



Herbal Approaches for Alzheimer Disease: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

"Plague of the Twenty-First Century," or "Alzheimer disease" is a neuro-degenerative disease that influenced the world's elderly population. The prevalence of Alzheimer's disease is expected to increase to one hundred thirty-five million by 2050, with no treatment(s) currently available to cure or monitor the disease's progression. The current treatment(s) have less capability to manage symptoms or delay disease development, and they can cause serious side effects. The cost of overall treatment is high for both the patients and their caregivers or family members. As an example, there is a serious requirement to find safer alternative treatments for better management of Alzheimer's disease. The various Indian herbal medicines such as *Centella asiatica*, *Celastrus paniculatus*, *Curcuma longa*, *Clitoria ternatea*, *Bacopa monnieri*, *Withania somnifera*, has been reviewed in this article. *Eclipta alba*, *Desmodium gangeticum*, *Evolvulus alsinoides*, *Moringa oleifera*, and *Convolvulus pluricaulis* are among the plants that have shown promising effect in the treatment related to cognitive disability.

Keywords: Ayurveda; herbal medicine; memory; brahmi.

1. INTRODUCTION

A German psychiatrist in 1906, and neuropathologist (Alois Alzheimer), first identify

the neurodegenerative disease, Alzheimer's disease [1]. It causes a person's intellect and memory to deteriorate, eventually leading to the loss of their ability to carry out day-to-day tasks

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independently. It is the most prevalent form of dementia, accounting for 60–70% of cases [2]. The onset of the disease is associated with ageing and is seldom found in the people of young age [3]. It is generally seen in people around the age of 65 or more. Currently, there is no treatment for Alzheimer's disease, which is considered the "Plague of the Twenty-First Century" since the number of cases is probable to rise from 48 million to 135 million by 2050 [4]. To successfully control and minimise the disease's proliferation, it is essential to find a cure or successful methods of prevention.

Alzheimer disease result in neuronal damage and death due to the disruption of some essential process as communication in neurons and with brain cells, repair, and regeneration and metabolism. In most cases, the condition gets worst with the increase in age. In the early phase, memory-related neurons in the allocortex area of brain and hippocampus are lost. After this stage this disease progresses to the next stages, affecting regions of the cerebral cortex responsible for thought, language, and social behaviour. This is a fatal disorder which also spreads to the other part of the brain, eventually make the patient unable to function and live independently which leads to death.

1.1 Molecular Mechanisms of Alzheimer

1. **Oxidative stress:** This term describes a condition in which the Oxidative stress in the body is caused by ROS (reactive oxygen species), which is particularly prevalent in disorders related to age like AD. In early phase's of AD, oxidative damage develops in the brain. It has an effect well before plaque pathology begins, as it occurs before amyloid-beta (A β) deposition and formation of intracellular neuro-fibrillary tau protein tangles are irregular. Reactive Oxygen Species play a role in neuronal death at the cellular and tissue levels and neurodegenerative processes [5].
2. **Occurrence of A β plaques:** The degradation of the A β PP results in the formation of A β proteins. These proteins start to stick together and lead to formation of plaques between neurons at abnormally high levels. Cellular function is eventually disturbed as a result of these aggregates [6].
3. **Neurofibrillary tangles formation:** When abnormally high levels of hyperphosphorylated tau protein build up within the neurons, neurofibrillary tangles

form. In healthy neurons, the tau protein is important for attaching to and stabilising microtubules. [7]. After tau detaches from microtubules, it links to other tau molecules and creates threads that connect to form tangles, which impair synaptic connection between neurons in AD [8]. The cleavage of a reversing barrier at the axon beginning section causes tau proteins in the axonal area of neurons to be missorted to the somato-dendritic section [9].

4. **Microglial cells:** Microglial cells act as brain macrophages, removing cell debris such as A β plaques, harmful chemical and damaged neurons. Furthermore, astrocytes help remove cell debris and plaques from the brain. In AD, these brain microglial cells gather around the neurons but are unable to fulfil their role of clearing debris. As a result of their accumulation, chemicals are released into the brain, causing chronic inflammation [10].
5. **Vascular causes:** Alzheimer disease can also lead to A build-up of plaque in the brain's arteries, as well as artery hardening (atherosclerosis), ministrokes, and other conditions [11], may retard flow of the blood and oxygen supply of oxygen to the brain and results in a degeneration and complicated loop i.e. a cause and consequence of Alzheimer's disease [12].
6. **Brain atrophy:** In AD, neurons are damaged and die. As a result, the neural network can break down, cause shrink in brain size [13].

The hippocampus of the medial temporal lobe, which is predominantly engaged in memory and emotion, suffers from the loss of brain function. The deterioration then accelerates impacting brain glucose metabolism and cause a decrease in neuronal processing in the parietal and temporal lobes on both sides [14]. The parietal lobe controls, self-awareness, memory retrieval, attention, sensation, and theory of mind [15–17]. The temporal lobe is involved in episodic memory, feelings, and mood [18]. As a result, memory, emotion, and perceptual control are all controlled by the brain regions afflicted by Alzheimer's disease.

1.2 Treatments Available Currently for Alzheimer's Disease

Currently only few medications are available to cure Alzheimer's disease, and most of them can treat the symptoms only. Symptoms such as memory loss, on the other hand, are slowed,

extending life and improving quality of life for those who are affected. Donepezil, rivastigmine, and galantamine are some of the drugs that are used to treat mild to severe Alzheimer's disease. These cholinesterase inhibitors, which stops acetylcholine from being broken down found essential for memory and learning. Memantine is an NMDA antagonist that is used to treat AD [19]. Memantine and donepezil is used for this in combination. Depression, rage, restlessness, and anxiety are all indications of AD, and other drugs are used to treat them. Among these are imipramine, mirtazapine, bupropion, citalopram, sertraline and duloxetine.

1.3 Alternative Therapies

As the world's population grows and people live longer, AD cases are on increasing all over the world. According to report conducted by WHO on dementia reveals that around 50 million people throughout the nation are suffering from dementia and every year new cases of 10 million are cont. adding to this no. which reflects that a person worldwide developing dementia in every three sec [21]. This fast onset of AD requires the advancement of new prevention and treatment methods for Alzheimer's disease. The new therapies are ineffective, have a high number of adverse effects, and suffer from low patient cooperation. These therapies are also costly for patients and providers, as the costs of continuing presence and hospital expenses regularly increasing year after year [22]. This necessitates the introduction of safer alternative of therapies that are being used as anti-AD therapies since ancient times and have been shown to be efficient. Ayurveda, traditional Chinese rituals, meditation, and exercise are all examples of such therapies. Many therapies focused at healing function of synapses and memory has shown to be helpful in reducing the progression of Alzheimer disease and increase effect of current therapy.

1.4 Herbal Drugs

Ayurveda, a Sanskrit term that means "scripture of immortality," is the philosophy of life and health that promotes a holistic approach to care to keep the body, mind, and soul in balance. The 5 fundamental tatva of the universe: fire, space, air, earth and water [23] are the foundations of this traditional medication system. Its roots can be found in India's Indus Valley Civilization and the Indian subcontinent (about 3,000 BC).

Several herbal medicines that has been used to treat neuro-degenerative diseases all over the world. For example *Salvia officinalis* and *Salvia lavandulaefolia* are used in European regions to improve memory since 16th century [24] and found to be affected with the help of different clinical trials [25,26]. The Ayurvedic tradition has long used *Bacopa monniera* (water hyssop) to aid memory and cognitive abilities. The rejuvenative tonic *Withania somnifera* root is also mentioned in Traditional Books like Ayurveda for the cognition improvement. [27-30]. Various traditional remedies are attaining popularity as a result of their perceived efficacy, protection, and affordability. Indeed, experimental studies have only recently begun to provide indication and justification of choosing herbal therapy in cognitive disabilities.

When offered as a prophylactic treatment, numerous Indian herbal medicines that are CNS active such as *Withania somnifera*, *Celastrus paniculatus*, *Centella asiatica*, and *Bacopa monnieri* possess activity of cognitive improvement in different pharmacological experiment models of AD [31-35].

Brahmi



Fig. 1. Leaves of *Bacopa monniera*

1.5 Biological Source

Bacopa monnieri (*B. monniera*) is a minor, ever growing creeping herb with a number of branches, leaves are oblong, and flowers can be light purple or can also be white belonging to Scrophulariaceae. In India it is popularly known as Brahmi and can be used for its revitalising and nootropic properties; it also improves cognition power and intellectual abilities. It also has been utilised to cure a range of diseases by practitioners of India's traditional medicine for thousands of years.

1.6 Chemical Constituent

Bacosides, which are triterpenoid saponins, are the most important chemical constituents of *B. monniera*. This plant also contains the alkaloids brahmine, nicotine, and herpestine. Bacopasides I–XII, which are new saponins, have also been discovered.

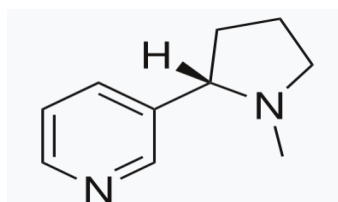


Fig. 2. Nicotin

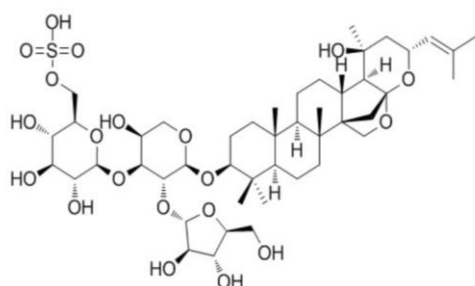


Fig. 3. Bacopasides I

1.7 Effect of Brahmi in AD

According to a study on olfactory bulbectomized mice by Le et al., this plant helps in by protecting cholinergic nerve cells in the medial septal nucleus that extend in hippocampus of our brain. A rat model of Alzheimer's disease showed that alcoholic Brahmi extracts inhibited cholinergic neuron degeneration, implying that the medication could be used therapeutically. According to these findings, the plant extracts have a cholinergic effect comparable to existing therapies such as donepezil, rivastigmine, and galantamine [37,38]. The plant extract diminishes the deposition of A β and hippocampus

damage due to stress and signalling potential therapeutic effect in Alzheimer's disease[39,40].

Gotu kala



Fig. 4. Leaves of Gotu kala

1.8 Biological Source

Centella asiatica, an annual plant, belonging to Apiceae that is also known as jalbrahmi or mandukparni, is found throughout India. It bears small oval fruit and possess green leaves with fan like shape and the flowers are white or light purple and can also be pink [41].

The Ayurvedic method of medicine has used the leaves of mandukparni as a memory enhancer [42]. Its use has also been recorded in traditional Chinese medicine and the African medical system. It's used to slow down the ageing process, avoid memory problems, and improve memory when combined with milk [43].

1.9 Chemical Constituents

Asiaticosides, madasiatic, asiatic acid, madecassoside, and acid are the chief chemical components of *C. asiatica*. and centelloside, brahminoside, thankuniside, isothankuniside, Brahmoside and are among the chemical compounds extracted from Gotu kala.

Table 1. Pharmacological activity of Brahmi

System	Pharmacological activity	References
CNS	Anti-convulsant, Anti-depressant, Anxiolytic	[37]
Respiratory	Bronchodilator	[38]
GIT	Hepato-protective	[39]
Other	Analgesic, antioxidant, antimicrobial, anticancer.	[40]

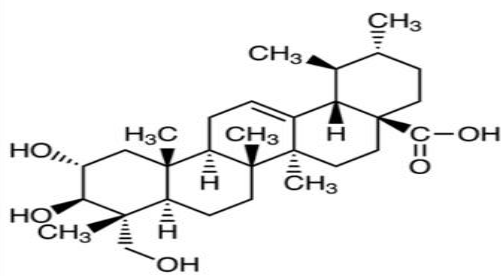


Fig. 5. Asiatic acid

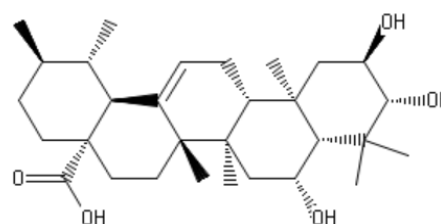


Fig. 6. Madasiatic acid

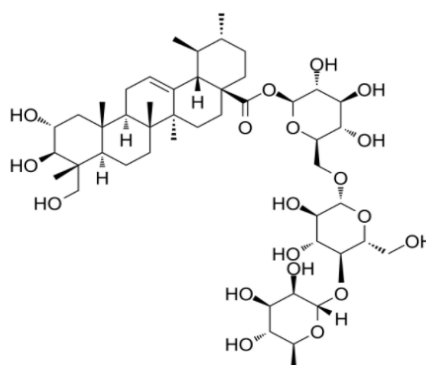


Fig. 7. Asiaticoside acid

Table 2. Pharmacological activity of Gotu kala

System	Pharmacological activity	Reference
CNS	Neuroprotective	[40]
	Antidepressant	
	Anticonvulsant	
	Sedative	
	Nootropic	
GIT	Antiulcer	[40]
	Hepatoprotective	
	antidiabetic	
CVS	Cardioprotective	[40]
Immune system	Immunostimulant, antiviral	[40]
General	Antibacterial, antifungal, insecticide, antitumor, anti-psoriatic.	[40]

1.10 Effect of Gotu kala in AD

Due to its high antioxidant properties, this neurodegenerative adaptogen aids in the prevention of cognitive impairments and the alleviation of oxidative stress associated with AD [44]. It's a better alternative to AChE inhibitors, which is used as the 1st-line therapy for AD[45]. It can also help lower phospholipase A2 levels. This herb's antioxidant activity may affect a natural process that contributes to dementia, mitochondrial dysfunction[46]. Its active ingredients are saponins and Asiatic side

derivatives, which substantially reduce death of cell caused by H₂O₂, lower the level of free radical, and prevent neural cell death mediated by Aβ (in vitro). As a result, it may be useful in preventing and treating Aβ toxicity as well as AD [47, 48].

A study of 28 stable elderly people found that Gotu kola extracts could help with mood disorders and age-related cognitive decline [49]. It's generally safe to use; however, over-dose can cause lethargy [50].

Ashwagandha



Fig. 8. Leaves of ashwagandha

1.11 Biological Source

Withania somnifera (W. somnifera) is a small woody shrub that belongs to the Solanaceae family and is widely cultivated in India. The herb is also known as Indian ginseng, winter cherry, or ashwagandha. It has greenish or yellowish flowers that are about a centimetre long [51,52].

1.12 Chemical Constituents

It contains withaferins, isopelletierine, anaferine, sitoindoside 7 and 8, and anferine, withanoloids are some of the most important phytoconstituents found in *W. somnifera*. somniferine, Withanine, cuscohygrin, withananine, pseudo-withanine, tropine, somniferinine, pseudo-tropine, 3-allyloxytropine, somnine, choline, and are some of the other chemical compounds [53–55].

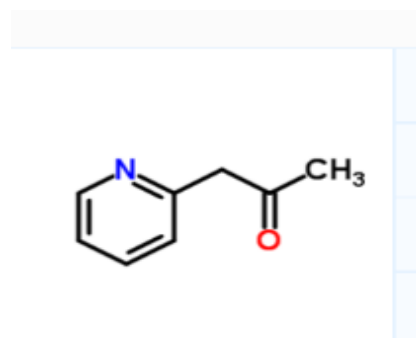


Fig. 9. Isopelletierine

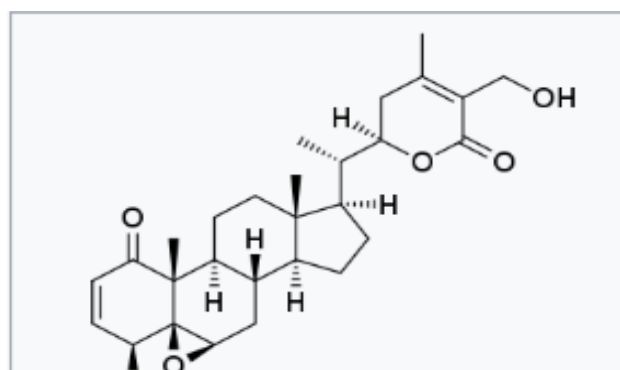


Fig. 10. Withaferin

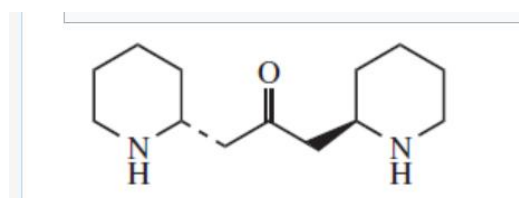


Fig. 11. Anaferine

Table 3. pharmacological activity of Ashawagandha

System	Pharmacological activity	References
CNS	Anti-Parkinson	[56]
	Anxiolytic	
	Antistress	
	Antidepressant	
CVS	Anti-Ischemiac	[56]
GIT	Antiulcer	[56]
	Nephroprotective	
Respiratory	Diabetes	
	Anti-hypoxiac	[56]
Other	Anti-inflammatory	[56]
	Antioxidative stress	
	Anticancer	

1.13 Effect of Ashwagandha in AD

The roots helps in the suppression of the nuclear factor (NF- κ B), and regulates the expression of genes involved in inflammatory mediators and oxidative stress parameters and thereby producing anti-inflammatory and antioxidative effect by preventing the development of A β . It helps in the regeneration of synaptic function and the decrease apoptosis. It encourages nuclear factor related to E2-related factor 2 (Nrf2) to migrate to the nucleus, resulting in an increase in antioxidant enzyme expression and neuroprotective proteins like haeme oxygenase-1, demonstrating antioxidant effects that are beneficial in the treatment and prevention of AD [57,58].

Turmeric



Fig. 12. leaves of Turmeric

1.14 Biological Source

Curcuma longa (*C. longa*) Linn also known as turmeric, is a perennial plant in the Zingiberaceae family. It is derived from the plant's rhizome and is widely used as a food flavouring and colouring agent in India. In South and Southeast Asia, it is grown for commercial purposes.[59-61].

1.15 Chemical Constituents

Curcuminoids, which include curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin, are the major chemical constituents of turmeric. Alpha- and beta-turmerone, arturmerone, alpha- and γ -atlantone, curlone, zingiberene, and curcumol are some of the other chemical constituents found in the plant [62].

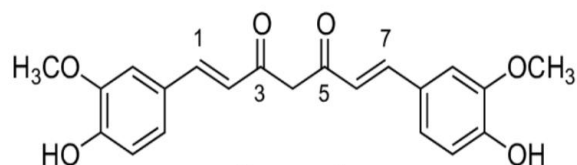


Fig. 13. Curcumin

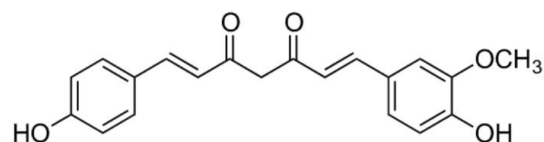


Fig. 14. Demethoxycurcumin

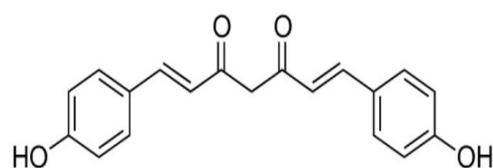


Fig. 15. Bisdemethoxycurcumin

1.16 Effect of Turmeric in AD

Curcumin has anti-inflammatory properties by inhibiting the development of TNF- α , IL-1 β , and further pro-inflammatory cytokines in astrocytes and microglia, such as IL-8, MIP1 β , and MCP-1. By modifying the Nrf2-Keap1 (Kelch-like ECH-associated protein 1) pathway, the oxidative damage is reduced and improves functions that are cognitive, particularly in the case of ageing. By modulating the Nrf2-Keap1 (Kelch-like ECH-associated protein 1) pathway, it reduces oxidative damage and improves cognitive function, particularly in the case of ageing [64]. When curcumin binds to Keap1, Nrf2 attaches to Keap1 and present in the cytoplasm is released.

A study found that daily curry eaters beat those who had never or only sometimes eaten it on a typical Montreal Cognitive Assessment (Mini-Mental State Examination, MMSE) [65]. It can also limit microglia development, lower the level of cholesterol, inhibit AChE, modulate the signalling pathway of insulin, prevent brain dysregulation induced by bio-metal poisoning, and inhibit acetylcholinesterase [66,67].

Table 4. Pharmacological activity of turmeric

System	Pharmacological activity	References
CNS	Neuroprotective	[63]
GIT	Antihepatotoxic	[63]
	Antidiabetic	
	Antidiarrheal	
	carminative	
Urinary system	Diuretic	[63]
CVS	Anti-thrombolytic	[63]
	Hypotensive	
Immune system	Antiviral, antirheumatic,	[63]
Other	Antimicrobial	[63]
	Antioxidant	
	Larvicidal	
	Antiproliferative	
	Antivenomous	
	Anti-tyrosinase	

The extensive consumption of turmeric in the Indian population has also been linked to lower rates of AD, implying a neuroprotective effect for haldi [68]. It is also used in food preparation and is completely healthy, along with the exception of diarrhoea, nausea, dizziness, or stomach upset if eaten in large amounts.

Shankpushpi



Fig. 16. leaves and flower of shankpushpi

1.17 Biological Source

Convolvulus pluricaulis is a species of *Convolvulus* (*C. pluricaulis*) Choisy is a perennial, wild, prostrate herb that is innate to Northern India and belongs to the *Convolvulaceae* family. In the ancient system of medicine, it also known as shankpushpi and have activity as a tonic to boost memory and brainpower [69].

1.18 Chemical Constituents

It contains Alkaloids that is shankpushpine and convolamine, volatile oils, flavanoid-kampferol, phytosterol, amino acids, fatty acids, scopoletin, and beta-sitosterol that is SethiyaNKare the main chemical components [70].

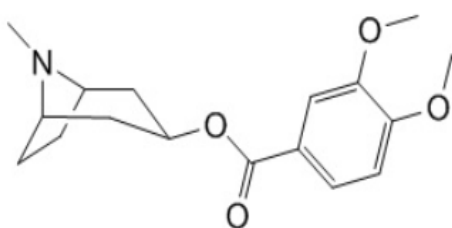


Fig. 17. Convolamine

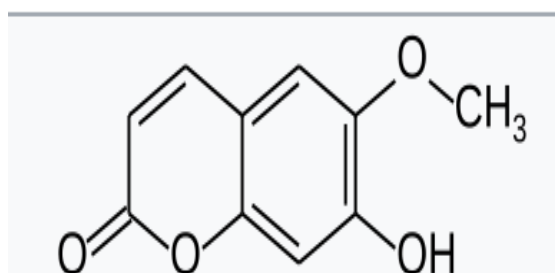


Fig. 18. Scopoletin

Table 5. Pharmacological activity of Shankpushpi

System	Pharmacological activity	References
CVS	Cardioprotective	[70]
CNS	Nootropic	[71-74]
	Inhibit stress	
	Antidepressant	
	Anti-convulsant	
	Anxiolytic	
	Sedative	
	Inhibit Amnesia	
GIT	Catatonic	
	Antiulcer	[74]

1.19 Effect of Shankpushpi in AD

Its aqueous extracts protect a *Drosophila* model of AD against early mortality by neutralising human microtubule-associated tau protein mediated neurotoxicity. The tau protein in tauopathy is greatly reduced by Shankpushpi extracts. increases antioxidant enzyme activity and reduces oxidative- stress mediated by tau protein [75]. The ethanolic extracts of Shankpushpi increase neurite outgrowth, which improves memory [76]. The action of *C.pluricaulis* can be triggered by adding it to daily food. Its small leaves, flowers, and roots, as well as the paste produced from them, can be eaten on a regular basis.

Drumstick Tree



Fig. 19.leaves of drumstick tree

1.20 Biological Source

Moringa oleifera (*M. oleifera*), a member from the Moringaceae family, is the utmost widely distributed plant. It's commonly referred to as a drumstick. This plant is instinctive to India, and trees can grow up to height of 10 metres in length.

1.21 Chemical Constituents

It contains Vitamins i.e.vitamin A and C, alkaloids, isothiocyanates, tannins, and saponins

and polyphenols i.e. flavonoids, chlorogenic acid, glucosinolates, and phenolic acids are the main chemical constituents in *M. oleifera* [77].

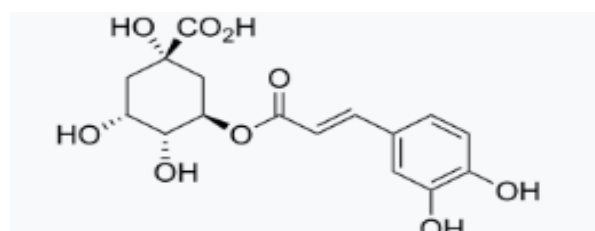


Fig. 20. Chlorogenic acid

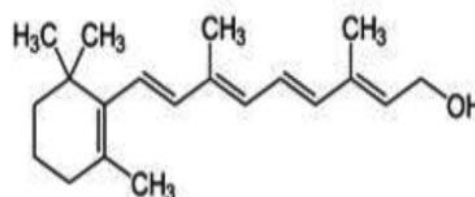


Fig. 21. Retinol

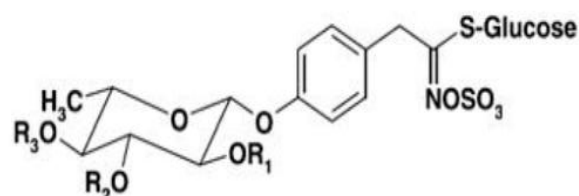


Fig. 22. Glucosinolates

1.21 Effect of Drumstick tree in ADS

It reversed the effects of colchicine on NE, 5-HT, and DA levels in the brain. Its antioxidant effect has been linked to improvements in learning and memory. Other studies have also shown that *M. oleifera* protects in contrast to memory loss in laboratory models for dementia.

Table 6. Pharmacological effect of Drumstick

System	Pharmacological activity	References
CNS	Nootropic Memory Enhancer	[78,79]
Other	Anti-inflammatory Anti-diabetic Inhibit obesity Anticancer	[80-82]

2. CONCLUSION

Alternative medicine is used in the treatment of Alzheimer's disease from ancient times, and many extractions of medicinal plants and herbal formulae showed potential. Medicinal plants provide fertile ground for novel drug development due to the availability of diverse chemical ingredients and their capacity to work on a different type of biological targets. The no. of persons suffering by age-related diseases such as Alzheimer's disease will substantially increase as the world's population grows. The number of AD cases is expected to increase to 135 Million by 2050 in the ageing population. As a result, advanced research and development of effective preventive and therapeutic methods are gaining increasing interest. This paper has mentioned some of herbs related to the AD and their effect. However, more work is still needed in order to convert this potential into actual treatment. Multi-centre clinical trials should be done to confirm the effectiveness of the herbal medications alone or in the form of formulations for the treatment of AD.

NOTE

The study highlights the efficacy of "Ayurveda " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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