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Centella Asiatica in Dermatology

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Abstract

Centella asiatica herb is recommended in the treatment of dermatoses and skin lesions such as excoriations, burns, hypertrophic scars or eczema as well as in non-dermatological diseases like gastric ulcers, gastric mucosal lesions (Shinomol and Muralidhara, 2011), anxiety (Wijeweera et al., 2006) and for improving cognition in neurodegenerative disorders (Subathra et al., 2005). *C. asiatica* has also been found beneficial in chronic venous insufficiency, mainly by improvement of microcirculation (Chong and Aziz, 2013). *C. asiatica* extract (International Nomenclature of Cosmetic Ingredients, INCI) is used also as an ingredient of cosmetics (Bylka et al., 2013).

Many studies present activity of *C. asiatica*, but until now there have been no reviews presenting the scientific information about the usage of *C. asiatica* in dermatological diseases. For this reason, this study provides an overview of the current knowledge on the in vitro and in vivo experiments, focused on the activity of *C. asiatica* extracts and individual compounds in facilitating the process of healing wounds, psoriasis and scleroderma lesions. The mechanisms of the above-mentioned activities as well as the potential side effects are discussed.

Introduction

Chemical constituents

Ursane type pentacyclic triterpenoids known as centelloids, mainly: asiaticoside, madecassoside (brahminoside), asiatic acid and madecassic acid (brahmie acid) were the most important constituents isolated from *C. asiatica*. Other triterpenoids in *Gotu kola* include: asiaticoside C, D, E, F; centellasaponin B, C; isothankunic acid and oleanane type saponins, e.g. terminolic acid; centellasaponin D. *C. asiatica* contains about 0.1% essential oils with α -humulene, germacrene B/D, β -caryophyllene, flavonoids, sesquiterpenes, steroids (Brinkhaus et al., 2000; James and Duebery, 2009; James and Duebery, 2011; Nhiem et al., 2011). Saponins may account for 1% to 8%, according to the European Pharmacopoeia, not less than 6.0% (Ph.Eur. 2011).

Pharmacological and clinical studies were carried out on the defined extracts as well as undefined aqueous or alcohol extracts. However, information on the medicinal products suggests that all extracts: titrated extract of *C. asiatica* (TECA), total triterpenoid fraction of *C. asiatica* (TTFCA), total triterpenic fraction (TTF), as well as *C. asiatica* total triterpenic fraction (CATTF) and estratto titolato di *C. asiatica* (ETCA) are different acronyms of the same extract, contained in the used preparations: Madecassol®, Centellase® or Blastestimulina®. These extracts include 40% of asiaticoside and a 60% mixture of asiatic and madecassic acids (Brinkhaus et al., 2000; EMEA (European Medicines Agency), 2012).

One to two tablets (10 mg/tab.) three times a day for adults and a half of this dose for children under 3 years of age are recommended by the European Medicines Agency (EMA) in the case of non-healing wounds, hypertrophic scars or keloids in the active phase. For external use, to support the local treatment and to improve the granulation phase of non-healing ulcers and wounds, 1% cream is recommended. Disinfection of the wound/ulcer is required before treatment with TTFCA. Moreover, 1% ointment and 2% powder are available for the treatment of non-healing wounds.

In vitro experiments

Wound healing. Wound healing is a complex biological process involving coagulation, inflammation, cytokine production, cell migration, proliferation and differentiation, angiogenesis, synthesis and remodeling of extracellular matrix (including collagen production and deposition). Type I and III collagen are the major components of the skin extracellular matrix. Both types play an important role in the wound healing process. As a result, proliferation of epithelial cells and wound contraction occur (Lu et al., 2004a, 2004b; Liu et al., 2008).

C. asiatica extracts, individual triterpene compounds and the mixture of triterpenoids from *C. asiatica* have been proven to support wound healing in a large number of scientific reports. A statistically significant increase in the percentage of collagen and cell layer fibronectin in cultures of human skin fibroblasts, after application of TTFCA extract (25 µg/mL), was detected (Tenni et al., 1988).

The TECA and its components including asiatic acid, madecassic acid and asiaticoside have been studied on human foreskin fibroblast monolayer cultures. TECA increased the collagen synthesis in a dose-dependent manner. In addition, TECA and all terpenes increased the intracellular free proline level, but this effect was independent of the stimulation of collagen synthesis (Maquart et al., 1990).

The influence of asiatic acid, madecassic acid and asiaticoside on human skin fibroblast type I collagen synthesis was investigated in vitro separately for each agent and in combination. Additionally, the culture was or was not stimulated with ascorbic acid. In the presence of ascorbic acid, secretion of type I collagen was higher for each individual component and for the mixture, than in the absence of ascorbic acid (Bonté et al., 1994).

To determine secretion of type I and III collagen in human fibroblast culture with or without stimulation with asiaticoside and madecassoside, the enzyme-linked immunosorbent assay (ELISA) was performed. The secretion of type I collagen was increased for 25–30% with asiaticoside and madecassoside. Authors concluded that *C. asiatica* extracts may facilitate maturity of a scar by increasing the amount of type I collagen and thus increasing the type I:III collagen ratio (Bonté et al., 1995).

Lee et al. (2006) have shown that asiaticoside significantly induced type I collagen synthesis in human dermal fibroblast.

The influence of asiaticoside on collagen synthesis and keloid-derived fibroblast proliferation was also investigated by Tang et al. (2011). The ethanolic extract of *C. asiatica* enhanced three-fold collagen synthesis of human fibroblast cells compared to the control. The highest collagen synthesis was found at 50 mg/mL of *C. asiatica* extract. This extract demonstrated significant DPPH-radical scavenging activity with 84% inhibition at a concentration 1 mg/mL. The activity was compared to that of grape seed extract and vitamin C (Hashim et al., 2011).

Asiaticoside enhanced periodontal tissue healing on human periodontal ligament cells (HPDLs). Dose-dependent increases in the levels of mRNA and protein of fibronectin and type I collagen, as well as attenuated metalloproteinase-I mRNA expression, were observed when HPDLs were treated by asiaticoside. Further-more, asiaticoside promoted osteogenic differentiation of HPDLs (Nowwarote et al., 2013).

Clinical study

Scleroderma. Guseva et al. (1998) studied the efficacy of orally/topically administered madecassol in patients with systemic sclerosis (SSc) and localized scleroderma (LS). They found that 6 month oral course (30 mg/day) caused softening of the skin lesions, lightening of hyperpigmentation and improvement of general condition of 12 SSc patients.

Wound healing. *C. asiatica* extract can shorten the healing process of wound in diabetic patients. The randomized control study included 200 diabetic patients, treated with two capsules of *C. asiatica* extract (50 mg asiaticoside/capsule) three times a day. Results showed that wound contraction was better than in the placebo group. Moreover, the extract suppresses the formation of scar tissue (Paocharoen, 2010).

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Conclusion

The effectiveness of *C. asiatica* and its preparation in facilitating the wound healing. Moreover, available literature does not clarify the best route and dosage of administration of the *C. asiatica* extract. In order to evaluate the usefulness of the plant in this area, clinical trials should be carried out.

Reference

1. Shinomol GK, Muralidhara K, Bharath MM. 2011. Exploring the role of Brahmi (*Bacopa monnieri* and *Centella asiatica*) in brain function and therapy. *Recent Pat Endocr Metab Immune Drug Discov* 5: 33–49.
2. Wijeweeraa P, Arnasona JT, Koszycki D, Merali Z. 2006. Evaluation of anxiolytic properties of Gotukola – (*Centella asiatica*) extracts and asiaticoside in rat behavioral models. *Phytomedicine* 13: 668–676.
3. Subathra M, Shila S, Devi SM, Panneerselvam C. 2005. Emerging role of *Centella asiatica* in improving age-related neurological antioxidant status. *Exp Gerontol* 40: 707–715.
4. Chong NJ, Aziz Z. 2013. A Systematic Review of the Efficacy of *Centella asiatica* for Improvement of the Signs and Symptoms of Chronic Venous Insufficiency. *Evid Based Complement Alternat Med*. 2013: 627182, 10.
5. Bylka W, Znajdek-Awizeń P, Studzińska-Sroka E, Brzezińska M. 2013. *Centella asiatica* in cosmetology. *Postep Derm Alergol* 30: 46–49.
6. Ph. Eur. 2011. European Pharmacopoeia 7th ed. Council of Europe: Strasburg.
7. EMEA (European Medicines Agency). 2012. Science Medicines Health. <http://www.ema.europa.eu> 04.06. 2012.
8. Brinkhaus B, Lindner M, Schuppan D, Hahn EG. 2000. Chemical, pharmacological and clinical profile of the East Asian medical plant *Centella asiatica*. *Phytomedicine* 75: 427–448.
9. James JT, Duebery IA. 2009. Pentacyclic triterpenoids from medicinal herb, *Centella asiatica* (L.) Urban. *Molecules* 14: 3922–3941.
10. James J, Dubery IA. 2011. Identification and Quantification of Triterpenoid Centelloids in *Centella asiatica* (L.) Urban by Densitometric TLC. *J Planar Chromatogr* 24: 82–87.
11. Nhiem NX, Tai BH, Quang TH, et al. 2011. A new ursane-type triterpenoid glycoside from *Centella asiatica* leaves modulates the production of nitric oxide and secretion of TNF- α in activated RAW 264.7 cells. *Bioorg Med Chem Lett* 15: 1777–1781.
12. Liu M, Dai Y, Li Y, Huang F, Gong Z, Meng Q. 2008. Madecassoside isolated from *Centella asiatica* herbs facilitates burn wound healing in mice. *Planta Med* 74: 809–815.
13. Lu L, Ying K, Wei S, et al. 2004a. Asiaticoside induction for cell-cycle progression, proliferation and collagen synthesis in human dermal fibroblasts. *Intern J Dermatol* 43: 801–807.
14. Lu L, Ying K, Wei S, Liu Y, Lin H, Mao Y. 2004b. Dermal fibroblast - associated gene induction by asiaticoside shown in vitro by DNA microarray analysis. *Br J Dermatol* 151: 571–578.

15. Tenni R, Zanaboni G, De Agostini MP, Rossi A, Bendotti C, Cetta G. 1988. Effect of the triterpenoid fraction of *Centella asiatica* on macromolecules of the connective matrix in human skin fibro-blast cultures. *Ital J Biochem* 37: 69–77.
16. Maquart FX, Bellon G, Gillery P, Wegrowski Y, Borel JP. 1990. Stimulation of collagen synthesis in fibroblast cultures by a triterpene extracted from *Centella asiatica*. *Connect Tissue Res* 24: 107–120.
17. Bonté F, Dumas M, Chaudagne C, Meybeck A. 1994. Influence of asiatic acid, madecassic acid, and asiaticoside on human colla-gen I synthesis. *Planta Med* 60: 133–135.
18. Bonté F, Dumas M, Chaudagne C, Meybeck A. 1995. Comparative activity of asiaticoside and madecassoside on type I and III collagen synthesis by cultured human fibroblasts. *Ann Pharm Fr* 53: 38–42.
19. Lee J, Jung E, Kim Y, et al. 2006. Asiaticoside induced human col-lagen I synthesis through TGF β Receptor I Kinase (T β RI Kinase) – independent smad signaling. *Planta Med* 72: 324–328.
20. Tang B, Zhu B, Liang Y, et al. 2011. Asiaticoside suppress collagen expression and TGF- β /Smad signaling through inducing Smad7 and inhibiting TGF- β RII in keloid fibroblast. *Arch Dermatol Res* 303: 563–572.
21. Hashim P, Sidek H, Helan MHM, Sabery A, Palanisamy UD, Ilham M. 2011. Triterpene composition and bioactivities of *Centella asiatica*. *Molecules* 16: 1310–1322.
22. Nowwarote N, Osathanon T, Jitjaturunt P, Manopattanasoontorn S, Pavasant P. 2013. Asiaticoside induces type I collagen synthesis and osteogenic differentiation in human periodontal ligament cells. *Phytother Res* 27: 457–462.
23. Paocharoen V. 2010. The efficacy and side effects of oral *Centella asiatica* extract for wound healing promotion in diabetic wound patients. *J Med Assoc Thai* 93, suppl 7: S166–70.
24. Guseva G, Stravoitova MN, Mach ES. 1998. Madecassol treatment of systematic and localized scleroderma. *Ter Arkh* 70: 58–61.