Chapter 3.22

Gotu Kola (*Centella asiatica*)

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INTRODUCTION

Plants as a source of food, herbs, and medicines have been used for thousands of years in many traditional medicine systems. Growth in research on plant-based herbal products has increased exponentially both in developed and developing nations (Gohil et al., 2010; Vaidya, 1997). Possible reasons for this could include its therapeutically safe and effective action against mild and chronic diseases, and also its increased use as a dietary supplement (Gohil, 2011).

Centella asiatica L. is a perennial herb that belongs to the Apiaceae family. The species is commonly known as "mandukaparni" in Sanskrit, "brahmi" in Hindi, "Indian pennywort" in English, and "gotu kola" in many others parts of the world. The plant is tasteless, odorless, and is mainly found in and around water (Fig. 3.22.1). It has been used by many ancient cultures and tribal groups of various countries in their traditional medicinal systems to cure various types of ailments such as anemia, epistaxis, and hepatitis amongst others, and it is most popular for its use as a "brain tonic" agent, according to the World Health Organization (WHO). It has been used for hundreds of years in Indian Ayurveda, Malaysian, and Chinese herbal medicine, as well as being used in other parts of Asia (Brinkhaus et al., 2000). It also helps improve memory and treat mental fatigue, anxiety, and eczema (Gupta et al., 2003; Hamid et al., 2002; Kartnig, 1988). The species is currently being cultivated in many parts of the world due to its high medicinal value and wide range of uses (Imada, 2012; Matsuda et al., 2001). This chapter discuss detailed information regarding *C. asiatica* distribution, bioactive compounds and bio-activity, interaction with other known drugs, toxicity studies, as well as listing *C. asiatica* major products dealing with wide therapeutic activity.

DISTRIBUTION

C. asiatica is distributed throughout tropical and subtropical countries from 200 to 2100 m a.s.l. (Hedge and Lamond, 1992; Samant and Pant, 2006) (Table 3.22.1). It is native to Asia, Africa, America, and Oceania as shown in Fig. 3.22.2.

BIOACTIVE COMPOUNDS

C. asiatica has been extensively studied for identification of its bioactive compounds. It is a rich source of amino acids (e.g., alanine, serine, aspartate, and glutamate), phenols (e.g., kaempferol and quercetin), terpenoids (e.g., asiaticoside, centelloside, madecassoside, and brahmoside), and carbohydrates (e.g., glucose, mesoinositol, and centellose) among others (Table 3.22.2), which have found wider applications as both health and food supplements.

THERAPEUTIC ACTIVITY

C. asiatica was known as "brain food," due to its various well-known neuroprotective activities. It has also been used as an antiinflammatory (Somchit et al., 2004), an antipsoriatic (Sampson et al., 2001), and antiulcer treatment (Cheng et al., 2004; Cheng and Koo, 2000), as a hepatoprotective treatment (Antony et al., 2006), an anticonvulsant (Visweswari et al., 2010), a sedative (Wijeweera et al., 2006), an immunostimulant (Wang et al., 2003), as a cardioprotective treatment (Gnanapragasam et al., 2004), an antidiabetic treatment (Mutayabarwa et al., 2003), as a cytotoxic and antitumor treatment (Bunpo et al., 2004; Xu et al., 2012), an antiviral (Yoosook et al., 2000), an antibacterial (Oyedeji and Afolayan, 2005), an

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FIG. 3.22.1 *Centella asiatica* **in its natural habitat at Surya Kunj (GBPNIHESD, Kosi-Katarmal, Almora, Uttarakhand).**

TABLE 3.22.1 Distribution of *Centella asiatica* Across the World

S. No.	Region	Country	References
1.	Africa	Angola, Madagascar, Zambia, Zimbabwe, Senegal, Sudan, Mali, Tanzania, Somalia, Nigeria, Mozambique, Mauritius, Congo, Kenya, Republic, Botswana, Malawi, Cameroon, South Africa, Central Africa	Biswas and Mukherjee (2003); Caldas and Machado (2004); Jamil et al. (2007); Zainol et al. (2003); Singh et al. (2010); Jana et al. (2010) and Gupta (2013)
2.	North America	United States, Mexico	Jamil et al. (2007); Gupta (2013)
3.	Asia	Vietnam, Taiwan, Pakistan, Nepal, Malaysia, China, Japan, Korea, Thailand, Bhutan, Indonesia, Yemen, Bangladesh, India, Myanmar, Saudi Arabia, Sri Lanka	Biswas and Mukherjee (2003); Jamil et al. (2007); Jana et al. (2010); Singh et al. (2010) and Gupta (2013)
4.	Australia		Gupta (2013)
5.	South America	Venezuela, Brazil, Colombia, Eastern South America	Caldas and Machado (2004); Jamil et al. (2007)
6.	Europe	France	Caldas and Machado (2004)

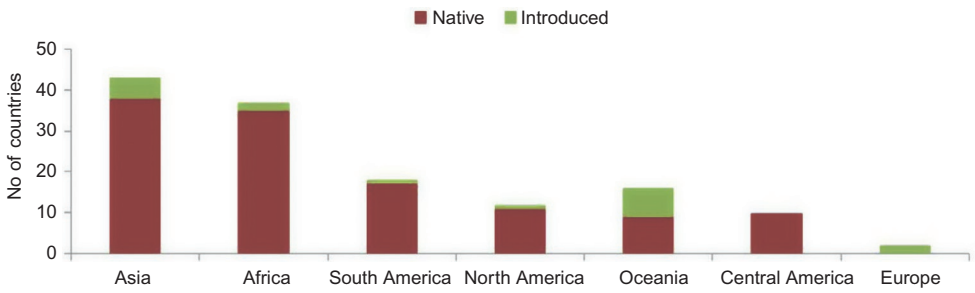

FIG. 3.22.2 Native and nonnative distribution of *Centella asiatica* **among within different continents.** *(Data taken from: www.cabi.org/isc/datasheet/12048).*

insecticidal (Rajkumar and Jebanesan, 2005), an antifungal (Dash et al., 2011), an antioxidant (Hamid et al., 2002), and a venous deficiency treatment (Cesarone et al., 2001; Pointel et al., 1987). These activities have been tested in both in vitro and in vivo models and are discussed in Table 3.22.3.

TOXICITY AND INTERACTIONS

Today, millions of people use herbs either as food or medicines along with prescription and nonprescription medications. These herbs are examined for their toxicity and interaction with a wide range of drugs and foods. As such, *C. asiatica* has been examined for toxicity and interactions, which are discussed in this section.

In an earlier paper from 1969, the saponoside fraction of the plant extract containing brahmic acid and its derivatives were found to cause infertility in both human and rat sperm (Singh and Rastogi, 1969). In 2010, Oruganti carried out a

TABLE 3.22.2 Bioactive Compounds Isolated From *Centella asiatica*

Class	Compound name	References
Triterpene acid	asiatic acid, asiaticoside, madecassic acid, madecassoside, terminolic, centic, centellic, centoic acid, indocentoic acid, isobrahmic, brahmic, betulic, and madasiatic acid	Rastogi et al. (1960); Singh and Rastogi (1969); Asolkar et al. (1992) and Schaneberg et al. (2003)
Polyphenolic compounds	quercetin, quercitrin, kaempferol, luteolin, chlorogenic acid	Bhandari et al. (2007)
Alkaloids	hydrocotylin	Chopra et al. (1956)
Volatiles and fatty acids	glycerides of oleic, palmitic, stearic, lignoceric, linoleic, and linolenic acids	Chopra et al. (1956)
Glycosides	asiaticoside A, asiaticoside B, madecassoside, centelloside, brahmoside, brahminoside, thankuniside, glycoside D, and glycoside E	Datta and Basu (1962); Singh and Rastogi (1969); Chopra et al. (1992) and Schaneberg et al. (2003)
Others	iligosaccharide centellose, stigmasterol, sitosterol, campsterol, polyacetylenes, carotenoids, vitamin B and C, vellarine, pectic acid, tannins, sugars, inorganic acid, and resins	Chopra et al. (1956); Singh and Rastogi (1969) and Kapoor (2005)

TABLE 3.22.3 List of Some of the Pharmacological Activities of *Centella asiatica*

Pharmacological/ therapeutic activity	Type of study and model used	Results	Mechanism	References
Antiproliferative	Effects of water extract from *C. asiatica* on the mortality of human lung cancer cells (A549) with the use of novel 3-D scaffolds infused with CMC hydrogel.	*C. asiatica* extract showed antiproliferative activity against A549 and there were no cytotoxic effects on human normal fibroblast cells IMR90.	*C. asiatica* extract induces apoptosis and mortality in A549 cells.	Aizad et al. (2015)
Cognitive functions (memory enhancer, etc.)	Protective effect of *C. asiatica* fresh leaf aqueous extract on learning and memory of albino rats.	Revitalize the brain and nervous system thus exhibit significant effect on learning and memory process.	Decreasing level of norepinephrine, dopamine, and 5- HT in the brain.	Nalini et al. (1992)
	Aqueous extract of *C. asiatica* tested against streptozotocin-induced cognitive impairment and oxidative stress in rats.	Cognitive enhancing and antioxidant properties.		Veerendra and Gupta (2002, 2003)
	Effect of different extracts (aqueous, methanolic and chloroform extracts) of *C. asiatica* on cognition and markers of oxidative stress in rats.	Improved learning and memory and increased antioxidant property.	Decreasing lipid peroxidation and augmenting the endogenous antioxidant enzymes in brain.	Kumar and Gupta (2002)

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TABLE 3.22.3 List of Some of the Pharmacological Activities of *Centella asiatica*—cont'd

Pharmacological/ therapeutic activity	Type of study and model used	Results	Mechanism	References
Antiinflammatory	Effect of asiatic acid and asiaticoside isolated from the leaves of *C. asiatica* on LPS-induced NO and PGE (2) production in macrophage cells.	Positive antiinflammatory effect.	Inhibition of enzyme (iNOS, cyclooxygenase-2 (COX-2), interleukins (IL-6, IL-1β), cytokine tumor necrosis factor (TNF-α)) expression through the downregulation of NF-κB activation.	Yun et al. (2008)
	Antinociceptive and antiinflammatory activity of *C. asiatica* aqueous extract tested in acetic acid–induced writhing and hot-plate method in mice.	Significant antinociceptive and antiinflammatory activity in both models.		Somchit et al. (2004)
	Antirheumatoid arthritic activity of madecassoside tested in type II collagen-induced arthritis (CIA) in mice models.	Madecassoside substantially prevented CIA in mice.	Reduced serum level of anti-CIIIgG, suppressed delayed type hypersensitivity, and moderately suppressed CII-stimulated proliferation of lymphocytes.	Liu et al. (2008)
Anticancer	Effects of *C. asiatica* leaf extract on decreasing the number of benzo(a) pyrene induced lung tumor nodules and determining the histopathological features of mice.	Extract of *C. asiatica* leaves in some doses could decrease the number of lung tumor nodules in mice induced by benzo(a)pyrene.	*C. asiatica* increased the phosphorylation of cyclic AMP response element binding protein (CREB) in neuroblastoma cultured cells that expressed beta amyloid 1-42(A beta). Thus, was preventing cell proliferation toward malignancy	Hamid et al. (2016); Gohil et al. (2010)
	U-87 MG human glioblastoma cell death induced by asiatic acid (AA) from *C. asiatica*.	AA induces cell death by both apoptosis and necrosis, with Ca^{2+}-mediated necrotic cell death predominating.	AA-induced glioblastoma cell death is associated with decreased mitochondrial membrane potential, activation of caspase-9 and caspase-3, and increased intracellular free Ca^{2+}.	Cho et al. (2006)
	Effect of *C. asiatica* extract and its purified fractions on tumor-bearing mice.	Retards the development of tumors and increases the life span of mice.	Cytotoxic and antitumor effect involve direct action on DNA synthesis.	Xu et al. (2012)
	Effect of *C. asiatica* extract and its purified fractions on solid and Ehrlich Ascites tumor-bearing mice.	Retards the development of tumors and increases the life span of mice.	Induces apoptosis.	Babu et al. (1995); Babu and Paddikkala (1993)

TABLE 3.22.3 List of Some of the Pharmacological Activities of *Centella asiatica*—cont'd

Pharmacological/ therapeutic activity	Type of study and model used	Results	Mechanism	References
Antioxidant	Cytoprotective effect of asiatic acid (AA) against oxidative stress by the t-BHP-induced model in HepG2 cells.	AA has a cytoprotective effect against t-BHP-induced cell damage via suppressing cytotoxicity, ROS generation, and apoptosis.	AA activates Nrf2 signal in HepG2 cells. It is well known that Nrf2 promotes transcriptional activation of a variety of antioxidant genes through binding to ARE, such as HO-1, NQO-1, GCLC, and GCLM.	Zhimin et al. (2017)
	Effect of *C. asiatica* methanolic extract against oxidative stress in lymphoma-bearing mice models.	Prevents oxidative stress.	Increased antioxidant enzymes (SOD, CAT, GSHPx).	Jayashree et al. (2003); Gohil et al. (2010)
	Kaempferol and quercetin from *C. asiatica* tested for in vitro DPPH activity.	DPPH activity as IC50 vales of 9.64 and 11.97 μg/ml for kaempferol and quercetin, respectively.	Scavenging DPPH radical.	Dewi and Maryani (2015)
Neuroprotective	Effect of *C. asiatica* leaf extract on hippocampal CA3 neurons.	Protects the hippocampal CA3 neurons from degeneration in stressed mice.	In the present study the cytoprotective and antioxidant property of CA may be responsible for the neuroprotection against cell death and the deleterious effects of stress and hence increased dendritic arborization.	Hemamalini and Rao. (2016)
	Asiatic acid neuroprotective activity tested on cultured cortical cells by exposure to excess glutamate.	Asiatic acid proves to be effective in protecting neurons.	Enhanced cellular oxidative defense mechanism	Kumar et al. (1998)
	Effect of *C. asiatica* extract against rotenone-induced Zebrafish model.	Maintain neuronal motility.	Increasing dopamine level.	Khotimah et al. (2015)
	Effect of asiaticoside derivatives against beta-amyloid induced neurotoxicity on B103 cell culture and hippocampal slices.	Protect neurons from beta-amyloid toxicity.	Strong inhibition of beta-amyloid and free radical–induced cell death.	Mook-Jung et al. (1999); Gohil et al. (2010)

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TABLE 3.22.3 List of Some of the Pharmacological Activities of *Centella asiatica*—cont'd

Pharmacological/ therapeutic activity	Type of study and model used	Results	Mechanism	References
Antiulcer	Antiulcerogenic activity of ethanol extract of *C. asiatica* against ethanol-induced gastric mucosal injury in rats.	Inhibited significantly gastric ulceration induced by cold and restraint stress in Charles-Foster rats.	Reduction of ulcer areas in the gastric wall as well as the reduction or inhibition of edema and leucocyte infiltration of submucosal layers.	Abdulla et al. (2010)
	Effect of ethanolic extract of *Tinospora cordifolia* and *C. asiatica* on animal model.	A dose of 100 mg/kg per day produced a protective effect against stress-induced ulceration.	Strengthened mucosal barrier and reduced damaging effect of free radicals.	Sarma et al. (1995); Cheng and Koo (2000)
	Fresh juice of *C. asiatica* tested against experimental ulcer models.	Significant protection against ulcer.	Strengthening of mucosal defensive factors.	Sairam et al. (2001)
Wound healing	Animal model	Asiaticoside from *C. asiatica* facilitates wound healing.	Increase in peptidic hydroxyproline content, tensile strength, collagen synthesis, angiogenesis, and epitheliazation.	Bonte et al. (1994); Shukla et al. (1999)
	Animal model	Asiatic acid and madecassic acid facilitates wound healing.	Increase in peptidic hydroxyproline and an increased remodeling of collagen synthesis.	Bonte et al. (1994); Maquart et al. (1999)
	Aqueous *C. asiatica* extract tested on open wounds in rats.	The treated wounds recover faster compared to untreated wounds.	Increased cellular proliferation and collagen synthesis resulted in increased tensile strength.	Gohil et al. (2010); Kumar et al. (1998)
	Activity of asiaticoside was studied in normal as well as delayed (diabetic)-type wound healing in rats.	Both types of wound healing activity have been recorded under treatment.	Increase in tensile strength, collagen content, hydroxyproline content, and better epithelisation.	Suguna et al. (1996); Gohil et al. (2010)

study to assess safety levels for oral doses of *C. asiatica* given to albino rats. After an extensive study for 30 days, a dose-dependent increase in serum biomarkers was reported. A dose of 1000 mg/kg increased the weight of the spleen and caused a high level of apoptosis in hepatic and renal tissues (Oruganti et al., 2010). In another chronic toxicity study on Wistar rats (male and female) receiving 20 mg/kg per day, 200 mg/kg per day, 600 mg/kg per day, and 1200 mg/kg per day of *C. asiatica* for 6 months, the rats displayed no sign of a significant alteration in body weight, blood chemistry, clinical chemistry, or histopathology when compared to a control group (Chivapat et al., 2004). In 2011, the same author carried out another toxicity study using ECa 233 (a standardized extract of *C. asiatica*) on male and female Wistar rats. After a study period of 14 days no lethality was observed at a dose of 10 g/kg along with an absence of any form of toxic damage to any organs. Subchronic toxicity of the standardized extract on a group of 24 Wistar rats led to no difference in their average weight, nor did they show any signs of abnormal behavior. On autopsy of the study animals, it was found that all the ECa 233 treated animals displayed no damage to their organs and there was no difference in their organ weights, except for the male rat group that was given ECa 233 (10 mg/kg per day), this group showed lower relative right adrenal weight when compared to the control group (Chivapat et al., 2011). In 1991, Dandekar et al. carried out studies on the interaction between phenytoin (an antiepileptic drug) and an Ayurvedic formulation (sankhapushpi) in which *C. asiatica* is the second most abundant component. The study was carried out on random-bred Sprague-Dawley rats of both sexes, with weights

ranging between 100 and 150 g. The study showed that plasma phenytoin levels lowered significantly when sankhapushpi was coadministered with phenytoin orally, twice daily, for 5 days, hence the combination was not recommended (Dandekar et al.,1992). However, when *C. asiatica* extract was administered in mice along with phenytoin (13 mg/kg), valproate (104 mg/kg), and gabapentin (310 mg/kg) in combination, the anticonvulsant activity increased with a significant decrease in the effective dose of drugs of 62%, 72%, and 75%, respectively (Vattanajun et al., 2005). In a case study carried by Izu et al. (1992), the occurrence of allergic contact dermatitis with topical application of creams containing *C. asiatica* extracts was observed. Also, *C. asiatica* was postulated to interfere with blood glucose level when coadministered with hypoglycemic therapy (Gohil et al., 2010). The excessive amont of *C. asiatica* consumed when taken orally can cause headaches and transient unconsciousness. Moreover, the continuous use of *C. asiatica* for more than 6 weeks can cause spontaneous abortion in women, an is therefore not recommended (Gohil et al., 2010).

TRADE AND TRENDS

C. asiatica has great market potential attributed to its rich medicinal properties. Due to its high medicinal value, it has been among the 25 top selling medicinal herbs in the United States (Randriamampionona et al., 2007). In traditional as well as commercial medicinal products, leaves, stems, and whole plants have been used (Jamil et al., 2007; Samant and Pant, 2006). Many scientific studies on *C. asiatica* have demonstrated its different pharmacological and therapeutic properties, that is, as an antioxidant, an antibacterial, an antifungal, an antiviral, as an antiulcer and antidiabetic treatment, as an antiinflammatory, as a cytotoxic, demonstrating protection of the skin as well as being a cardioprotetive, radioprotective, and neuroprotective, having immunomodulatory properties, enhacing memory, and being able to heal wounds. In light of this, various market products having *C. asiatica* as an active ingredient have been introduced, some of them are listed in Table 3.22.4.

TABLE 3.22.4 List of Commercial Products Having *Centella asiatica* as an Active Ingredient

S. No.	Product name	Uses	Approximate price (US$)	Manufacturing company
1	Way 4 Organic Pure *Centella asiatica* raw powder	Enhances the overall immune system	2.95/100 g	Genius Nature Herbs Pvt. Ltd, India
2	Vallarai (*Centella asiatica*) powder	Memory enhancer, used to cure hair, skin, and stomach problems as well as curing stress and depression	7.4/100 g	Neotea DCBS ideas, India
3	Gotu Kola	Balances the effects of aging, increases healing power for longevity, and is a neuroprotective	7.59/500 mg	Morpheme Remedies, India
4	Organic India Organic Brahmi capsules	Used to cure venous insufficency, leg edema, stress, lack of concentration, memory decline	2.60/60 g	Shop Organikos, Punjab, India
5	Skin 1004 *Centella asiatica* ampoule	Skin nourishment	80.13/454 g	Skin Industries, Korean cosmetics, Korean beauty
6	Xhekpon Face Neck & Decolleté Anti-ageing Cream	Skin nourishment	52.86/40 g	XHEKPON, Spain
7	*Centella asiatica* facial cleaning gel	Skin nourishment	75.60/150 g	Thai herb, Thailand
8	Richelth capsules	Rich antioxidant support for health and longevity	4.78/100 g	CharakPharma Pvt. Ltd, India

(Continued)

TABLE 3.22.4 List of Commercial Products Having *Centella asiatica* as an Active Ingredient—cont'd

S. No.	Product name	Uses	Approximate price (US$)	Manufacturing company
9	Green Tea Brahmi	Promotes Relaxation. Maintains mental health	4.15/50 g	Biosap, Rajasthan, India
10	Contorno Occhi (eye gel)	Antioxidant as well as an antiinflammatory agent	117.14/15 ml	L'ERBOLARIO, Italy
11	Patanjali Sharbat Brahmi	Effective in the treatment of edema, urinary disorders, anaemia, and fever	1.48/750 ml	Patanjali Ayurved, India
12	Gotu Kola extract	Dietary supplement	29.75/120 ml	Hawaii Pharm LLC., Honolulu, Hawaii, USA
13	Capisol	Dietary supplement	29.45/380 mg	R.I. Group srl, Cornuda (TV), Italy

(Data taken from: amazon.in, amazon.com, renacoitalia.net)

CONCLUSIONS

C. asiatica is one of the most potent herbal supplements for treating central nervous system (CNS)-related disorders. It has a balancing effect on mood and also increases concentration. Clinical evidence suggests that it can be used to treat venous and arterial problems, as it showed beneficial effects in strengthening vascular systems and connective tissues. Further studies on clinical activities need to be carried out on *C. asiatica* to explore its wider possibilities in treating disease conditions.

Due to its diverse potential health applications, *C. asiatica* is being exploited at a faster rate than previously thought, and as a result is listed as a highly threatened plant species by the International Union for Conservation of Nature. There is a need for continuous production of *C. asiatica* on a large scale, grown in vitro, to meet the demands of the herbal industry. Further investigations on the effect of environmental and bioprocess factors on the accumulation of secondary metabolites in *C. asiatica* would strengthen its utilization for industrial purposes. Also, genetic characterization, by means of genetic fingerprinting, is needed to further understand the diversity seen in *C. asiatica*. This will involve understanding the genetic variability and heritability of *C. asiatica*, thereby helping to improve the component yield of the plant.

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