PHYTOCHEMISTRY AND MEDICINAL PROPERTIES OF CENTELLA ASIATICA

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Contents

Summary

Plants have been demonstrated extraordinary source of medicine, and recently focus on medicinal plant research has increased. *Centella asiatica* is well known for its traditional uses and medicinal properties for the treatment of many diseases. The published literatures mention the use of this plant as whole and bioactive compounds isolated are widely used in the treatment of various human ailments. *C. asiatica* reported to possess various pharmacological activities: antimicrobial activity, anticancer activity, wound healing activity, neuroprotective activity, immunomodulatory activity, anti-inflammatory activity, hepatoprotective activity, insecticidal activity, and antioxidant activity. *C. asiatica* is also rich in flavonoids and terpenoids compounds among them asiatic acid, asiaticoside, madecassoside is well characterized for its pharmacological value. Many natural compounds isolated from *C. asiatica* showed promising pharmacological study candidate based on the invivo animal, and insilico study. There is widespread information on phytochemistry, isolated and characterized

bioactive compounds, pharmacological properties, in vitro propagation, and traditional uses of the important medicinal plant *C. asiatica*. *C. asiatica* is also marketed now as an oral supplement as well as a cosmetic ingredient due to its various health benefits. The therapeutic role of *C. asiatica* needs to be clarified through further preclinical studies and randomized controlled trials. Based on available reports, in this contemporary review chapter we discuss phytochemical analysis of plant-extracts and the pharmacological activities of bioactive compounds to understand their therapeutic potentialities and mechanism of action.

1. Introduction

Medicinal plants are an important episode in the medical sector. Around 5000 species have specific therapeutic value among 2,50,000 higher plant species on earth (Joy et al. 1998). Among the many medicinal plants *Centella asiatica*, an ancient Ayurvedic remedy, is useful tonic and cleansing herb for skin problem and digestive disorders (Chevallier 2001) and effective treatment for stomach ulcers, mental fatigue, diarrhea, epilepsy, hepatitis, syphilis, and asthma (Goldstein and Goldstein 2012). Such traditional uses and reputation of this species cross over the boundary limit of Bangladesh, India, and Srilanka and now extensively used in the West (Chevallier 2001; Meulenbeld and Wujastyk 2001). *C. asiatica* and *Hydrocotyle asiatica,* belongs to family Apiaceae previously known as (Umbelliferae) are used synonymously and commonly known as (Singh et al. 2010):

- *Thankuni* (Bengali),
- *Bemgsag/ Brahma-Manduki/ Gotukola/ Khulakhudi/ Mandookaparni* (Hindi),
- Indian Pennywort/ Marsh Pennywort/ *Gotu kola* (English)

C. asiatica is creeping, perennial herb with up to 2m long slender and tender horizontal reddish prostrate stolons, characterized by long rooting internodes (Jamil et al. 2007; Koh et al. 2009). Glabrous leaves, 1-3 arising from each node of the stems, are green, fan-shaped, or round renifrom, 1.4 cm by 1.7 cm with crenate or dentate margin (Jamil et al. 2007; Koh et al. 2009). Flowers occurring in July-September are umbels with 3-4 white or light purple-to-pink petals bearing 4mm long oval to globular shaped fruit (Chauhan 1999; Jamil et al. 2007; Koh et al. 2009). The used part for medicinal purposes is dried whole plant or herb, mainly leaves and stems. *C. asiatica* plant is indigenous to Bangladesh, India, America West Pakistan, China, Japan and the pacific (Koh et al. 2009). This plant is commonly seen in moist, sandy, or clayey soils waste places throughout India up to an altitude of 600m (Jamil et al. 2007).

The genetic diversity and structure of eighty *C. asiatica* from southern India were studied using ten genomic microsatellites, which revealed high intra-population variation, prevalent inbreeding, and population divergence (Mathavaraj and Sabu 2021). Entire chloroplast genome (CP) of *C. asiatica* was 154,771 bp in length, consisting of a large single copy (LSC) region with 86176 bp, a small single copy (SSC) region with 18107 bp, and a pair of inverted repeats (IR) regions with 25,343 bp (Li et al. 2020). A total of 227 conserved and 109 novel microRNAs were identified from the libraries made from *C. asiatica* total RNA giving the insight of first elaborated glimpse of miRNA pool (Ranjith et al. 2020).

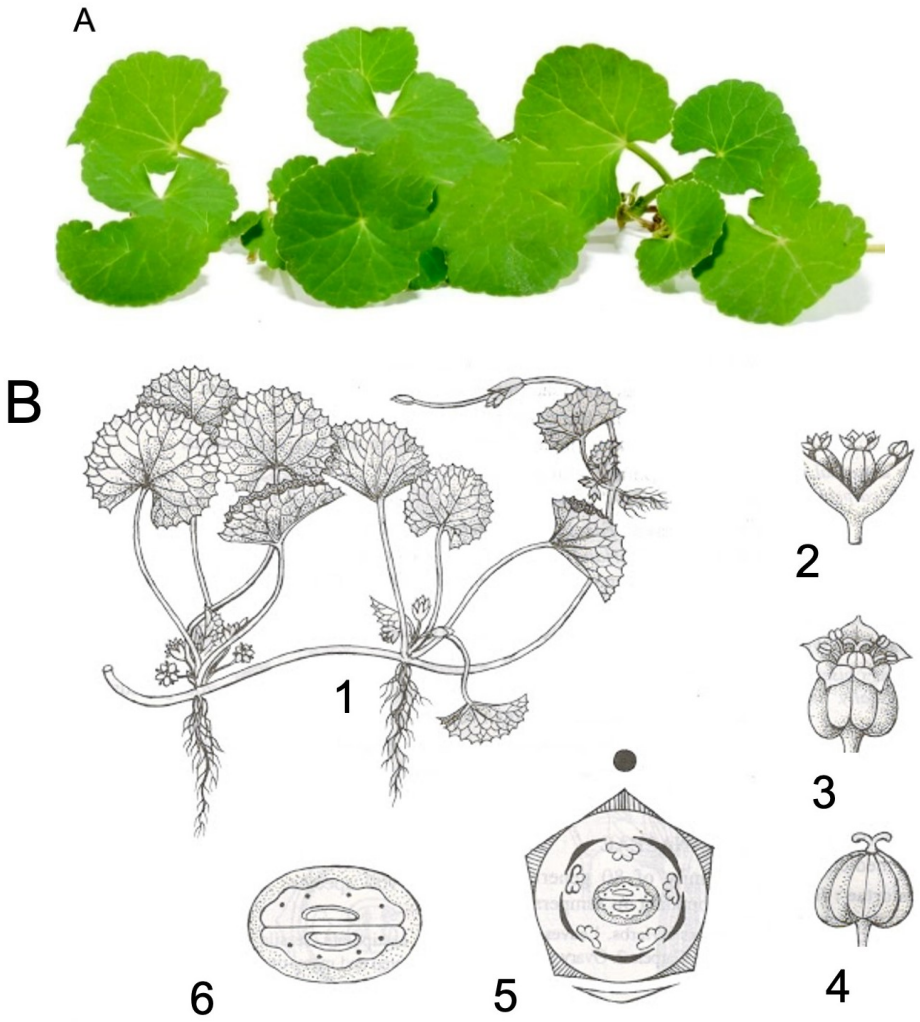


Figure 1. A. *Centella asiatica*. B. (1) drawing of plant with flower, (2) inflorescence, (3) flower, (4) fruit, (5) transection of fruit, (6) floral diagram.

2. Phytochemistry

C. asiatica is a rich source of amino acids, flavonoids, terpenoids, essential oils, alkaloids etc. The chemical constituents are listed in the following:

- Carbohydrates
- Amino acids
- Phenols
- Terpenoids
- Volatile oils and Fatty oils
- Vitamins
- Minerals
- Others

The above are described in groups in Table 1. Most of the studies were on aerial parts especially on leaves but other parts (stems and roots) were also studied, and it was

observed that the constituents of this plant vary depending upon the geographical distribution (Chong and Aziz 2011).

Main groups	Constituents	References
Amino acids	Alanine and serine (major components), aminobutyrate, aspartate, glutamate, histidine, lysine, threonine, arginine, leucine, iso-leucine, valine, methionine, tyrosine, phenylalanine, proline, cystine, glycine. The root contains greater quantities than the herb.	(Barnes and Anderson 2007; Chong and Aziz 2011)
Carbohydrates	Glucose, mesoinositol, Centellose, Pectin, arabinogalactan	(Chong and Aziz 2011)
Phenols	Flavonoids: Kaempferol, kaempferol-3-o-β-d-glucuronide, castilliferol, quercetin, quercetin-3-o-β -d-glucuronide, castillicetin, Apigenin, Rutin, Luteolin, Naringin	(Bhandari et al. 2007; Chong and Aziz 2011; Zheng and Qin 2007.)
	Phenylpropanoids: Rosmarinic acid, chlorogenic acid, 3,4-di-*o*-caffeoyl quinic acid, 1,5-di-*o*-caffeoyl quinic acid, 3,5-di-*o*-caffeoyl quinic acid, 4,5-di-*o*-caffeoyl quinic acid, isochlorogenic acid	(Chong and Aziz 2011)
	Tannin: Tannin, phlobatannin	(Chong and Aziz 2011)
Terpenoids	Triterpenes, asiaticoside, centelloside, madecassoside, brahmoside and brahminoside (saponin glycosides). Aglycones are referred to as hydrocotylegenin A–E, compounds A–D are reported to be esters of the triterpene alcohol R_1- barrigenol. Asiaticentoic acid, centellic acid, centoic acid, madecassic acid, terminolic acid and betulic acid.	(Barnes et al. 2007; Jamil et al. 2007)
Volatile oils and fatty oils	Various terpenoids including β-caryophyllene, trans β-farnesene and germacrene D (sesquiterpenes) as major components, α-pinene and β-pinene. Fatty acids (e.g. linoleic acid, linolenic acid, lignocene, oleic acid, palmitic acid, stearic acid), The major terpenoid is stated to be unidentified.	(Barnes et al. 2007; Jamil et al. 2007)
Vitamins	Ascorbic acid, nicotinic acid, β-carotene	(Chong and Aziz 2011)
Mineral	Calcium, phosphorus, iron, potassium, magnesium, manganese, zinc, sodium, copper	(Chong and Aziz 2011)

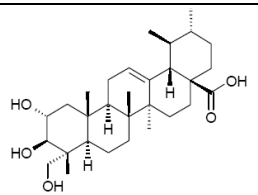
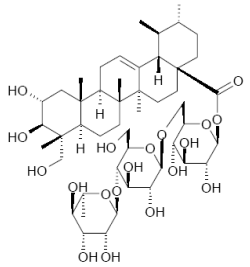
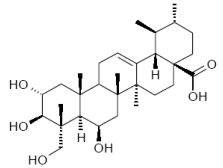
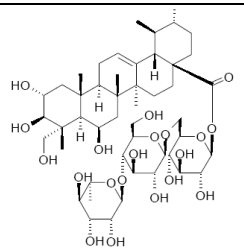
Other constituents	Hydrocotylin (an alkaloid), vallerine (a bitter principle), phytosterols (e.g. campesterol, sitosterol, stigmasterol), resin. The underground plant parts of thankuni have been reported to contain small quantities of at least 14 different polyacetylenes (such as 8-acetoxycentellynol, cadiyenol, dotriacont-8-en-1-oic acid, 11-oxoheneicosanyl cyclohexane).	(Barnes et al. 2007; Chong and Aziz 2011)

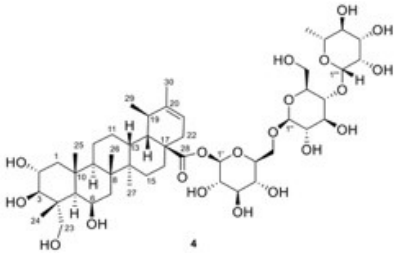
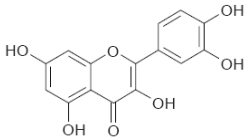
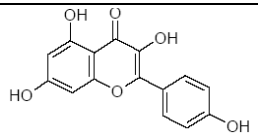
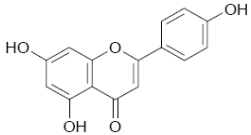
Table 1. Chemical constituents of *C. asiatica*

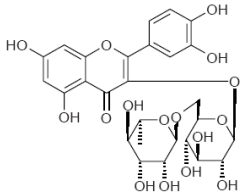
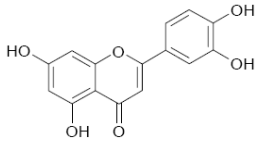
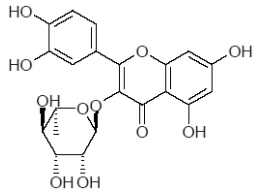
3. Bioactive Compounds

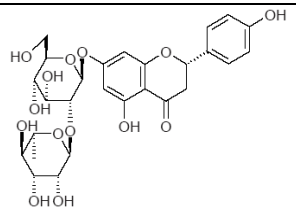
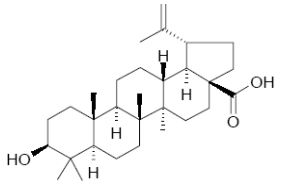
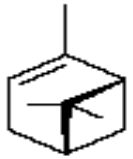
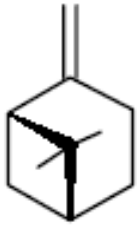
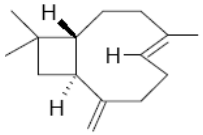
Since the time *C. asiatica* is being used as a natural source of medicine as it contains some bioactive compounds which show biological activity in human and animal body. Some bioactive compounds which show biological activities reported in published literature are summarized in Tables 2 with their physical properties and biological activities. The bioactive compounds from *C. asiatica* are as follows:

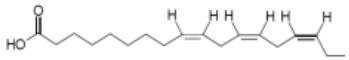
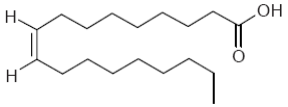
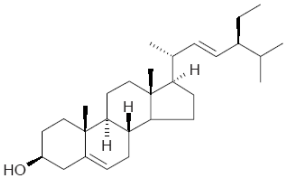
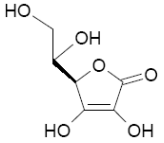
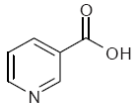
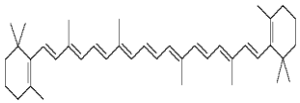
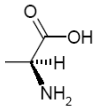
- β-Caryophyllene
- Linolenic acid
- Kaempherol
- Oleic acid
- Stigmasterol
- Ascorbic acid
- Nicotinic acid
- β-Carotene
- Alanine
- Chlorogenic acid
- Asiaticside G
- 23-O acetylasiaticoside
- 23-O acetylmadecassoside
- Asiatic acid
- Asiaticoside
- Madecassic acid
- Madecassoside
- Isomadecassoside
- Quercetin
- Apigenin
- Rutin
- Luteolin
- Quercitrin
- Naringin
- Betulic acid
- α-Pinene
- β-Pinene

Name of the compounds	Structure	Biological activity	References
Asiatic acid ($C_{30}H_{48}O_5$; mw = 488.71)		Aids in generation of neuroglia; promotes wound healing (external use); promotes cuticle cornification; stimulates granulation; induces gene expression changes (hmn fibroblast, IC90 = (60±5) µg/mL)	(Hambali et al. 2021; Zhou, Xie, and Yan 2011c)
Asiaticoside ($C_{48}H_{78}O_{19}$; mw = 959.15; mp = 230~233ºC)		Anti-inflammatory; induces gene expression changes (hmn fibroblast, IC90 >400µg/mL)	(Hambali et al. 2021; Zhou, Xie, and Yan 2011d)
Madecassic acid ($C_{30}H_{48}O_6$; mw = 504.71; mp = 293ºC)		Induces gene expression changes (hmn fibroblast, IC90 = (175±20)µg/mL)	(Hambali et al. 2021; Zhou et al. 2011c)
Madecassoside ($C_{48}H_{78}O_{20}$; mw = 975.14)		Induces gene expression changes (hmn fibroblast, IC90 > 400µg/mL)	(Hambali et al. 2021; Zhou et al. 2011c)

Isomadecassoside		Artikel I. Reduces Nitrite Levels in LPS-Stimulated Macrophages	(Chianese et al. 2021)
Quercetin ($C_{15}H_{10}O_7$**;** mw = 302.24; mp = 313~314ºC)		Anti-HIV-1, antiasthmatic, antibacterial, antihepatotoxin, antihypertensive, anti-inflammatory, antitussive, antiviral, coronary vasodilator, antihypercholesterolemic, 5-HT inhibitor, smooth muscle relaxant, platelet aggregation inhibitor, 3',5'-cAMP-phosphodiesterase inhibitor, fatty acid synthetase inhibitor, aldose reductase inhibitor (eye lens), protein kinase C inhibitor; antihypertensive, reduces blood capillary brittleness, antioxidant	(Chong and Aziz 2011)' (Zhou et al 2011a)
Kaempferol ($C_{15}H_{10}O_6$**;** mw = 286.24; mp = 274~278ºC)		Anti-HIV-1, antibacterial; anti-inflammatory, antitussive to cure trachitis, antioxidant, Δ^5 -lipoxygenase inhibitor; iodinate thyronine deiodinase inhibitor; aldose reductase inhibitor	(Chong and Aziz 2011; Zhou et al. 2011e)
Apigenin (C15H10O5**;** **mw** = 270.24; mp = 344~347ºC)		Antibacterial, antiulcerative, antispasmodic (smooth muscle), diuretic, aldose reductase inhibitor, antihypertensive, nodulation signal for metabiosis of pea and *Rhizobium leguminosarum*, anti-	(Bhandari et al. 2007; Zhou et al. 2011c)

		inflammatory, antioxidant	
Rutin ($C_{27}H_{30}O_{16}$; mw = 610.53; mp = 188~190ºC)		Anti-inflammatory, antiviral, aldose reductase Inhibitor, insect antifeedant (*Heliothis zea*), insect phagostimulant (*Gastrophysa atrocynea*), antioxidant, inhibits cancer cell invasion inactive (MM1 cells, *in vitro*, 10µg/mL), reduces blood capillary permeability and brittleness (used in treatment of blood capillary ailments)	(Bhandari et al. 2007; Zhou et al. 2011a)
Luteolin ($C_{15}H_{10}O_6$; mw = 286.24; mp = 328~330ºC)		Antiallergic, antibacterial, antifungal, cytotoxic, anti-inflammatory, antispasmodic, antitussive, antiviral, enhances arterial tension and lowers intravenous tension, enhances blood capillary permeability, immunoenhancer, increases coronary flow; dihydrocoenzyme I (NADH) oxidase inhibitor, iodine-induced thyronine deiodinase inhibitor, aldose reductase inhibitor, anti-inflammatory, anti-HIV	(Bhandari et al. 2007; Zhou et al. 2011c)
Quercitrin ($C_{21}H_{20}O_{11}$; mw = 448.39; mp = 166~168ºC)		Antibacterial, antineoplastic, antihepatotoxin, anti-inflammatory, antimutagenic, antiviral, diuretic, Hemostatic, aldose reductase inhibitor, antioxidant, insect antifeedant (*Bombyx mor*), insect phagostimulant (*Gastrophysa atriocyaea*), hepatoprotective, ACE inhibitor, APN inhibitor inactive, inhibitory	(Bhandari et al. 2007; Zhou et al. 2011e)

		activity against NFAT transcription	
Naringin ($C_{27}H_{32}O_{14}$; mw = 580.55; mp = 82ºC, 171ºC)		Antibacterial, anti-inflammatory, antiviral, aldose reductase inhibitor, passive cutaneous anaphylaxis inhibitor	(Zheng and Qin 2007.; Zhou et al. 2011e)
Betulic acid ($C_{30}H_{48}O_3$; Mw = 456.72; mp = 285~287ºC)		Antineoplastic, cytotoxic, antitubercular, antibacterial	(Jamil et al. 2007; Zhou et al. 2011d)
***α*-Pinene** ($C_{10}H_{16}$; mw = 136.24; bp = (+) 155~156ºC/755mmHg, (−) 155~156ºC/746mmHg, (±) 156.2ºC/741mmHg)		Antifungal, antitussive, irritant.	(Barnes et al. 2007; Zhou et al. 2011d)
***β*-Pinene** ($C_{10}H_{16}$; mw = 136.24; bp = (+) 162~166ºC, (−) 163.5~164.0ºC/746mmHg)		Antifungal, anti-inflammatory, antitussive	(Barnes et al. 2007; Zhou et al. 2011c)
β-caryophyllene ($C_{15}H_{24}$; mw= 204.36); bp =		Flavorant	(Barnes et al. 2007; Zhou et al. 2011d)

129~130ºC/14mmHg)			
Linolenic acid ($C_{18}H_{30}O_2$; mw = 278.44)		Nutrient, inhibits cancer cell invasion, 5α-reductase inhibitor	(Jamil et al. 2007; Zhou et al. 2011c)
Oleic acid ($C_{18}H_{34}O_2$; mw = 282.47; mp = 16ºC; bp = 285.5~286.0ºC/100 mmHg)		Increases absorption through skin, dermatitis, inhibits cancer cell invasion	(Jamil et al. 2007; Zhou et al. 2011b)
Stigmasterol ($C_{29}H_{48}O$; mw = 412.71; mp = 170ºC)		Antihypercholesterolemic, antimutagenic, cytotoxic inactive, antileishmanial, antimalarial, antitrypanosomal, platelet aggregation inhibitor, antiviral	(Barnes et al. 2007; Zhou et al. 2011b)
Ascorbic acid ($C_6H_8O_6$; mw = 176.13; mp = 190~192ºC)		Antioxidant, antibacterial, anti-infective, antidote, antihypercholesterolemic, inhibits production of Carcinogen, induces tissue to produce collagen, hematopoietic	(Chong and Aziz 2011; Zhou et al. 2011d)
Nicotinic acid ($C_6H_5NO_2$; mw = 123.11; mp = 236ºC)		Antihypercholesterolemic, vasodilator (peripheral)	(Chong and Aziz 2011; Zhou et al. 2011b)
***β*-Carotene** ($C_{40}H_{56}$; mw = 536.89). mp = 184ºC)		EBV-EA activation inhibitor, anti-tumor promoter, ultraviolet screen, pigment, food additive	(Chong and Aziz 2011; Zhou et al. 2011d)
Alanine ($C_3H_7NO_2$; mw = 89.09)		Food additive, reverses glucopenia and ketosis caused by starvation, glucagon secretion promotor	(Barnes et al. 2007; Zhou et al. 2011d)

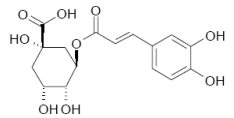
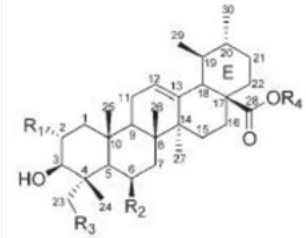
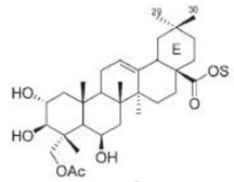
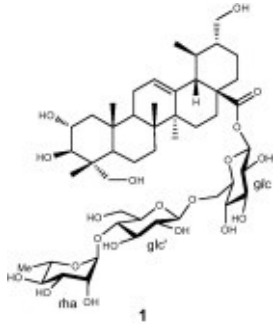
Chlorogenic acid ($C_{16}H_{18}O_9$; mw = 354.32; mp = 208~209ºC)		Antioxidant, antineoplastic, cytotoxic, antimutagenic, antiviral, choleretic, hemostatic, leukopoietic, antimalarial,	(Chong and Aziz 2011; Zhou et al. 2011d)
23 -*O*-acetylmadecassoside		Not reported	(Rumalla et al. 2010)
23 -*O*-acetylasiaticoside		Not reported	(Rumalla et al. 2010)
Asiaticoside G		Modulates the production of nitric oxide and secretion of TNF-α in activated RAW 264.7 cells	(Nhiem et al. 2011)

Table 2. Individual functions and properties of some bioactive compounds isolated from *C. asiatica.*

Recent technological developments have been used to extract bioactive compounds in an updated and precise manner. The green extraction can produce high-quality extracts with less solvent, time, and energy, while keeping the environment in mind. A green extraction method of *C. asiatica* was explored to produce triterpenoids-enriched extracts for the pharmaceutical and cosmeceutical industries and for the quantitative analysis of triterpenoids in raw materials (Thong-on et al. 2021). Furthermore, six new pentacyclic triterpenoid saponins, centelloside F, centelloside G, 11-*oxo*-asiaticoside B, 11-*oxo*-madecassoside, 11 (β)-methoxy asiaticoside B, and 11 (β)-methoxy madecassoside, along with seven known ones, asiaticoside, asiaticoside B, madecassoside, centellasaponin A, isoasiaticoside, scheffoleoside A, and centelloside E, were separated from the 80% methanol extract of the whole plant of *C. asiatica* (Wu et al. 2020). Recently a specific, sensitive, and validated method has been developed based on UHPLC-ESI-MS-MS-MRM tandem mass spectroscopy for accurate determination of major triterpenes and chlorogenic acid in C. asiatica in a shorter period (Sabaragamuwa, 2022).

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