

Centella asiatica in cosmetology

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Abstract

Centella asiatica known as Gotu Kola is a medicinal plant that has been used in folk medicine for hundreds of years as well as in scientifically oriented medicine. The active compounds include pentacyclic triterpenes, mainly asiaticoside, madecassoside, asiatic and madecassic acids. *Centella asiatica* is effective in improving treatment of small wounds, hypertrophic wounds as well as burns, psoriasis and scleroderma. The mechanism of action involves promoting fibroblast proliferation and increasing the synthesis of collagen and intracellular fibronectin content and also improvement of the tensile strength of newly formed skin as well as inhibiting the inflammatory phase of hypertrophic scars and keloids. Research results indicate that it can be used in the treatment of photoaging skin, cellulite and striae.

Key words: *Centella asiatica*, triterpenes, wound healing, cosmetic preparation.

Introduction

Centella asiatica (L) Urban., synonym: *Hydrocotyle asiatica* L. (Eng. *Indian Pennywort*, Fr. *Hydrocotyle asiatique*, Ger. *Asiatischer Wassernabel*), also known by common names as: *Gotu kola* or *Tiger Grass*, belongs to the *Apiaceae* family. It grows in Asia, mainly in India, Pakistan, Madagascar, equatorial Africa, central America and in the tropical region of Oceania [1]. The *C. asiatica* herb was already used as a "panacea" three thousand years ago in China, India, Africa, the Philippines, Sri Lanka and Madagascar. In the 19th century, *C. asiatica* and *C. asiatica* extract were included in the *Indian Pharmacopoeia*. Due to the medicinal properties of the plant it was gradually incorporated into other Pharmacopoeias: *British Herbal Pharmacopoeia*, *Chinese Pharmacopoeia*, *Dutch Pharmacopoeia*, *German Pharmacopoeia*, *Homöopathisches Arzneibuch*, *Martindale European Pharmacopoeia*, *Pharmacopoe française*, *La Farmacopea Italiana X*, *European Pharmacopoeia VI* and into *Polish Pharmacopoeia IX* edition [1-3]. According to European and Polish Pharmacopoeias, *Centella* (*Centellae asiaticae herba*) consists of dried, fragmented aerial parts of *Centella asiatica* (L Urban.), contains not less than 6.0 per cent of total triterpenoid derivatives expressed as asiaticoside [2, 3].

In traditional Asian medicine, the herb of *C. asiatica* has been used for hundreds of years, especially in dermatolo-

gical conditions, to improve small wounds, scratches, burns, hypertrophic wounds healing, and as an anti-inflammatory agent, particularly in eczema. It is also recommended as an antipyretic, diuretic, rheumatic, antibacterial, antiviral drug, in the treatment of vein insufficiency and for improving cognition, relieving anxiety and as an anti-cancer agent [1, 4, 5]. Formerly, *C. asiatica* was also used in epilepsy, hysteria, leprosy, and in minor itching and insect bites [5].

This review presents the results of activity of *C. asiatica* in facilitating the healing of wounds, compounds responsible for activity and mechanism of action, also contraindications and potential side effects. So far studies in the use of this plant as an ingredient in cosmetic preparations applied on photoaging skin, in cellulite and striae have also been presented.

Chemical composition

The most important constituents isolated from *C. asiatica* were triterpenoid saponins known as centellobiosides. Saponins may account for 1% to 8% of all *C. asiatica* constituents [6]. The variable quantity mainly depends on the origin of the plant and can be established using the HPLC-UV method [7].

Centellobiosides are primarily ursane- and oleanane-type pentacyclic triterpenoid saponins. The most important compounds, due to their pharmacological activity, are asiati-

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coside, madecassoside, asiatic acid and madecassic acid. Other centellosides occurring in *C. asiatica* include triterpenic acids, for example: brahmic acid, madasiatic acid, terminolic acid, centellic acid as well as their glycosides: brahminoside, madasiaticoside and centelloside [6]. *Centella* also contains other components, including volatile oils (0.1%), flavonoids, tannins, phytosterols, amino acids and sugars [1, 8].

Preparations

Pharmacological, biochemical and clinical studies were related to undefined aqueous or alcohol extracts and defined extracts. Pharmacological research included the following extracts: titrated extract of *Centella asiatica* (TECA), total triterpenoid fraction of *Centella asiatica* (TTFCA), both containing asiatic acid (30%), madecassic acid (30%), asiaticosides (40%) and total triterpenic fraction (TTF) which comprises asiatic acid and madecassic acid (60%) as well as asiaticosides (40%) [1]. However, information coming from licensed medicinal products says that all of the above mentioned TECA, TTFCA, TTF as well as CATTFF and ETCA are different acronyms to designate the same extract, commercially known as Madecassol®, Centellase® or Blastostimulina®, containing 40% of asiaticoside and a 60% mixture of asiatic and madecassic acids [1, 9].

Clinical trials were performed using TECA and ETCA (Estratto Titolato di *Centella asiatica*) or commercially produced extracts: *Centella asiatica* total triterpenic fraction (CATTFF) and TTFCA as well as isolated triterpenoid saponins, mainly asiaticoside, madecassoside and asiatic acid [1, 9].

The *C. asiatica* preparations used in conventional medicine are applied in an oral form (tablets and drops), topical medication (ointments and powder), in the form of injections (*s.c.*, *i.m.*) and external or internal homeopathic preparations [1].

Biological activity

Centella asiatica is effective in treatment of wounds, even in infected wounds, as well as burns and postoperative hypertrophic scars [10-13]. Triterpene compounds: asiatic acid, madecassic acid, asiaticoside and madecassoside are the principal components of *C. asiatica*, responsible for wound healing. The action has been demonstrated both for the extracts as well as triterpene compounds in a large number of scientific reports involving *in vitro* and *in vivo* experiments [14, 15].

The terpenoids (TTF) cause a significant increase in the percentage of collagen and cell layer fibronectin. The most beneficial effects are the stimulation of scar maturation by the production of type I collagen, decrease in the inflammatory reaction and myofibroblast production [16].

According to Maquart *et al.*, wounds treated with TECA and its separated components: asiatic acid, madecassic acid and asiaticoside increased total protein, collagen, and

peptic hydroxyproline content. As a result, the increase of fibroblast proliferation by stimulation of cell migration from the surrounding tissues and/or the expression or activation of some growth factors in the wound was observed. The triterpenoid components were also able to stimulate glycosaminoglycan, especially hyaluronic acid synthesis [17].

The saponins from *C. asiatica* administered orally or subcutaneously to the rats, during 3 weeks caused the reduction of the scar granuloma, whereas the rupture, tensile strength and the collagen content in the scar tissue increased [1].

The ethanolic extract of the *C. asiatica* facilitated the wound-healing in both normal and dexamethasone suppressed wound healing. The study was done in Wistar albino rats using incision, excision and dead space wounds models. The extract increased the wound breaking strength in incision wound model, accelerated the epithelization and the rate of wound contraction. Granulation tissue and hydroxyproline content in a dead space wound also increased. The extract attenuated dexamethasone healing effect in all wound models [18].

Madecassol® was found to have a preventive effect on burn and postoperative hypertrophic scars [13].

Madecassoside was active in burn wound healing, through increasing antioxidative activity and enhancing collagen synthesis, and influencing angiogenesis. Oral administration of this compound at doses of 6 mg/kg, 12 mg/kg and 24 mg/kg to mice facilitated wound closure in a time-dependent manner and complete wound closure took place on the 20th day in the group receiving 24 mg/kg of madecassoside. The compound caused dermal proliferation of fibroblasts and increased the level of hydroxyproline (used as an indicator of collagen synthesis in burned skin) which resulted in enhanced epithelization. These results confirm a positive effect on fibroblast proliferation and collagen synthesis during burn wound repair [11].

Asiaticoside also stimulated angiogenesis so that the increase in tension and elasticity of blood vessels was observed [19].

Studies on rats have shown that this compound (0.2%) applied topically increases the levels of enzymatic and non-enzymatic antioxidants in the newly created tissues [20].

Asiaticoside caused an increase in hydroxyproline and also in tensile strength, a rise in collagen content and better epithelization of punch/puncture wounds in guinea pigs or on delayed-type wounds of guinea pigs with experimentally induced diabetes [19].

The mechanism of action of asiaticoside is the induction of type I collagen synthesis in human dermal fibroblast cells by phosphorylation of both Smad 2 and Smad 3, also binding Smad 3 and Smad 4. Studies show that asiaticoside can induce type I collagen by activation of tumor growth factor β (TGF- β) receptor I kinase – independent Smad pathway [21].

The facilitation of burn wound healing, observed after 20 days of local application of asiaticoside at a dose of 10 µg, 1 ng, or 100 ng/wound area on the backs of mice, took place through influence on the level of various cytokines produced in the place of the burn wound. The improvement in burn wound healing might be an outcome of angiogenesis promotion during wound healing in the injured area occurring as a result of the stimulation of vascular endothelial growth factor (VEGF) production [22].

Eventually, proliferation of epithelial cells and wound contraction occur. In contraction, the wound is made smaller by the activity of myofibroblasts [10-12].

Centella asiatica herb water extracts also shows the anti-psoriatic activity [23], exerts a beneficial effect in treating systemic scleroderma and focal scleroderma [24].

In cosmetology *C. asiatica* has been used as an effective anti-photoaging agent, mainly due to enhancement of type I collagen, which amount in skin decreases with age. The action was confirmed in a randomized, double blind clinical trial conducted among 20 female participants (45-60 years old) with photoaged skin to examine the impact of topically applied 0.1% madecassoside in conjunction with 5% vitamin C on their skin. Six-month treatment resulted in a significant improvement in firmness, elasticity and skin hydration, which was confirmed by appropriate biometrological tests. It is considered that the beneficial effect of *C. asiatica* on improving the condition of skin was due to madecassoside, a known inducer of collagen expression by activating the SMAD signaling pathway. In the previous study, the same investigators confirmed the beneficial effect of 5% vitamin C on photoaged skin, which resulted from stimulation of collagen synthesis in fibroblasts and control of matrix metalloproteinase enzymes responsible for degradation of collagen, while in photoaged skin, the level of vitamin C in tissues was significantly reduced. Thus, it follows that the mixture of vitamin C and madecassoside is an attractive combination of two active compounds characterized by different mechanisms of activity, which exert an additive or synergistic effect "causing the remodeling of the superficial dermis" [25].

Centella asiatica is a common ingredient of cosmetics used in cellulite and striae. Cellulite, known as liposclerosis, is a non-inflammatory change within the subcutaneous adipose tissue caused by an increase in the volume of fat cells or by increased division of the connective tissue, which causes constriction of small blood vessels. The result is a disorder of metabolism in the subcutaneous adipose tissue, resulting in "distended" fat cells in this tissue, particularly around hips, buttocks, abdomen, thighs and arms. Cellulite is an ailment that affects many people, most frequently women, especially obese and leading stationary lifestyle, but may even be encountered in children.

Preparations that affect the adipose tissue, connective tissue and improve microcirculation are applied in the treatment of cellulite. They can be used topically, internally and transdermally. It is recommended to include medicines of

plant origin in the fight against cellulite. Methylxanthines (caffeine, theobromine, theophylline) have a lipophilic effect, while the extract of *C. asiatica* normalizes the metabolism occurring in the cells of the connective tissue, shows anti-inflammatory and draining activity and regulates microcirculation.

The study confirmed the influence of triterpenes of *C. asiatica* on increasing the metabolism of lysine and proline, the amino acids building the collagen molecule. In addition, these compounds increased the synthesis of tropocollagen, and mucopolysaccharide in the connective tissues. The results obtained showed the impact of *C. asiatica* on improving nutrition of tissues and connective vascular stimulation [26].

The positive effects of the treatment of cellulite with the *C. asiatica* extract were confirmed by a few clinical studies that used different methodologies. These experiments, however, used non-standard criteria to evaluate the progress of the treatment and most of them lacked a control group. The histopathological study performed in a double-blind trial, involving 35 patients evaluated the size of adipocytes in the gluteofemoral region and in the deltoid region. Twenty people participating in the experiment were administered 60 mg of the dry extract of *C. asiatica* orally once a day, for 90 days. Other participants of the experiment group took a placebo. The results showed that in the patients taking the Gotu Kola extract, the diameter of fat cells (or adipocytes) decreased in both studied regions of the body with a predominance of positive changes in the gluteofemoral region. In this study, a reduction in interadipocyte fibrosis was also observed [27].

In the experiment on a group of 60 people with cellulite, the influence of Madecassol® applied four times a day for 4 months was studied. The results clearly showed a beneficial effect of the Gotu Kola extract on inhibiting the progression of cellulite and a significant improvement in the skin condition in 85% of the experiment participants. The preparation was well tolerated [1].

Other experiments conducted on 65 patients with advanced cellulite showed that oral intake of the preparation Madecassol together with simultaneous reduction in diet for 3 months caused a significant decline in cellulite in 58% of the patients, whereas in 20% of the volunteers the effects were only satisfactory [28].

A randomized, double-blind, placebo-controlled trial of the cream Trofolastin®, containing an extract of *C. asiatica*, α -tocopherol, hydrolyzed collagen and elastin, was carried out on 100 pregnant women. Half of the women, who qualified for the study, received a placebo, the other half were applied a tested cosmetic preparation. The cream was applied daily on breasts, abdomen, buttocks and hips, starting from the third month of pregnancy. The test lasting 30 months was carried through by 80 of the women (39 in the placebo group and 41 in the group using the cream). The results indicated that in the placebo group, striae occurred in 56% of the women (22 patients), whereas in the group that

used the cream with the extract of *C. asiatica*, the problem affected 14 women only. The study also assessed the severity of striae on a scale of 0-3. Among the patients using the cream the average numerical value of the parameter adopted was 1.42, and 2.13 among those receiving the placebo. The tested cream provided significant protection for the women who had had striae during puberty (89% of the women) [29].

Toxicity

Centella asiatica applied in the recommended doses is not toxic and possible side effects are rare. *Centella asiatica* may cause: local allergic reactions and burning, especially when used externally and subcutaneously. Skin problems such as eczema on fingers and hands after external use of Madecassol® for a period of 3 months, and a vesicular reaction with pruritus after 20 days of application of Centelase® were observed [30].

Conclusions

Centella asiatica (Gotu kola) is effective in treatment of wounds, also in infective wounds, burns, and hypertrophic scar. The active compounds include pentacyclic triterpenes, mainly asiaticoside, madecassoside, asiatic and madecassic acids.

The mechanism of action involves promoting fibroblast proliferation and increasing the synthesis of collagen as well as acidic mucopolysaccharides, increasing intracellular fibronectin content and mitotic activity in the germ layer, significantly improving the tensile strength of newly formed skin as well as by inhibiting the inflammatory phase of hypertrophic scars and keloids.

Some studies suggest that the use of *C. asiatica* or its components may be useful in the treatment of psoriasis and scleroderma. *Centella asiatica* is a common ingredient of cosmetics applied on photoaging skin also in cellulite and striae.

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