25

Ethnobotany, Phytochemistry and Pharmacological Features of *Centella asiatica*: A Comprehensive Review

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Abstract

Centella asiatica (CA) or Gotu cola is an herbal plant from the Apiaceae family with a long history of usage in different traditional medicines. It has long been used for the treatment of various ailments such as central nervous system (CNS), skin and gastrointestinal disorders especially in the Southeast Asia. This chapter focused on the phytochemical constituent and pharmacological activities of CA based on preclinical and clinical studies. Additionally, botanical description and distribution, traditional uses, interactions, and safety issues are reviewed. Electronic data-

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bases of Google Scholar, Scopus, PubMed, and Web of Science were searched to obtain relevant studies on the pharmacological activities of CA. Approximately, 124 chemical compounds including triterpenoids, polyphenolic compounds, and essential oils have been isolated and identified from CA. Ethnomedicinal applications of CA mostly include treatment of gastrointestinal diseases, wounds, nervous system disorders, circulatory diseases, skin problems, respiratory *ailments*, diabetes and sleep disorders in various ethnobotanical practices. Pharmacological studies revealed a wide range of beneficial effects of CA on CNS, cardiovascular, lung, liver, kidney, gastrointestinal, skin, and endocrine system. Among them, neuroprotective activity, wound healing and treatment of venous insufficiency, as well as antidiabetic activity seem to be more frequently reported. At the moment, considering various health benefits of CA, it is marketed as an oral supplement as well as a topical ingredient in some cosmetic products. Additional preclinical studies and particularly randomized controlled trials are needed to clarify the therapeutic roles of CA.

Keywords

Centella asiatica · Herbal plant · Ethnobotany · Phytochemistry · Pharmacology · Clinical studies

25.1 Introduction

Medicinal plants perhaps are the main source for new chemical entities or may be used in their intact form as a medicine. They have proven their therapeutic potentials along the time and nowadays investigates for active compounds, by *in vivo*, *in vitro*, and clinical studies for confirming their usages as a medicine or an adjuvant or a supplement for standard treatments of diseases [1].

Centella asiatica (L.) Urb. is anayurvedic (an Indian system of medicine) and Chinese traditional medicine plant belonging to Apiaceae family (previously known as Umbelliferae) (Fig. 25.1) [2]. It also named *Hydroctyle asiatica* and Indian pennywort, GotuKola (Europe and America), Pegaga (Malaysia), Mandukaparni (India), Kaki Kuda or Pegagan (Indonesia), Gong Gen or Tung chain (China) are its other common names in different countries [3, 4]. *Centella asiatica* (CA) has been listed in the Indian Herbal Pharmacopoeia, the Pharmacopoeia of the People's Republic of China, the European Pharmacopoeia, and the German Homeopathic Pharmacopoeia as a drug [5].

Fig. 25.1 An illustration of *Centella asiatica*. Note: This figure was published in the internet

It traditionally is applied for different conditions such as some infectious and inflammatory diseases, seizure, tumor, and also psychosis [6, 7]. CA also improved some neurological and psychological conditions such as general anxiety disorder, dementia and cognitive disorders [8, 9]. It is established that extract of CA is an antioxidant and an anti-inflammatory agent and also it has showed anti-hyperglycemia and anti-hyperlipidemia effects in various studies [10–13]. It promoted wound healing and improved filtration and some other functions of venous and general circulation in diabetic and hypertensive patients or patients who have venous insufficiency or other disorders such as anal fissure [14–17]. It was helpful for treatment of some dermal disorders like erythema, edema, crust, excoriation and lichenification [8, 18]. CA seems to

be safe for human use [15, 19, 20]. So, CA logically has enough potential for investigation as a medicinal herb for different applications.

In present chapter, we attempt to incorporate a comprehensive, detailed, and up to date findings about its ethnobotanical uses, phytochemistry, preclinical and clinical studies, interactions, and safety issues, focusing on the pharmacological and pharmacognostic aspects.

25.2 Botanical Description and Distribution

The genus *Centella* L. is a member of the Apiaceae family (formerly Umbelliferae) with important medicinal species, containing a total of 59 accepted species worldwide [21]. Among them, the most popular and commercially important is *Centella asiatica* (L.) Urb., which naturally found in the tropical and subtropical regions, of the Old and New World [22, 23]. *Centella asiatica* is a stoloniferous perennial plant, with a height which can reach up to 15 cm. The stem is creeping and glabrous. The leaves are orbicular or reniform, 1–3 from each node of stems, sheathing leaf base, crenate margins, glabrous on both sides. The flowers are fascicled umbels, each umbel consisting of 3–4 white to purple flowers. The fruit is schizocarp with oblong and globular shape of 5 cm long. The seeds have pendulous embryo [22]. It is commonly found in the damp and marshy areas of South-Southeast Asia, Australia, Madagascar, Southern and Central Africa, some Pacific Islands and several regions of South Eastern United States and South Central America [24].

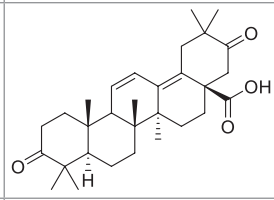
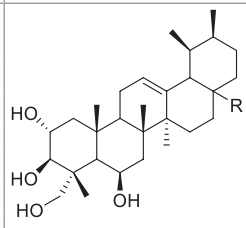
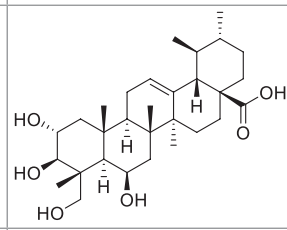
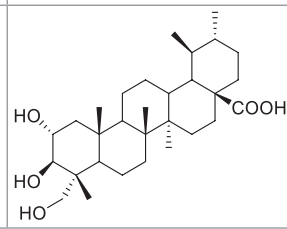
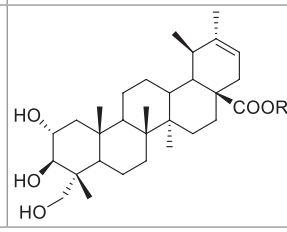
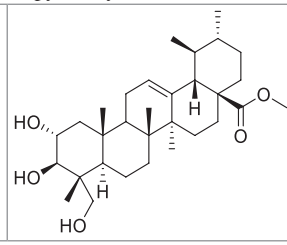
25.3 Phytochemistry Study

Phytochemical studies on CA indicate the presence of several categories of chemical compounds such as triterpenoids, polyphenolic compounds, and essential oils. These compounds are shown in Table 25.1.

25.4 Ethnobotanical and Ethnomedicinal Uses

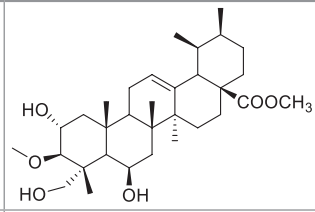
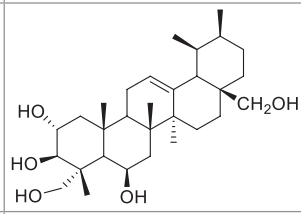
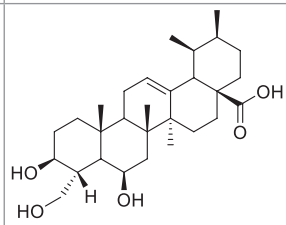
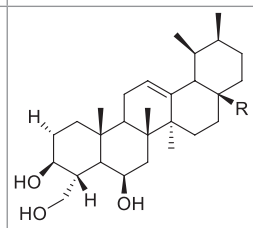
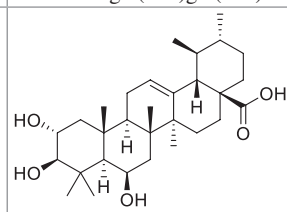
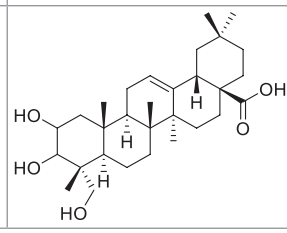
Centella asiatica (L.) Urb. has a long history of uses both as edibles and as ethnomedicinal plant in different ethnobotanical practices around the world. *Literature review demonstrates that*, CA, as the most famous species of the *Centella* genus, has noticeable traditional applications which mainly originate from Asia, Africa and Europe continents. In Asian countries, particularly India, Nepal, Bangladesh and China, there are remarkable reports on the traditional applications of CA. In India, it is applied as a traditional drug to treat asthma [25]. In the Indian Traditional Medicine, its leaves commonly known as Vallarai, which are widely employed as for children as a memory enhancer [26]. Furthermore, the whole plant is used for the treatment of stomach worm, and its leaf is also taken as an effective treatment for leucorrhoea, epilepsy and mental disorder [27]. In Pakistan, its leaves commonly known as Barhami, are considered very useful in the treatment of skin diseases, syphilitic, rheumatism, dysentery and fevers [28]. In China, CA is considered very useful in the treatment of hepatitis [29]. In the *Traditional* Chinese *Medicine*, it is also consumed as heat-clearing, detoxification, sunstroke and gallstones cleaning [30]. In Nepal, the paste of whole plant is applied to relieve muscular swelling and joint pains. It is also used to cure skin diseases such as eczema and pimples. Moreover, a decoction of it is given to cure fever, indigestion, uric acid and dysentery. It is also recommended for children to enhance memory power [31]. In addition, the leaves and roots of CA are extensively used in folk medicine to treat wound, gastritis and anorexia by local communities of the Kali Gandaki Watershed Area, Nepal [32]. In Bhutan, traditional medicine practitioners recommended it as appetizer [33]. In Bangladesh, the decoction of its leaves are used for curing of hypertension. Leaf paste is applied for healing of wounds, burns, and skin lesion [34]. In Philippines, its leaves are recommended to treat of urination difficulty, sore eyes and burns [35].

Table 25.1 Chemical composition of *Centella asiatica*

No.	Name of compounds	Structures	Plant parts	Ref. erences
		Triterpenoids		
1	Papyriogenin A		Leaves	[106]
2	Madecassoside (brahminoside)	 R = COO-glc(1–6)glc(1–4)rha	Leaves	[106, 107]
				[108]
				[109]
				[53]
				[110]
			Leaves	[111]
			Whole plants	[112]
3	Madecassic acid		Leaves	[106, 111]
4	2α,3ß,20,23-tetrahydroxy-urs-28-oic acid			[108]
				
5	2α,3ß,23-trihydroxy-urs-20-en-28-oic acid: R = H			[108]
6	2α,3ß,23-trihydroxy-urs-20-en-28-oic acid O-α-L-rhamnopyranosyl- (1–4)-O-ß-D-glucopyranosyl-(1–6)-O-ß-Dglucopyranosyl ester: R = rha(1–4)-glc(1–6)-glc-			[108]
7	Methyl asiatate			[108]

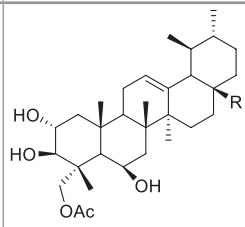
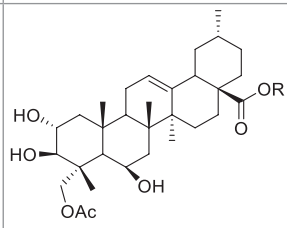
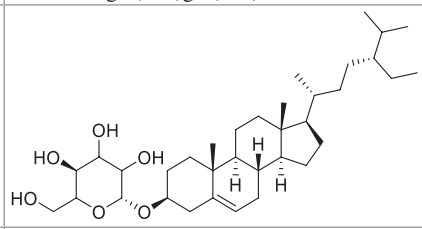
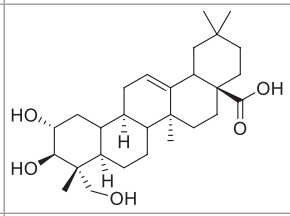
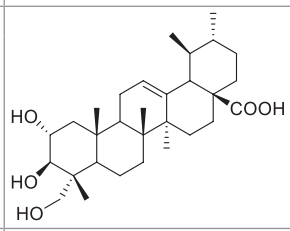
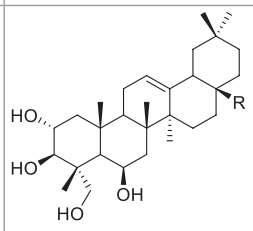
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
8	Methyl brahmate			[108]
9	Brahmol			[108]
10	Isothankunic acid (3α,5α,6ß,24-tetrahydroxy-urs-12-en-28-oic acid)			[108]
11	Isothankuniside	 R = COO-glc(1–6)glc(1–4)rha		[108]
12	Madasiatic acid			[108]
13	2,3,23-trihydroxy-olean-12-en-28-oic acid			[108]

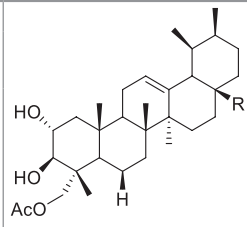
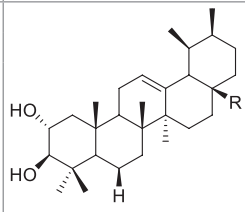
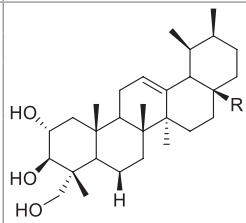
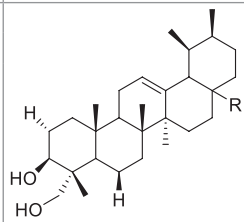
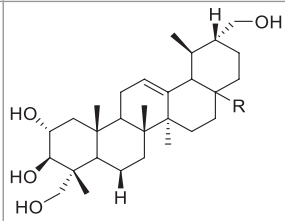
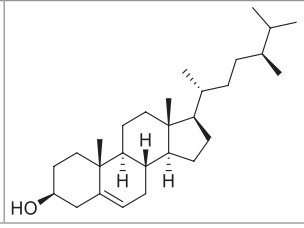
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
14	23-O-acetylmadecassoside	 R = COO-glc(1–6)glc(1–4)rha	Leaves	[111]
15	23-O-acetylasiaticoside B	 R = COO-glc(1–6)glc(1–4)rha	Leaves	[111]
16	Sitosterol 3-O-β-glucoside		Leaves	[111]
17	Arjunolic acid			[2]
18	Asiatic acid (2α,3ß,23-trihydroxy-urs-12-en-28-oic acid)			[53] [108] [24] [110]
19	Asiaticoside B	 R = COO-glc(1–6)glc(1–4)rha		[108] [53]

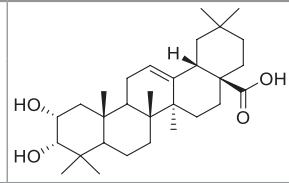
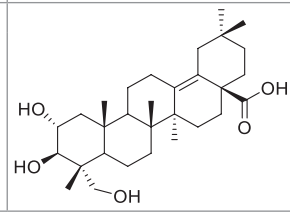
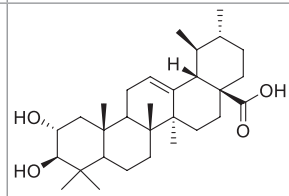
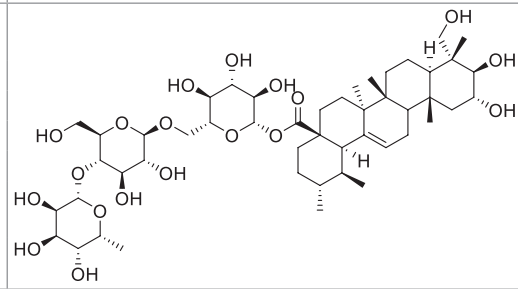
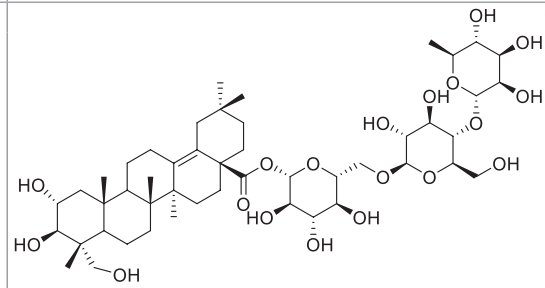
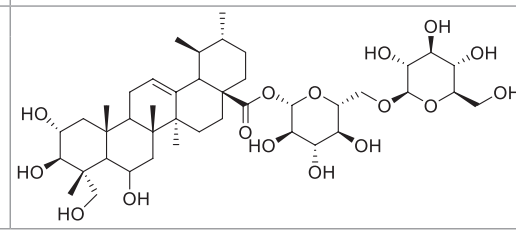
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
20	Asiaticoside C	 R = COO-glc(1–6)glc(1–4)rha		[108]
			Whole plants	[112]
			Leaves	[111]
21	Asiaticoside D	 R = COO-glc(1–6)glc(1–4)rha		[2]
				[108]
			Whole plants	[112]
22	Asiaticoside E	 R = COO-glc(1–6)glc		[2]
				[108]
			Whole plants	[112]
			Fresh mature plants	[113]
23	Asiaticoside F	 R = COO-glc(1–6)glc(1–4)rha		[108]
				[2]
			Whole plants	[112]
			Leaves	[111]
24	Asiaticoside G	 R = COO-rha(1–4)glc(1–6)glc		[2]
25	Campesterol			[24]

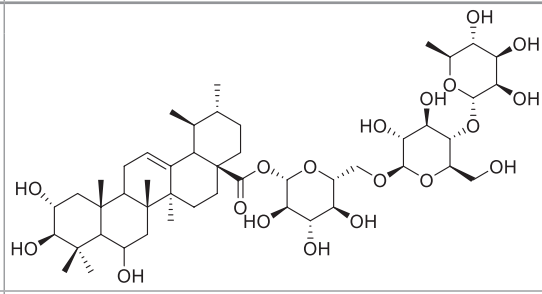
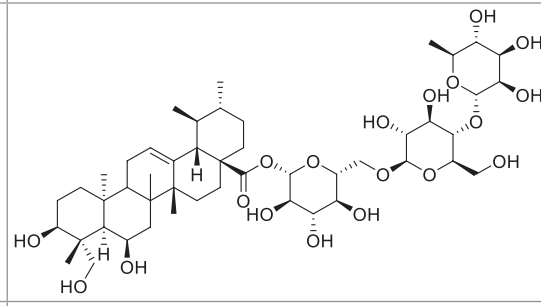
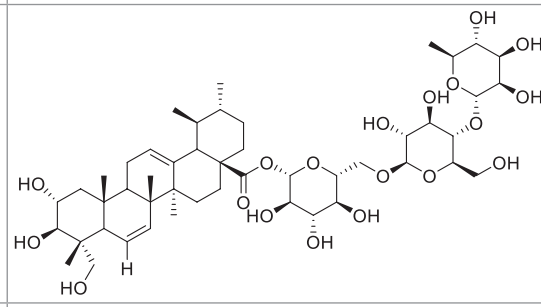
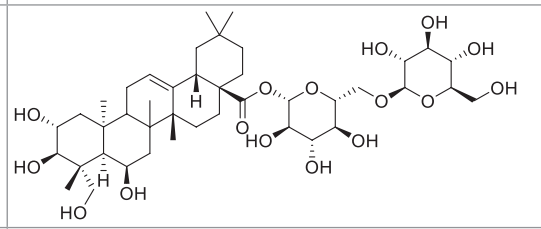
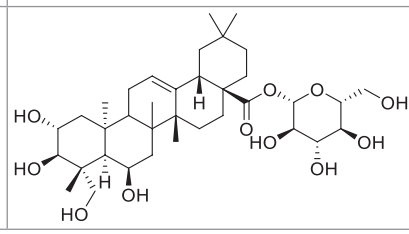
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
26	3-epimaslinic acid		Aerial parts	[114]
				[24]
27	Centellasapogenol A			[2]
				[108]
28	Corosolic acid		Aerial parts	[114]
29	Asiaticoside		Leaves	[106, 107]
				[115]
				[109]
				[53]
				[110]
			Whole plants	[112]
			Leaves	[111]
30	Centellasaponin A			[108]
				[2]
31	Centellasaponin B			[2]
				[108]

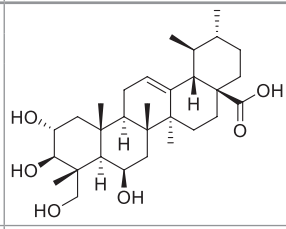
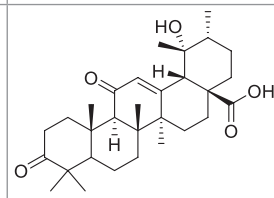
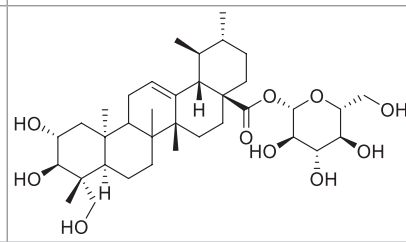
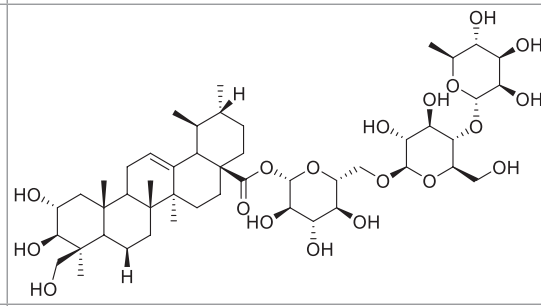
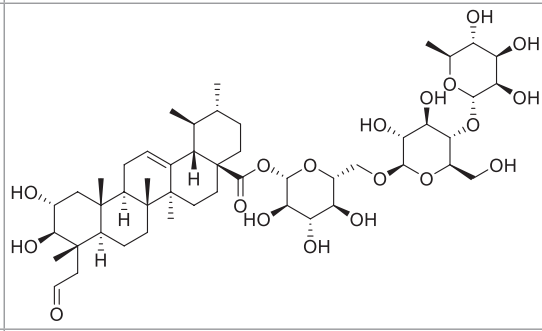
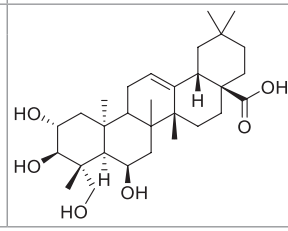
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
32	Centellasaponin C			[2] [108]
33	Centellasaponin D			[108] [2]
34	Centelloside E			[2]
35	Centelloside D			[2]
36	Chebuloside II			[2]

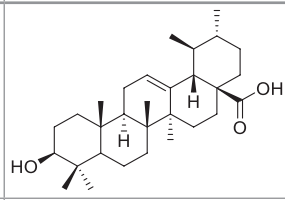
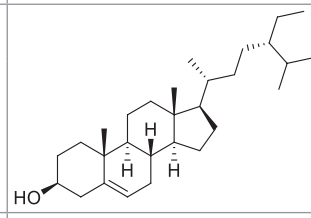
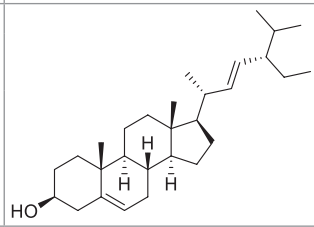
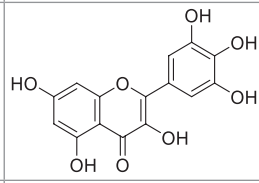
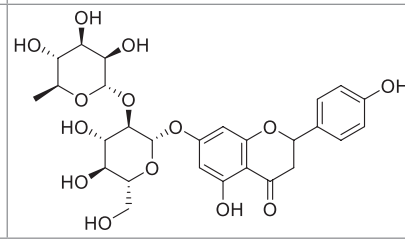
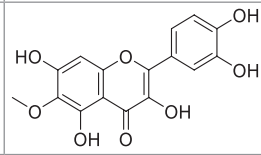
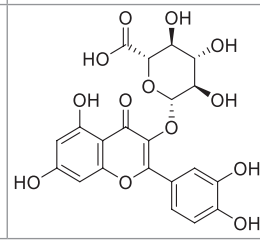
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
37	Madecassic acid (brahmic acid)			[53] [108] [110]
38	Pomolic acid		Aerial parts	[114]
39	Quadranoside IV			[2]
40	Scheffuroside F			[2]
41	Scheffuroside B			[108]
42	Terminolic acid			[53] [108]

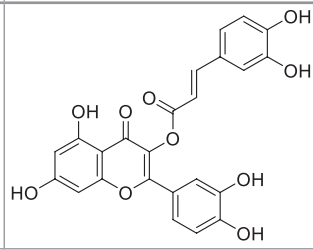
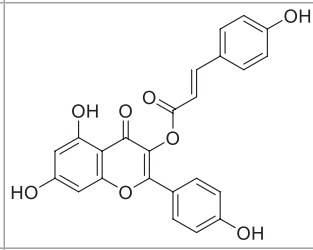
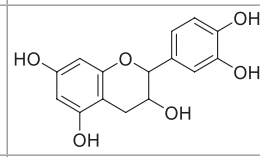
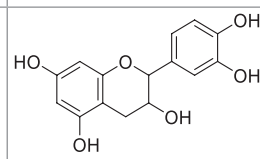
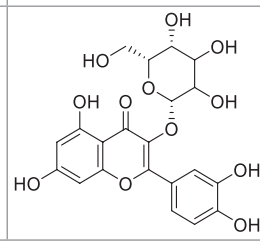
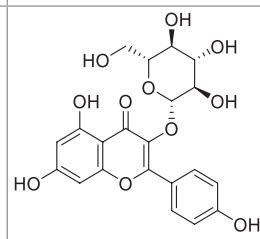
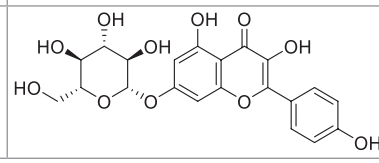
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
43	Ursolic acid		Aerial parts	[114]
44	Sitosterol		Aerial parts	[114]
			Aerial parts	[116]
45	Stigmasterol			[110]
			Aerial parts	[116]
				[115]
		Polyphenolic compounds		
46	Myricetin			[110]
47	Naringin		Leaves	[117]
48	Patuletin			[110]
49	Querectin-3-O-β-D-glucuronide		Leaves	[111]

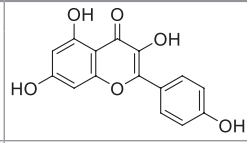
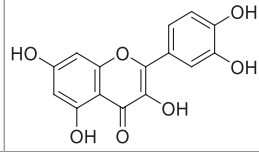
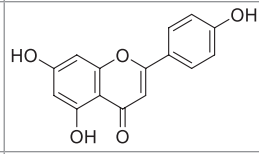
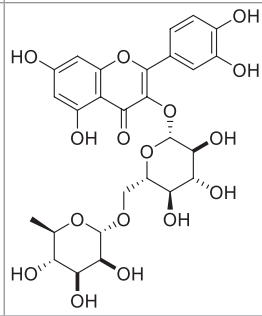
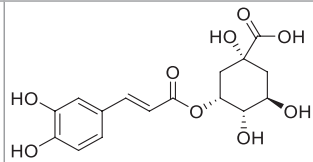
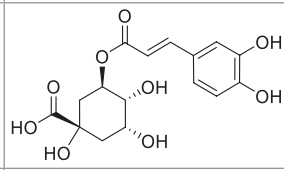
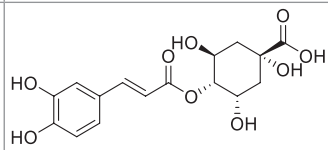
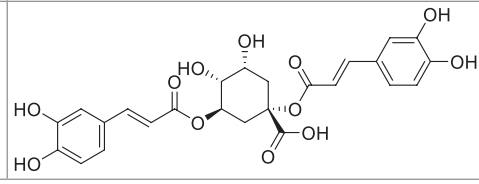
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
50	Castillicetin			[110]
51	Castilliferol			[110]
52	Catechin			[24]
53	Epicatechin			[24]
54	3-glucosylquercetin			[110]
55	3-glucosylkaemferol			[110]
56	7-glucosylkaemferol			[110]

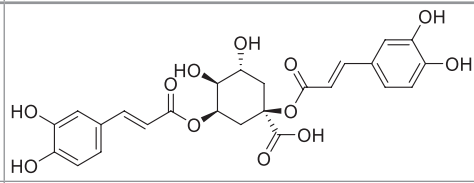
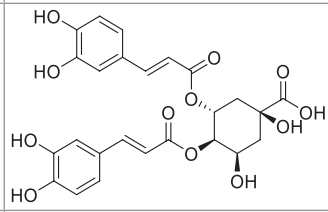
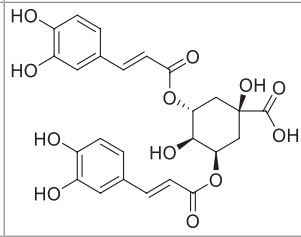
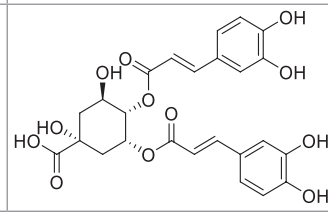
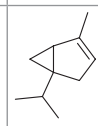
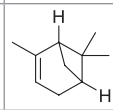
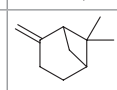
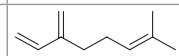
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
57	Kaempferol			[110]
				[24]
58	Quercetin		Leaves	[117]
				[110]
59	Apigenin			[110]
60	Rutin		Leaves	[117]
				[110]
61	Neochlorogenic acid (5-O-dicaffeoylquinic Acid)		Leaves	[23]
62	Chlorogenic acid (3-O-caffeoylquinic acid)		Leaves	[23]
63	Cryptochlorogenic acid, (4-O-caffeoylquinic acid)		Leaves	[23]
64	1,3-dicaffeoylquinic acid		Leaves	[23]

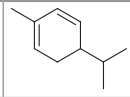
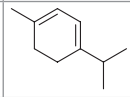
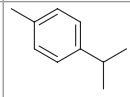
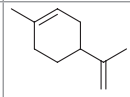
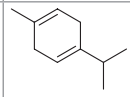
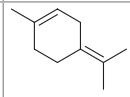
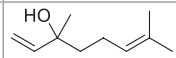
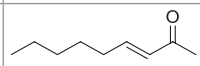
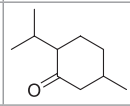
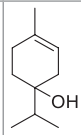
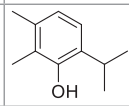
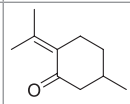
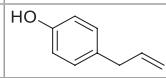
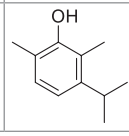
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
65	1,5-dicaffeoylquinic acid		Leaves	[23]
66	3,4-dicaffeoylquinic acid (isochlorogenic acid B)		Leaves	[23]
67	3,5-dicaffeoylquinic acid (isochlorogenic acid A)		Leaves	[23]
68	4,5-dicaffeoylquinic acid (isochlorogenic acid C)		Leaves	[23]
		Essential oils		
69	α-Thjuene		Fresh mature plants	[113]
70	α-Pinene		Fresh mature plants	[113]
71	Camphene		Fresh mature plants	[113]
72	β-Pinene		Fresh mature plants	[113]
73	Myrcene		Aerial parts	[114]
				[53]
			Fresh mature plants	[113]

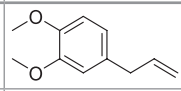
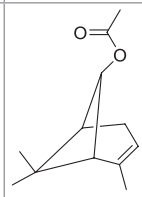
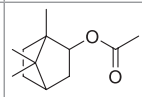
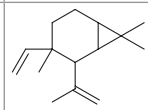
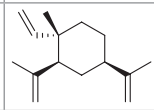
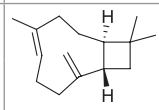
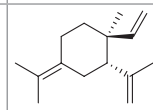
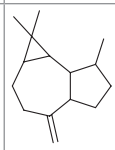
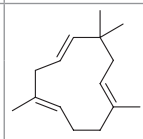
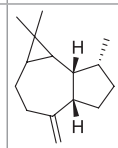
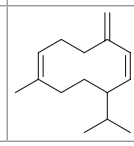
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
74	α-Phellandrene		Fresh mature plants	[113]
75	α-Terpinene		Fresh mature plants	[113]
76	p-cymene		Fresh mature plants	[113]
77	Limonene		Fresh mature plants	[113]
78	γ-Terpinene		Fresh mature plants	[113]
79	Terpinolene		Fresh mature plants	[113]
80	Linalool		Fresh mature plants	[113]
81	3-nonen-2-one		Fresh mature plants	[113]
82	Menthone		Fresh mature plants	[113]
83	Terpinen-4-ol		Fresh mature plants	[113]
84	Methyl thymol		Fresh mature plants	[113]
85	Pulegone		Fresh mature plants	[113]
86	Chavicol			[53]
87	Methyl carvacrol		Fresh mature plants	[113]

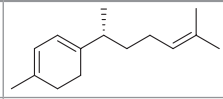
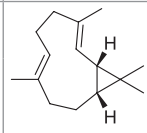
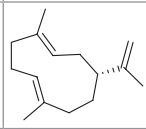
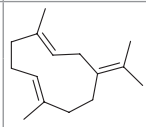
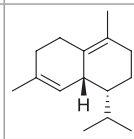
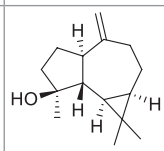
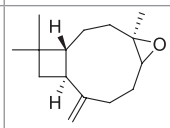
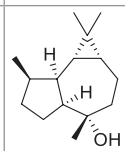
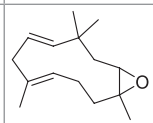
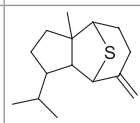
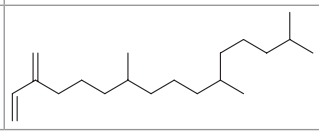
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
88	Methyleugenol			[53]
89	Chrysanthenyl acetate		Fresh mature plants	[113]
90	Bornyl acetate		Fresh mature plants	[113]
91	Bicycloelemene		Fresh mature plants	[113]
92	β-Elemene		Fresh mature plants	[113]
93	β-Caryophyllene		Aerial parts	[114]
			Fresh mature plants	[113]
94	γ-Elemene		Fresh mature plants	[113]
95	Aromadendrene		Fresh mature plants	[113]
96	α-Humulene		Aerial parts	[114]
			Fresh mature plants	[113]
97	Allo-aromadendrene		Fresh mature plants	[113]
98	Germacrene D		Fresh mature plants	[113]

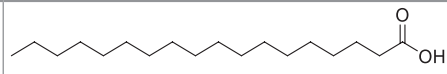
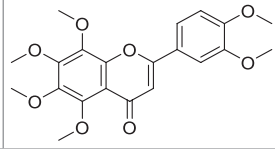
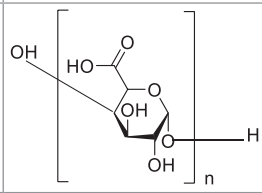
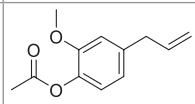
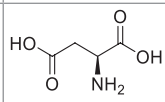
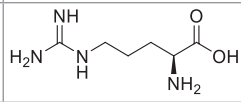
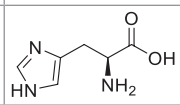
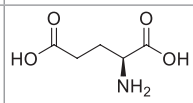
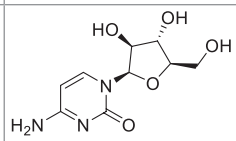
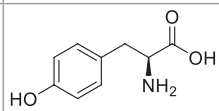
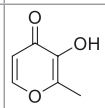
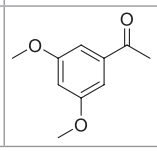
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
99	γ-Curcumene		Fresh mature plants	[113]
100	Bicyclogermacrene		Aerial parts	[114]
			Fresh mature plants	[113]
101	Germacrene A		Fresh mature plants	[113]
102	Germacrene B		Aerial parts	[114]
			Fresh mature plants	[113]
103	δ-Cadinene		Fresh mature plants	[113]
104	Spauthulenol		Fresh mature plants	[113]
105	Caryophyllene oxide		Fresh mature plants	[113]
106	Viridiflorol		Fresh mature plants	[113]
107	Humulene epoxide		Fresh mature plants	[113]
108	Mintsulfide		Fresh mature plants	[113]
109	Neophytadiene		Fresh mature plants	[113]

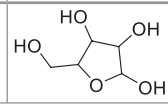
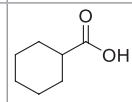
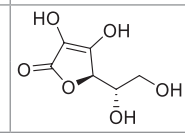
(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
110	n-octadecanoic acid		Whole aerial parts of	[118]
		Other compounds		
111	Nobiletin		Leaves	[106]
112	Pectic acid			[115]
113	Eugenol acetate			[53]
114	Aspartic acid		Aerial parts	[116]
115	Arginine		Aerial parts	[116]
116	Histidine		Aerial parts	[116]
117	Glutamic acid		Aerial parts	[116]
118	Arabinoside			[108]
119	Tyrosine		Aerial parts	[116]
120	Methyl pyromeconic acid (maltol)		Leaves	[106]
121	3′,5′-dimethoxyacetophenone		Leaves	[106]

(continued)

Table 25.1 (continued)

No.	Name of compounds	Structures	Plant parts	Ref. erences
122	Beta-D-ribofuranoside		Leaves	[106]
123	Cyclohexanecarboxylic acid		Leaves	[106]
124	Ascorbic acid		Aerial parts	[116]
				[115]

It is also well-documented for its remarkable uses in the African Traditional Medicine. In Tanzania, the decoction of whole plant is believed to be efficacious in the treatment of malaria [36]. In Cameroon, its leaves are applied to treat pharyngitis and dysmenorrhoea convulsion [37]. Furthermore, the decoction of whole plant, is also taken as an effective treatment for vomiting and appendicitis [38]. In Uganda, the decoction of its leaves are used traditionally in the treatment of Ulcers [39]. In Guinean traditional medicine, the decoction of whole plant is prescribed for diabetes [40]. In Nigeria, its root decoction is taken as an effective treatment for haemorrhoids [41]. In South Africa, the root of CA is used by Bapedi traditional healers to treat diabetes mellitus [42]. Its root and leaves commonly known as Inyongwane, are also reported as a traditional drug to treat stomach disorders, dysentery and diarrhoea [43].

CA is also a well-known ethnomedicinal plant in the European Traditional Medicine. In Greece, its leaves commonly known as Sentella, which are widely applied as blood circulation stimulant and as a remedy for hypertension, phlebitis, uric acid, cellulites, and menstruation disorders [44]. In Russia, the leaves and barks of CA are employed as a traditional drug to treat depression [45]. In Turkey, its aerial parts are considered very useful in the treatment of neurological disorders [46].

Furthermore, in different geographical areas of American continent, remarkable reports of its traditional uses, are found. In Brazil, the leaves and barks of CA are extensively used in folk medicine to treat hypertension and as dermal lesions [47]. It is also taken as an effective treatment for weight loss among Mexican-American women [48]. In other geographical regions like Madagascar, its leaves popularly known as Viliantsahona, are applied externally to treat pimples [49]. In the folk phytotherapy of the Yaegl Aboriginal community in northern New South Wales, Australia, the leaves of it, also are prescribed for the treatment of arthritis [50].

The most frequent ethnomedicinal applications of CA appears to be treatment of gastrointestinal diseases, wounds, nervous system disorders, circulatory diseases, skin problems, respiratory *ailments*, diabetes and also as sedative in various ethnobotanical practices throughout the world. In addition to its medicinal usages, it is commonly eaten as fresh vegetable in Malaysia, China, Sri Lanka, India and Indonesia [51]. In Thailand, its aerial parts are eaten as wild food plant [52].

25.5 Pharmacological Aspects

So far, many *in vivo* and *in vitro* pharmacological studies have been investigated different biological activities of CA, mostly about its traditional uses. These studies, mainly focused on titrated extract of CA(TECA), total triterpenoid fraction of CA (TTFCA), total triterpenic fraction (TTF)

or each triterpene derivative, alone such as Asiatic acid, Asiaticoside, Madecassic acid, and Madecassoside [53].

It is revealed that CA acts on central nervous system (CNS) as neuroprotective agent, memory enhancer, tranquilizer, anxiolytic, sedative, antidepressant, anticonvulsant, and nerve regenerator in Alzheimer and Parkinson disease [54].The neuroprotective effects of CA has been revealed to be due to different mechanisms, such as reduction of oxidative stress parameters and inhibition of acetylcholine esterase activity [55], decrease of amyloid-β plaques and protection of cornu ammonis pyramidal neurons in the hippocampus [56, 57], modulation of neurotransmitter activity in the synaptic gap [58], and etc.

It also has lots of beneficial effects to prevent and reduce the complications of metabolic syndrome, considering its positive effects on the lipid profile [13], as the aqueous leaf extract of CA reduced the level of total cholesterol, triglyceride (TG), low-density lipoprotein (LDL) and elevated the level of high-density lipoprotein (HDL) in a high cholesterol-fed rat model. In an *in vitro* model of tumor necrosis factor alpha (TNF-α)-induced atherosclerosis in human aortic endothelial cells, Asiatic acid significantly reduced endothelial hyper-permeability and secretions of cell adhesion molecules [59]. Asiatic acid in a rat model of renovascular hypertension, ameliorated hemodynamic alterations, renin-angiotensin system (RAS) activation, inflammation and oxidative stress comparable with captopril (an angiotensin-converting enzyme (ACE) inhibitor) [60]. In a rat model of spontaneous type 2 diabetes, administration of Asiatic acid decreased insulin resistance and blood glucose and also protected islet cells from fibrosis [61].

Protective effects of CA against fibrosis, inflammation and hypertrophy in heart, kidney, liver and lung have been proven in some studies. Progression of myocardial remodeling and left ventricular hypertrophy attenuated with oral administration of Asiatic acid in a mouse model of cardiac hypertrophy [62]. Alcoholic extract of CA in a rat model of isoniazid induced-hepatorenal damage, significantly improved the histology of the liver and kidney, reduced the hematological and oxidative parameters and also lowered liver and kidney function markers to near-normal levels [63]. Also oral administration of Madecassoside in a mouse model of pulmonary fibrosis mediated by bleomycin, ameliorated the pathological changes and reduced the collagen deposition in the lungs [64].

It dramatically heals and prevents gastric ulcers in models of gastric lesions. Aqueous leaf extract of CA in a rat model of indomethacin-induced gastric ulceration, significantly protected and also accelerated the ulcer healing process [65]. Leaf extract of CA demonstrated anti-*Helicobacter pylori* activity both *in vivo* and *in vitro* [66] and also the work of Guo et al. (2015) showed that Asiatic acid had beneficial influences in amelioration of ulcerative colitis through anti-inflammatory effects [67].

CA is effective in acceleration of small, hypertrophic, diabetic or burn wound healing and also in treatment of scleroderma, psoriasis, cellulite, photoaging skin and striae gravidarum [68]. Dermatologic effects of the CA has been suggested to result from elevation of intracellular fibronectin content and collagen synthesis, increasing the fibroblast proliferation and epithelization, promotion of the tensile strength and also inhibition of inflammatory response in keloids and hypertrophic scars [69].

Furthermore, there are two studies carried out about the beneficial effects of Madecassoside and Asiaticoside in prevention of osteoporosis. Results showed that they suppressed receptor activator of nuclear factor-κB ligand (RANKL)-induced bone resorption and osteoclast differentiation in a dose-dependent manner [70, 71].

Taken together, it seems that CA performs beneficial effects in the most parts of body (Fig. 25.2), and plays a positive role in the human health. We attempt to provide a summary of CA pharmacological activities and mechanisms of action, categorized according to the body organs or systems which are presented in Tables 25.2 and 25.3.

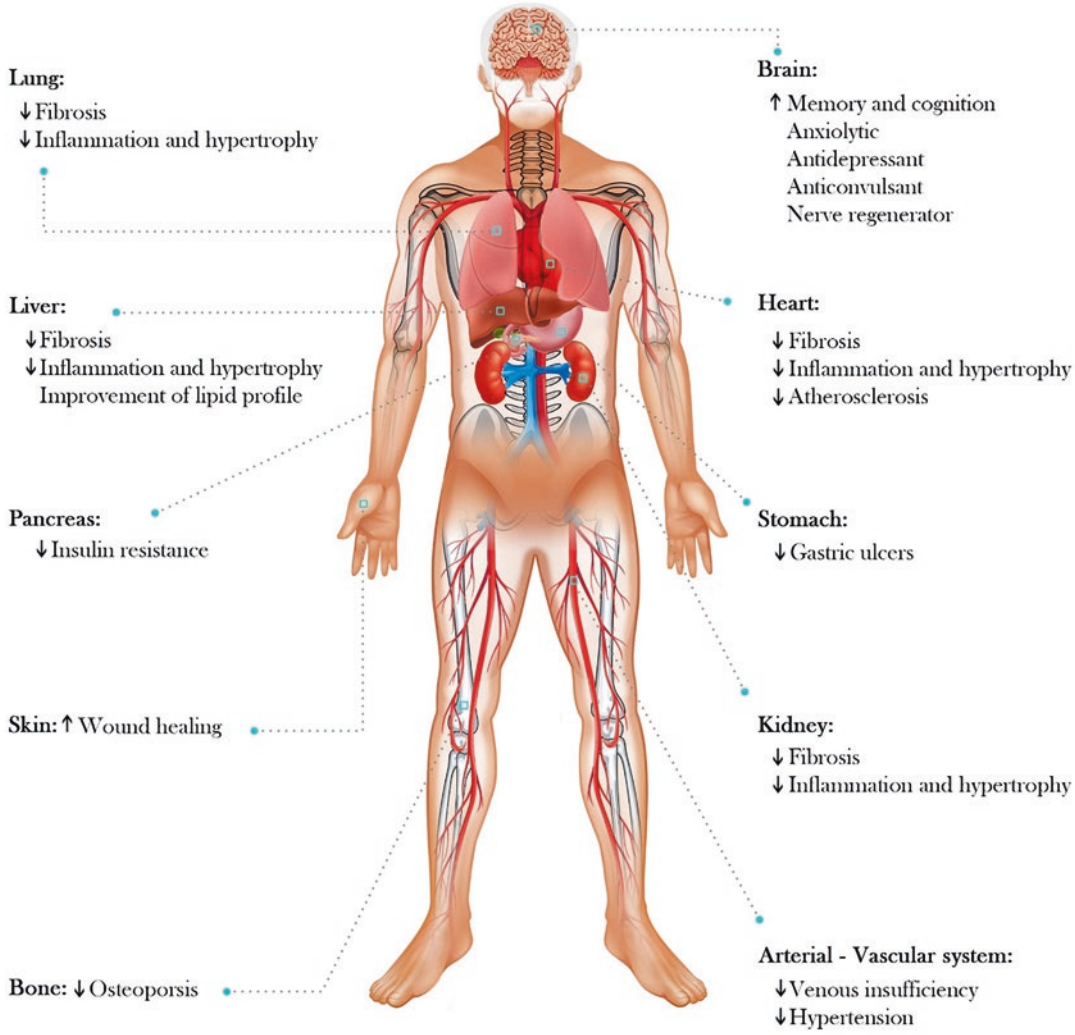


Fig. 25.2 Activity sites of *Centella asiatica* in human body. Note: This figure provided with the authors

25.6 Clinical Studies

Despite many *in vivo* and *in vitro* studies have been carried out about different pharmacological and traditional uses of CA, but there are only a limited number of clinical studies about some effects of CA. Most of these clinical studies include CNS, cardiovascular, and dermatological effects, which are categorized in details in Table 25.4.

The results of a systematic review and meta-analysis about the effects of CA on cognitive function and mood related outcomes extracted from eleven randomized controlled trials, demonstrated that CA improves mood and decreases anger. However, it's revealed that CA doesn't have significant effect on cognitive function in comparison with placebo, at all [72].

Daily oral administration of selected triterpenes of CA (120 to 240 mg) for 52 weeks in 43 type 2 diabetic patients significantly reduced total symptom scores of neuropathy and paresthesia [73]. Topical administration of Madecassoside 0.1% with vitamin C 5% cream for 6 months twice daily in 20 healthy postmeno-

Table 25.2 *In vivo* studies of *Centella asiatica*

Activity/Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	References
Central nervous system					
Anti-depressant	Extract of CA	Mouse and rat model	Anti-depressant activity	Modulation of D_2 receptor and cholinomimetic activity	[119]
Anti-anxiety	Aqueous extract of CA (25 mg/kg)	Mouse model,i.p.	↓spontaneous motor activity and delayed pentylenetetrazole-induced convulsions	–	[120]
Learning and memory	Fresh leaf aqueous extract of CA	Rat model / two compartment passive avoidance task	Improvement of learning and memory	↓norepinephrine, dopamine, serotonin and their metabolites	[121]
Cognitive Impairment	Aqueous extract CA (200 mg/kg)	Rat model, oral, QD, 14 days	↑learning and memory	↓lipid peroxidation, ↑endogenous antioxidant enzymes in brain	[122]
Anticonvulsant	Crude drug, methanolic and solubulised extract of CA (500, 1000 mg/kg)	Rat model, oral, 1, 3, 6, 24 hours	Anticonvulsantactivity comparable with phenytoin (30 mg/kg)	–	[123]
Cognitive impairment	Aqueous extract of CA (200, 300 mg/kg)	Rat model, oral, QD, 21 days	↑cognition	↓malondialdehyde, ↑glutathione and catalase	[124]
Cognitive impairment and epilepsy	Aqueous extract of CA (300 mg/kg)	Rat model, oral	↓seizure score, ↑learning and memory	–	[125]
Anti-depressant	TTFCA	Mouse model / forced swimming test	↓immobility time,	Amelioration of imbalance of amino acid levels	[126]
Anticonvulsant	Hydroalcoholic leaf extract of CA (100 and 200 mg/kg)	Mouse model, oral	Anticonvulsant, antioxidant, and central nervous system depressant actions	–	[127]
Nerve regeneration	Ethanolic extract of CA (300–330 mg/kg)	Rat model, oral, QD, 18 days	↑functional recovery, ↑axonal regeneration	–	[128]
Cognition	Aqueous extract of CA (200 mg/kg)	Mouse model, oral, QD, 15 days	↑learning and memory,	↑acetylcholine esterase activity, ↑dendritic arborization of hippocampal CA3 neurons	[129]
Anticonvulsant	Ethyl acetate fraction of CA	Mouse model, oral	Synergism with antiepileptic drugs (phenytoin, valproate, and gabapentin)	–	[130]
Anti-depressant	TTFCA	Rat model	↓corticosterone level in serum and ↑serotonin, norepinephrine, dopamine and their metabolites in brain	Ameliorating the function of HPA axis, ↑monoamine neurotransmitters	[131]

Anxiolytic	Methanolic and ethyl acetate extracts of CA and Asiaticoside	Rat model	Anxiolytic activity	–	[132]
Neuronal dendritic growth	Fresh leaf juice of CA (4 and 6 mL/kg)	Rat model, oral, QD, 4 and 6 weeks	↑dendritic length and dendritic branching in amygdaloid neurons	–	[133]
Neuronal dendritic growth	Fresh leaf extract of CA (v6 mL/kg)	Rat model, oral, QD, 6 weeks	↑dendritic length and dendritic branching in hippocampal CA3 neurons	–	[134]
Cognitive impairment	Aqueous extract of CA (150 and 300 mg/kg)	Rat model, oral, QD, 25 days	↓memory impairment	↓oxidative damage, ↑acetylcholinesterase activity	[135]
Alzheimer's disease	Extract of CA (2.5, 5 g/kg)	Mouse model, oral, QD, 2 and 8 months	↓amyloid β plaques in hippocampus	↓amyloid β neurotoxicity and antioxidant properties	[136]
Cerebral ischemia	Asiatic acid (30, 75, 165 mg/kg)	Mouse model, oral, 1 and 7 days	↓infarct volume and improvement of neurological outcome	↓blood–brain barrier permeability, ↓mitochondrial injury	[137]
Parkinson's disease	Aqueous extract of CA (300 mg/kg)	Rat model, oral, QD, 21 days	Neuroprotective effect	↓mitochondrial damage and oxidative stress	[138]
Epilepsy	n-hexane, chloroform, ethyl acetate and n-butanol extract of CA (200 mg/kg)	Rat model, oral, QD, 1 week	Anticonvulsant and neuroprotective activity	↑Na^+/K^+, Mg^{2+} and Ca^{2+} -ATPase activities	[139]
Parkinson's disease	Asiaticoside (15, 30 and 45 mg/kg)	Rat model, oral, QD, 14 days	Neuroprotective effects	Antioxidant activity, maintaining the metabolic balance of dopamine, and ↑ ratio of Bcl-2/Bax	[140]
Alzheimer's disease	Aqueous extract of CA (200 mg/kg)	Mouse model, oral, 2 weeks	Improvement of behavioral deficits	Attenuation of amyloid-β associated behavioral abnormalities	[141]
Alzheimer's disease	Aqueous extract of CA (100 mg/kg)	Rat model, oral, 6 weeks	↑time spent in goal quarter, ↓memory deficits	Antioxidant action	(121)
Anxiolytic and anti-depressant	Asiatic acid (30 mg/kg)	Rat model, i.p.	↑open arm time, ↓time mobile, ↑mean movement time, ↓fecal pellet output	Modulation of benzodiazepine site on the $GABA_A$ receptor	[142]
Migraine	Asiaticoside (10 and 30 mg/kg, 100 μg/rat)	Rat model, oral and nasal, acute and 7-days subacute	Significant anti-nociception activity, reversal of the nitroglycerine-induced hyperalgesia, ↓number of vocalization	Modulation of 5-HT1A and 5-HT1B	[58]
Cognitive impairment	Aqueous extract of CA (2 mg/mL) in drinking water	Mouse model, 5 weeks	↑cognition	↑expression of mitochondrial and antioxidant response genes in the brain and liver	[143]
Anxiolytic	ECa233	Mouse model	Anxiolytic activity	Modulation of neuronal activity on intercalated neurons of amygdala	[144]

(continued)

Table 25.2 (continued)

Activity/Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	References
Neuroprotection	Asiatic acid (30 mg/kg)	Rat model, oral, QD, 20 and 40 days	Inhibition of p21 (cell cycle arrest) and MDA (lipid peroxidation product) in the hippocampus that produced by 5-fluorouracil	↑Notch1, SOX2, nestin, DCX, and Nrf2 expression in the hippocampus	[145]
Cognitive impairment	Aqueous extract of CA (2 mg/mL) in drinking water	Mouse model, 2 weeks	Improvement of memory and executive function	↑synaptic density, ↓mitochondrial dysfunction, ↓oxidative stress	[146]
Learning And memory	Ethanolic extract of CA (30 mg/kg)	Rat model, oral, QD, 14 days	Improvement of spatial learning and memory, not significant effect on locomotor activity	↑AMPA receptor GluA1 subunitin the CA1 and CA2 sub regions of the hippocampus	[147]
Parkinson's disease	ECa 233 (10, 30, 100 mg/kg)	Rat model, oral, QD, 20 days	Protection of locomotor deficits, ↓dopaminergic neuronal death in the substantianigra	↑mitochondrial complex I activity, ↑antioxidants activity	[148]
Alzheimer's disease	Aqueous extract of CA (200, 400, 800 mg/kg)	Rat model, oral, QD, 70 days	Alleviation of cognitive impairments	↓pathological changes in the hippocampus CA1 pyramidal cells	[149]
Alzheimer's disease	Aqueous extract of CA(2 mg/mL) in drinking water	Mouse model, 14 days	↑learning and memory	↓amyloid-β plaques in the hippocampus, ↓mitochondrial dysfunction, ↓oxidative stress	[56]
Learning and memory	Hydroalcoholic extract of CA (100, 300, 600 mg/kg)	Rat model, oral, QD, 14 days	↑learning and memory	↑expression of AMPA receptors GluA1 and GluA2 subunits, differential expression of NMDA receptors GluN2 A and GluN2B subunits in the hippocampal subfields and entorhinal cortex	[57]
Learning and memory	ECa 233 (10, 30 mg/kg)	Rat model, oral, BID, 30 days	↑learning and memory	↑synaptic plasticity and plasticity-related proteins in hippocampus	[150]
Neuroprotection	Ethanolic leaf extract of CA (150,300, 600 mg/kg)	Rat model, oral, QD, 28 days	Neuroprotection in the hippocampus	↓TNF-α and ↑brain-derived neurotropic factor in the hippocampus	[151]
Alzheimer's disease	Hydroalcoholic extract of CA (200, 400, 800 mg/kg)	Rat model, QD, 10 weeks	↓cognitive deficits, ↓morphological aberrations in the CA3 region of hippocampus	↓GSK-3β, ↑protein phosphatase2	[149]
Amnesia	Ethanolic extract of CA (250, 500 mg/kg)	Mouse model, oral, 14 days	Neuroprotective effects	↑antioxidant activity, inhibition of acetylcholine esterase	[152]

Gastrointestinal					
Gastric ulcer	CA	Rat model	Significantly inhibition of gastric ulceration mediated by cold restraint stress	GABAergic activity of CA	[153]
Gastric ulcer	Alcoholic root extract of CA (100 mg/kg)	Rat model, oral, QD, 16 days	↓number and severity of the ulcers	Anti-stress activity of CA	[154]
Gastric ulcer	Aqueous leaf extract of CA (250, 500 mg/kg)	Rat model, oral, QD	Inhibition of gastric ulceration, 42.6% and 100%, respectively	–	[155]
Gastric ulcer	Aqueous extract of CA (50, 250, 500 mg/kg)	Rat model, oral, QD	Prevention of gastric lesions	Anti-inflammatory effect through reduction of mucosal MPO	[156]
Gastric ulcer	Fresh juice of CA (200, 600 mg/kg)	Rat model, oral, BID, 5 days	Significantly inhibition of gastric ulceration	Augmentation of defensive mucosal factors (↑gastric mucin secretion and mucosal cell glycoproteins)	[157]
Gastric ulcer	Aqueous extract of CA (100, 250 mg/kg) or Asiaticoside (5, 10 mg/kg)	Rat model, oral, QD, 7 days	Accelerating the ulcer healing process	Anti-inflammatory effect through reduction of iNOS synthesis	[158]
Gastric ulcer	Aqueous leaf extract of CA (10, 20 mg/kg)	Rat model, oral, QD	Prevention of gastric ulceration mediated by indomethacin	–	[159]
Gastric ulcer	Alcoholic leaf extract of CA (100, 200, 400 mg/kg)	Rat model, oral, QD	Significantly protection of the gastric mucosa	–	[160]
Gastric ulcer	CA, *Hericiumerinaceus* and *Amomumvillosum*	–	Significantly inhibition of gastric ulcer	–	[161]
Ulcerative colitis	Asiatic acid (3, 10, 30 mg/kg)	Mouse model, oral, QD, 10 days	Significantly ameliorates ulcerative colitis	↓inflammatory cytokines (IFN-γ, TNF-α, IL-1β, and IL-6), ↓caspase-1 activation in peritoneal macrophages	[67]
Anti-*Helicobacter pylori*	Leaf extract of CA (50 mg/kg)	Mouse model, oral, 3 weeks	↓*H. pylori* colonization in mice gastric mucosa	–	[66]
Gastric ulcer	Aqueous leaf extract of CA (50, 250 mg/kg)	Rat model, oral, QD	Significantly gastroprotective	↓malondialdehyde, TNF, COX-2 and iNOS	[65]
Cardiovascular					
Cardiomyopathy	Aqueous extract of CA (200 mg/kg)	Rat model, oral	Restored the enzyme activities to near normal levels	–	[162]
Myocardial Infarction	Alcoholic extract of CA (100–1000 mg/kg)	Rat model, oral	↓necrosis of the myocardium, ↓lipid peroxide levels in serum and heart tissue	Free radical scavenging activity or enhancing the endogenous antioxidants level	[163]

(continued)

Table 25.2 (continued)

Activity/Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	References
Myocardial failure	Aqueous extract of CA (200 mg/kg)	Rat model, oral	Cardioprotective effect against myocardial failure	Inhibition of oxidative stress and mitochondrial dysfunction	[164]
Hyperlipidemia	CA (1000, 2000 mg/kg)	Rat model, oral, QD	↓TG and total cholesterol	–	[10]
Cardiac hypertrophy	Asiatic acid (100 mg/kg)	Mouse model, oral, 2 weeks	↓(heart weight to body weight, interventricular septal end-diastolic dimension, left ventricular end diastolic posterior wall dimension and left ventricular end-diastolic diameter)	Inhibition of TGF- β1	[165]
Cardiac hypertrophy	Asiatic acid)100 mg/kg)	Mouse model, oral	Attenuation of the pressure overload progression of left ventricular hypertrophy and heart failure	Blocking the activation of mitochondrial and death receptor-dependent apoptotic signaling pathways, blocking of TGF-β1/Smad and IL-6 signaling activation	[62]
Myocardial infarction	Asiatic acid)5, 25, 50 mg/kg)	Rat model, oral, QD, 4 weeks	Preservation of cardiac function and inhibition of left ventricular remodeling	Blocking the phosphorylation of p38 MAPK and ERK1/2 in the infarct border zone of the ischemic myocardium	[166]
Hyperlipidemia	Aqueous extract of CA (0.25, 0.5, 1 g/kg)	Rat model, oral, QD, 4 weeks	↓(TG, total cholesterol, LDL), ↑HDL	–	[13]
Hypertension	Asiatic acid (30 mg/kg)	Rat model, oral, QD, 4 weeks	Amelioration of hemodynamic alterations, RAS activation, inflammation and oxidative stress	Direct effect on RAS activation, inflammation and oxidative stress and/or ACE inhibitory effect on Angiotension II-AT_1 receptor-NADPH oxidase-NF-κB pathway	[60]
Myocardial ischemia/reperfusion	Asiatic acid (2.5, 5, 10 mg/kg)	Rat model of ischemia/reperfusion, oral, single dose pretreatment	↑cardiac function indexes, ↓size of myocardial infarction, ↓LDH and ↓creatine kinase activities, ↓cardiomyocyte apoptosis	Activation of Akt/GSK-3β signaling pathway in the myocardium to inhibit glycogen breakdown through PPARɣ activation and GLUT4 translocation	[167]
Liver					
Liver fibrosis	Total glucosides of CA	Rat model, 6 weeks	Improvement of histology, ↓AST, ALT and hyaluronic acid to near-normal levels	–	[168]
Liver damage	Aqueous extract of CA (100 mg/kg)	Mouse model	Preserves hepatocytes from abnormality, ↓binucleated cells	–	[169]

Acute liver injury	Asiaticoside (5, 10, 20 mg/kg)	Mouse model, QD, 3 days	Decrease of the magnitude of hepatocytes necrosis and leukocyte infiltration, ↓TNF-α, ALT, AST, caspase-3 activity and MAPK	Inhibition of TNF-α and MAPKs	[170]
Liver fibrosis	Asiatic acid (0.5, 2, 8 mg/kg)	Rat model, oral, QD, 6 weeks	Anti-fibrotic activity	Blocking of TGF-β/Smad signaling pathway	[171]
Liver injury	Aqueous extract of CA (200 mg/kg)	Rat model, oral, QD, 7 days	Significantly restored marker enzyme levels, total protein and albumin levels	Antioxidant action	[172]
Liver and immune organ damage	Triterpenesaponins of CA (250 mg/kg)	Rat model, oral, QD, 30 days	Improvement of histology of the liver and immune organs	Restoring the cytokine production and antioxidant system	[107]
Liver and kidney damage	Ethanolic extract of CA (100 mg/kg)	Rat model, oral, QD, 30 days	Improvement of histology, ↓(hematological parameters, oxidative status, liver and kidney function markers to near-normal levels)	–	[63]
Liver injury	Aqueous leaf extract of CA (100, 200 mg/kg)	Rat model, oral, QD, 5 days	Hepatoprotective	↑antioxidant enzymes, ↓inflammatory mediators	[173]
Cardiac and hepato-renal injury	Asiatic acid (5, 10, 20 mg/kg)	Rat model, oral, QD, 7 days	Improvement of histology, ↓(oxidative stress, serum creatinine and serum blood urea nitrogen)	↑Nrf2 protein expression	[174]
Liver fibrosis	Asiatic acid (5, 10 mg/kg)	Rat model, 6 weeks	Attenuates liver injury and fibrosis	Regulation of Bcl-2/Bax and PI3K/AKT/mTOR signaling pathway	[175]
Acute liver failure	Madecassoside (20, 40 mg/kg)	Mouse model, oral, QD, 10 days	Suppressing the production of inflammatory cytokines and recovering antioxidant enzyme activity, ↓iNOS and COX-2	Inhibition of p38/NF-κB and activation of Nrf2/HO-1 signaling pathways	[176]
Kidney					
Chronic renal failure	CA	Rat model, enema, QD, 30 days	Improvement of electrolyte levels, hematocrit, RBC counts and hemoglobin content	–	[177]
Diabetic nephropathy	Asiatic acid	Rat model	Protective effects	Upregulation of nephrin in the podocyte, inhibition of JNK signaling pathway	[178]
Tubulointerstitial fibrosis	Asiatic acid (4, 16 mg/kg)	Mouse model, oral, QD, 6 days	↓tubular injury, fibroblast activation and extracellular matrix accumulation	↓α-smooth muscle actin by inhibition of Smad-dependent TGF-β1 signaling pathway	[179]
Nephropathy	Asiatic acid (8, 16, 32 mg/kg)	Rat model, oral, QD, 4 weeks	Improvement of histology, ↓proteinuria, ↓total cholesterol, ↑serum albumin,	↑mRNA and protein levels of synaptopodin, nephrin and podocin, ↓mRNA and protein levels of desmin	[180]

(continued)

Table 25.2 (continued)

Activity/Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	References
Renal fibrosis	Asiatic acid (5 mg/kg) and naringenin	Mouse model, i.p., QD, 7 days	Anti-fibrotic effect on unilateral ureteral obstruction nephropathy	Rebalancing of TGF-β/Smad signaling pathway	[181]
Diabetic nephropathy	CA (5.6, 11.2, 16.8 mg/kg)	Rat model, oral, QD, 16 weeks	Prevention and cure of diabetic nephropathy	Regulating of TGF-β1/Smad signaling pathway	[182]
Diabetic nephropathy	Asiatic acid (10, 20, 40 mg/kg)	Rat model, oral, QD, 8 weeks	Protection of podocytes	Antioxidant effect, protection of podocytes, ↓activation of JNK signaling pathway	[183]
Acute kidney injury	Asiatic acid (50 mg/kg or 100 mg/kg)	Mouse model, i.p., single dose pretreatment	↓(serum creatinine, blood urea nitrogen and histological changes)	Anti-apoptosis and anti-inflammation mechanisms with upregulation of the apoptosis inhibitor survivin and suppression of IL-1β, TNF-α, MCP-1, caspase-1, and upregulation of Smad7	[184]
Lung					
Pulmonary fibrosis	Madecassoside (40 mg/kg)	Mouse model, oral, QD, 21 days	Amelioration of Bleomycin-induced pulmonary fibrosis	Increases the activity of PPAR-γ, which subsequently increases hepatocyte growth factor expression in colonic epithelial cells	[64]
Acute lung injury	Asiatic acid (25, 50, 100 mg/kg)	Mouse model	Inhibition of LPS-induced acute lung injury	Inhibition of the inflammatory cytokines production via blocking of the TLR4/NF-κB signaling pathway	[185]
Pulmonary inflammation	Asiatic acid (15, 30 mg/kg)	Mouse model, oral, QD, 11 days	Effectively inhibits pulmonary inflammatory response	Suppression of inflammatory mediators	[186]
Scleroderma	Asiatic acid (2, 8 mg/kg)	Mouse model, oral, QD, 2 weeks	Prevents the development of interstitial lung disease mediated by hypochlorous	Inhibition of Smad2/3 activation	[187]
Endocrine					
Diabetes	Asiatic acid (25 mg/kg)	Rat model, oral, QD, 2 weeks	↓blood glucose, ↑serum insulin	Preserves β-cells in the pancreatic islet by inducing AKT kinase activation expression and Bcl-xL expression	[170]
Diabetes	Ethanolic extract of CA (200 mg/kg)	Rat model, oral, QD, 15 days	Significantly anti-diabetes activity but not significantly influence on the level of serum insulin	–	[188]
Diabetes	Asiatic acid (5, 10, 20 mg/kg)	Rat model, oral, QD, 45 days	↓ blood glucose, ↑ insulin secretion from β-cells and modulated hepatic enzymes including AST and ALT and ALP responsible for glucose metabolism to near-normal levels	–	[189]

Diabetes	Asiatic acid (20 mg/kg)	Rat model, oral, QD	↓lipid peroxidation and hyperglycemia, ↑antioxidant status	–	[190]
Diabetes	Ethanolic extract of CA(250, 500, 1000 mg/kg)	Rat model, oral, BID, 4 weeks	↓(hyperglycemia, serum LDL and cholesterol), ↑HDL	Inhibition of intestinal disaccharidase enzymes and α-amylase, glucose fiber binding	[191]
Hypoglycemic activity	CA (1000, 2000 mg/kg)	Rat model, oral	↓plasma glucose	–	[10]
Diabetes	Madecassic acid (0.05% and 0.1% diets)	Mouse model, oral, QD, 6 weeks	↓(plasma glucose, TG, cholesterol, oxidative and inflammatory stress), ↑plasma insulin	—	[192]
Spontaneous type 2 diabetes	Asiatic acid (25 mg/kg)	Rat model, oral, QD, 4 weeks	Improvement of insulin resistance, ↓glucose level and islet fibrosis	Inhibition of fibronectin (a key protein related to islet fibrosis)	[61]
Diabetes	CA (300 mg/kg)	Rat model, oral, QD, 4 weeks	Reversed the glucose and lipid levels, tricarboxylic acid cycle and amino acid metabolic disorders, ↑production of insulin	–	[193]
Type 2 diabetes	Methanolic leaf extract CA (500, 1000 mg/kg)	Rat model, oral, QD, 14 days	↑activity of muscle glycolytic enzymes, ↑glycogenesis in the skeletal muscle, ↓histological damage of skeletal muscle fibers	↑skeletal muscle glycogen with target muscle glucose and glycogen metabolism	[194]
Skin					
Wound healing	Cothyline®; Asiaticoside	Guinea pig model, topical, TDS, 1 week	Accelerated the healing process	–	[195]
Wound healing	Aqueous extract of CA (1%)	Rat model, topical ointment, cream and gel, TDS, 24 days	↑cellular proliferation, collagen synthesis and tensile strength	–	[196]
Wound healing	Asiaticoside (0.2, 0.4%)	Rat model, topical solution, BID, 7 days	↑(hydroxyproline content, tensile strength, collagen content and epithelization)	↑levels of enzymatic and non-enzymatic antioxidant	[197, 198]
Wound healing	Asiaticoside (0.2%)	Guinea pig model, topical solution, BID, 7 days	↑(hydroxyproline content, tensile strength, collagen content and epithelization)	–	[197]
Wound healing	Asiaticoside (1 mg/kg)	Guinea pig model, oral, 7 days	↑(hydroxyproline content, tensile strength, collagen content and epithelization)	–	[197]
Wound healing	TECA (asiatic acid, madecassic acid and asiaticoside)	Rat model, SC, 28 days	↑(dry weight, DNA, protein, hydroxyproline, collagen, peptidichydropr oline,glycosaminoglycan synthesis)	–	[199]

(continued)

Table 25.2 (continued)

Activity/Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	References
Wound healing	Ethanolic leaf extract of CA	Rat model, oral, 10 days	↑(epithelization, contraction, tensile strength)	–	[200]
Burn wound healing	Madecassoside (6, 12, 24 mg/kg)	Mouse model, oral, 20 days	Significant wound-healing activity	Antioxidant activity, collagen synthesis and angiogenesis	[201]
Burn wound healing	Asiaticoside (100 mg)	Mouse model, topical ointment, 19 days	Burn wound healing most strongly at very low concentrations	↑angiogenesis	[202]
Wound healing	Hexane, methanolic, ethyl acetate and aqueous extracts of CA	Rat model, topical, 14 days	↑wound healing in both incision and burn wounds	–	[203]
Wound healing	Methanolic extract of CA	Rat model, electrospun gelatin Nanofibers containing CA	Presented the highest recovery rate	Promoting fibroblast proliferation and collagen synthesis and exhibits antibacterial activity	[204]
Burn wound healing	Asiaticoside or madecassoside (500 μL)	Rat model, topical, QD, 14 days	↑wound healing	–	[205]
Others					
Osteoporosis	Madecassoside (10 mg/kg)	Mouse model of ovariectomy,i.p., QOD, 6 weeks	Protection and prevention of estrogen deficiency-inducedbone loss	Inhibition of osteoclast activity	[70]
Glaucoma	Asiatic acid (2×10^{-5} and 2×10^{-4} μmol)	Rat model, intravitreally injection	↑retinal ganglion cell survival and function, prevention of retinal ganglion cell apoptosis	Upregulating the expression of the antiapoptotic protein Bcl-2 and downregulating the expression of the pro-apoptotic proteins Bax and caspase-3	[206]

Table 25.3 *In vitro* studies of *Centella asiatica*

Activity / Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	Ref. erences
Central nervous system					
Neuronal damage	Ethanolic extract of CA (100 μg/mL)	Human SH-SY5Y cell lines	↑neurite outgrowth	–	[128]
Alzheimer's disease	Hydroalcoholic extract of CA (100–150 μg/mL)	Spectrophotometric method of Ellman	Inhibition of acetylcholinesterase with IC50 values of 19.87 μg/mL in comparison with Physostigmine (IC50 value of 0.076 μg/mL)	–	[207]
Anxiolytic	Aqueous and ethanolic extracts of CA (1 mg/mL)	Rat brain homogenate assay, spectrophotomethric method	Stimulation of glutamic acid decarboxylase activity by over 40%	–	[208]
Alzheimer's disease	Leaf extract of CA (1, 5, 10, 100, 200 μg/mL)	Neuroblastoma cell line expressing amyloid-β and rat embryonic cortical primary cell culture	↑phosphorylation of cAMP response element binding protein (CREB)	ERK/RSK signaling pathway	[209]
Neuropsychiatric disease	Aqueous extract of CA (125–500 mg/mL)	Rat cerebellum, radio-enzymatic assay	Inhibition of Ca^{2+}-independent PLA_2 and cytosolic PLA_2	–	[210]
Alzheimer's disease	Aqueous leaf extract of CA (100 μg)	Thioflavin-T assay and transmission electron microscopy	Not inhibition of amyloid-β aggregation, not disintegration of preformed fibrils	–	[211]
Alzheimer's disease	Aqueous extract of CA (200 μg/mL)	SH-SY5Y and MC65 human neuroblastoma cells	Protection of SH-SY5Y and MC65 cells from toxicity induced by exogenously added and endogenously generated amyloid-β, respectively, prevention of intracellular amyloid-β aggregate formation in MC65 cells	–	[141]
Neuroprotection	Caffeoylquinic acid andaqueous extract of CA (50 and 100 ug/mL)	MC65, SH-SY5Y and neuroblastoma cells	↓intracellular ROS and Ca^{2+} levels, ↑expression of antioxidant response genes	Attenuation of amyloid-β-induced oxidative stress and mitochondrial dysfunction	[212]
Parkinson's disease	Asiatic acid (0.01, 0.1, 5, 10, and 100 nM)	SH-SY5Y cells	↓ ROS, mitochondrial dysfunction and apoptosis	Antioxidant, mitoprotective and anti-apoptotic properties	[55]
Gastrointestinal					
Ulcerative colitis	Asiatic acid	Human monocytic THP-1 cells	Inhibition of NLRP3 inflammasome (multi-protein complexes which activates caspase-1 and maturates pro-inflammatory cytokine IL-1β), ROS and mitochondria dysfunction	–	[67]

(continued)

Table 25.3 (continued)

Activity / Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	Ref. erences
Anti-*Helicobacter pylori*	Leaf extract of CA (2 mg/mL)	Agar dilution method	Inhibition of *H. pylori*	–	[66]
Cardiovascular					
Arteries and vascular disease	Alcoholic extract of CA	Normal human colon fibroblasts cells	↑fibroblast cell attachment and tissue plasminogen activator	–	[213]
Hyperlipidemia	Alcoholic extract of CA (20 µL)	Pancreatic lipase solution (6 µL)	Anti-lipase activity with IC_{50} of 759.14 µg/mL	–	[10]
Cardiac hypertrophy	Asiatic acid (2.5–30 µM)	Neonatal rat ventricular myocytes	Significantly attenuation of hypertrophic response in cardiomyocytes	↓ANP mRNA expression, ↓TGF-β1-stimulated increase in the levels of p38 and ERK1/2 phosphorylation, ↓NF-κB binding activity	[165]
Atherosclerosis	Asiatic acid (10–40 µM)	Human aortic endothelial cells	↓endothelial hyper-permeability and secretions of cell adhesion molecules protein expression that triggered by TNF-α (10 ng/ml)	Inhibition of NFκB-activation	[59]
Liver					
Liver fibrosis	Asiatic acid (20, 30 µM)	Hepatic stellate cell line	Significantly inhibition of TGF-β1-inudced collagen I and α-smooth muscle actin mRNA expression	Blocking of TGF-β/ Smad signaling pathway	[171]
Kidney					
Anti-fibrotic	Methanolic extract of CA (1250 µg/mL)	Normal renal mammalian fibroblasts	Induced apoptosis	–	[214]
Renal fibrosis	Asiatic acid (20, 30 µM)	Renal tubular epithelial cells	Anti-fibrotic effect	Inhibition of Smad3 phosphorylation	[181]
Endocrine					
Hypoglycemic activity	CA (50 µg/mL)	Differentiating 3 T3-L1 adipocytes	↑lipogenesis as did Troglitazone (an anti-diabetic drug)	Reverses lipid metabolism disorders	[215]
Hypoglycemic activity	Alcoholic extract of CA (25, 50 µL)	Colorimetric method	Inhibition of α-glucosidase with IC_{50} of 42.27 µg/mL and α-amylase with IC_{50} of 536.51 µg/mL	–	[10]
Vascular complications of diabetes	CA (10, 25 µg/mL)	Human umbilical vein endothelial cells	↓expression and exposure of vascular adhesion molecules, ↑vascular reactivity	Inhibition of nitro-oxidative stress and down-regulation of MAPK and NF-κB activation	[216]

Skin					
Wound healing	TTFCA (25 μg/mL)	Human skin fibroblast	↑collagen and fibronectin synthesis	–	[217]
Wound healing	TECA (Asiatic acid, Madecassic acid and Asiaticoside)	Human foreskin fibroblast monolayer cultures	↑proline level and collagen synthesis	–	[199]
Wound healing	Asiatic acid, Madecassic acid, Asiaticoside (4.5, 4.5, 6 μg/mL respectively)	Human skin fibroblast	↑type I collagen synthesis	–	[218]
Wound healing	Asiaticoside, Madecassoside	Human fibroblast culture	↑type I and III collagen synthesis	–	[219]
Wound healing	Asiaticoside (40 μg/disk)	Chick chorioallantoic membrane model	↑angiogenesis	–	[197]
Wound healing	TECA (Asiatic acid, Madecassic acid, Asiaticoside, Madecassoside)	Human fibroblasts, DNA microarrays analysis	Stimulation of wound healing	Changes of genes expression responsible for angiogenesis and wound healing	[220]
Wound healing	Asiaticoside (30 μg/mL)	Human dermal fibroblasts, DNA microarray analysis	↑fibroblast proliferation and extracellular matrix synthesis	Changes of genes expression involved in cell proliferation, cell cycle and extracellular matrix	[221, 222]
Wound healing	Asiaticoside (10 μM)	Human dermal fibroblasts	↑type I collagen synthesis	Activation of TβR1 kinase-independent Smad pathway	[223]
Burn wound healing	Madecassoside (10, 30, 100 μmol/L)	Rat aortic ring assay	↑endothelial cell growth	–	[201]
Wound healing	Asiaticoside	THP-1 and human keratinocyte cell line	Influence on the level of cytokines, ↑angiogenesis, stimulation of VEGF production, MCP-1, IL-1	–	[202]
Wound healing	Ethanolic leaf extract of CA (50 mg/mL)	Human fibroblast cells	↑collagen synthesis	–	[224]
Hypertrophic scar	Asiaticoside (100, 250, 500 mg/L)	Keloid-derived fibroblasts, RT-PCR and Western blot and MTT	Normalization of healing process	Suppresses collagen expression and TGF-b/Smad signaling through inducing Smad7 and inhibiting TGF-βRI and TGF-βRII in keloid fibroblasts	[225]
Wound healing	Asiaticoside (62.5, 125, 250, 500, 1000 μM)	Human skin fibroblasts	↑migration and proliferation of the fibroblasts, ↑extracellular matrix synthesis	–	[226]
Wound healing	Aqueous extract of CA (1000 ppm)	Rabbit corneal epithelial cells	↑cell migration, changes of proliferation and cell cycle	–	[227]

(continued)

Table 25.3 (continued)

Activity / Disease	Active constituent	Study design	Result(s)	Proposed mechanism(s)	Ref. erences
Burn wound healing	Asiaticoside or Madecassoside (100 ng/mL)	The human acute monocytic leukemia cell line (THP-1)	↑monocyte chemoattractant protein-1 production, but not significant effect on vascular endothelial growth factor production	–	[205]
Anti-psoriatic	Aqueous extract of CA (210, 238 mg/mL) or Asiaticoside (8.4 μM) or Madecasosside (8.6 μM)	SVK-14 keratinocytes	Inhibition of growth of SVK-14 keratinocytes	–	[228]
UVB protection	TECA (1, 2, 5 μg/mL)	Normal human HaCaT keratinocytes	↓UVB toxicity	mRNA alteration caused inhibition of apoptosis and cell proliferation	[227]
Skin whitening	TECA (10, 25, 50, 100, 200 μg/mL), Asiatic acid (50 μM), Madecassic acid (200 μM), or Asiaticoside (200 μM)	B16F10 mouse melanoma cells	↓hyperpigmentation	↓melanin content in melanocytes by inhibition of tyrosinase mRNA expression	[229]
Others					
Periodontal tissue healing	Asiaticoside (25, 50, 100 mg/mL)	Human periodontal ligament cells	↑type I collagen synthesis and osteogenic differentiation	↑mRNA and proteins of fibronectin and type I collagen, ↓metalloproteinase-I mRNA expression	[230]
Osteoporosis	Madecassoside (5, 10 μmol/L), 5 days	Bone marrow monocytes	Suppression of RANKL-induced osteoclast differentiation dose-dependently	Inhibition of osteoclastogenesis via inhibition of NFATc1, c-Fos and blocking of Ca^{2+} oscillation, MAPK and NF-κB signaling pathways	[70]
Osteoporosis	Asiaticoside (5, 10, 20 μmol/L)	Bone marrow macrophages	Suppression of RANKL-induced bone resorption and osteoclast formation dose-dependently	Inhibition of Ctsk, Atp6v0d2, Nfatc1, Acp5, Dc-stamp and blocking of Ca^{2+} oscillation, NF-κB and NFATc1 signaling pathways	[71]

Table 25.4 Clinical studies of *Centella asiatica*

Activity /Disease	Active constituent	Study design	Participants	Result(s)	Ref. erences
Central nervous system					
Cognition	Extract of CA (250, 500, 750 mg)	Randomized, placebo-controlled, double-blind study, QD, 2 months	28 healthy elderly participants	↑cognition and mood	[231]
Mild cognitive impairment	CA (50 mg/kg)	Cross-design clinical study, 2 months	41 healthy middle age and elderly adults	Attenuate age-related decline in memory function	[232]
Mild cognitive impairment	Aqueous extract of CA (500 mg)	Oral, BID, 6 months	60 elderly subjects of age group 65 years and above	Improvement of mild cognitive impairment	[233]
Generalized anxiety disorder	Hydroalchoholic extract CA (500 mg)	Hamilton's brief psychiatric rating scale, oral, BID, 60 days	33 participants	↓anxiety related disorders, stress and depression	[9]
Gastrointestinal					
Gastric ulcer	Fresh juice of CA (60 mg/kg)	Oral, QD	15 patients with peptic or duodenal ulcer	Improvement in subjective symptoms (93%) and ulcers healing (73%)	[234]
Cardiovascular					
Vascular disease	TTFCA (60 mg/day)	Comparative clinico-instrumental study, 30 days	80 patients with venous insufficiency of the lower limbs	Improvement of venous reflux	[235]
Vascular disease	Extract of CA	Randomized controlled trials, TDS, 4 weeks	17 patients with chronic venous insufficiency	Improvement of clinical observations of venous insufficiency and venous tone	[236]
Vascular disease	TTFCA (60, 120 mg/day)	Randomized, double blind, placebo controlled, 8 weeks	94 patients with venous insufficiency of the lower limbs	↓pain, heaviness, edema and improve in venous distensibility	[237]
Vascular disease	TTFCA (60 mg/day)	Oral, QD, 3 months	20 patients with varicose vein	↑vascular integrity	[238]
Venous hypertension	TTFCA (60 mg)	Oral, TDS, 2 weeks	44 patients with venous hypertension	↑microcirculation and capillary permeability	[239]
Post phlebitic syndrome	TTFCA	Oral, QD, 3 weeks	Patients with postphlebitic syndrome	Significantly returned circulating endothelial cells to the normal level	[240]
Vascular disease	TFCA (30, 60 mg)	Randomized controlled trials, BID, 60 days	87 patients with chronic venous hypertensive microangiopathy	Effective	[15]

(continued)

Table 25.4 (continued)

Activity /Disease	Active constituent	Study design	Participants	Result(s)	Ref. erences
Vascular disease	CA, tocopherol, rutin and melilotus	Clinical practice, 30 days	30 patients with chronic venous insufficiency	Significantly improvement of the clinical symptom	[241]
Vascular disease	TTFCA (60 mg)	Randomized controlled trials, BID, 8 weeks	40 patients with severe venous hypertension, ankle swelling, and lipodermatosclerosis	↑microcirculation, ↓leg volume	[242]
Venous hypertension	TTFCA (30, 60 mg)	Prospective, placebo-controlled, randomized, TDS, 4 weeks	62 patients with venous hypertension	↓capillaryfiltrationrate, anklecircumferenceandankleedema	[243]
Vascular disease	TTFCA (60, 120 mg/day)	A single-blind, controlled, randomized placebo-study, 8 weeks	99 patients with venous hypertensive microangiopathy	Significantly improve of venous hypertensive microangiopathy	[242]
Atherosclerosis	TTFCA (100 mg) and Pycnogenol	Observational pilot substudy, oral, QD, 30 months	824 patients with femoral or carotid stenosing plaques	↓plaques progression, events (hospital admission, specialized care), the need for risk factor management and oxidative stress	[77]
Liver					
Chronic hepatic disorder	Titrated extract of CA	–	12 patients	Therapeutic effects in 5 patients	[244]
Endocrine					
Diabetic microangiopathy	TTFCA (60 mg)	Clinical prospective randomized trial, oral, BID, 6 months	50 diabetic microangiopathy patients	↑microcirculation, ↓ capillary permeability	[245]
Diabetic microangiopathy	TTFCA (60 mg)	Clinical prospective randomized trial, oral, BID, 12 months	50 diabetic microangiopathy patients	↓capillary filtration and edema	[14]
Diabetic wound	Capsule of Asiaticoside (100 mg),	Prospective randomized control study, oral, TDS, 21 days	200 diabetic wound patients	Effective in the wound healing promotion and suppresses the scars	[17]
Diabetic cystoid macular edema	CA (30 mg) with flavonoids and Melilotus	Prospective, interventional, controlled study, oral, QD, 14 months	40 diabetic cystoid macular edema patients without macular thickening	Preserving retinal sensitivity	[246]

Diabetic foot ulcer	Cream of CA and *Plectranthusamboinicus*	Single-center, randomized, topical, BID, 2 weeks	24 diabetic patients with foot ulcer	Slightly improvement but not significant	[247]
Diabetic cystoid macular edema	CA (15 mg) with flavonoids and Melilotus	Prospective, interventional, controlled study, oral, QD, 36 months	70 diabetic cystoid macular edema patients without macular thickening	Preserving retinal sensitivity	[19]
Diabetic neuropathy	Selected triterpenes of CA (120 escalated to 240 mg)	Randomized, double-blind, placebo-controlled, pilot clinical study, oral, 52 weeks	43 type 2 diabetic patients	↓total symptom score and paresthesia	[73]
Skin					
Wound healing	Asiaticoside	Topical, TDS	20 patients with dirty wounds and chronic or recurrent atony refractory	Accelerated the healing process	[195]
Wound healing	Madecassoside (0.1%) with vitamin C (5%)	Randomized double-blind study, topical, BID, 6 months	20 healthy postmenopausal female volunteers with actinically aged facial, neck and forearm skin	Significantly improved the clinical score of deep and superficial wrinkles, suppleness, firmness, roughness and skin hydration	[74]
Striaegravidarum	Cream of CA triterpenes, hydroxyprolisilane-C, rosehip oil and vitamin E	Randomized, double-blind, placebo-controlled trial, topical, BID, 30 days	183 pregnant women	↓severity of the striae during pregnancy, prevents the appearance of new striae and halts progression	[248]
Scleroderma	Madecassol; tablet (10 mg), ointment, powder	TDS for tablet and BID for ointment, 6 months	54 patients with systemic and focal scleroderma	↓indurative lesions, hyperpigmentation, vascular trophic disorders	[75]
Healing of skin graft	Cream of CA (7%)	Prospective randomized, controlled, double-blind trial, topical, BID, 12 weeks	30 adult patients with a split-thickness skin graft, 2 weeks after completion of epithelialization	Significant improvement of Vancouver scar scale	[249]
Cutaneous stretchmarks	Centellicum®; CA (250 mg)	Oral, TDS, 6 weeks	78 women with stretchmarks, 6 months postpartum	↓visible stretchmarks, ↑skin thickness, ↑collagen components, improve of the grey scale median, skin perfusion, temperature and elasticity	[250]

pausal female volunteers with actinically aged facial, neck and forearm skin, significantly improved the clinical score of deep and superficial wrinkles, suppleness, firmness, roughness and skin hydration [74]. Also topical and oral formulations of Madecassol in 54 patients with systemic and focal scleroderma significantly reduced indurative lesions, hyperpigmentation and vascular trophic disorders after 6 months of administration [75]. The efficacy of CA for the treatment of chronic venous insufficiency was investigated in a systematic review according to eight randomized controlled trials. Qualitative data of three study showed that CA significantly reduced pain, leg heaviness and oedema. Also quantitative data of five other studies, indicated significant improvement of microcirculatory parameters including venoarteriolar response, severity of ankle swelling and transcutaneous partial pressure of O_2 and CO_2 [76]. Furthermore, daily oral administration of 1000 mg TTFCA with Pycnogenol (the extract of French maritime pine bark) for 30 months in 824 patients with femoral or carotid stenosing plaques, significantly lowered plaques progression and events regarding to atherosclerosis [77].

25.7 Herb-Drug Interactions

According to *in vitro* studies, ethanolic extract of CA competitively inhibited cytochrome P450 (CYP) 1A2 and CYP2C9 and noncompetitively inhibited CYP3A4. Inhibition of CYP1A2 and CYP3A4 may be due to flavonoids of the plant. Methanolic extract of CA has noncompetitive inhibitory effect on CYP2D6 [78, 79]. An *in vitro* study showed that standardized extract of CA, ECa233, only inhibited CYP3A4, CYP2D6 and CYP2B6. Similar standardized extract was found inhibitor of CYP2B1 and CYP2B2 and decreased sulfotransferase activity of liver in rats [80–82]. These effects may explain reduction of clearance and increase of the area under the curve (AUC) of amitriptyline by CA in rats. So, it seems that CA may increase concentration of medicines metabolized by these enzymes [83]. Some data suggested ethyl acetate extract of the plant had additive antiepileptic effect in combination with gabapentin, valproate, phenytoin, and reduced effective dose of these medicines but, that was determined some constituents of CA may decline protective effect of phenytoin, phenobarbital and carbamazepine against seizure [84, 85]. Nevertheless, there is no herb-drug interaction documented in human study. Due to CNS depression activity of CA, it is advised to avoid concomitant use of this plant with CNS depressant medications. Data suggested that CA theoretically may increase effect of hypoglycemic agent and hepatotoxicity of medicines determined hepatotoxic [86–88]. Taken together, more data is needed to confirm herb-drug interactions of CA.

25.8 Pregnancy and Lactation

CA perhaps was found to be safe in pregnant female rats and was not teratogenic for male rats [89, 90]. Human studies suggested topical application of CA is possibly safe but, due to limitation of teratology data and some abortions reported from chronic oral use of the plant in rats, pregnant and nursing mothers are advised to avoid to ingestion of formulations congaing CA [91–93].

25.9 Toxicology

In human clinical studies, no serious adverse effect was reported from CA in oral or topical use. In clinical studies, the usual dose for oral administration was two capsule containing 500 mg hydro-ethanolic extract of CA once a day for up to 60 days or three capsule containing 50 mg of extracted Asiaticoside for up to 21 days. In another study volunteers took one capsule containing standardized extract of CA in dose up to 500 mg for 7 days and show no adverse effect [9, 17, 83, 91, 94–96]. Asiaticoside isolated from CA and oral administration of 1 g/kg showed no toxicity in previous human studies [97–99]. However, it may cause allergy in some patients, especially in topically application. So, it is important to care about probable contact dermatitis.

There was a report from hepatotoxicity effect following ingestion of CA resulting in jaundice in human. This adverse reaction was resolved after discontinuation of the plant [87].

In animal studies, CA made no toxicity up to 1000 mg orally in a single dose or daily for up to 90 days. In these studies, CA increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), *blood urea nitrogen* (BUN) and creatinine significantly after a month, but all parameters still were within normal range and no death occurred. According to this, perhaps the medium lethal dose (LD50) and no-observed-adverse-effect-level (NOAEL) for its standardized extract is greater than 2000 mg/kg or even 4000 mg/kg and 1000 mg/kg respectively in rats. The standardized extract causes no acute toxicity sign in dose up to 10 g/kg in mice. These results were reported from single dose, acute and subchronic evaluations of CA toxicity [20, 100–103]. Some data from animal studies suggested CA may have antifertility effect in male rat and also may cause abortion in female rat [92, 104, 105].

25.10 Conclusions

In summary, CA is a herbal medicine which is found almost all over the world and has been used since prehistoric and immemorial times in many traditional systems of medicine as a curative agent for a wide range of ailments. In recent years, CA significantly drawn the attention of researchers because of its health-promoting potentials. According to the results of our study, CA demonstrated to have CNS, cardiac, pulmonary, liver and kidney protective, antiulcer, wound healing, and antidiabetic effects. On the basis of the experimental evidence, some chemical isolates and herbal preparations of CA have been launched in the market as oral supplements or topical ingredients in cosmetic products.

Although a large number of studies have investigated the biological activities and underlying mechanisms of CA over the past decades, documented data and findings of these studies are still limited. Similarly, there is limited information about interactions, adverse effects and toxicity of CA. Hence, it seems that further scientific studies and organized clinical trials are required to validate and justify the safety and efficacy of CA.

Conflict of Interests None.

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