The seeds also increase myelination and brain phospholipids content [21–23].

SALVIA OFFICINALIS

Salvia officinalis family Lamiaceae. The leaves of *Salvia officinalis L.* (sage) are well known for their antioxidant properties. The biological source of *Salvia officinalis* is Europe. Like mint, it is cultivated worldwide. It is also known for its laxative effect. Patients with mild Alzheimer' disease (65 to 80 years old) treats *S. officinalis* and Placebo Therapy. It works by psychodynamic rather than pharmacodynamic means and often produces responses equivalent to the active drug. *S. officinalis* may reduce agitation in patients. Leaf extracted with flavonoids, aldehyde, monoterpenes, polyphenol (rosmarinic acid), which leads to moderate dementia.

UNCARIARHYNCHOPHYLLA

It is also known as cat's claw and belongs to the family Rubiaceae. It is a common herbal medicine known as Gou-teng in Chinese. It is used in the treatment of diseases like convulsions, hypertension, epilepsy, eclampsia and other cerebral diseases. The main constituents of Uncariarhynchophylla are alkaloid, terpenoids and flavonoids. It consists of alkaloid Rhynchophylline which is mainly studied to treat neurodegenerative disorders, such as AD. (+)-Catechin and (-)-epicatechin also found in Uncariarhynchophylla. Rhynchophylline contains several different compounds, such as corynoxeine, isorhynchophylline, isocorynoxeine, geissoschizine methyl ether, hirsuteine, and hirsutine. The extracts from U rhynchophylla have significant inhibitory and destabilizing effects on Aβ fibril than other Chinese medical herbs (Table 1). According to several studies 70% aqueous ethanol extract of Uncariarhynchophylla gives protection against D-galactose (D-gal)-induced cognitive deficits in mice. Mice were given a subcutaneous injection of D-gal (50 mg/kg) and orally administered EUR (100, 200, or 400 mg/kg) daily for 8 weeks) [24–38].

Table 1. Conventional marketed formulation.

Herbal Plant	Active Compounds	Therapeutic Effects	Common Uses in Traditional Medicine
Ginseng	*Triterpene saponins* (Ginsenosides)	Improves brain cholinergic function, restores damaged neural networks, enhances learning abilities in animals	Used as a general tonic, to boost energy, and improve mental performance
Ashwagandha	Alkaloids, steroidal lactones, Sitoindosides, acylsterylglucosides	Nervine tonic, aphrodisiac	Traditionally used for stress relief, increasing vitality, and enhancing fertility
P. tenuifolia	Triterpenoid saponins, xanthone glycosides, phenolic glycosides	Neuroprotective, anti-inflammatory, enhances central cholinergic system	Used in Chinese medicine for calming the mind and improving memory
Centella asiatica	Saponins, sterols, flavonoids, tannins, essential acids, phytosterols	Sedative, anxiolytic, antidepressant, antiepileptic, improves cognitive functions	Applied in Ayurveda for skin healing, mental clarity, and as a rejuvenative herb
Huperzia serrata	Huperzine A	Inhibits acetylcholinesterase activity	Employed in traditional Chinese medicine to enhance memory and treat fevers
Brahmi (*Bacopa monnieri*)	Saponins, triterpenoid bacosaponins	Enhances memory, neuropharmacological effects, nootropic action	Widely used in Ayurveda to improve intellect, memory, and cognitive function
Emblica officinalis	Hydrolyzable tannins, gallic acid, ellagic acid	Memory retention	Known as Amla in Ayurveda, it is used to promote longevity, enhance digestion, and support mental health
Malkangani (*Celastrus paniculatus*)	Compounds counteracting H_2O_2-induced oxidative stress and glutamate neurotoxicity	Improves learning and memory, radical scavenging, increases myelination, enhances brain phospholipid content	Used in traditional medicine for enhancing cognitive function and treating joint pain
Salvia officinalis	Flavonoids, aldehydes, monoterpenes, polyphenols (rosmarinic acid)	Antioxidant properties, laxative	Commonly used in herbal remedies for digestive issues, sore throats, and as a mild tonic
Uncaria rhynchophylla	Alkaloids, terpenoids, flavonoids, (+)-Catechin, (-)-Epicatechin	Antioxidant, treats neurodegenerative disorders	Utilized in traditional Chinese medicine for calming the spirit and treating convulsions

CONCLUSION

We have several systems of medicine, viz. Nature cure, Ayurveda, Homeopathy, Siddha and Unani being actively practiced in different parts of the country. When a patient gets seriously ill, he desperately desires relief from discomfort at the earliest irrespective of the system of medicine. In other words, patients are open to accept any medication, if relief is guaranteed. In such a situation, herbal plants are best placed to work out an integrated system of medicine taking advantage of both modern technology and traditional therapies. Extracellular Aβ plaque formation and intracellular accumulation of NFT are the main pathological features of AD which lead finally to neuronal death and synaptic loss. Different herbal plants, their active constituent like triterpenesaponin and sapogenins, sterols, flavonoids, and other components and activities like anti-Aβ, anti-inflammatory, and enhancing central cholinergic system are effective for prevention and treatment of AD. Herbal plants provide a fertile ground for new drug discovery because of the presence of various chemical constituents. The present article reviewed the reported efficacy of herbal medicines in the treatment of AD.

REFERENCES

1. Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: A review. Alzheimer's Res Ther. 2012;4(1):1–9.
2. Kim HG, Oh MS. Herbal medicines for the prevention and treatment of Alzheimer's disease. Curr Pharm Des. 2012;18(1):57–75.
3. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2006;21(2):113–18.
4. Khoury R, Patel K, Gold J, Hinds S, Grossberg GT. Recent progress in the pharmacotherapy of Alzheimer's disease. Drugs Aging. 2017;34(11):811–20.
5. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer report 2016: Improving healthcare for people living with dementia: coverage quality and costs now and in the future. Alzheimers Dis Int. 2016.
6. Grover JK. Medicinal plants of India with antidiabetic potential. J Ethnopharmacol. 2002;81(1):81–100.
7. Malik J, Choudhary S. Indian traditional herbs and Alzheimer's disease: Integrating ethnobotany and phytotherapy. Evidence Based Validation of Traditional Medicines: A Comprehensive Approach. 2021;1129–51.
8. Bent S, Ko R. Commonly used herbal medicines in the United States: A review. Am J Med. 2004;116(7):478–85.
9. Soheili M, Karimian M, Hamidi G, Salami M. Alzheimer's disease treatment: the share of herbal medicines. Iran J Basic Med Sci. 2021;24(2):123–30.
10. Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: A review. Alzheimer's research & therapy. 2012 Jun;4:1–9.
11. Maccioni RB, Calfío C, González A, Lüttges V. Novel nutraceutical compounds in Alzheimer prevention. Biomolecules. 2022;12(2):249.
12. Guo P, Zhang B, Zhao J, Wang C, Wang Z, Liu A, Du G. Medicine-food herbs against Alzheimer's disease: A review of their traditional functional features, substance basis, clinical practices, and mechanisms of action. Molecules. 2022;27(3):901.
13. Mathur A. Who owns traditional knowledge? Econ Polit Wkly. 2003;38(42):4471–81.
14. Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, Brinker A, et al. Plants and human health in the twenty-first century. Trends Biotechnol. 2002;20(12):522–31.
15. Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, Van Dyck CH, Weiner MF, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008;300(15):1774–83.
16. Heo JH, Lee ST, Chu K, Oh MJ, Park HJ, Shim JY, et al. An open-label trial of Korean red ginseng as an adjuvant treatment for cognitive impairment in patients with Alzheimer's disease. Eur J Neurol. 2008;15(8):865–70.
17. Akram M, Nawaz A. Effects of medicinal plants on Alzheimer's disease and memory deficits. Neural Regen Res. 2017;12(4):660–70.

18. Kite GC, Howes MJ, Leon CJ, Simmonds MS. Liquid chromatography/mass spectrometry of malonyl-ginsenosides in the authentication of ginseng. Rapid Commun Mass Spectrom. 2003;17(3):238–44.
19. Lee ST, Chu K, Sim JY, Heo JH, Kim M. Panax ginseng enhances cognitive performance in Alzheimer disease. Alzheimer Dis Assoc Disord. 2008;22(3):222–6.
20. Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. Br J Pharmacol. 2005;144(7):961–71.
21. Russo A, Izzo AA, Cardile V, Borrelli F, Vanella A. Indian medicinal plants as antiradicals and DNA cleavage protectors. Phytomedicine. 2001;8(2):125–32.
22. Pike CJ, Cummings BJ, Cotman CW. beta-Amyloid induces neuritic dystrophy in vitro: similarities with Alzheimer pathology. Neuroreport. 1992;3(9):769–72.
23. Lv J, Jia H, Jiang Y, Ruan Y, Liu Z, Yue W, et al. Tenuifolin, an extract derived from tenuigenin, inhibits amyloid-β secretion in vitro. Acta Physiol. 2009;196(4):419–25.
24. Meda L, Cassatella MA, Szendrei GI, Otvos L, Baron P, Villalba M, et al. Activation of microglial cells by β-amyloid protein and interferon-γ. Nature. 1995;374(6523):647–50.
25. Dandona P, Ghanim H, Chaudhuri A, Dhindsa S, Kim SS. Macronutrient intake induces oxidative and inflammatory stress: potential relevance to atherosclerosis and insulin resistance. Exp Mol Med. 2010;42(4):245–53.
26. González-Scarano F, Baltuch G. Microglia as mediators of inflammatory and degenerative diseases. Annu Rev Neurosci. 1999;22:219–40.
27. Spelman K, Burns JJ, Nichols D, Winters N, Ottersberg S, Tenborg M. Modulation of cytokine expression by traditional medicines: A review of herbal immunomodulators. Altern Med Rev. 2006;11(2):128–39.
28. Wang Q, Wang LW, Liu XM. Brief review about compatibility and their pharmacological effects of Chinese material medica as tranquilizer. Zhongguo Zhong Yao Za Zhi. 2007;32(22):2342–6.
29. Park CH, Choi SH, Koo JW, Seo JH, Kim HS, Jeong SJ, Suh YH. Novel cognitive improving and neuroprotective activities of Polygala tenuifolia Willdenow extract BT-11. J Neurosci Res. 2002;70(3):484–92.
30. Shin EJ, Oh KW, Kim KW, Kwon YS, Jhoo JH, Jhoo WK, et al. Attenuation of cocaine-induced conditioned place preference by Polygala tenuifolia root extract. Life Sci. 2004;75(23):2751–64.
31. Chen YL, Hsieh CL, Wu PH, Lin JG. Effect of Polygala tenuifolia root on behavioral disorders by lesioning nucleus basalis magnocellularis in rat. J Ethnopharmacol. 2004;95(1):47–55.
32. Ikeya Y, Takeda S, Tunakawa M, Karakida H, Toda K, Yamaguchi T, et al. Cognitive improving and cerebral protective effects of acylated oligosaccharides in Polygala tenuifolia. Biol Pharm Bull. 2004;27(7):1081–5.
33. Xue W, Hu JF, Yuan YH, Sun JD, Li BY, Zhang DM, et al. Polygalasaponin XXXII from Polygala tenuifolia root improves hippocampal-dependent learning and memory. Acta Pharmacol Sin. 2009;30(9):1211–9.
34. Koo HN, Jeong HJ, Kim KR, Kim JC, Kim KS, Kang BK, et al. Inhibitory effect of interleukin-1α-induced apoptosis by Polygala tenuifolia in Hep G2 cells. Immunopharmacol Immunotoxicol. 2000;22(3):531–44.
35. Kim HM, Lee EH, Na HJ, Lee SB, Shin TY, Lyu YS, et al. Effect of Polygala tenuifolia root extract on the tumor necrosis factor-α secretion from mouse astrocytes. J Ethnopharmacol. 1998;61(3):201–8.
36. Yabe T, Tuchida H, Kiyohara H, Takeda T, Yamada H. Induction of NGF synthesis in astrocytes by onjisaponins of Polygala tenuifolia, constituents of kampo (Japanese herbal) medicine Ninjin-yoei-to. Phytomedicine. 2003;10(2–3):106–14.
37. Lee HJ, Ban JY, Koh SB, Seong NS, Song KS, Bae KW, et al. Polygalae radix extract protects cultured rat granule cells against damage induced by NMDA. Am J Chin Med. 2004;32(4):599–610.
38. Goossaert V. Bureaucratic Charisma: The Zhang Heavenly Master Institution and Court Taoists in Late-Qing China. Asia Major. 2004 Jan 1:121–59.

