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THERAPEUTIC EFFICIENCY OF *Centella asiatica* (L.) Urb. AN UNDERUTILIZED GREEN LEAFY VEGETABLE : AN OVERVIEW

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ABSTRACT

Centella asiatica (L.) Urb. is one of the important medicinal and nutraceutical herbs being used by ethnic people since prehistoric times. It accumulates large amount of pentacyclic triterpenoid saponins which forms the major store house of secondary metabolites providing active compounds stimulating cell rejuvenation, improving physical and mental health. *C. asiatica* also serves dietetic purpose in the form of green leafy vegetable and in the preparation of juice, drink and other food products. The present review is an attempt to emphasize its ecology, phytochemistry, traditional and pharmacological applications of *C. asiatica.*

KEYWORDS: ***Centella asiatica*, medicinal plant, cognitive impairment, pharmacology, therapeutic uses.**

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INTRODUCTION

Plants have been enumerated as an eminent basis of medicine since immemorial past. Drugs based on the plants are of prime importance for several remedies in traditional and conventional medicine throughout the world and serves as a substitute for drug supply in modern medicine. Now a days world markets are turning towards plants as the source of ingredients in manufacturing health care products. Secondary metabolites obtained from the plants are found to be an important source of various phytochemicals that could be used directly or as an intermediate for the production of pharmaceuticals[1, 2] in food or drink supplements as well as in the form of preservatives. In the developing countries, approximately 80% of the populations still rely on the traditional medicine derived from the plants for health care needs [3-5]. Thus the demand for herbal medicines is continuously increasing day by day due to lesser side effects in comparison to the synthetic drugs. Unfortunately, in the present day, precipitous economic development and suburbanization resulted in overexploitation and loss of valuable natural resources, including the medicinally important plants. As a result, many of the plant species are endangered or threatened with extinction leading to severe depletion of biodiversity[6-8]. *C. asiatica* L. (Fig. 1) is one of the threatened medicinal herb[9-11] generally endemic to Western Ghats of South India[12].

Figure 1
***Centella asiatica* (L.) Urb.**

NOMENCLATURE

Kingdom	Eukaryota
Subkingdom	Embryophyta
Division	Spermatophyta
Subdivision	Angiospermae
Class	Dicotyledonae
Subclass	Rosidae
Suborder	Aralianae
Order	Araliales
Family	Apiaceae
Subfamily	Hydrocotyle
Genus	Centella
Species	*Centella asiatica*

VERNACULAR NAMES IN DIFFERENT REGIONS

C. asiatica has been named by an array of vernacular names throughout the world[13].

In India

Region/Language	Vernacular name
Hindi	Brahme-manduki, Mandookparni, Gotukola, khulakhudi
Malayalam	Kodangal, kodagam, Kutakm, kuttanal, Muthal, Muttil,
Telgu	Bokkudu,Saraswataku,Saraswati plant, Bekaparnamu
Sanskrit	Bhekaparni,Brahmananduki,Manduki, Supriya, Tvasthi
Marathi	karinga,karivana
Oriya	Thalkudi
Tripura	Thankuni,Thunimankuni
Assam	Manimuni
Bihar	Chokiora
Urdu	Brahmi
Gujarati	Barmi, Moti Brahmi
Tamil	Babassa,Vallarai
Bengal	Thankuni,Tholkuri
Deccan	Vallarai
Meghalaya	Bat-meina
Sinhalaese	Hingotukola
Kanarese	Bhramisoppu,Urage,Vandelaga-illikiwigidda, Vondelaga

Out of India

USA	Indian Pennywort, Marshy Pennywort
Hawaii	Pohekula
Cook Islands	Kapukapu
Fiji	Totodro
China	Fo-ti-tieng,Chi-hsueuh-tsao
Samoa,Tonga	Tono
Tahiti	Tohatupou

MORPHOLOGY

C. asiatica L. is a small stonoliferous perennial creeping aromatic herb belonging to the family Apiaceae (Umbelliferae) and subfamily Mackinlaya[14] previously included in hydrocotyle[15]. The leaves are 2-5 cm wide, hastate or cordate or palmately lobed or reniform, arranged in an alternate fashion in form of clusters at stem nodes having long stalk and sheathing leaf bases. The petiole is long and stipules are small in size. Leaf blades are dentate, crenate consisting of thick radiate veins and are green in colour. The peduncle occurs in pairs of 3, less than 1 cm in length which bears small sessile flowers which are dark pink in colour. They arise in the form of simple umbels consisting of 3-6 flowers from the axils of the leaves which are shorter than petioles. The fruit is minute, clusted at joint, ovoid in shape, white or green coloured with more or less similar 9 longitudinal ridges. The fruit is bitter in taste, pungent, nauseous having an aromatic odour if bruised. Seeds are laterally compressed, solitary in each mericarp and having pendulous embryo.

ECOLOGY

C. asiatica L. is one of the ubiquitous species of *Centella. C. asiatica* grows plentifully in moist or damp or swampy areas[16-18] in many parts of the world including India, China, Madagascar, Africa, Australia, Japan, Venezuela, Columbia and the eastern region of South America[19-21]. *C. asiatica* ranges from sea level to high elevation. In Himalayan region, it occurs upto an altitude of 700 metre[22]. *C. asiatica* grows very well in

sandy and clay soil[23] rich in humus and organic matter. It grows within a broad range of climatic conditions but it is more abundant in those communities where secondary succession occurred[24].

TRADITIONAL USES

C. asiatica L. is a classic ethnomedicinal species used by tribal groups and also by ancient civilizations. In India and other Far East countries, *Centella* is traditionally used in the form of cover crop in rubber and tea plantations. It is also one of the constituents of summer drink popularly known as "thandaayee"[25]. Besides, *Centella* is generally eaten as green leafy vegetable in the form of salad and ulam among the Malay and Javanese people[26]. The salad is affluent in micronutrients comprising of vitamins and mineral elements and suggested to assuage micronutrient malnutrition and therefore serves as an appetizer. It can also be used as soup. Being bitter in taste due to the presence of Vellarine, it is served along with coconut milk or sometimes with sweet potatoes. In Thailand, *C. asiatica* leaves are blended and used in the form of cordial drink[27] and also in tea and juice[28]. In Srilanka, the leaves of *C. asiatica* are used as "mallung" which is a traditional curry and in the porridge known as "kolakenda" to combat malnutrition[29]. Extract of the *C. asiatica* is also used in the production of food products, i.e. herbal noodles[30]. In China, it is used in the form of cooling drink[31-33].

Nutritive composition of Centella asiatica

Quantitative interpretation reveals that *C. asiatica* comprises high amount of water. Besides, it also serves as a good source of various macro and micronutrients, proteins and vitamins, such as ascorbic acid, thiamine and carotene[34]. The details of composition are listed in table 1.

Table 1
Nutritional composition of Centella asiatica

Composition	Value
Moisture	84.6%
Protein	2.4%
Fiber (per 100 g) (insoluble dietary)	5.43g
Soluble dietary	0.49g
Mineral content	
Ca (mg/ 100 g)	174
P	17
K	345
Na	107.8
Mg	87
Fe	14.86
Zn	0.97
Cu	0.24
Cr	0.046
Vitamins (mg/ 100g)	
Ascorbic acid	11
Thiamine	0.04
Carotene	25.93
β Carotene	3.90

Phytochemistry of Centella asiatica

The chemical composition of *C. asiatica* plays an important role in medicinal and nutraceutical application which is due to the presence of primary active constituent's *viz*., triterpene saponins[35]. In general, terpenes can be biosynthetically divided into four different stages. There are two major pathways leading to the biosynthesis of the isoprene unit[36]. Mevalonic acid pathway 1-deoxyxylose pathway First step involves formation of isopentenyl diphosphate, an isoprene unit. Second step involves association of isoprene units to form $(C_5)_n$ isoprenoid which is the backbone of the terpene families. Third step involves cyclisation of these isoprene units to generate carbon skeleton. Fourth step comprises interrelationship involving the hydroxylation and oxidation step leading to the formation of terpenoids[37, 38] (Fig. 2).

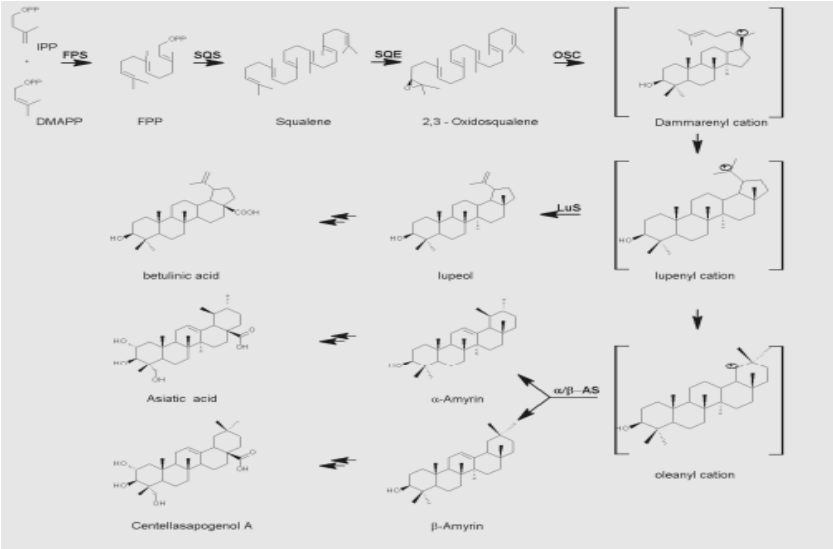
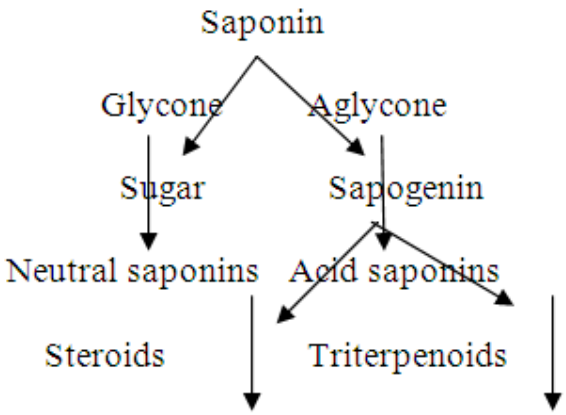


Figure.2.

A simplified scheme of triterpenoid biosynthesis in C. asiatica. Farnesyl diphosphate synthase (FPS) isomerizes isopentyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) to farnesyl diphosphate (FPP), which squalene synthase (SQS) converts to squalene. Squalene epoxidase (SQE) oxidises squalene to 2,3-oxidosqualene. Oxidosqualene cyclase (OSC) enzymes cyclize 2, 3-oxidosqualene through cationic intermediates (e.g. dammarenyl cation) to one or more cyclic triterpene skeletons. Other enzymes involved include α/β-amyrin synthases (α/β-AS) which can also form the lupenyl cation but further ring expansion and rearrangements are required before the deprotonation to α/β-amyrin, the precursors of the sapogenins, to generate the products.

In C. asiatica triterpenoid saponins are synthesised via the isoprenoid pathway to produce a hydrophobic triterpenoid structure (aglycone) containing a hydrophilic sugar chain (glycone) by cyclization of 2-3 oxidosqualene to give primary oleanane (beta amyrin) or dammarene triterpenoid skeleton[39] (Fig. 3).

Figure 3
Group of Saponin glycosides.



These triterpenoid saponins are required for plant growth and development having an ecological role in regulating the interactions between plant and their environment where the predominant group is pentacyclic triterpenoid derivatives and their sapogenins[38]. These triterpenoid saponins are the secondary metabolites that can be defensive substances such as phytoanticipins, antifeedant, attractants, phytoalexins and pheromones[40].

The triterpene of *C. asiatica* composed of several compounds which include asiatic acid, madecassic acid, asiaticoside, madecassoside, brahmic acid, thankunoside, isothankunoside, centelloside, sceffoleoside, madsiatic acid, centic acid and centillic acid[20,41-43] and alkaloid hydrocotylin[44,45]. Some of the chemicals and the class to which they belong[46] are represented in Fig. 4.

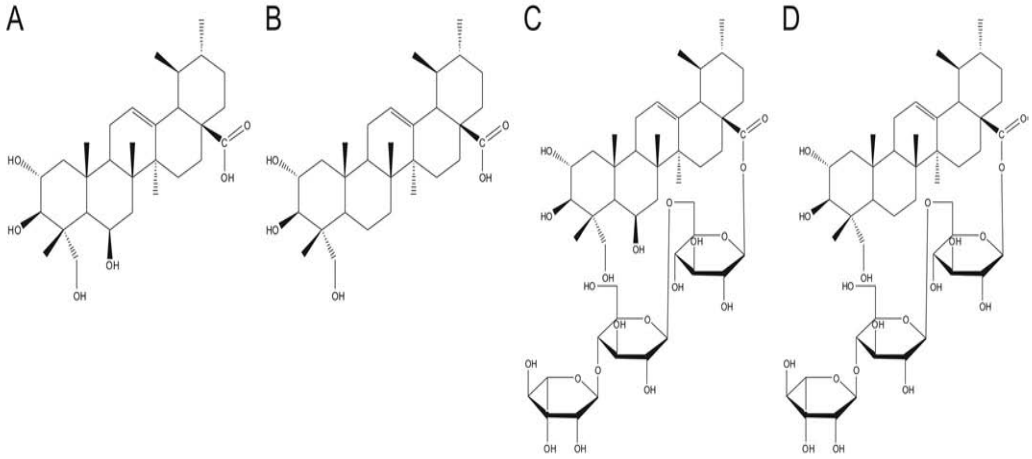


Figure 4
Structures of the main identified active components in *Centella asiatica* which are claimed to have medicinal properties: (A) madecassic acid (MW 504.17), (B) asiatic acid (MW 488.70), (C) madecassoside (MW 975.1), and (D) asiaticoside (MW 959.12).

In addition to these bioactive components it also contains high phenolic content[47] which is contributed by the flavonoids such as quercetin, kaempherol, catechin, rutin, apigenin and naringin[30, 48-49], sugars[50,51], tannins and Vellarine[52]. The plant also possess amino acids

i.e. glycine, glutamic acid, α-alanine, phenylalanine[53] and other resinous substances. Among the triterpenes, the most important biologically active compounds are the asiatic acid, madecassic acid, asiaticoside and madecassoside[54]. In case of *C. asiatica*, these triterpene saponins are used as the biomarker components for quality assessment[20]. The total triterpernoid content of dried leaf vary from 1 to 8 percent[49]. Asiaticoside comprises about 40% of the total triterpenoid[55]. It is also reported that asiaticoside content varies depending upon genetic resources and habitat environment[56, 57]. High level of asiaticoside is obtained from the plant having 2-B chromosomes growing in the Himalayan region in the sub temperate area[58] .

Essential oil

The major constituent present in *C. asiatica* oil comprises of terpenic acetate while other prominent constituents were β-caryophelene, farnesene, trans β-farnesene, gemacrene-D, α-humulene, bicyclogermacrene, sesquiterpene and p-cymol[59,60]. The chemical composition of essential oil of *C. asiatica*[61] is represented in table 2.

Table 2
Chemical composition of essential oil of C. asiatica

KI[a]	Constituents %	Composition
935	α-Thjuene	0.20
940	α -Pinene	3.49
962	Camphene	0.86
984	β-Pinene	0.37
994	Myrcene	6.55
1005	α -Phellandrene	0.19
1019	α -Terpinene	0.47
1033	p-Cymene	0.71
1038	Limonene	1.00
1061	γ-Terpinene	5.77
1096	Terpinolene	0.59
1101	Linalool	0.20
1150	3-Nonen-2-one	0.49
1162	Menthone	1.43
1199	Terpinen-4-ol	0.24
1235	Methyl thymol	0.22
1248	Pulegone	0.21
1250	Methyl carvacrol	0.64
1266	Chrysanthenyl acetate	0.59
1291	Bornyl acetate	1.44
1341	Bicycloelemene	0.62
1391	β -Elemene	1.99
1442	β -Caryophyllene	19.08
1456	γ -Elemene	1.58
1470	Aromadendrene	0.20
1483	α-Humulene	21.06

1484	allo-Aromadendrene	0.45
1485	Germacrene D	4.01
1486	γ-Curcumene	1.48
1494	Bicyclogermacrene	11.22
1495	Germacrene A	0.24
1523	δ-Cadinene	0.34
1551	Germacrene B	6.29
1576	Spauthulenol	1.44
1588	Caryophyllene oxide	1.66
1590	Viridiflorol	0.26
1592	Humulene epoxide	0.27
1645	Isopauthenol	0.27
1748	Mintsulfide	0.76
1840	Neophytadiene	0.24
Total (%)	99.12	

[a] = Calculated retention time (Kovát indices) on an HB-5 capillary column at 5˚/min from 70 to 240˚C.

Centella asiatica as medicine

C. asiatica L. has been used for several hundred years in folk medicines. In Indian Ayurveda literature, *C. asiatica* is considered as one of the recognised drugs used for "Rasayana'' purpose[62]. In Chinese medicine, *C. asiatica* is used for treatment of vomiting, epistaxis, urinary calculi, scabies and jaundice. In homeopathic medicine, it is used for treating ascariasis, elephantiasis and in granular cervicites. Clinical tests have formulated several benefits of *C. asiatica* extracts in terms of wound healing[63,64], burns[65,66] and in skin diseases[67,68], in gastrointestinal disorders[15,69] and in treatment of leprosy, lupus, scleroderma, eczema, veins diseases[70] and for treatment of psoriasis. It gives protection against diseases by enhancing immunity of the body. The extract of the whole plant is reported to have anticancerous activity[71] and the methanolic extract of aerial parts of *C. asiatica* inhibit the growth of human uterine carcinoma, human gastric carcinoma, and murine melanoma cells *in vitro*[72]. *C. asiatica* is also used as nervine tonic[73], along with antibacterial, antifeedant and antileptic property[74]. It is also efficient in promoting fast growth of skin and keratinization[75]. It also possesses anti-inflammatory[76] and memory enhancing property[73, 77-78]. It also finds application in controlling anxiety and thereby imparting mental calmness[79].

Pharmacological uses

Besides these activities, *C. asiatica* L. is claimed to possess wide range of applications:

Wound healing

Increased cellular proliferation and collagen synthesis, angiogenesis and epithealization at wound site is brought about by madecassol, extract of *C. asiatica* containing asiatic acid, madecassic acid and asiaticoside by increasing peptidic hydroxyproline content. Asiaticoside, one of the active constituent of *C. asiatica* induces antioxidant activity at the initial stage thus playing important role in wound healing[80].

Memory enhancement

In vivo studies have shown that the aqueous extract of the leaves of the *C. asiatica* revitalize the brain and nervous system thus exhibit significant effect on learning and memory process by increasing the level of norepinephrine, dopamine and 5- HT in the brain[81].

Neuroprotective

Clinical studies have reported that *C. asiatica* found its efficacy in giving protection to neurons against oxidative damage by giving exposure to excess glutamate[82]. Studies have also shown that upon oral administration *C. asiatica* proves it's utility in accelerating damaged neurons by promoting neurite elongation[83]. Likewise, other preclinical studies have reported the use of *C. asiatica* leaf extract enhanced hippocampal CA3 neuronal dendritic arborization in rats during the growth spurt period[84].

Immunomodulatory

With reference to *C. asiatica*, triterpenoid saponins present in it possesses immunomodualtory activity[85, 86].

Preclinical studies performed in mice have reported that the alcoholic extract of the *C. asiatica* when injected intravenously known to possess stimulatory effect on reticuloendothelial system followed by 24 hour latency period[87].

Antidepressant

The triterpenoid saponins present in the plant exhibit antidepressant activity by reducing corticosterone level in serum[88].

Venous insufficiency

The triterpenoid saponins present in *C. asiatica* strenghthen weakened veins by improving wall alterations in chronic venous hypertension and thereby protecting venous endothelium[89]. It also plays important role in stabilizing connective tissue growth by stimulating the production of hylauronidase and chondriotin sulfate and also imparts balancing effect on connective tissue[90].

Autoimmune

Madecassol, component isolated from *C. asiatica* found to be efficacious in the treatment of chronic or subchronic systemic scleroderma and advanced focal scleroderma[91].

Cardiovascular

In case of Postphlebitic syndrome *C. asiatica* decreases the number of circulating endothelial cells[92].

Hepatoprotective

With reference to *C. asiatica*, studies have shown that before administration of ethanol, *C. asiatica* extract (0.05, 0.25 and 0.50 g/kg) protects gastric mucosa by inhibiting ethanol-induced gastric lesions and by decreasing mucosal myeloperoxidase due to its free radical scavenging activity in a dose dependent manner[93].

Additional studies have also stated that the administration of the alcoholic extract of the *C. asiatica* (20 and 40 mg/kg/d) for three months with intraperitoneal injection of Carbon tetrachloride (1 ml/kg) protects Sprague Dawley rats against CCL_4 induced hepatic damage by inhibiting decrease in serum albumin and protein level and elevation in serum marker enzyme – AST, ALT and ALP[94].

Studies have also revealed that one dose (5, 10, 20 mg/kg/d) of asiaticoside (the active ingredient present in *Centella asiatica*) if administered consecutively for three days in case of mice before injecting LPS/D-GaIN possesses remarkable hepatoprotective effect on LPS/ D-GaIN induced liver injury in a dose dependent manner by decreasing the level of aminotransferases, caspase-3 and hepatocytes apoptosis[95].

Anticancer

Preclinical studies have shown that methanolic extract of *C. asiatica* causes inhibition in breast cancer cells by inducing apoptosis in different cancer cell lines HeLa, HepG2 and SW48 and MCF-7. Out of which MCF-7 found to be most sensitive line for *in vitro* growth inhibitory activity which is marked by decrease in cell viability that is concentration dependent based on MTT assay[96].

Similar studies have also shown the chemopreventive potential of *C. asiatica* extract on DMBA induced skin tumorigenesis in male Swiss albino mice. Upon oral

administration *C. asiatica* (500 and 1000 mg/kg) exhibits significant decrease in the level of tumor incidence, weight, cumulative number of papillioma in comparison to carcinogen control group[97].

Antidiabetic

Clinical studies have revealed that the two glycosides present in *Centella asiatica* (L.) viz. bhramoside and brahminoside exert sedative and hypoglyacemic effect[98] .

Likewise, studies have also investigated that the polyphenolic polymers present in *C. asiatica* serve as antioxidants, potentiate insulin action and thus is advantageous in regulating glucose intolerance and diabetes[99].

CONCLUSION

In the present time, research on plants have been enthralled throughout the world to emblematize the tremendous potential of medicinal plants. Medicinal plants are the important source of life saving drug for 80% of world's population which constitutes a vast, undocumented and overexploited economic resource not only in the form of traditional medicine but also as trade commodities. In recent years, due to its wide prospects and potential, its demand has led to a quantum increase which plays a vital role in alleviating human sufferings due to lesser side effects, easy availability at affordable cost and being non-narcotic. Sometimes, it is the only source of health care available to the poor. *C. asiatica* L. is one such medicinally important herb with well known biological activities in terms of immunomodulatory, memory enhancer, antidepressant etc., proved by clinical studies. However, further research on *C. asiatica* must be explicit in terms of recognition and quantification of active ingredients, making it readily approachable for implementation to upgrade the eminence of life and also to explore the therapeutic efficiency of *C. asiatica* in order to use it in the form of standard drug through massive exploration of bioactivity of various compounds, their mode of action , toxicity, pharmacotherapeutics and clinical trial. In the near future, it is of immense potential in terms of neutraceuticals. In addition to this, studies should be premeditated regarding the investigation of underutilized green leafy vegetable, substantial to permeate nutritional ailments.

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