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Review Article

Role of Centella asiatica in Alzheimer's Disease: A Comprehensive Review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, affecting millions worldwide. As synthetic medications often prove ineffective or cause severe side effects, natural remedies are gaining attention. This review explores the potential of Centella asiatica, a herb traditionally used in oriental medicine, in the treatment of Alzheimer's disease. Centella asiatica contains various bioactive compounds, including triterpenoids, asiaticoside, and madecassoside, which contribute to its medicinal properties. Studies suggest that Centella asiatica may enhance cognitive function through multiple mechanisms, such as inhibiting acetylcholinesterase activity, reducing phospholipase A2 activity, protecting against β-amyloid formation, and modulating oxidative stress responses. The plant's effects on neuronal morphology, learning performance, and memory retention have been demonstrated in animal models. Additionally, Centella asiatica extract has shown promise in attenuating Aβ plaque-associated oxidative stress in the hippocampus and cortex. While these findings are encouraging, further research is needed to fully elucidate the herb's mechanisms of action and evaluate its efficacy in human clinical trials. This review highlights the potential of Centella asiatica as a promising natural intervention for Alzheimer's disease and emphasizes the need for continued investigation into its therapeutic applications.

INTRODUCTION

Throughout the life span, many diseases affect the human body with suitable remedies available in nature. When synthetic medications fail to be effective or show severe side effects,
they are a natural medicinal system sourced from plants that provide safety and comfort to patients during therapy [1]. Alzheimer's disease (AD) is the most common type of dementia. It can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures [2]. Three cases illustrate the clinical spectrum of AD. Case A highlights AD that is determined genetically, Case B represents a language variant of AD, usually occurring at a younger age under 70 years and Case C is a typical amnestic variant, more commonly seen in patients older than 70 years [3]. There are around 50 million AD patients worldwide; this number is projected to double every 5 years and reach 152 million by 2050 [2]. *Centella asiatica* is a great multipurpose miracle herb used in oriental medicine [4]. *Centella asiatica* is used in Indian systems of medicine for enhancing memory and for the treatment of skin diseases and nervine disorders [5]. In India, the plant is commonly known as 'Mandukaparni'. In Sri Lanka and Indonesia, it is given the name 'Thankuni Sak'. In classical Indian Ayurveda literature, it is considered to be one of 'Rasayana' (rejuvenator) drugs and it is said to improve the texture of skin, enhance memory and prolong life [6]. This review aims to understand the role of *Centella asiatica* in the treatment of AD. By analyzing various data, it was found that *Centella asiatica* played a major role in boosting memory power. This article also gives the picture of other pharmacological actions of the plant.

TAXONOMY [7]

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Apiales
Family	Apiaceae
Genus	*Centella*
Species	*asiatica*

Fig:1 Centella asiatica Plant

DESCRIPTION OF PLANT

Centella asiatica is a clonal, perennial herbaceous creeper found throughout India growing in moist places up to an altitude of 1800 m. It is found in most tropical and subtropical countries growing in swampy areas, including parts of India, Pakistan, Sri Lanka, Madagascar, and South Africa and South pacific and Eastern Europe. It has small fan-shaped green leaves with white or light purple-to-pink or white flowers and it bears small oval fruit [8]. The stems are slender, creeping stolons, green to reddish green in color, interconnecting one plant to another. It has long-stalked, green, reniform leaves with rounded apices which have smooth texture with palmately netted veins. The leaves are borne on pericladial petioles, around 20 cm. The rootstock consists of rhizomes, growing vertically down. They are creamish in color and covered with root hairs [7]. This plant grows naturally in wet, shaded areas up to 7000 feet and is frequently observed along the banks of rivers, streams, ponds, and irrigated fields. About 20 species of Gotu kola have been reported to grow in most tropical or moist pantropical environments, such as rice paddies, as well as rocky and higher elevations [9].

CHEMICAL CONSTITUENTS

The major chemical constituents found in the plant are triterpenoids, vallarine, asiaticoside, sitosterol, tannin, oxyasiaticoside [10]. *C. asiatica* is rich in pentacyclic triterpene glycosides and the medicinal efficacy of the plant is mainly attributed to these primary active constituents, asiaticoside and madecassoside as well as their respective aglycones (sapogenins), asiatic acid and madecassic acid. Other compounds derived from the herb include phenolic acids, triterpene steroids, volatile oils, flavonoids, tannins, phytosterols, vitamins, essential oils, amino acids and sugars [11]. *C. asiatica* also shows the presence of isoprenoids (sesquiterpenes, plant sterols, pentacyclic triterpenoids, and saponins) and phenylpropanoid derivatives (eugenol derivatives, caffeoylquinic acids, and flavonoids) [12]. The leaves of *C. asiatica* contain various types of terpenes such as monoterpenes, sesquiterpenes and triterpenes. The aerial parts of *C. asiatica* contain triterpenes, phenols and cadiyenol while the root also contain monoterpenes, sesquiterpenes and triterpenes in addition to some minerals [13].

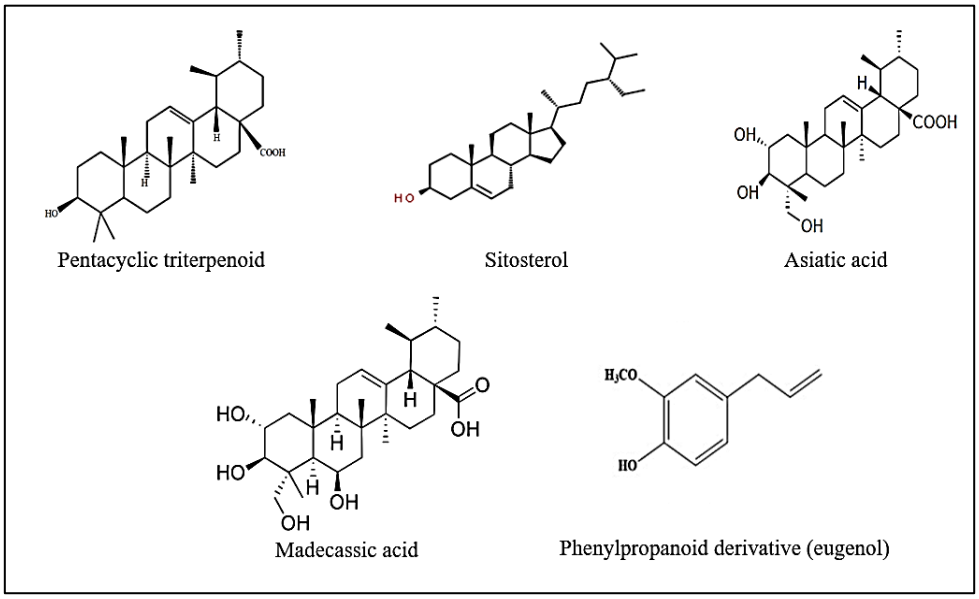

Fig.2: Chemical constituents of *Centella asiatica*

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

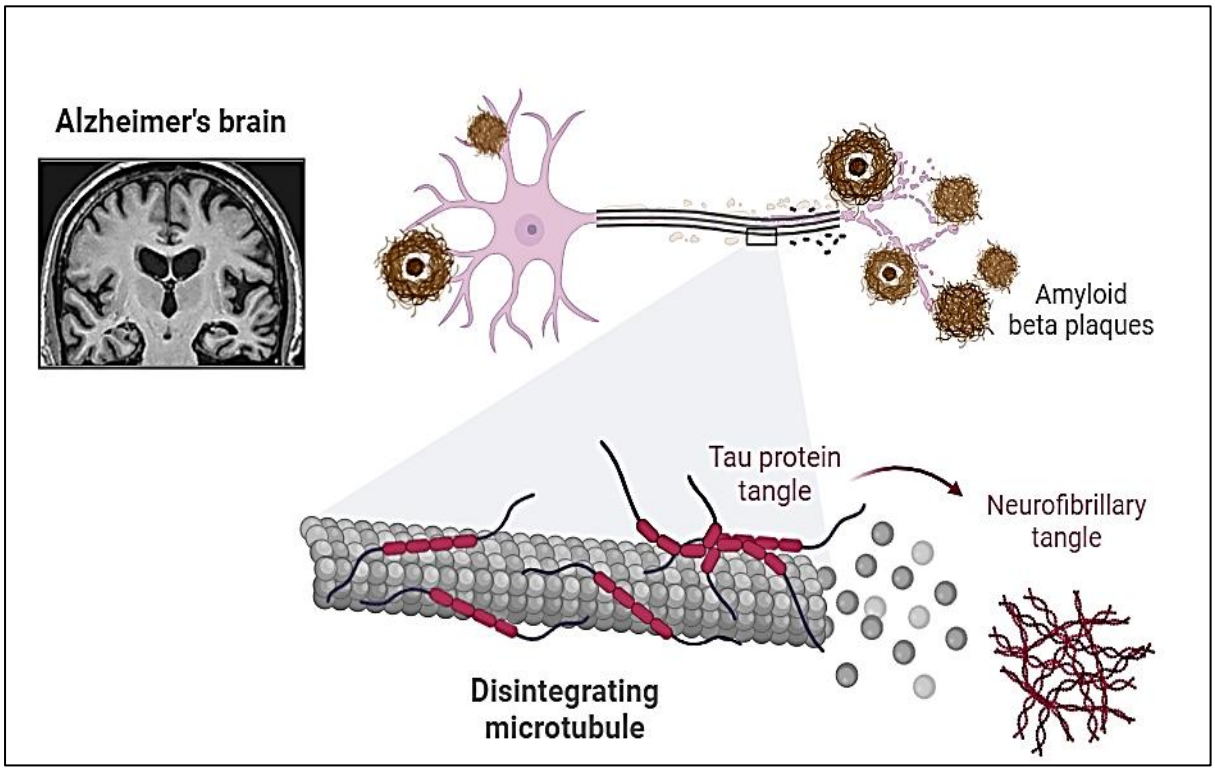

Fig.2: Pathophysiology of Alzheimer's disease

Alzheimer's disease (AD) is caused due to the accumulation of abnormal neuritic plaques and neurofibrillary tangles in the brain. These pathological changes are accompanied by a loss of neurons, particularly cholinergic neurons in the basal forebrain and the neocortex [14]. The clinical manifestation of AD is dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating [15]. In Alzheimer's disease, however, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, which harms the synaptic communication between neurons [16]. There is diffuse atrophy of the cerebral cortex and secondary dilatation of the ventricles. The deposits are found more at the hippocampus, temporal cortex and nucleus basalis of Meyernet. There is loss of neurons due to the pathological changes leading on to reduced levels of neurotransmitters especially acetylcholine causing cognitive deficits in these patients [15].

Two main hypotheses were proposed to explain the cause for AD, cholinergic and amyloid hypotheses [2]

1. The Cholinergic Hypothesis proposes that the reduced levels of acetylcholine (ACh) in the brain, resulting from neuronal loss in the Nucleus Basalis of Meynert, play a significant role in AD development.
2. The amyloid hypothesis suggests that amyloid beta (Aβ) peptide is derived from amyloid precursor protein (APP) through the actions of β- and γ-secretase enzymes. Usually, APP is cleaved by either alpha or beta-secretase, and the tiny fragments formed by them are not toxic to neurons. However, sequential cleavage by beta and then gamma-secretase results in 42

amino acid peptides (Aβ42). Elevation in levels of Aβ42 leads to aggregation of amyloid that causes neuronal toxicity [14].

MECHANISM OF ACTION OF *Centella asiatica* IN ALZHEIMER'S DISEASE

Centella asiatica is a plant used for centuries to enhance memory [17]. Important indications for *C. asiatica* in Ayurveda include its use for cognitive properties as a brain tonic, in the treatment of mental disorders, and as a memory-enhancing agent. *C. asiatica* was shown to improve neuronal morphology and learning performance and enhance memory retention in animal models. Several mechanisms of action of *C. asiatica* were demonstrated for enhancing cognitive function, such as the inhibition of acetylcholinesterase activity, reduction of phospholipase A_2 (PLA_2) activity, protection against ß-amyloid formation, and protection from brain damage [18]. Studies showed administration of *Centella asiatica* extracts might improve learning and memory function by the enhancing neuronal dendrites in growth spurt rats and altering amyloid β pathology in the brains and modulating components of the oxidative stress responses in neurodegenerative mice [19].

NRF2 pathway signaling is part of a larger cellular response to oxidative stress, a response which includes the key regulator of ROS content, superoxide dismutases. Elevated SOD expression is indicative of the high levels of oxidative stress associated with Aβ plaques in Alzheimer's disease brains. Analysis revealed that *Centella asiatica* water (CAW)extract treatment was associated with a reduction in Aβ plaque-associated oxidative stress in the hippocampus and cortex. CAW provides a neuroprotective effect against Aβ toxicity through the attenuation of oxidative stress and possible mitigation of neuritic dystrophy around the plaques [18].

OTHER PHARMACOLOGICAL ACTIONS AND TRADITIONAL USE

WOUND HEALING ACTIVITY

It was revealed that, the ethanolic extract of *C. Asiatica* leaves accelerated the healing process of excision wounds after the extracts were applied at various concentrations to the wound-inflicted experimental Wistar rat [20]. Wound healing is a complex process, which starts immediately after injury and consists of different phases: inflammation, proliferation, maturation, and re-epithelization. *Centella asiatica* is widely used in treating infectious skin diseases and accelerating the healing of skin ulcers and wounds. *Centella asiatica* shows the presence of pentacyclic ursane type triterpenoid centellosides namely madecassic acid, asiatic acid, asiaticoside, and madecassoside. Amongst these, madecassoside has strong anti-inflammatory action through enhanced secretion of collagen type III, whereas asiaticoside supports wound healing by stimulating fibroblast proliferation and synthesis of collagen type-I [21].

ANTIFUNGAL ACTIVITY

Various studies showed that extracts of *C. asiatica* had been determined against different microorganisms, *A. niger*. The extracts of *C. asiatica* showed a significant preservative effect against *A. niger* at 5% and 1% solution. In these findings, 5% extracts showed a maximum inhibitory effect than the control group and 1% solution [22].

IN SKIN DISEASES

Atopic dermatitis (or atopic eczema) is one of the most common allergic inflammatory skin diseases. *C. asiatica* on 2,4-dinitrochlorobenzene (DNCB)-induced skin inflammation has been tested using in vitro and in vivo models of atopic dermatitis, and the results illustrated strong protective activity of *C. asiatica* extract by it inhibiting pro-inflammatory cytokines to effectively suppress dermatitis symptoms [11].

TRADITIONAL USES

The use of *Centella* in food and beverages has increased over the years. Besides being used as a traditional and alternative medicine, *Centella asiatica* is commonly as vegetables and drinks as in tea or juice. Due to its mild bitterness, it is always cooked and served with the addition of coconut milk or shredded coconut and sometimes sweet potatoes and potatoes are added. In Sri

Lanka, the *Centella* leaves are used in their traditional curry called “mallung”, and in their porridge known as “kola kenda” [23,24]. Apart from this the extract of *Centella asiatica* is used as anti-skin aging agent [25]. *Centella asiatica* can help to improve skin hydration, making the skin around the eyes appear plumper and reducing the appearance of dark circles and fine lines [26]. The dried Brahmi leaves are made into powder form and can be used as supplement with any dish, which helps to enhance the nutritional value of the foods [27].

FUTURE DIRECTIONS

Future research on *Centella asiatica* should focus on elucidating its precise mechanisms of action in cognitive enhancement, particularly its interactions with the NRF2 pathway and oxidative stress responses. Large-scale clinical trials are necessary to establish its efficacy and safety in human Alzheimer's patients. Efforts should be made to isolate and identify the most potent bioactive compounds, develop optimized drug delivery systems, and explore potential synergistic effects with existing treatments. Long-term studies on its preventive effects in aging populations, standardization of extracts, dose-response studies, and investigation of its potential in other neurodegenerative disorders are also crucial. Additionally, sustainable cultivation practices should be developed to meet potential increased demand. These multifaceted approaches will help advance our understanding of *Centella asiatica* therapeutic potential and facilitate its development as a promising treatment for Alzheimer's disease and related cognitive disorders.

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