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Centella asiatica (Gotu Kola): A Natural Solution for Neurodegenerative Disorders

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Abstract: Diseases prevalent in an ageing society are often chronic and neurodegenerative. The growing recognition of the role of nutrition in healthy ageing has stimulated research into the therapeutic potential of traditional foods and medicinal plants. *Centella asiatica* (Gotu kola), a perennial herb native to Southeast Asia, has long been used in both Indian and Chinese traditional medicine and is now increasingly recognized for its neuroprotective potential against neurodegenerative disorders such as Parkinson's, Alzheimer's, and Huntington's diseases. Traditionally regarded as a brain tonic, *C. asiatica* has been shown to alleviate anxiety and depression, while at the cellular level, it exhibits protective effects against oxidative stress and inflammation. Several studies have demonstrated that its plant-derived metabolites support neuronal growth, survival, and repair by inhibiting apoptosis and neurotoxicity. These effects are attributed to bioactive compounds including asiaticoside, asiatic acid, madecassoside, and madecassic acid. The herb exerts its neuroprotective action through multiple disease-modifying pathways, including inhibition of acetylcholinesterase activity, which reduces amyloid plaque formation in the brain. Preclinical investigations indicate that *C. asiatica* enhances cognitive function, improves memory, and promotes neuronal growth and regeneration. Its antioxidant properties enable the neutralization of free radicals, while its anti-inflammatory effects suppress pro-inflammatory cytokines and microglial activation. Additionally, its anti-apoptotic activity protects neurons by modulating key cell survival signaling pathways. *In vivo* studies further demonstrate the amelioration of cognitive deficits and the enhancement of synaptic plasticity. Although clinical evidence remains limited, available trials suggest improvements in cognitive performance and reductions in anxiety and depression among elderly populations, underscoring its potential in the management of age-related neurodegenerative conditions. This chapter provides an overview of *Centella asiatica*, its major bioactive constituents, and their mechanisms of action, while highlighting the need for further rigorous research to validate and optimize the therapeutic use of these compounds in the treatment of neurodegenerative disorders.

Keywords: Neurodegeneration, Acetylcholinesterase inhibitory, *Centella asiatica*, Degenerative diseases, Neuroprotectant, Neurotoxicity.

1. Introduction

The nervous system comprises highly complex and specialized structures, including the brain, spinal cord, and peripheral nerves, which are particularly vulnerable to a wide range of diseases and traumatic injuries. Disorders affecting the nervous system can severely impair sensorimotor and cognitive functions and, in acute cases, may pose life-threatening risks. Unfortunately, owing to the intricate organization and limited regenerative capacity of nervous tissue, spontaneous repair and recovery are extremely restricted. These challenges, combined with the high cost of long-term patient care and associated socio-economic burdens, have intensified global research efforts aimed at understanding and managing neurological disorders.

While the role of a balanced and nutritious diet in maintaining neurological health cannot be overstated, increasing awareness among health-conscious consumers has driven demand for foods rich in antioxidants and other neuroprotective components. In this context, medicinal plants have emerged as promising candidates for the development of novel neuroprotective therapies [1]. Since ancient times, plants have been closely associated with human health and well-being, and even animals have been observed to instinctively consume specific herbs or plant parts to aid recovery from illness and injury [2-4]. With advances in modern scientific methodologies and analytical instrumentation, research focus has increasingly shifted toward experimental validation and mechanistic understanding. This shift has contributed to transforming many previously fatal neurological conditions into manageable and in some cases treatable diseases.

Centella asiatica (L.), commonly known as mandukparni, Indian pennywort, jalbrahmi, or Gotu kola, possesses a rich medicinal history spanning several millennia. It is formally recognized in major pharmacopoeias, including the German Homeopathic Pharmacopoeia, the Pharmacopoeia of the People's Republic of China, the European Pharmacopoeia, and the Indian Herbal Pharmacopoeia, for its therapeutic applications in a variety of ailments [5]. Despite decades of scientific investigation into its bioactive constituents and mechanisms of action, a comprehensive and conclusive understanding of its full therapeutic potential remains incomplete. Traditionally, *C. asiatica* has been used to treat infections, inflammation, seizures, tumors, and psychosis.

In recent years, its role in improving neurological and psychological conditions such as anxiety, dementia, and cognitive impairment has gained increasing attention. Extracts of the plant have demonstrated a broad pharmacological profile, including antihyperglycemic, antihyperlipidemic, antioxidant, anti-inflammatory, and wound-healing properties. Traditional consumption has also shown benefits in metabolic and vascular conditions such as diabetes, hypertension, venous insufficiency, and anal fissures. Additionally, *C. asiatica* has been widely used in the treatment of dermatological conditions, including erythema, edema, crusting, excoriation, and lichenification. Importantly, the plant exhibits a favorable safety profile for human use, further strengthening its potential as a therapeutic agent across multiple disease domains, including neurological disorders. This chapter explores the multifaceted nature of *Centella asiatica*, focusing on its pharmacological properties, bioactive compounds, and therapeutic potential in neurodegenerative disorders. Emphasis is placed on elucidating the mechanisms underlying its neuroprotective actions, drawing upon evidence from both preclinical and clinical studies.

The genus *Centella* L., belonging to the family Apiaceae (formerly Umbelliferae), comprises approximately 59 recognized species worldwide, many of which possess medicinal value. Among these, *Centella asiatica* (L.) Urb. is the most extensively studied and commercially significant species. It is a stoloniferous perennial herb that typically grows up to 15 cm in height and thrives in moist and marshy habitats. The plant is widely distributed across Australia, Central Africa, Madagascar, the Pacific Islands, South and Southeast Asia, South-Central America, the southeastern United States, and Southern Africa. Morphologically, *C. asiatica* features a creeping, smooth stem with round to kidney-shaped leaves, usually one to three per node. The leaves have sheathing bases, scalloped margins, and smooth surfaces on both sides. The plant produces fascicled umbels bearing two to four small flowers, which range in color from creamy white to pale purple. The fruit is a schizocarp, oblong to globular in shape, measuring approximately 5 mm in length, and contains seeds with pendulous embryos [6].

2. Traditional and Ethnomedicinal Uses of *Centella asiatica*

Centella asiatica possesses a long-standing history of use as both a nutritional and ethnomedicinal plant, underscoring its significance in traditional healthcare systems worldwide. Owing to its extensive antiquity of use, the plant occupies a prominent position in diverse cultural medicinal practices. Numerous ethnobotanical records indicate that *C. asiatica* is among the most widely recognized species within the genus, with particularly extensive applications in Asian traditional medicine, and notable use in African and European regions as well [7]. As a dietary component, the fresh leaves and aerial parts are commonly consumed as vegetables, while medicinally, the entire plant is utilized for the management of a broad spectrum of ailments. These include arthritis, circulatory and cardiovascular disorders, diabetes, gastrointestinal disturbances, nervous system disorders, respiratory conditions, skin diseases, wound healing, and as a mild sedative [8-9]. The wide range of traditional applications reflects the plant's multifaceted therapeutic potential. **Table 1** summarizes the region-specific traditional uses of *C. asiatica* across different cultures.

Table 1: Region-based Traditional Uses of *Centella asiatica*.

Country	Traditional Uses
India	Treats asthma, enhances memory in children (known as Vallarai), treats stomach worms, leucorrhoea, epilepsy, mental disorders
Pakistan	Treats skin ailments, syphilis, dysentery, rheumatism, and fevers (known as Barhami)
China	Treats hepatitis, used to treat gallstones, sunstroke, detoxification, and heat (Traditional Chinese Medicine)
Nepal	Relieves muscular swelling and joint pain, treat skin diseases (eczema, pimples), cures fever, indigestion, uric acid, dysentery, enhances memory, treats wounds, gastritis, anorexia
Bhutan	Recommended as an appetizer
Bangladesh	Treats hypertension, wounds, burns, skin lesions
Philippines	Treats urination difficulty, sore eyes, burns
Tanzania	Treats malaria (whole plant decoction)
Cameroon	Treats pharyngitis, dysmenorrhea, convulsions (leaves), vomiting, appendicitis (whole plant decoction)
Uganda	Treats ulcers (leaf decoction)
Guinea	Treats diabetes (whole plant decoction)
Nigeria	Treats haemorrhoids (root decoction)
South Africa	Treats diabetes mellitus (root, Bapedi traditional healers), treats stomach disorders, dysentery, diarrhoea (known as Inyongwane)
Greece	Stimulates blood circulation, and treats hypertension, phlebitis, uric acid, cellulitis, and menstruation disorders (known as Sentella)
Russia	Treats depression (leaves and bark)
Turkey	Treats neurological disorders (aerial parts)
Brazil	Treats hypertension, dermal lesions (leaves and bark)
Mexico	Used for weight loss among Mexican-American women
Madagascar	Treats pimples externally (known as Viliantsahona)
Australia (Yaegl Aboriginal community)	Treats arthritis (leaves)
Malaysia, China, Sri Lanka, India, Indonesia	Eaten as a fresh vegetable
Thailand	Aerial parts consumed as a wild food plant

In traditional Chinese medicine, *C. asiatica* is prescribed for gallstones, sunstroke, heat exhaustion, and hepatitis. In Nepal, a paste prepared from the whole plant is applied topically to treat skin disorders such as eczema and acne, as well as to alleviate joint and muscle pain [10]. Decoctions are commonly used to treat fever, diarrhoea, flatulence, and elevated uric acid levels, and are also administered to enhance memory in children. In the Kali Gandaki watershed region of Nepal, the plant is traditionally used to treat anorexia, gastritis, and wounds. In Bhutan, it is recommended as an appetiser, while in Bangladesh, leaf decoctions are used to manage hypertension, wounds, burns, and various skin lesions [11]. In Pakistan, where the plant is known as Barhami, the leaves are used to treat skin ailments, rheumatism, dysentery, syphilis, and general malaise. African traditional medicine also documents extensive applications of *C. asiatica*. In Tanzania, a syrup-like decoction prepared from the whole plant is used in the treatment of malaria. In Cameroon, leaf preparations are employed to manage pharyngitis, dysmenorrhea, and convulsions, while decoctions of the whole plant are used to treat vomiting and appendicitis. In Uganda, leaf decoctions are prescribed for ulcers, whereas in Guinea and Nigeria, whole-plant decoctions are traditionally used in the management of diabetes and haemorrhoids. In South Africa, Bapedi traditional healers utilize the root to treat diabetes mellitus, and both the roots and leaves—locally known as Inyongwane—are used to treat stomach disorders, dysentery, and diarrhoea [8]. In Madagascar, where the plant is referred to as Viliantsahona, the leaves are applied externally to treat pimples. In European traditional medicine, *C. asiatica* is also highly valued.

In Greece, where it is known as Sentella, leaf preparations are used to stimulate blood circulation and treat conditions such as cellulitis, hypertension, menstrual disorders, phlebitis, and elevated uric acid levels. In Russia, leaves and bark are traditionally used to manage depression, while in Turkey, the aerial parts are employed in the treatment of neurological disorders. Across the American continent, *C. asiatica* exhibits diverse traditional applications. In Brazil, leaf and bark preparations are used to treat hypertension and dermatological lesions, while among Mexican-American communities, the plant is traditionally consumed for weight loss purposes. In the Indian subcontinent, particularly in remote forest regions, both tribal and non-tribal communities rely heavily on traditional medical systems such as Ayurveda, Siddha, and Unani for primary healthcare [12]. Within these systems, *C. asiatica* is widely utilized in the form of fresh leaves, herbal teas, or as a component of classical formulations [13], as detailed in **Table 2**. For instance, Vallarai, an Ayurvedic preparation made from *C. asiatica* leaves, is traditionally administered to enhance memory and cognitive function in children.

Table 2: *Centella asiatica* formulations that conventional doctors recommend to treat neurological conditions.

S. No	*Centella asiatica* Plant part	Formulation	Application
1.	Whole plant	Turned into a paste by crushing it with cow's milk.	Externally, on the head for depression treatment.
2.	Whole plant with Rauwolfia roots	Ground and tablet are prepared	Oral for epilepsy treatment
3.	Whole plant with *Eclipta prostrata* leaves	Cooked in coconut oil after being crushed.	Externally on the head for epilepsy treatment.
4.	Whole plant with *Hibiscus rosasinensis* flowers	Mashed, followed by cooking in sesame oil	Externally on the forehead for insomnia treatment.
5.	Whole plant with *Trigonella foenum-graecum* Seeds	Pulverised and heated in coconut oil	Externally on the forehead for paralysis treatment.
6.	Leaves with *Cynodon dactylon* entire plant	Minced, dried, and combined with honey.	Orally in psychosis treatment

3. Bioactive Compounds and Health Benefits of *Centella asiatica*

The leaf transcriptome of *Centella asiatica* provides a comprehensive map of the genes involved in the biosynthesis of secondary metabolites, which are abundantly present in the roots, aerial parts, and rhizomes. To date, 57 secondary metabolites have been identified in this herb and classified based on structural similarity. Compounds derived from the isoprenoid pathway are grouped into four clusters: pentacyclic triterpenoids, plant sterols, saponins (comprising approximately 8% of total dry mass), and sesquiterpenes. Phenylpropanoid-derived compounds are categorized into three clusters: caffeoylquinic acids, eugenol derivatives, and flavonoids. *Centella asiatica* is particularly renowned for its centelloids, a class of pentacyclic triterpenoids divided into two subtypes, oleanane and ursane series, distinguished by the methyl substitution pattern on C-19 and C-20. The most abundant pentacyclic triterpenoids include asiatic acid, madecassic acid, and their corresponding aglycones.

The primary saponins are asiaticoside and madecassoside. Essential oils extracted from the aerial parts exhibit antibacterial activity due to their content of monoterpenoids and sesquiterpenes such as myrcene, germacrene-D, bicyclogermacrene, β-caryophyllene, and α-humulene, along with oxygenated monoterpenes, oxygenated sesquiterpenes, and sulfur-containing sesquiterpenoids [14]. Caffeoylquinic acids include isomeric dicaffeoyl esters such as 1,3-dicaffeoylquinic acid and 3,5-dicaffeoylquinic acid [15]. Flavonoid biosynthesis occurs *via* a combination of the shikimate and acetate pathways, leading to the production of naringenin derivatives, flavones, and flavanols. Additionally, the esterification of cinnamic acid derivatives with quinic acid generates chlorogenic acids, another major bioactive constituent. The diverse array of secondary metabolites in *C. asiatica* underpins its wide-ranging medicinal properties. Notably, pentacyclic triterpenoids, together with chlorogenic acids, have demonstrated potent antioxidant and anti-inflammatory effects, which are critical for enhancing cognitive function and mitigating the onset or progression of neurodegenerative diseases such as Parkinson's and Alzheimer's disease [16].

3.1 Neuroprotective Action of Specific Phytoconstituents Present in *Centella asiatica*

The principal bioactive compounds in *Centella asiatica*, collectively known as centelloids, include asiaticoside, madecassoside, asiatic acid, and madecassic acid as depicted in **Figure 1**. These molecules are well-recognized for their neuroprotective, antioxidant, and anti-inflammatory activities, making them key contributors to the herb's therapeutic potential in neurodegenerative disorders.

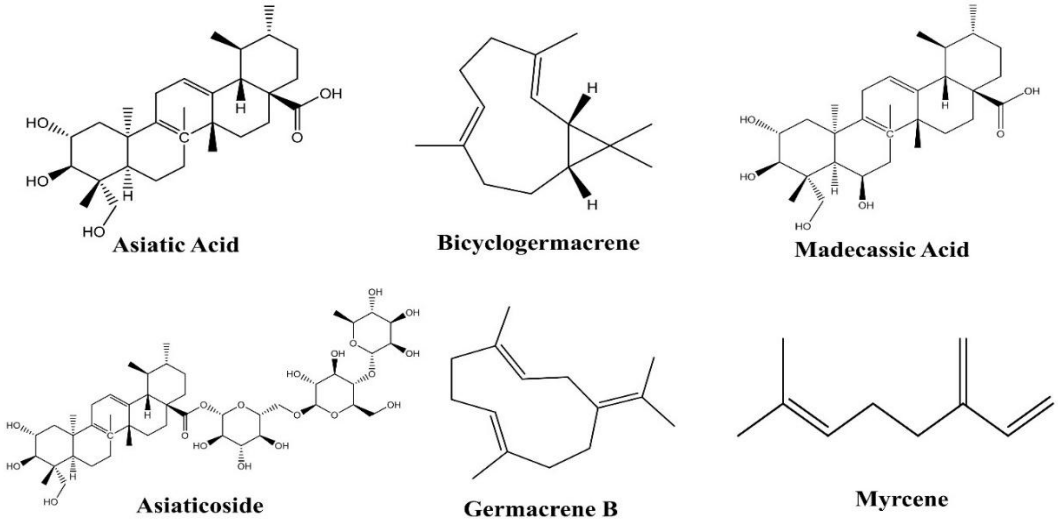

Figure 1: Phytoconstituents present in *Centella asiatica*

3.1.1 Centellin

Among the phyto-components abundant in *Centella asiatica*, centellin has demonstrated notable neuroprotective and phytorestorative properties. It is proposed that centellin exerts its effects by enhancing the expression of brain-derived neurotrophic factor (BDNF) and through potent antioxidant and anti-inflammatory mechanisms. These actions collectively support neuroplasticity and promote neuronal survival [17-18]. Centellin has also shown efficacy in mitigating key processes of neurodegeneration, including impaired synaptic transmission, by inhibiting amyloid-β deposition, a hallmark feature of Alzheimer's disease [19]. Furthermore, this phytoconstituent appears to improve mitochondrial function and protect neurons against glutamate-induced excitotoxicity, which may further enhance its neuroprotective potential [20]. Although these findings are promising, current evidence remains limited, and further research is essential to fully elucidate the mechanisms of centellin in human neurological disorders.

3.1.2 Centellicin

Centella asiatica (Gotu kola) contains the pentacyclic triterpene centellicin, which imparts significant neuroprotective effects. Studies have demonstrated that centellicin can cross the blood-brain barrier (BBB), exhibit potent free radical scavenging activity, and protect against oxidative stress-induced neuronal damage [14]. It has also been shown to inhibit acetylcholinesterase activity, enhance cholinergic neurotransmission, and improve cognitive function [8]. Additionally, centellicin contributes to anti-inflammatory effects within the central nervous system, which may reduce the risk or progression of neurodegenerative disorders. Research further suggests that centellicin promotes neuronal differentiation, supporting neuroplasticity and indicating potential applications in neuronal repair and rejuvenation [21-22]. While these findings are promising, most studies remain at the preclinical stage. Further investigation is necessary to fully elucidate the mechanisms of centellicin and to advance its potential pharmacological applications for the treatment of various neurological disorders.

3.1.3 Asiatic Acid

Asiatic acid, a pentacyclic triterpene present in *Centella asiatica*, demonstrates notable neuroprotective properties. Studies have shown that asiatic acid can attenuate oxidative stress and inflammation in the brain,

thereby safeguarding neurons from damage [23]. By promoting neuronal growth and enhancing synaptic connectivity, asiatic acid has been observed to improve memory and cognitive functions in animal models [24-25]. It mitigates glutamate-induced cognitive deficits and restores antioxidant levels in the hippocampus and cortex [26]. Additionally, asiatic acid has been reported to inhibit the formation of β-amyloid plaques and reduce tau protein accumulation in rats and mice, highlighting its potential as a therapeutic agent for neurodegenerative diseases [27]. Other studies suggest that it protects neurons from glutamate-induced excitotoxicity and enhances mitochondrial function [28]. Although these findings are promising, further research is required to validate the therapeutic potential of asiatic acid for human neurological disorders.

3.1.4 Bicyclogermacrene

Although research on bicyclogermacrene, a sesquiterpene, is still in its early stages, this compound has demonstrated potential anti-inflammatory and antioxidant activities, which may contribute to its neuroprotective effects. By reducing oxidative stress and inflammation—key factors in the pathogenesis of various neurodegenerative disorders—bicyclogermacrene may help protect the central nervous system. Animal studies suggest that it can influence neurotransmitter systems and exhibit anxiolytic-like effects [29]. However, most investigations have used essential oils or crude plant extracts rather than the isolated compound, and therefore, further research is necessary to elucidate the specific mechanisms underlying its neuroprotective actions.

3.1.5 Madecassic Acid

Madecassic acid, a pentacyclic triterpene, exhibits neuroprotective properties similar to those of asiatic acid and bicyclogermacrene. Its actions include the reduction of oxidative stress and inflammation in neurons, enhancement of memory and cognitive functions, inhibition of β-amyloid plaque formation, reduction of tau protein accumulation, protection against glutamate-induced excitotoxicity, and improvement of mitochondrial function in neuronal cells [11, 30].

3.1.6 Asiaticoside

As a triterpene saponin, asiaticoside exhibits notable pharmacological properties. Studies have demonstrated its ability to reduce oxidative stress and inflammation in the brain, enhance cognitive functions, and improve memory by promoting neurogenesis and synaptic plasticity [31]. Asiaticoside also exerts restorative effects by attenuating neurodegenerative processes, including the inhibition of β-amyloid formation and tau hyperphosphorylation. Furthermore, it protects against glutamate-induced excitotoxicity and enhances overall neuronal function. Notably, asiaticoside has been shown to support nerve cell regeneration [22]. Beyond Alzheimer's disease, it also exhibits neuroprotective effects in models of Parkinson's disease, likely through the inhibition of neuroinflammatory cascades that contribute to disease progression.

3.1.7 Germacrene B

Germacrene B, a sesquiterpene, has also been reported to exhibit neuroprotective properties, which are thought to arise from synergistic interactions with other bioactive compounds. It possesses antioxidant and anti-inflammatory activities [32]. Some studies suggest that Germacrene B may cross the blood-brain barrier, although this has not been definitively confirmed. It is presumed that, if this occurs, its neuroprotective effects may involve modulation of neurotransmitter systems. Similar to other phytochemicals in *Centella asiatica*, further research is needed to elucidate the precise mechanisms of action underlying its neuroprotective effects.

3.1.8 Myrcene

Similar to Germacrene B, further investigation is required to fully elucidate the mechanism of action of Myrcene. Nonetheless, its ability to enhance cellular defenses has been demonstrated through upregulation of antioxidant enzymes, such as catalase and superoxide dismutase, alongside effective free radical scavenging [27]. Additionally, Myrcene has been associated with inhibition of pro-inflammatory cytokines and attenuation of inflammatory signaling pathways, including NF-κB, thereby reducing neuronal stress. Its neuroprotective effects are also presumed to involve modulation of neurotransmitter systems, particularly GABAergic transmission, contributing to anxiolytic and protective outcomes. Furthermore, Myrcene has been shown to regulate glutamate receptors, mitigating excitotoxicity in neuronal cells [33].

4. Clinical evidence for neuroprotective effects of *Centella asiatica*

Extracts of *Centella asiatica*, such as Titrated Extract of *C. asiatica* (TECA), Total Triterpenic Fraction (TTF), Total Triterpenoid Fraction of *C. asiatica* (TTFCA), as well as individual triterpene derivatives including Asiatic Acid, Asiaticoside, Bicyclogermacrene, Centellicin, Germacrene B, and Madecassic Acid, have demonstrated significant neuroprotective effects. These compounds exhibit anxiolytic, antidepressant, nerve-regenerating, sedative, anticonvulsant, tranquilizing, and memory-enhancing properties in neurodegenerative conditions such as Alzheimer's and Parkinson's disease. The therapeutic effects are attributed to multiple mechanisms, including modulation of redox potentials in key cellular components, inhibition of acetylcholinesterase, reduction of amyloid-β plaque formation, and regulation of neurotransmitter activity within synaptic junctions. **Table 3** provides a comprehensive summary of *C. asiatica* pharmacological activities in neurological disorders along with their proposed mechanisms of action [5].

Table 3: *C. asiatica* pharmacological activities in neurological disorders.

Pharmacological activity	Type of CA extract (Dose)	Animal Model used (M-Mouse, R-Rat) [Route]	Mechanism
Anti-depressant	Aqueous extract (100mg/kg)	M and F / forced swimming test	Modulation of D_2 receptor and cholinomimetic activity, decreased immovability time, and improvement of unevenness of amino acid stages
Anti-anxiety	Aqueous extract (25 mg/kg)	M and F [I.P. route]	Decreased spur-of-the-moment motorized activity and delayed pentylene-tetrazole-derived convulsions
Memory and learning	Leaf aqueous extract	R/ 2-compartment passive avoidance model	Decreased norepinephrine, dopamine, serotonin and all the metabolites, Improvement of Memory and learning
Cognitive Impairment	Aqueous extract (200 mg/kg)	R [oral, QD, 14 days]	Decreased lipid peroxidation, increased endogenous anti-oxidant enzymes in the brain
Anticonvulsant	Methanolic and Hydroalcoholic leaf extract (100, 200,500, and 1000 mg/kg)	M and R [oral, alternate hours]	Anti-convulsant, anti-oxidant, and central nervous system sedative actions, Synergistic with anti-epileptic drugs (valproate, phenytoin, and gabapentin)
Nerve regeneration	Ethanolic extract (300-350 mg/kg)	R [oral, QD] for 18 days	Increased functional recovery, increased axonal regeneration
Epilepsy and cognitive decline	Aqueous extract (200, 300 mg/kg)	R [oral, QD for 15-21 days]	Decreased malondialdehyde, increased glutathione and catalase, decreased seizure score, increased learning and memory, increased ACh esterase action and Dendritic arborization of hippocampal CA-3 nerves,

In addition, **Table 4** summarises human trial studies assessing the efficacy of *Centella asiatica* in neurodegenerative disorders [21].

Table 4: Human Trials Assessing *Centella asiatica* in Neurodegenerative Disorders.

Capsules filled with CA	Trial study location	Study Design (Control)	Dose (Duration)	Subjects	Evaluation	Trial remarks

Dried leaves powders	India	Open-label type (None)	500 mg Twice (180 days)	60 senior citizens with modest dementia.	GDS, MMSE, caretaker interviews, ADL scale, and IADL	MMSE score improved; diastolic blood pressure down; hunger, mood, and sleep improved; peripheral neuritis and anxiety reduced
Crude herb Powder	Malaysia	Randomized; blinding (Corn starch placebo)	500 mg / 10kg body mass daily (60 days)	41 mid-aged, healthy individuals	Test of Cognitive Abilities by Woodcock and Johnson III	Increased intellectual capacity scores (3/8 for men and 5/8 for women)
70% hydroethanolic extract of dried aerial parts	India	Open-label type (None)	500 mg twice daily after meals (60 days)	33 adult patients diagnosed with GAD	Validated stress, anxiety, and depression scales; validated adjustment and attention scales; SF-36 health questionnaire for surveys	Lower depression index, higher self-perceived stress, lower anxiety, better adjustment index, and higher degree of attention
Combined aqueous leaf extract with sugar (Patent 4721; Thailand)	Thailand	Double-blind; randomized (Placebo)	250, 550, or 750 mg daily (90 days)	80 well-aged, in good health	Hand grip, six-minute walk test, 30-second chair stand test, and SF-36 overall quality of life questionnaire.	With 500 and 750 mg dosages, there was an increase in weakness in the lower extremities and a life satisfaction subscale.
Ghava-Satva powder with leaves	India	Open-label (None)	500 mg twice daily after meals with lukewarm water (90 days)	Ages 20–25 with MMSE<25	Vitals, carer interviews, and the MMSE	MMSE score improvement and a drop in mean diastolic and systolic blood pressure
70% hydro-ethanolic whole herb extract dried powder	Indonesia	Non-randomized Double-blind; (3 mg folic acid)	1000 or 750 mg daily (28 days)	48 people who had vascular cognitive impairment following a stroke	MoCA-Ina	Better memory for delayed recall

ADL = Activities of Daily Living; CDR = Clinical Dementia Rating; GDS = Geriatric Depression Scale; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; MoCA-Ina = Montreal Cognitive Assessment-Indonesian version;

Table 4 summarizes human clinical trials assessing the efficacy of *Centella asiatica* in neurodegenerative disorders [21]. These studies investigated various formulations, dosages, and designs, evaluating cognitive and neuroprotective benefits across different populations. The table includes details on trial locations, dosages, control measures, duration, subject demographics, and assessment methods. Results indicate improvements in cognitive function, reduction in anxiety, enhanced well-being, and other health-related outcomes, providing a foundation for understanding the therapeutic potential of *C. asiatica* and emphasizing the need for further research to confirm its efficacy and safety in larger, more diverse populations. Beyond neuroprotection, oral administration of *C. asiatica* has demonstrated beneficial effects in animal models, including alleviation of myocardial remodeling and left ventricular hypertrophy in cardiac hypertrophy models. Aqueous leaf extracts in high-cholesterol-fed rats reduced low-density lipoprotein (LDL), triglycerides (TG), and total cholesterol while increasing high-density lipoprotein (HDL), likely *via* suppression of tumor necrosis factor-alpha (TNF-α)-induced atherosclerosis, reduced endothelial hyper-permeability, and modulation of cell adhesion molecules, showing comparable effects to captopril. Additional studies in animal models report protective effects on pancreatic islet cells (diabetes), liver and kidney oxidative parameters, pulmonary fibrosis (bleomycin-induced), gastric ulcers (indomethacin-induced), ulcerative colitis, and skin conditions such as cellulite, photoaging, psoriasis, scleroderma, and pregnancy-associated striae. *C. asiatica* has also been reported to prevent osteoporosis. Collectively, these findings highlight the broad therapeutic potential of *C. asiatica* for human health [34].

5. Possible Mechanisms of Neuroprotective Properties of *Centella asiatica*

Compounds in *Centella asiatica* have been shown to penetrate the blood-brain barrier in animal models, supporting their potential neuroprotective effects against Parkinson's disease (PD) and Alzheimer's disease (AD) [35-36]. The accumulation of these bioactive compounds in the brain is believed to underlie their beneficial effects, including cognitive enhancement, improved memory, and protection against hippocampal dysfunction. These effects are associated with modulation of excitatory neurotransmission and synaptic plasticity, promoting neuronal survival and overall brain health. The mechanisms underlying *C. asiatica* neuroprotective actions include anti-inflammatory activity, attenuation of oxidative stress, enhancement of mitochondrial function, upregulation of brain-derived neurotrophic factors (BDNFs), and support for neuronal regeneration, as depicted in **Figure 2** [37].

5.1 Anti-Inflammatory Effects

Neuroinflammation is a key feature in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). AD pathology is characterized by the formation of neurofibrillary tangles and β-amyloid plaques, whereas PD involves neuronal damage in the substantia nigra pars compacta, often mediated by glial cell activation and the release of pro-inflammatory cytokines. *Centella asiatica* has been shown to reduce the production of nitric oxide (NO), TNF-α, and reactive oxygen species in activated microglial cells. These anti-inflammatory effects are proposed to be mediated via inhibition of the PI3K/AKT and ERK1/2 signaling pathways, thereby preventing NF-κB activation [38].

5.2 Reduction of Oxidative Stress

The brain's high oxygen consumption and limited antioxidant capacity make it particularly vulnerable to oxidative stress, especially in regions such as the hippocampus and cortex. Oxidative stress can impair cholinergic function by increasing acetylcholinesterase (AChE) activity, which accelerates acetylcholine breakdown and contributes to cognitive deficits. *Centella asiatica* has been shown to modulate key antioxidant systems by enhancing the activities of glutathione (GSH), superoxide dismutase (SOD), and protein carbonyl (PC), while reducing AChE activity, thereby improving cholinergic transmission. Additionally, it decreases oxidative markers such as malondialdehyde (MDA), reactive oxygen species (ROS), and hydroperoxides, while restoring GSH levels and enhancing glutathione-S-transferase activity, collectively strengthening the brain's antioxidant defenses [26].

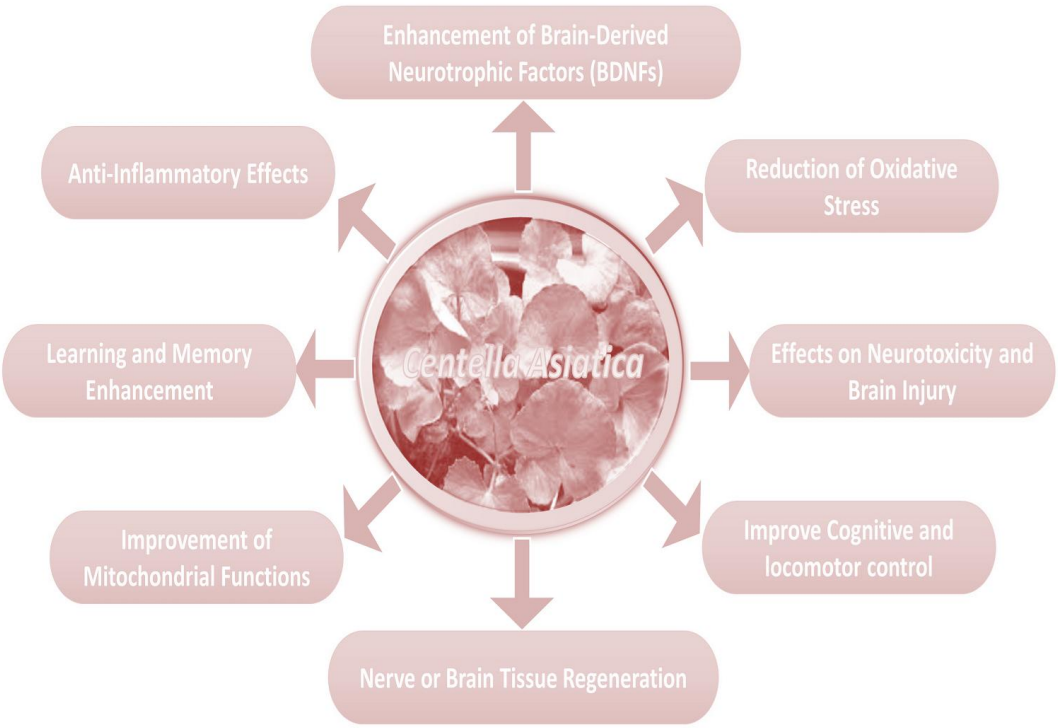

Figure 2: Insights for the mechanism of action of *Centella asiatica*

5.3 Improvement of Mitochondrial Functions

Mitochondrial dysfunction is a hallmark of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and ageing-related neuronal decline. Impairments in mitochondria disrupt cellular energy metabolism, immune responses, and apoptotic pathways. Protein aggregation, increased mitochondrial fragmentation, and excessive production of reactive oxygen species (ROS) further exacerbate mitochondrial damage. Research indicates that *Centella asiatica* enhances mitochondrial function by modulating key mitochondrial enzymes, thereby improving overall cellular bioenergetics and resilience, even in the absence of β-amyloid pathology [38].

5.4 Enhancement of Brain-Derived Neurotrophic Factors (BDNFs)

Brain-derived neurotrophic factors (BDNFs) are essential for neuronal maintenance, survival, and neurotransmitter regulation, playing a pivotal role in synaptic growth, learning, and memory. In neurodegenerative diseases, BDNF levels are often reduced, potentially due to chronic neuroinflammation. *Centella asiatica* has been shown to elevate BDNF levels in the hippocampus by upregulating both BDNF protein and mRNA expression. Moreover, bioactive compounds such as asiatic acid and madecassic acid may enhance neuronal differentiation by modulating neurofilament expression and activating MEK signaling pathways [39].

5.5 Nerve Tissue Regeneration

Extracts of *Centella asiatica* have demonstrated significant potential in promoting nerve and brain tissue regeneration. For instance, ethanolic extracts facilitated recovery and enhanced axonal regeneration following sciatic nerve crush in Sprague-Dawley rats, with increases in myelinated axons and axon diameter, thereby accelerating peripheral nerve repair. In dose- and duration-dependent studies, rat models exhibited enhanced dendritic branching and increased dendritic length in amygdaloid and hippocampal CA3 neurons [40]. Furthermore, in middle cerebral artery occlusion (MCAO) rat models, which simulate stroke-induced ischemia, *C. asiatica* treatment reduced neuronal tissue damage, as evidenced by the preservation of hippocampal and cortical neurons [39]. Asiatic acid, a key bioactive compound, has also been reported to mitigate glutamate-induced cognitive deficits and restore antioxidant levels in the hippocampus and cortex [26].

6. Conclusion

Although *Centella asiatica* has demonstrated neuroprotective and neuro-regenerative properties in animal models, further research is needed to fully identify its bioactive compounds and elucidate their mechanisms of action. Standardization of extraction methods, biochemical profiling, and dosage determination should be prioritized. Supported by both traditional use and modern studies, *C. asiatica* exhibits a broad spectrum of neuroprotective effects, including antioxidant, anti-inflammatory, neuroregenerative, and anti-neurotoxic activities. Its ability to reduce amyloid plaque accumulation, modulate the GABAergic system, and inhibit acetylcholinesterase contributes to anti-anxiety, antidepressant, and cognitive-enhancing effects, highlighting its potential as a versatile therapeutic agent. However, translating these findings into clinical application requires rigorous scientific evaluation. This includes understanding synergistic interactions among active compounds, developing efficient extraction and stabilization methods, and ensuring effective delivery across the blood-brain barrier. Addressing these challenges will enable *C. asiatica* to be harnessed effectively in the management of neurodegenerative disorders, offering a natural and promising approach to supporting neurological health.

7. References

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