Review: The Bioavailability Activity of *Centella asiatica*

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Abstract
Centella asiatica (Bao-bog, Tiger Herbal, Pennywort, Gotu kola) has been announced as one of five "Thailand Champion Herbal Products (TCHP)" by the Department for Development of Thai Transitional and Alternative Medicine, Ministry of Public Health. *C. asiatica* has been investigated for its bioavailability activity, antimicrobial activity, antioxidant activity, anti-inflammatory activity, wound healing activity and anticancer activity. *C. asiatica* contains many types of active compounds: terpenoids, terpenoids and phenols. Thus, *C. asiatica* has high potential to be applied in pharmaceutical, cosmetic and food industries.

Keywords: *Centella asiatica*, Phytochemistry, Bioactivity, Herbal product

1 Introduction

Centella asiatica (Bao-bog, Tiger Herbal, Pennywort, Gotu kola) is used as a traditional drug to decrease blood pressure, heal fresh wounds, heal bruises and treat diuretic symptoms [1]. Normally, most parts of *C. asiatica* are used, including the stems, leaves and aerial parts. In Ayurveda, an Indian system of medicine, *C. asiatica* is used for the management of central nervous system, skin and gastrointestinal disorders [2]. The major biologically active compounds of *C. asiatica* extracts are monoterpenes, sesquiterpene and triterpenoids [3]. The major active compounds of *C. asiatica* are the polyphenols [4] and triterpenes [5]. In addition to terpenoids, *C. asiatica* also has high phenolic and flavonoid contents, such as quercetin, kaempherol, catechin, rutin, apigenin, naringin and volatile oils (such as caryophyllene, farnesol and elemene) [4], [6]. *C. asiatica* has been demonstrated in many studies to have wound healing activity [7], anticancer activity [8], antioxidant activity [4], antimicrobial activity [9], [10] and antileprotic activity [11]. The enhancement of collagen synthesis by the effect of asiaticoside in *C. asiatica* had been suggested as being able to be applied in functional cosmetics [12]. *C. asiatica*'s active biological activities have been scientifically proved and verified, which indicates that *C. asiatica* has high potential for use in pharmaceutical, cosmetic and food applications.

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2 Phytochemistry and Bioactive Compounds of *C. asiatica*

C. asiatica is considered as an enriched source of different active compounds as shown in table 1. The main active compounds of *C. asiatica* are pentacyclic triterpenes (asiatic acid, madecassic acid, asiaticoside and madecassoside) [13].

Table 1: Main active compounds of *C. asiatica*

Main groups	Active compounds	References
Terpenoids	triterpenes, asiaticoside, centelloside, madecassoside, brahmoside, brahminoside (saponin glycosides), asiaticentoic acid, centellic acid, centoic acid, madecassic acid, terminolic acid and betulic acid.	[14], [15]
Terpenoids	various terpenoids: β-caryophyllene, trans β-farnesene and germacrene D (sesquiterpenes), α-pinene and β-pinene.	[14], [15]
Phenols	flavonoids: kaempferol, kaempferol-3-o-β-d-glucuronide, castilliferol, quercetin, quercetin-3-o-β-d-glucuronide, castillicetin, apigenin, rutin, luteolin, naringin	[16]–[18]
Phenols	phenylpropanoids: rosmarinic acid, chlorogenic acid, 3,4-di-o-caffeoyl quinic acid, 1,5-di-o-caffeoyl quinic acid, 3,5-di-o-caffeoyl quinic acid, 4,5-di-o-caffeoyl quinic acid, isochlorogenic acid	[18]
Phenols	tannin: tannin, phlobatannin	[18]

3 Antimicrobial Activity

The crude extracts of *C. asiatica* obtained from various types of extraction solvents exhibited antimicrobial activities. The ethanolic crude extract of *C. asiatica* showed antibacterial activity against enteric pathogens [19], *Bacillus cereus* and *Listeria monocytogenes* (under normal, osmotic stress and low pH) [9], [10]. Using ethanol, chloroform and hexane as the extraction solvents, crude extracts showed antibacterial activity against *Salmonella enterica* Typhimurium U302, *S. enterica* Enteritidis, *S. enterica* 4,5,12:I human (US clone), *B. cereus* and *B. subtilis* [3]. Based on disc assay (containing 1,000 μg/disc), hot methanolic crude extracts of *C. asiatica* were moderately effective on inhibition of Staphylococcus aureus and methicillin-resistant *S. aureus* [20]. *Mycobacterium tuberculosis* and *M. leprae* were also reported to be sensitive to treatment of asiatocoside (in the form of liposomal particles) obtained from of *C. asiatica* [21].

4 Antioxidant Activity

C. asiatica extracts have comparable level of antioxidant activities to rosemary extracts, sage extracts [22], vitamin C [23] and grape seed extract [24], hence they are a good target to be investigated to produce natural antioxidants. Interestingly, extraction method has an effect on the level of antioxidant activity. It was found that among three solvents, including water, ethanol and light petroleum, ethanol showed the highest antioxidant activities, followed by water, while light petroleum yielded negative activities [25]. The antioxidant activity of *C. asiatica* was hypothesized to be the result of the reduction of hydroperoxide that inactivates free radicals and/or chelates metal ions [4]. The antioxidants activities of the *C. asiatica* could be classified to different functional properties, such as scavenging of the reactive oxygen species (quercetin and catechins) [26], inhibition of the free radicals generation, inhibition of chain-breaking activity (p-coumaric acids) [27] and metal chelation [28]. The degree of antioxidant activity could be determined by using Folin-Ciocalteu method based on the phenolic contents [3]. Previously, it was shown that ethanolic extract contains the highest phenolic content followed by chloroform extract and hexane extract, respectively (23.802 ± 0.524a, 22.172 ± 0.140a and 7.961 ± 1.635b μg GAE/mg, respectively). Additionally, Ferric reducing antioxidant value of ethanolic extract was greater than those of chloroform extract and hexane extract (6.401 ± 0.039a, 3.478 ± 0.674b and 1.769 ± 0.128c mmol Fe2+/mg, respectively) [3].

5 Wound Healing Activity

For the therapeutic application, *C. asiatica* extracts were applied on the treatments of chronic wound infections [29]. Aqueous extracts that were formulated as cream and gel were tested in rats to observe the wound healing effect and resulted with the faster epithelialisation and higher rate of wound contraction [30]. Dexamethasone suppressed wound in Wistar albino rats were healed by application of ethanolic leaf extracts of *C. asiatica* [31]. In a recent study at

the Department of Surgery, Thammasat University Hospital, diabetic patients gained positive results from taking capsules containing *C. asiatica* extractes without any adverse effect [32]. The effects of asiaticoside in human periodontal ligament cells (HPDLs) proliferation, protein synthesis, and osteogenic differentiation were investigated and showed enhanced periodontal tissue healing [33]. At low concentrations, aqueous extracts of *C. asiatica* promoted epithelium wound healing in rabbit corneal epithelial (RCE) cells [34]. Ultra-fine cellulose acetate fiber mats containing asiaticoside (in crude extract or pure form) were evaluated for wound dressings and found that they were stable up to 4 months and promoted proliferation and upregulation of the collagen production [35]. Madecassoside showed enhance wound-healing and diminished keloid formation in primary keloid-derived fibroblasts originating from human earlobe keloids [36].

6 Effect on Skin

Asiaticoside in *C. asiatica* stimulated synthesis of skin aging inhibitor type 1 collagen in human dermal fibroblast cells therefore it was recommended to be used in the treatment of hypertrophic scars and keloids [37], [38]. Alcoholic extract of *C. asiatica* showed positive effects in pruritis and other skin diseases [39]. Hydroalcoholic extracts were mixed with other four medicinal plants (*Curcuma caesia*, *Areca catechu*, *Cinnamon zeylanicum* and *Tamarindus indica*) as herbal creams and their effects were shown to increase skin hydration, sebum level, viscoelasticity, and to decrease melanin content [40]. Asiaticoside improved skin cell behaviours in wound healing process by increasing migration rate of skin cell, enhancing the initial skin cell adhesion and inducing an increase in the number of normal human dermal fibroblasts [41]. Aqueous extract as a nanoencapsulated form within gelatin efficiently reduced the expression of matrix metalloproteinase (MMP)-1 in UV-irradiated cells and inhibited hyaluronidase expression in mouse skin [42].

7 Anti-inflammatory Activity

Asiatic acid and madecassic acid in *C. asiatica* showed anti-inflammatory effect via the inhibition of enzymes (iNOS, cyclooxygenase-2 (COX-2)), interleukins (IL-6, IL-1β) and cytokine tumor necrosis factor (TNF-α) expression through the down-regulation of NF-κB activation in lipopoly saccharide-induced murine macrophage cells [43], [44]. Madecassoside prevented collagen II (CII)-induced arthritis (CIA) in mice [45]. In experimental animal, asiaticoside inhibited lipopolysaccharide-induced fever and inflammatory response, including production of serum TNF-α and IL-6, liver myeloperoxidase (MPO) activity, brain COX-2 protein expression and prostaglandin production [46]. Asiaticoside G was also reported to have anti-inflammatory property in LPS-stimulated RAW 264.7 cells [47].

8 Anticancer Activity

Different solvent extracts of *C. asiatica* had anti-cancerous activity with specificity to different types of cell lines as described here. Methanolic extract of *C. asiatica* induced apoptosis in human breast cancerous MCF-7 cells *in vitro* [48]. Aqueous extracts induced apoptosis in colonic crypts and exerted chemopreventive effect on colon tumorigenesis in male F344 rats [49]. Asiatic acid induced apoptosis in human melanoma SK-MEL-2 cells which responded for skin cancer and SW480 human colon cancer cells [50], [51]. Asiaticoside in *C. asiatica* enhanced anti-tumor activity of vincristine in cancer cells [52]. Methanol extract inhibited the proliferation of human gastric adenocarcinoma (MK-1), human uterine carcinoma (HeLa), and murine melanoma (B16F10) cells [53].

9 Design of Nanotechnology-based Drug Delivery Systems

Nanoparticles could be used as drug delivery vehicles. They are generally smaller than 100 nm in at least one dimension, and produced from different biodegradable materials, such as natural or synthetic polymers, lipids, or metals. Nanoparticles are taken up by cells with higher efficience than larger micromolecules and therefore, could be used as effective transport and delivery systems. The strategy of applying nanotechnology to plant extracts has been widely used, because nanostructure systems could enhance activity of plant extracts, promote consistent release of active constituents, reduce the required dose, decrease side effects, and improve activity [62], [63].

Several nanotechnology strategies, such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursors systems for liquid crystals (PSLCs), liposomes, and microemulsions, have been proposed and tested. Herbal extracts in nanoparticle form influent substances to present consistent formulation, and may even modify substance's properties and behaviors in a biological environment [64]. These technological discoveries have revolutionized drug delivery. The new drug delivery systems have the ability not only to increase the effectiveness of active components, but also to reintroduce other components that were discarded because they were not useful in formulation [64]. Moreover, the ability to improve new substances, such as by increasing selectivity and efficacy, protecting against thermal- or photo-degradation, reducing side effects, and controlling the release of active constituents, before they are introduced to the market or used therapeutically, makes this approach even more attractive [65]–[67]. However, there are just a few numbers of researches in *C. asiatica* nanoparticles. The *C. asiatica* ethanolic extract E/O/W multiple emulsion was stable to phase separation after storage at 25°C for 7 days [68]. The nanoparticles of *C. asiatica* extract were prepared by using ionic gelation [69]. It was found the ratio of chitosan to alginate strongly affects the size of *C. asiatica* extract particles [69]. It was found that *C. asiatica* gelatin nanoparticles inhibited hyaluronidase expression (>60%) at a concentration of 0.5 mg/ml, which was higher than the levels produced by the unencapsulated crude extracts [42].

Table 2: Bioactive compound of *C. asiatica* and its biological property

Bioactive compound	Biological property	References
Asiatic acid	Aids in generation of neuroglia; promotes wound healing, promotes cuticle cornification; stimulates granulation; induces gene expression changes, enhancing learning and memory properties, antinociceptive activity, anti-inflammation activity, acetylcholinesterase inhibitory activity, anti-apoptotic activity	[36], [54]–[58]
Asiaticoside	Anti-inflammatory; antioxidant induces gene expression changes, wound healing, reduces scar formation, neuroprotective activity, improve collagen biosynthesis	[33], [38], [41], [57], [59], [60]
Madecassoside	Induces gene expression changes, protection of endothelial cells from oxidative injury	[57], [61]
Quercetin	Anti-HIV-1, antiasthmatic, antibacterial, antihepatotoxin, antihypertensive, anti-inflammatory, antitussive, antiviral, coronary vasodilator, antihypercholesterolemic, 5-HT inhibitor, smooth muscle relaxant, platelet aggregation inhibitor, 3',5'-cAMP-phosphodiesterase inhibitor, fatty acid synthetase inhibitor, aldose reductase inhibitor (eye lens), protein kinase *C* inhibitor; antihypertensive, reduces blood capillary brittleness, antioxidant	[18], [57]
Quercitrin	Antibacterial, antineoplastic, antihepatotoxin, anti-inflammatory, antimutagenic, antiviral, diuretic, Hemostatic, aldose reductase inhibitor, antioxidant, insect antifeedant (Bombyx mor), insect phagostimulant (Gastrophysa atriocyaea), hepatoprotective	[16], [57]
Kaempferol	Anti-HIV-1, antibacterial; anti-inflammatory, antitussive to cure trachitis, antioxidant, Δ5-lipoxygenase inhibitor; iodinate thyronine deiodinase inhibitor; aldose reductase inhibitor	[18], [57]
Apigenin	Antibacterial, antiulcerative, antispasmodic (smooth muscle), diuretic, aldose reductase inhibitor, antihypertensive, anti-inflammatory, antioxidant, nodulation signal for metabiosis of pea and Rhizobium leguminosarum	[16, 57]
Luteolin	Antiallergic, antibacterial, antifungal, cytotoxic, anti inflammatory, antispasmodic, antitussive, antiviral, enhances arterial tension and lowers intravenous tension, enhances blood capillary permeability, immunoenhancer, increases coronary flow; dihydrocoenzyme I (NADH) oxidase inhibitor, iodine-induced thyronine deiodinase inhibitor, aldose reductase inhibitor, anti-inflammatory, anti-HIV activity	[16], [57]
Naringin	Antibacterial, anti-inflammatory, antiviral, aldose reductase inhibitor, passive cutaneous anaphylaxis inhibitor	[17], [57]
Betulic acid	Antineoplastic, cytotoxic, antitubercular, antibacterial	[15], [57]
α-Pinene	Antifungal, antitussive, irritant	[14], [57]
β-Pinene	Antifungal, anti-inflammatory, antitussive	[14], [57]
Ascorbic acid	Antioxidant, antibacterial, anti-infective, antidote, antihypercholesterolemic, inhibits production of Carcinogen, induces tissue to produce collagen, hematopoietic activity	[18], [57]
Chlorogenic acid	Antioxidant, antineoplastic, cytotoxic, antimutagenic, antiviral, choleretic, hemostatic, leukopoietic, antimalarial	[18], [57]

10 Conclusions

C. asiatica has valuables bioavailability properties, such as antimicrobial, antioxidant, wound healing activity, anti-inflammatory activity, and anticancer activity. These bioavailability properties indicate that *C. asiatica* has high potential to be used as the active ingredient in high valued industry products. In order to get single active compound from *C. asiatica*, the number of complicated steps in the purification and separation processes are required. These purification and separation steps become unnecessary major capital cost in industries. Furthermore, purification and separation lead to partial loss of activity due to the removal of target substances. Additionally, purification yield is often too low for commercial production. Therefore, researchers have begun to examine the method of using crude extract of *C. asiatica*. This approach has several advantages, for example, only a few simple steps are required and also it provides the synergistic effects due to the presence of multiple active molecules in the crude extracts. Nevertheless, there are some limitations in crude extracts as they showed good potential *in vitro* but less or none in vivo due to their poor lipid solubilities or improper molecular sizes or both, resulting in poor absorption, slow delivery, poor dosing and poor bioavailability. Theoretically, it is difficult for water-soluble active compounds to permeate through cell membrane of both human and pathogenic microorganisms, which have hydrophobic characteristics. Therefore, industries need the novel technology for utilizing the crude extract of *C. asiatica* to overcome these limitations to increase absorption, stability and solubility for better drug delivery system in pharmaceutical, cosmetic and food industries.

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