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Review Article

Perspective study on Pharmacological and Therapeutic potential of *Centella asiatica*

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Abstract

Centella asiatica (L.) is a perennial, climbing plant, barely fragrant and an expensive therapeutic herb worldwide. It is commonly disseminated all the way through humid and subtropical provinces. The appliance of *Centella* in foodstuff and beverages has improved in modern era due to its favourable functional properties. The plant and its synthetic constituents are recurrently utilized for the therapy of several nootropic disorders, cognitive disorder, platelets conglomeration, burn wounds, hypertonic scars, insomnia, psoriasis, skin cell reconstruction and curing. *Centella* determines the greater part of its pharmacological actions from four foremost bioactive triterpene glycosides specifically, asiatic acid, asiaticoside, madecassoside and madecassic acid (termed as centellosides). This current search have another look at focuses to impart inclusive information on pharmacology, various preclinical and clinical studies, safety precautions, mechanisms of action and present research scenario of the herb.

Keywords: phytoconstituents; pharmacological activities; triterpenoids; bioactive components

Introduction

Taxonomy, Nomenclature and Geographical distribution

Centella asiatica (CA), a clonal, perennial herbaceous creeper belongs to the family *Umbellifere* (*Apiceae*) and subfamily Mackinolayoideae, found all over India growing in humid condition up to an elevation of 1800 m. It is originate mainly in humid and subtropical countries mounting in muddy regions, as well as parts of India, Sri Lanka, South Africa, Madagascar, Eastern Europe, South pacific and Pakistan. Concerning 20 species related to CA grow in most parts of the tropic or wet pan tropical areas such as rice paddies, and also in rocky, higher elevations [1]. Almost 80 species of Centella have been recorded, many of which have older synonyms under the genus Hydrocotyle and in common English names are Indian Pennywort and Asian Pennywort. This creeping plant propagates by producing stolons. It consists of shovel shaped leaves among scalloped boundaries, borne on elongated petioles grouped at the stem nodes. The inconsequential green or pinkish-white flora are borne in intense umbels and the seeds are pumpkin fashioned nutlets 3-5mm in length. Due to its wide spread spectrum of activity, can be employed as a modern or traditional botanical medication in many countries and also found gastronomic utilize as a salad vegetable or in juices.

Binomial Classification

Kingdom	:	Eukaryota
Subkingdom	:	Embryophyta
Division	:	Spermatophyta
Subdivision	:	Angiospermae
Class	:	Dicotyledoneae

Subclass	:	Rosidae
Superorder	:	Aralianae
Order	:	Araliales (UmbelJifiorae)
Family	:	Apiaceae or UmbelJiferae
Subfamily	:	Hydrocotyle
Genus	:	Centella
Species	:	*Centella asiatica*

It is a unsavoury, fragrance-free plant that flourish in the region of water. It has diminutive fan-shaped green foliage with white or light purple-to-pink or white blossoms and it bears small oval fruit (Fig. 1). The entire plant is utilized for therapeutic applications [2]. It is broadly worn as a blood purifier as well concerning for treating hyper tension, for memory enhancement and promoting durability. In Ayurveda, CA is one of the imperative herbs for restorative the nerves and brain cells. Eastern healers relied on CA to indulgence emotional disorders such as gloominess, which were reflection to be deep-seated physical problems [3, 4]. In Western medication, for the period of the central of the twentieth century, CA and its alcohol extracts shown positive outcomes in the management of leprosy [5].

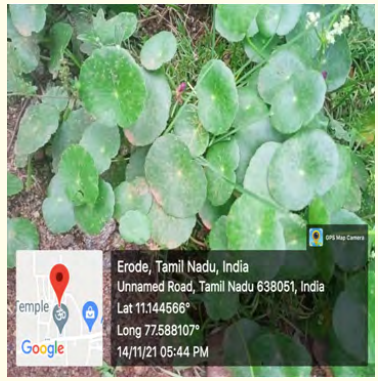

Figure 1: Habitat of *C.asiatica*.

Centella asiatica is universally recognized as Gotu Kola, Asiatic Pennywort or Brahmi in the herbal trade and is a vital components of more than hundred health care formulations sold in the marketplace. Plants posses as a minimum 2% content of asiaticoside and madecassoside are normally favoured by the herbal industries. In India, 500–1000 MT of *Centella* plant estimated at 0.4-0.5 US dollars/kg is exchanged annually. Similarly, several other restorative plants, over 90% of the inventory of C. asiatica spice to the industry is met throughout compilation from the wild strands, which is neither sustainable nor quality-driven. This herb is previously integrated in the International Union for Conservation of Nature and National Resources Red Data book of threatened species.

Phytochemical constituents

The pharmaceutical activity of herbs resides in their secondary metabolites which are located in the aerial portion of the plants, roots and rhizomes. A cytoscape linkage of 57 secondary metabolites naturally found in *C.asiatica* was reported by Kim et al [6]. Major groups of phytocompounds are depicted in Figure 2.

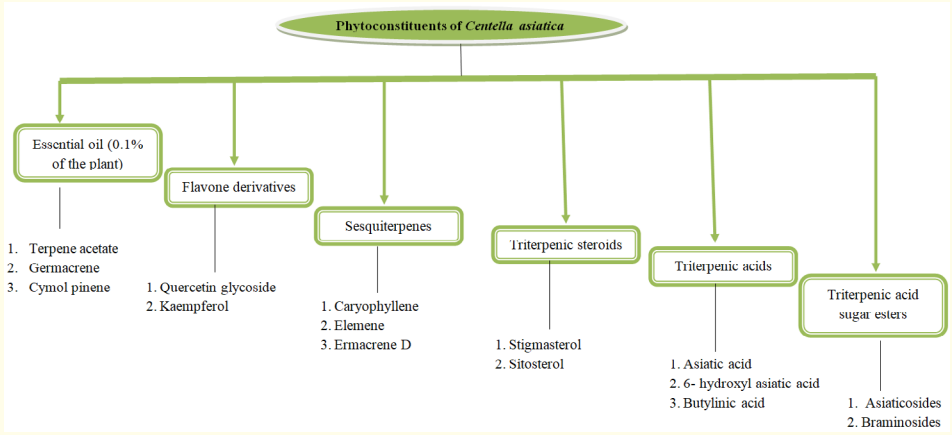

Figure 2: Classification of *Centella asiatica* major groups of phytoconstituents.

Saponins (triterpenoids) are the principal active ingredients of CA, which comprise asiaticosides (a trisaccharide moiety) connected to the aglycone asiatic acid, madecassoside, and madasiatic acid [7]. By interacting with collagen at the afflicted location, these triterpene saponins and their sapogenins are primarily responsible for wound healing and vascular effects. Other CA components, such as brahmoside and brahminoside, may be responsible for CNS and uterorelaxant effects, although clinical studies are needed to prove this. In mice, a crude extract comprising the glycosides isothankuniside and thankuniside had an antifertility effect [8, 9]. The use of centelloside and its derivatives in the treatment of venous hypertension is expected to be beneficial. There are also plant sterols, flavonoids, and other components in the whole extract that have no recognised pharmacological activity [10]. Tannins (20-25%), essential acids (0.1%), phytosterols (campesterol, sitosterol, stigmasterol), mucilages, resins, free aminoacids (alanine, serine, aminobutyrate, aspartate, glutamate, lysine, and threonine), flavonoids (derivates of quercetin and kaempferol), an alkaloid (hydrochotine), fatty acids (linoleic acids, linoleic, oleic, palmitic and stearic acids).

Nutritional properties

The nutritive analysis *C. asiatica* shows that *100* g of the leaves contain 34 calories, 89.3 g water, 1.6 g protein, 0.6 g fat, 6.9 g carbohydrates, 2 g fibre, 1.6 g ash, 170 mg Ca, 30 mg P, 3.1 mg Fe, 414 mg K, 6.58 mg beta carotene, 0.15 mg thiamine, 0.14 mg riboflavin, 1.2 mg niacin, and 4 mg ascorbic acid [11]. The proximate composition revealed that moisture (13.10 ± 1.07%), ash (16.5 ± 0.45%), proteins (8.35 ± 1.28%), lipid (1.20 ± 0.10%), fiber (17.0 ± 1.87%) and carbohydrate (43.81 ± 0.70%) contents shown in table - 1. Due to huge tremendous therapeutic potential, the claim for its usage is persistently rising in the worldwide market. *C. asiatica* is an imperative constituent of more than 100 traditional and modern herbal formulations. It is accessible in the marketplace as liposomal pills, fine particles, cream or tincture can be sold with various brand names.

S. No	Nutritional content	Concentration (%)*
1	Carbohydrates	43.81 ± 0.70
2	proteins	8.35 ± 1.28
3	Lipids	1.20 ± 0.10
4	Fibers	17.00 ± 1.87
5	Moisture content	13.10 ± 1.07
6	Ash content	16.55 ± 0.45

Note: * indicates the values are presented as mean ± standard error mean (SEM) of replicate determination.

Table 1: Nutritional composition of *Centella asiatica* leaves [12].

Effects of *C.asiatica* on various diseases of human beings

C.asiatica is a plant of reputation amid the numerous imperative therapeutic herbs that have been worn ever since pre-historic period for treating various diseases presented in figure 3.

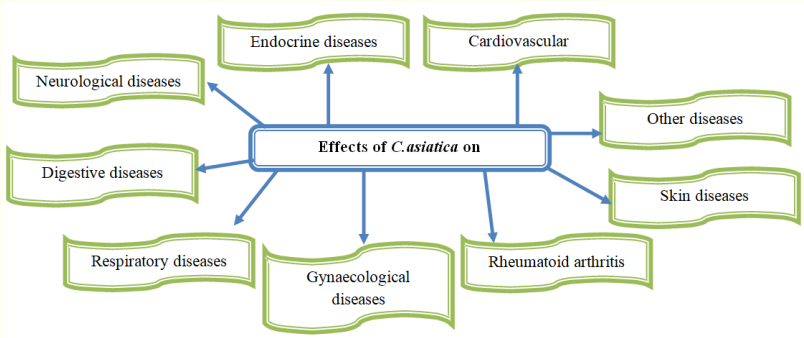

Figure 3: Effects of *C.asiatica* against various diseases of human beings.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory joint disease that usually affects women and elderly people. The main pathological change is persistent synovitis. Madecassoside as a triterpene component of *C.asiatica*, may have anti-arthritis effect, and the underlying mechanism is reduction in the level of inflammatory factors [13].

Gynaecological Diseases

C.asiatica can efficiently ameliorate endometriosis and reprieve pelvic inflammatory disease, along with exert anti-ovarian and anti-breast cancer functions. Pelvic inflammatory disease is a microbial infection of the upper reproductive tract. Infertility, chronic pelvic pain, rupture of a renal tubular ovarian abscess, and ectopic pregnancy are the most common consequences. Antibiotics are used in Western medicine to effectively control symptoms [14, 15]. Endometriosis is a widespread inflammatory disease repeatedly escort by pelvic pain and infertility.

Respiratory Diseases

The effects of *C.asiatica* on respiratory diseases are primarily reflected in its capacity to progress pulmonary fibrosis, obstructive pulmonary disease, lung injury and certain anti-lung cancer effects. The effective components of *C. asiatica* for respiratory diseases are asiatic acid and asiaticoside, and the foremost mechanism was anti- inflammation. Asiatic acid could reduce tumour volume, migration and differentiation. Additionally, it has the capacity to endorse tumour cell apoptosis [16, 17].

Digestive Diseases

C. asiatica and its triterpenoids have therapeutic effects on digestive problems, as evidenced by reduced *Helicobacter pylori* gastric colonisation and improved liver fibrosis, colitis, and gastric mucosal damage. *C.asiatica* improves digestive diseases in the liver, colon, and stomach by lowering inflammation, reducing oxidative stress, and increasing mitochondrial function [13].

Skin Diseases

Acne, baldness, vitiligo, atopic dermatitis, and wounds are all treated by *C. asiatica* extract and its triterpenoids [18-22]. *C.asiatica* and its triterpenoids have a variety of formulations that have been used to investigate therapy alternatives for skin illnesses, and it has been demonstrated that they may have a role in wound healing and skin inflammation. The anti-inflammation, anti-oxidation, and weakening of oxidative stress damage to mitochondria are the primary mechanisms of action of *C.asiatica* and its components in the treatment of skin problems.

Neurological Diseases

C. asiatica improves nervous system performance. Methanol, ethanol, and water all dissolve it. According to relevant literature on the nervous system, *C. asiatica* and its triterpenes are used to treat a variety of neurological illnesses, the best studied of which are Alzheimer's disease (AD) [23] and Parkinson's disease (PD) [24]. Neuroinflammatory activity [25], oxidative stress [26], mitochondrial dysfunction [27], and brain-derived neurotrophic factor malfunction [28] are all involved in the aetiology of these illnesses.

Cardiovascular Diseases

C. asiatica has anti-inflammatory and anti-cardiovascular properties. Asiaticoside and asiatic acid are the major components that affect the cardiovascular system. The most researched disorders are hypertension and atherosclerosis [29]. Improving the inflammatory response, lowering oxidative stress, and maintaining the endothelial barrier function have favourable impacts on the onset and progression of atherosclerosis. Asiatic acid and asiaticoside were found to have positive effects on cardiovascular disorders in numerous studies.

Effects on Endocrine Diseases

C. asiatica extracts show more promise in the treatment of endocrine illnesses, particularly type 2 diabetes and obesity. Asiatic acid was found to be useful in the treatment of obesity [30] and madecassoside as a possible option for the treatment of osteolytic bone disorders [31]. *C. asiatica* extract and asiatic acid help to (1) improve insulin resistance, (2) reduce oxidative stress, (3) lower blood sugar levels, (4) prevent weight gain, and (5) reduce inflammation. Furthermore, madecassoside cured osteoporosis by weakening osteoclast absorption and reducing osteoclast development.

Therapeutic potential of *C.asiatica*

Antioxidant activity, antibacterial, antifungal, and antiviral activity, antiulcer activity, antidiabetic activity, anti-inflammatory activity, cytotoxic activity, memory enhancing activity, cardio, neuro, and skin protective activities, immunomodulatory effect, radioprotective, and wound healing activity are just a few of the functional properties.

Antioxidant activity

C.asiatica is high in antioxidants such ascorbic acid, total and beta carotene, and total phenolics. According to Zainol, et al. [32], leaves of *C.asiatica* had the best antioxidant activity and the highest phenolic content when compared to other plant components. *Centella* works as a lipid peroxidation inhibitor as well as a scavenger of hydroxyl and superoxide radicals. According to Chanwitheesuk et al [33], Centella asiatica has a high antioxidant index and larger levels of natural antioxidants such as vitamin E, vitamin C, total carotenes, total xanthophylls, tannins, and total phenolics. According to Vimala et al. [34], *C.asiatica* leaves have been discovered to

have very strong antioxidant activity in three different pathways, including superoxide free radical scavenging activity. DPPH decreases linoleic acid peroxidation (98.2%) and exhibits radical scavenging properties (86.4%). (92.7 percent). Pittella et al [35]. Discovered that the aqueous extract of *C.asiatica* scavenged DPPH free radicals and had a good antioxidant activity. This activity could be explained by the presence of phenolic and flavonoid components.

Antimicrobial activity

C.asiatica is solitary of the very important plant suggests antibacterial recreation in opposition to extensive range of bacteria. Ullah et al, [36] used to be discovered the n-hexane, carbon tetrachloride, chloroform soluble fractions of methanol extract from the plant. C.asiatica confirmed antibacterial recreation towards five gram positive microorganisms (*Bacillus cereus*, *Bacillus megaterium*, *Bacillus subtilis*, *Staphylococcus aureus* and *Sarcina lutea*) and eight gram negative micro organisms (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella paratyphi*, *Salmonella typhi*, *Shigella boydii*, *Shigella dysenteriae*, *Vibrio mimicus* and *Vibrio parahemolyticus*). Wei et al, [37] used to be determined that methanol extract of *C. asiatica* complete plant confirmed inhibition region towards *V. alginolyticus*, *V. vulnificus* and *Streptococcus sp* whilst inhibition area was once determined in *C. freundii* and all *Vibrio sp*. Taemchuay et al, [38] was once locate out that crude extract of the selected plant, in particular extracted with water, had a promising antibacterial impact in opposition to *Staphylococcus aureus*. Ethanolic and petroleum ether extracts of *C. asiatica* plant suggests considerably greater price of antifungal endeavour towards quite a number fungal lines like *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans* when evaluate to water extracts [39]. Methanolic extract confirmed great inhibitory impact on spore germination in opposition to a range of fungal traces like *Alternaria*, *Cercospora*, *Curvularia*, *Drechslera* and *Fusarium*. The inhibitory impact on spore germination of the above fungus lines used to be multiplied proportionately with the expand in the attention of methanolic extracts of the leaves [40, 41]. Crude water extracts of mixtures every of Centella and *Mangifera indica* confirmed anti-herpes simplex virus things to do [42]. Alcoholic extract of whole plant confirmed antiprotozoal activity against *Entamoeba histolytica* [43].

Memory enhancing activity

Aqueous extract of *C.asiatica* confirmed great impact on studying and reminiscence enhancing and notably diminshed the ranges of norepineprine, dopamine and 5-HT and their metabolites in the brain.

Wound healing activity

Total triterpenoid fraction extracted from *C.asiatica* expanded the proportion of collagen in cell layer fibrnectin and for this reason can also assist in promoting wound recuperation [44]. Asiaticosides greater induction of antioxidant ranges at an preliminary stage of recovery which may also be a vital contributory element in its restoration properties [45]. Asiatic acid and asiaticoside had been more active than madecassic acid.

Sedative and anxiolytic properties

In Indian literature, *C.asiatica* was originally described as having CNS properties such stimulatory-nervine tonic, rejuvenant, sedative, tranquillizer, and intelligence enhancing property [46]. It has long been used as a sedative in many Eastern cultures; the sedative effect was once thought to be primarily due to the brahmoside and brahminoside constituents, while the anxiolytic activity is thought to be due in part to binding to cholecystokinin receptors (CCKB), a group of G protein coupled receptors that bind the peptide hormones cholesystokinin (CCK) or gastrin [47].

Gastric ulcer

C.asiatica has been found to be useful in preventing stomach lesions caused by ethanol administration [48]. The *C.asiatica* extract may help to strengthen the stomach mucosal barrier while also reducing the damaging effects of free radicals.

Radioprotection

Previous study has suggested that *C.asiatica* may help to avoid radiation-induced behavioural changes during clinical radiotherapy [49, 50].

Venous insufficiency

One of the most important effects of *C.asiatica* has been suggested to be on connective tissues by strengthening weaker veins [51]. *C.asiatica* was originally thought to aid in the protection of connective tissue [52]. It may also help in the treatment of scleroderma by stabilising connective tissue growth and reducing its formation by encouraging the formation of hyaluronidase and chondroitin sulphate, as well as exerting a balancing effect on connective tissue [52]. *C.asiatica* claimed to act on the connective tissues of the vascular wall, being efficacious in hypertensive microangiopathy and venous insufficiency and reducing capillary filtration rate by boosting microcirculatory parameters [53].

Pharmacodynamic effects

Madecassoside (pubchem CID: 131801373) is a pentacyclic triterpene saponin derived from *C.asiatica* that has a few medicinal properties. C48H78O20 has a molecular weight of 975.1 g/mol and a chemical formula of C48H78O20. It is widely distributed in the heart, liver, spleen, lung, brain, stomach, skin, and kidney following oral treatment, reaching maximal levels in 5–15 minutes [54]. Asiaticoside has a chemical formula of C48H78O19 and a molecular mass of 959.1 g/mol (pubchem CID: 52912190). It also achieves maximum levels in 5–15 minutes after being taken orally. Within 1 hour of dosage, Asiaticoside is widely disseminated in the brain, stomach, and skin [55]. Madecassic acid was identified in the plasma, brain, heart, liver, kidney, colon, and bladder following oral dosing, according to a previous study [56]. Asiatic acid (pubchem CID: 119034) has a chemical formula of C30H48O5 and a solubility in water of 5.98 102 mg/L at 25°C. Despite the fact that asiatic acid is absorbed mostly in the jejunum [57], it is also found in the plasma, brain, heart, liver, kidney, colon, and bladder [56]. They discovered that asiatic acid has physicochemical features that make it scarcely soluble in water but stable in saline. It has a considerable micelle concentration of 15 2M and a surface tension of 64.1 mN/m, respectively.

Furthermore, preclinical and clinical pharmacokinetic data revealed that asiatic acid should be dispersed throughout the body through binding to albumin. Although asiatic acid's bioavailability is limited, its derivatives have demonstrated a number of therapeutic benefits. Furthermore, modifying the asiatic acid's stamina chemically increased its bioavailability and biological activity [58, 59]. Glycosides contain physiologically active acids such as asiatic acid and madecassic acid. Although their content in tissues and plasma is low, they can be found in faeces 48 hours after oral administration of C. asiatica extract. The majority of triterpenoid glycosides are metabolised in the colon, according to this study [55].

Conclusion & future prospects

Various research findings on pharmacological investigations on *C. asiatica* as scrutinized in the present review emphasizes that this perennial potential herb is amenable and having totipotency in both *invitro* and *invivo* research studies. The main therapeutic components are centellosides of asiaticoside, asiatic acid, madecassoside and madecassic acid. These compounds such as herbal extracts and triterpenoids had more alleviate impacts on multisystem diseases like type 2 diabetes mellitus, gestational diabetes, sleep deprivation, hyperlipidemia, atopic dermatitis, liver injury, wound healing, baldness, gastric mucosal injury, drug induced liver toxicity, breast cancer, gastric ulcers, oral sub mucous fibrosis, leukaemia, migrainine etc. The bioactive therapeutic compound of *C.asiatica*, asiatic acid actively relieves Parkinson's disease, cognitive impairment, renovascular hypertension, myocardial ischemia/reperfusion injury, Alzheimer's disease, atherosclerosis, acute pancreatitis, colon carcinogenesis, ovarian carcinoma, lung cancer, hepatocellular carcinoma, endometriosis, pulmonary fibrosis, pelvic inflammatory, sepsis and periodontitis.

Due to its diverse potential health applications, *C.asiatica* is mortal demoralized at a more rapidly than formerly studied, and as a consequence, it was placed as a highly threatened plant species by the International Union for Conservation of Nature. There is an

emergence for incessant production on large scale, grown *invitro*, to meet the demands of the herbal industry. Further studies on clinical activities will be improved to explore its wider possibilities in treating disease conditions. Future investigations explore towards secondary metabolites efficiency which would strengthen its utilization in industrial purposes. In addition, genetic characterization in the form of genetic fingerprinting encouraged for the better understanding of diversity of *C.asiatica*.

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