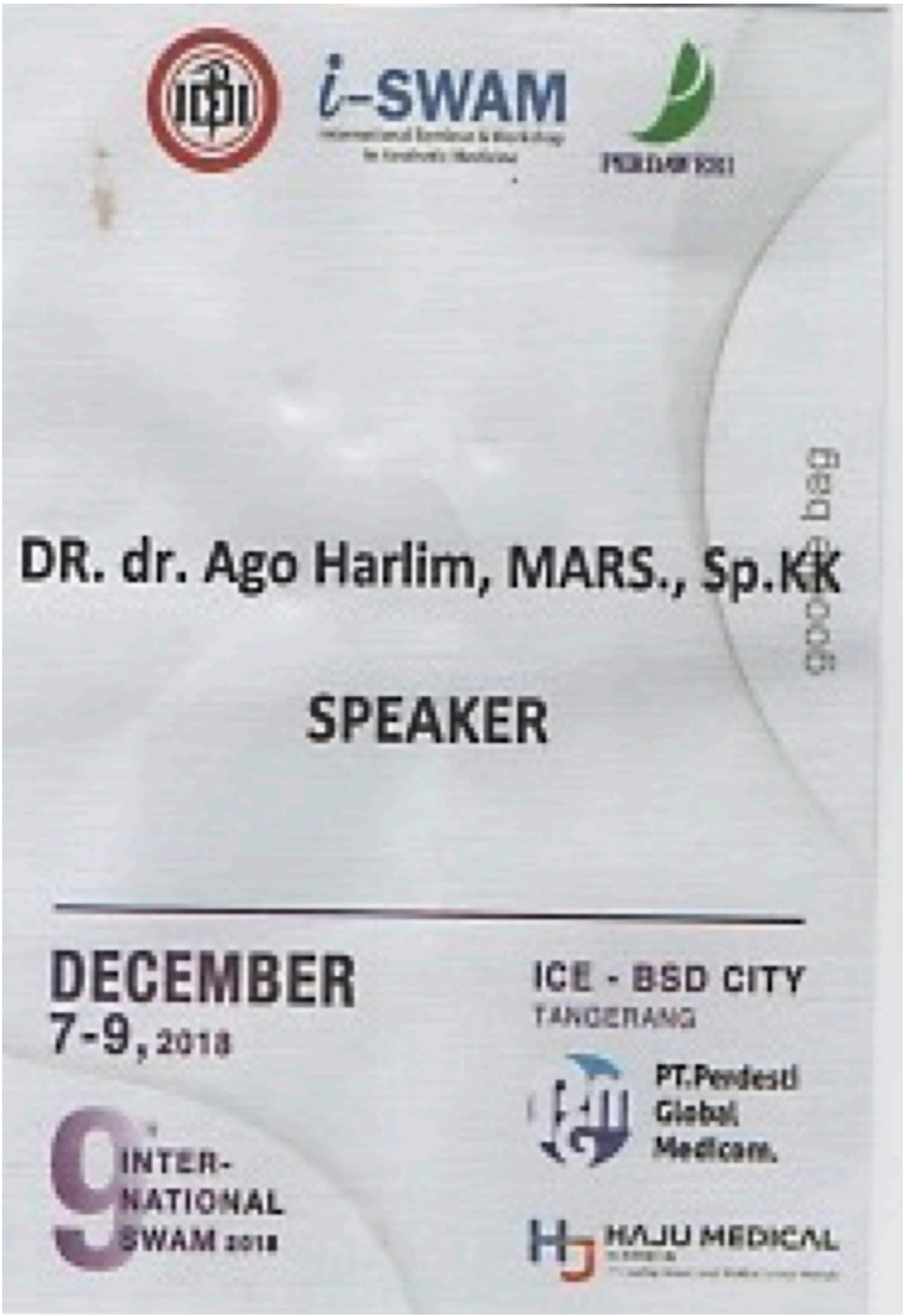

Centella asiatica in Dermatology

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C. 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 (Wijeweeraa et al., 2006) and for improving cog-nition 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 Ingre-dients, 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 H. asiatica in dermato-logical 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 activ-ities as well as the potential side effects are discussed.

CHEMICAL CONSTITUENTS

Ursane type pentacyclic triterpenoids known as centelloids, mainly: asiaticoside, madecasosside (brahminoside), asiatic acid and madecassic acid (brahmic acid) (Fig. 1) 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-caryphyllene, flavonoids, sesquiter-penes, steroids (Brinkhaus et al., 2000; James and Duebery, 2009; James and Dubery, 2011; Nhiem et al., 2011). Sapo-nins 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 alco-hol extracts (Table 1). However, information on the medicinal products suggests that all extracts: titrated ex-tract 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 acro-nyms of the same extract, contained in the used prepara-tions: Madecassol®, Centellase® or Blastoestimulina®. 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/tabl.) 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 (EMEA) in the case of non-healing wounds, hy-pertrophic 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 differentia-tion, angiogenesis, synthesis and remodeling of extracel-lular matrix (including collagen production and deposition). Type I and III collagen are the major com-ponents 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 con-traction 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 num-ber 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 syn-thesis 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 in-creasing the type I:III collagen ratio (Bonté et al., 1995).

Lee et al. (2006) have shown that asiaticoside signifi-cantly induced type I collagen synthesis in human der-mal 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 com-pared to the control. The highest collagen synthesis was found at 50 mg/mL of C. asiatica extract. This ex-tract 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 condi-tion of 12 SSc patients.

Wound healing. C. asiatica extract can shorten the healing process of wound in diabetic patients. The ran-domized 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. More-over, 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-Awiżeń 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 TGFβ Receptor I Kinase (TβRI 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-βRII 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.