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Chemistry, traditional uses and pharmacological effects of *Centella asiatica* (L.): A review

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Abstract

Centella asiatica (L.) is a valuable medicinal herb mainly distributed to Southeast Asian regions. Current study attempts to provide detailed information on morphology, chemistry, therapeutic uses, side effects and current herb research perspectives. This perennial creeper has been traditionally used for rheumatism, indigestion, diabetes, dysentery, fever, fractures, hepatitis, jaundice, constipation, wounds, and eye problems. Its medicinal values are attributed to the presence of tri-terpenes, carotenoids, glycosides, flavonoids, alkaloids, volatile and fatty oils. *In vivo* and *in vitro* investigations have demonstrated a number of biological effects such as wound healing, antiulcer, anti-leprotic, anti-tubercular, anti-cancer, memory enhancing, and immune-modulatory effects. However, absence of detailed scientific approach regarding to *Centella asiatica* health benefits hinders the perception of its benefits to develop new drugs. Moreover, composition of bioactive constituents is greatly affected by various biotic and abiotic factors that must be studied in detail to maximize the utilization of plant.

Key words: *Centella asiatica*, wound healing, memory enhancing, toxicity, tri-terpenes

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1. Botany

1.1. Introduction

Centella asiatica (L.) is an herb with reputation among many important medicinal plants that have been used since pre-historic times to treat many diseases. The *Centella genus* (Family: Apiaceae) includes over fifty species found in the sub-tropical and tropical areas of the world. The herb is indigenous to South America, Papua New Guinea, Sri-Lanka, Venezuela, Bangladesh, India, Madagascar, Malaysia, Indonesia, Mexico, Indonesia, Pakistan, and other Asian countries [1-3]. *Centella asiatica* is valued in the traditional medicine systems for curing several chronic diseases including Alzheimer's disease, venous insufficiency, intestinal ulcer, leprosy, some eczema, hypertonic scar, and keloids [4-7]. The herb is also known to have strong immune-modulatory, anti-ulcer, anti-asthmatic, anti-depressant, anti-cancer, anti-tubercular, radioprotective, and neuroprotective effects [8-10]. The medicinal values of *Centella asiatica* result from the presence of several phytonutrients like terpenoids, phenols, vitamins, minerals, and fatty acids. The relative concentration of these compounds is greatly influenced by the source of plant, its place of origin and climatic conditions [11-16]. Because of huge therapeutic potential, the demand for *Centella* asiatica is constantly growing on the world's herb market. According to a report from National Medicinal Plant Board (India), it is on the list of 178 medicinal plants which are utilized in amounts>100MT/year [17]. *Centella asiatica* is an essential ingredient of over 100 traditional and modern herbal preparations. It is commercially available in the form of liposome tablets, powder, and tincture or cream and is known by different vernacular names including Indian pennywort /marsh pennywort (English), sombrerito (Spanish), hydroctyle asiatique (French), ji xue cao (Chinese), asiatische sumpfpfennigkra (German), tsubo-kusa (Japanese), brahmi (Hindi), and gotu kola (Urdu). Limited cultivation and insufficient efforts to supplement nature reserves have led to a significant reduction of its wild resources and hence its insertion in the International Union for Conservation of Nature and National Resources [IUCN] list of endangered species.

1.2. History

Available literature discloses that *Centella asiatica* L. has been used as a medicine from ancient times. It was referred to in the ancient Chinese Shennong Herbal and in Indian Ayurvedic medicine about 2000 to 3000 years ago, respectively. It has been listed in *Susruta Samhita*, an ancient Indian medicinal text. In Ayurvedic medicine, *Centella* is reputed as a mental rejuvenator and a local stimulant of skin and thus is used to treat skin diseases such

as herpes, eczema, psoriasis, and wounds. In India and Indonesia, *Centella asiatica* was used to treat wounds and leprosy, enhance memory and prolong life span. In China, it is used for boils, contusions, fractures, snake-bites, strains, and turbid leucorrhoea. The use of *Centella asiatica* as a drug was first accepted in France in the 1980s. In India, *Centella asiatica* and its extracts were incorporated into the Indian Pharmacopoea in the 19th century. In 1884, *Centella asiatica* was referred to in the French Pharmacopoea, but regardless of its long history of conventional use, it only appeared in the Codex in 1884. First extract of *Centella asiatica* was created after 1941, and three years later, the French scientist, Boiteau isolated its triterpenoids. The use of its aerial parts in rheumatism and its topical application for leprous ulcers, indolent wounds, and post-surgical wound healing (cicatrization) are reported in the British Herbal Pharmacopoea. In Europe, therapeutic products containing triterpenic fractions extracted from *Centella asiatica* have been legitimized for cutaneous use (as a cream, powder ointment) since 1968. Oral tablets containing Madecassol have been permitted in Europe since 1969, but are only allowed in Belgium, France, Greece, Italy, and Portugal [18].

1.3. Demography/Location

Centella asiatica, a native to Asian countries, now grows widely in the West as well. The specie is widespread throughout tropical and sub-tropical countries worldwide including Angola, Austrailia, Bhutan, Central America, China, Congo, Indonesia, Iran, Kenya, Korea, Korea, Liberia, Madagascar, Malawi, Laos, Malaysia, South-America, South-Africa, Senegal, Sudan, Sri-Lanka, Thailand, Nepal, Nigeria, Yemen, Saudi Arabia, Taiwan, Zambia, Zimbabwe, and Pakistan.

1.4. Botany, Morphology, Ecology

Centella asiatica is a perennial, slender, prostrate, slightly aromatic, creeper, stoloniferous herb. It achieves a height of about 0.15m. Long and prostrate stem emerges from vertical rootstock; it is glabrous, striated, filiform, and reddish in color, with long internodes and rooting at the nodes. Leaves emerge alternately in clusters at stem nodes; 1.3 to 6.3 cm across, thin, long petiolated, 2 to 6cm long, and 1.5 to 5cm wide; there are several from each root stock, one to three from each node of the stem, orbicular-reniform, cupped, entire, crenate, and glabrous. Petioles are variable in length, 7.5 to 15cm long and channeled. The peduncle is about 6mm long with no pedicels; small bracts embrace the flowers. The inflorescence is in a single umbel, bearing one to five flowers, sessile, white or reddish. The fruits are small, compressed, 8mm long, the mericarps are longer than broad, curved, rounded at the top, seven to nine ridged, with secondary ridges as prominent as the primary, and reticulate between them. The pericarp is much thickened. Seeds contain a pendulous embryo that is compressed laterally. The plant develops quickly and extensively in shady, swampy, damp, and wet places. Sandy loam soil is the most fertile soil for regeneration. Plant grows along stone walls or other rocky areas upto an altitude of 2000 feet. Propagation is through seeds and stolons [18].

2. Chemistry

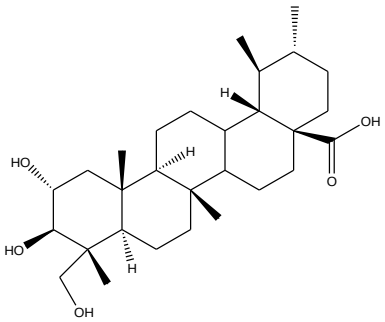
2.1. Nutritional composition

Basically, *Centella asiatica* leaves are a rich in essential minerals such as iron (Fe), magnesium (Mg), potassium (K), and calcium (Ca), and vitamins. They also contain various phyto-constituents such as β-carotene, lutein, neoxanthin, and zeaxanthin, which prevent eye damage caused by age-related issues. The macronutrients present in *Centella asiatica* are principally proteins, fibers and carbohydrates. In general, the plant is low in proteins (2-2.5%), carbohydrates (5.5-7%), and fats (<1). *Centella asiatica* contains approximately (85-87%) moisture, (4-6%) insoluble dietary fiber, and (<1%) soluble dietary fiber, and 0.017g/100g phosphorus (P), 0.014g/100 g iron (Fe) and 0.107g/100 g sodium (Na). These values may vary significantly depending upon the analytical procedure as well as abiotic and biotic factors. Nutrient composition values suggest that *Centella asiatica* is a worthy source of dietary fiber, which offers numerous health benefits. High fiber consumption reduces the risk of coronary heart disease, stroke, high blood pressure, diabetes, obesity, some gastrointestinal diseases, and provides many other health related benefits [19]. The total number of calories in 100 g of *Centella asiatica* is 37.0 kcal [20]. Generally, *Centella asiatica* contains high levels of calcium (171 mg) and potassium (345 mg). Consumption of potassium reduces the chances of cardiovascular disorders, stroke, and renal damages. Calcium is an essential bone component. Sufficient calcium intake throughout childhood is required to attain maximum bone weight in early stages of life which is an important indicator of bone mineral status in adulthood. *Centella asiatica* is also a rich source of ascorbic acid (48.5 mg/100 g), thiamine (0.09 mg/100 g), riboflavin (0.19 mg/100 g), niacin (0.1 mg/100 g), carotene (2649 μg/100 g), and retinol (442 μg/100 g) [20-21].

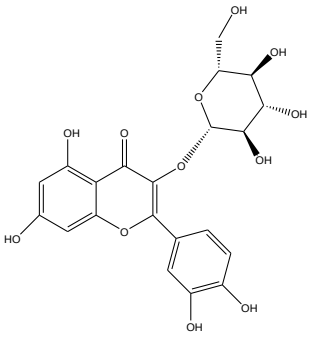
2.2. Phytochemistry

Centella asiatica comprises of a wide spectrum of bioactive constituents including tri-terpenes, alkaloids, carotenoids, fatty and volatile oils, flavonoids, and carotenoids. Major phytoactive constituents of *Centella asiatica* are terpenoids including saponins (madecassoside, asiaticoside), sapogenins (madecassic acid, asiatic acid), hydrocotylin, thankuniside, quercetin-3-glucoside, indocentellic acid, centellinic acid, brahminoside, glycerides of stearic acid, oleic acid, palmitic acid, linoleic acid, linolenic acid, pectic acid, glycine, α-alanine, phenylalanine, kaempferol-3-glucoside, and glutamic acid. Figure 1 shows structures of important phytochemicals found in *Centella asiatica*. Among various triterpenes, four major triterpene glycosides namely as centellosides (madecassic acid, madecassoside, asiatic acid, and asiaticoside), have been used as biomarkers to assess the quality of *Centella asiatica*

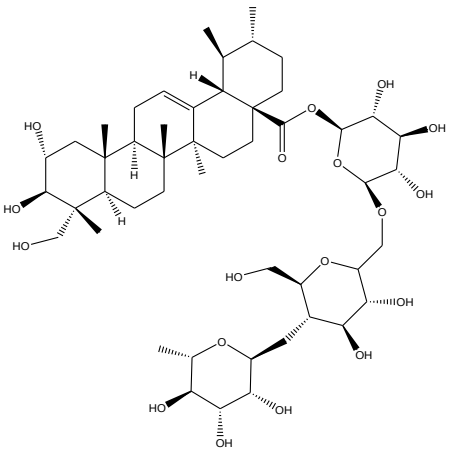
[22]. They are mainly concentrated in leaf and petioles [23]. According to World Health Organization, *Centella asiatica* should constitute (≥ 2%) of the glyceride triterpene esters saponins (madecassoside and asiaticoside). The European Pharmacopeia evaluation report also showed that saponin and sapogenin contents of the herb can vary from 1-8% depending on geographical location and harvesting conditions.



Asiatic acid



Quercitin 3-glucoside



Asiaticoside

Fig 1. Structures of important phytochemicals found in *Centella asiatica*

3. Traditional medicinal uses

Centella asiatica has been used traditionally for the treatment of various ailments in different countries. Traditional uses of *Centella asiatica* are enlisted in Table 1 [24].

Table 1. Traditional uses of Centella asiatica in different regions

Countries	Traditional uses
Brazil	Elephantiasis, uterine cancer, leprosy
China	Bleeding, scabies, skin ulcers, rash and redness, abdominal pain, diarrhea, dysentery, vomiting, red eyes, swollen throat, jaundice, infectious hepatitis, boils, fistulas, furuncles, toxic swelling, fever, trauma, contusion, fractures, asthma, childhood tidal fever, bronchitis, respiratory problems, tuberculosis, pleurisy, urinary infections, cold, dizziness, improve of appetite, digestion
Europe	Varicose veins
Fiji	Skin ulcers, rash and redness, pimples, bleeding ulcer, constipation, hemorrhoids, eye problems, fractures, painful and swollen joints, rib pain, post-partum weakness,
India	Eczema, skin ulcers, cataract, eye problem, cholera, abdominal tumor, anxiety, insanity, poor memory, general debility, blood disease
Indonesia	Wound, colic
Malagasy	Leprosy
Malaya	Dermatosis
Mauritius	Cancer
Nepal	Indigestion, rheumatism, syphilis, leprosy
Philippines	Dysentery, headache, fever, wounds
Turkey	Spasms, leprosy

4. Pharmacological 4. Pharmacological uses

4.1. Wound healing

The *Centella asiatica* extracts have traditionally been utilized for healing, and research is increasingly supporting these assertions [25]. A pre-clinical study found that various aqueous *Centella asiatica* extracts preparations (ointment, cream, and gel) administrated to open wounds in mice (3 times daily for 24 days) caused enhanced cell proliferation and collagen synthesis at the wound site, as indicated by an increased tensile strength and collagen content [26]. The researchers reported that *Centella asiatica* extract treated wounds epithelialized faster and the wound contraction rate was higher than untreated wounds. The cure was most evident with the gel product. It is thought to have an effect on keratosis, which helps thicken the skin in areas of infection [27]. Asiaticoside, a component of *Centella asiatica*, has been found to have healing action as it increases collagen formation and angiogenesis [28-29]. A study on laboratory animals examined the effect of asiaticoside on antioxidant levels because antioxidants were reported to play significant role in wound healing [30]. The researchers suggested that asiaticosides may have increased the induction of antioxidants in the early stage of healing, but continued use of the formulation does not appear to increase the level of antioxidants [31]. Another study evaluated the effect of oral and topical administration of *Centella asiatica* alcohol extract in rats. The extract enhanced cell proliferation and collagen content in granular tissues. Faster and better maturation and crosslinking of

collagen was reported in rats treated with the extract, as shown by the stability of acid-soluble collagen and the increase in aldehyde content and tensile strength.

4.2. Effect on central nervous system

Ethanolic extract of *Centella asiatica* (70%), administered intraperitoneally to mice has shown to produce anticonvulsant activity. In albino rats, *Centella asiatica* extracts have been reported to have imipramine like antidepressant activity and significant antistress effect comparable to diazepam [32]. Furthermore, another report also suggest the antianxiety effect of *Centella asiatica* which was comparable to diazepam as well as without affecting the behavioral despair [33]. On contrary, administration of *Centella asiatica* was also shown to exert adverse effects such as sedation, hypotheramia, besides being ineffective in protecting from metrazol-induced seizures and electroshock seizures [20]. In another investigation, trained rats treated with *Centella asiatica* extracts showed dose dependent effect comparable to chlorpromazine. It has been suggested that the extract causes impairment of muscular coordination and has a tranquilizing effect [34]. In a biochemical study, urinary metabolites of central monoamines, with the exception of 3 methoxy-4–hydroxyl phenyl glycol (MHPG), were found to be decreased with the treatment of *Centella asiatica* [35]. Similar decrease was also observed in brain homogenates indicating the overall decrease in the turnover of central monoamines explaining the possible mode of above mentioned CNS effects. However, these findings are not in concordance with the previous reports where anticonvulsant activity of *Centella asiatica* in rats was found to be accompanied with a significant increase in whole brain content of catecholamines and histamine and a significant decrease in acetyl choline levels based on the studies on neurochemistry of brains [34]. The drug has been found to exert weak sedative, cardio-depressant and hypotensive effect [34]. In a double blind clinical trial, conducted on 30 children, it has been found to improve the cognitive functions in mentally retarded children. The patients in the study were free from epilepsy and other neurological conditions. The drug was administered for 12 weeks and the results indicate a significant improvement in both general ability and behavioral patterns [34].

4.3. Antiulcer effect

A small clinical trial involving fifteen patients has demonstrated the antiulcer activity after oral administration of the extract of *Centella asiatica* at the dose level of 0.06g/kg daily. About 93% of the patients showed a significant improvement in subjective [36]. In an experimental study on albino rats, *Centella asiatica* has been found to produce antiulcer effect in cold restraint stress-induced gastric ulcer, aspirin-induced gastric ulcer and pyloric ligation-induced peptic ulcer models. The possible mechanism of action was proposed to be mediated through the enhancement of mucosal defensive factors. However, other reports suggest the possible involvement of GABA (γ-aminobutyric acid)-mediated action in the antiulcer activity of *Centella asiatica* [37].

4.4. Anti-leprotic and anti-tubercular effects

Oral administration of *Centella asiatica* or asiaticoside and potassium chloride capsules has been found to be effective against leprosy. In a clinical trial for the treatment of leprosy with *Centella asiatica* for one year, improvement has been found to be faster as compared to dapsone. The drug was well tolerated by the patients and the therapeutic effect was comparable to dapsone [38]. Hydroxyasiaticoside, when injected to guinea pigs inoculated with Mycobacterium, it reduced the size and number of tubercular lesions in the liver, lungs, nerve ganglion and spleen [39].

4.5. Anticancer and immune-modulatory effects

The antitumor activity of *Centella asiatica* extracts (crude and slightly purified) have been examined in both *in vitro* chemo-sensitivity tests and *in vivo* tumor models. The purified extract repressed the multiplication of transformed cell lines of Ehrlich ascites and Dalton's lymphoma ascites tumor cells more remarkably than crude extract [40].

4.6. Memory enhancing effect

Oral administration of *Centella asiatica* extract at dose level of 0.2g/kg enhanced brain function during postnatal development in adult and juvenile mice [41]. In another study, asiatic acid increased memory and learning properties of male Spraque–Dawley rats [42].

5. Toxicity and safety

At suggested doses (0.06–0.18g daily), *Centella asiatica* is recognized for its non-toxic nature with no or very rare adverse effects. However, at higher doses, burning sensation and skin allergy after topical application may occur, and oral administration may cause headache, nausea, indigestion, drowsiness, and dizziness [5]. Extended use of herb for over 1.5 months is not suggessted. The use of extracts of *Centella asiatica* is also not recommended for nursing mothers and its consumption during pregnancy may results in teratogenic effect on the fetus [43]. Researchers also suggested that utilization of *Centella asiatica* for over 20 to 60 days may lead to liver damage [44].

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