

Urticaria induced by Centella asiatica – case report

Pokrzywka indukowana *Centella asiatica* – opis przypadku

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Streszczenie

Wiele osób, szczególnie uczących się i starszych, chętnie korzysta z różnych metod poprawiających pamięć i koncentrację. Jedną z nich jest stosowanie preparatów ziołowych. Gotu kola, inaczej wąkrota azjatycka (łac. *Centella asiatica* L.) to roślina należąca do rodziny selerowatych (baldaszkowatych), której właściwości i lecznicze działanie od dawna są doceniane na całym świecie. Jej preparaty stosowane są zarówno zewnątrznie (np. owrzodzenia, egzema) i wewnątrznie (np. choroby przewodu pokarmowego, układu sercowo-naczyniowego). Ponadto uważa się, że ma ona właściwości odmładzające i wywiera pozytywny wpływ na funkcjonowanie mózgu. Za lecznicze właściwości *C. asiatica* najprawdopodobniej odpowiadają jej główne związki aktywne – saponiny triterpenoidowe. Artykuł opisuje przypadek reakcji alergicznej 25-letniej studentki, stosującej preparat wąkroty reklamowany jako produkt poprawiający krążenie obwodowe i mózgowie, tonizujący, powodujący odprężenie, wzmacniający pamięć, polecany szczególnie w stanach zwiększonego wysiłku umysłowego. (*Farm Współ* 2019; 12: 54-58)

Słowa kluczowe: Centella asiatica, wąkrota azjatycka, Gotu kola

Abstract

In order to improve cognitive abilities and memory, a lot of people regardless of age seek for beneficial properties of natural medicine. An herb, which may meet these demands, is *Centella asiatica* from the *Apiaceae* (*Umbelliferae*) family, which is widely used in traditional medicine of Far East and increasingly arouses interest in the West. *C. asiatica* has been successfully used in wound healing and other skin conditions such as eczema, psoriasis, lupus, leprosy or varicose ulcers but also for other ailments like diarrhea, fever, amenorrhea, and diseases of the female genitourinary tract. *C. asiatica* properties are also known for relieving anxiety and cognition improvement. Triterpenoid saponins, the primary constituents of *Centella asiatica* are mainly believed to be responsible for its wide therapeutic actions. This review describes the case of an allergic reaction of a 25-year-old female student using *C. asiatica* preparation as a product regarding its ability to improve peripheral and cerebral circulation as well as toning, relaxing and memory improving traits, especially in states of increased mental effort. (*Farm Współ* 2019; 12: 54-58)

Keywords: Centella asiatica, Asiatic pennywort, Gotu kola

Introduction

For ages people have been struggling to understand the mechanisms of the diseases or other ailments, and by trial and error, seek for the proper and the most available treatments in nature. Besides strictly therapeutic action of drugs, people also aspired to find remedies that would have a positive effect on ones' strength, vigour, and mind. That subsequently led to the development of various herbal drugs (for memory and concentration), which are nowadays in high demand among students, nevertheless

elderly people also draw benefits from these products, as along with the process of aging their memory might become weaker. Many of these products contain various herbs extracts (e.g., ginseng, ginkgo biloba, lemon balm) which are the source bioactive substances stimulating the brain functioning. Asiatic pennywort (*Centella asiatica*) belongs to this group, however the knowledge about the safety of its application remains insufficient.

Case report

Healthy, 25-year-old female student, whose intention was to improve her memory in a natural way, bought gotu kola herb (*C. asiatica*) via the Internet. According to the specifications and way of usage from the leaflet, she had been preparing an infusion (1-2 teaspoons of herb brewed in one glass of hot boiled water under the lid) to drink twice a day, in the morning and at noon. On the third day of use, skin changes appeared on the woman's body, which were diagnosed by a physician as urticaria. The patient was ordered to discontinue the use of the herb. The physician introduced a treatment with cetirizine in a daily dose of 10 mg and topical application of hydrocortisone for seven days with good results of clinical improvement. The interview excluded the use of other drugs at that time as well as earlier skin-related drug reactions.

Discussion

In recent times, plant research arouses interest afresh. *Centella asiatica*, known as Asiatic pennywort or Gotu kola is a popular medicinal herb, widely used in many Asiatic countries and gaining popularity in the West. *Centella asiatica*, belonging to the family *Umbellifere (Apiceae)*, is a perennial, clonal herbaceous creeper. This plant grows in most tropical and subtropical countries, in swampy areas, wetlands (e.g., rice paddies) and also in rocky, higher elevations up to an altitude of 1800 m. There are approximately 20 species of plants related to *C. asiatica* and their range includes parts of India, Pakistan, Sri Lanka, South Africa, Madagascar, South Pacific and Eastern Europe. In Poland, there is the common pennywort *Hydrocotyle vulgaris* L., which has a similar chemical composition and properties [1].

Regarding morphological characteristics, Asiatic pennywort has small fan-shaped green leaves and white or light purple-to-pink flowers, bearing small oval fruits. Moreover, this plant has neither taste nor odor. All parts of this herb may be used for medicinal purposes [1]. In the Far East medicine, the medicative materials derived from the Gotu kola are both leaves and the whole plant with roots. This herb has been used for ages to treat various impairments of the central nervous system (improvement of the brain cells activity, memory and consciousness enhancement, IQ increase, coping with depression), cardiovascular system (hypertension, peripheral artery disease), peptic ulcer disease, skin diseases, such as chronic non-healing wounds

[2,3]. In Ayurvedic medicine, preparations of *Centella asiatica* are being used externally and internally in chronic ulcers, eczema, psoriasis, leprosy, as well as in malaria and as a generally strengthening antidote. Brahmi is one of the forms of this medicine, also known as Rasayana- rejuvenating remedy, Characa Samhita- believed to boost intelligence and Bhavaprakasha – believed to prolong lifespan. For memory augmentation and mentality disorders, powder from dried leaves (at specified doses) with milk is used [2,4]. *Centella asiatica* exhibits a complex pharmacological action, which has been evaluated in several *in vitro* and *in vivo* studies. Detailed data concerning the experimental material and applied methods is provided in the cited literature. Among various types of diseases which have been successfully treated with the extracts of *C. asiatica*, a significant percentage of cases is associated with the affected functions of connective tissue and the central nervous system. Two main constituents of triterpenoid fraction- asiaticoside and madecassoside are biologically active components applied to promote wound healing and to enhance memory [5]. Gotu kola is also a nutritionally important plant (consumed as green leafy vegetable, or in the form of juice) as it is a source of vitamins B and C, minerals, proteins, carotenoids, flavonoids, tannins, polyphenol, and oils, which are standing behind antidiabetic, wound-healing, antimicrobial, antioxidant, neuroprotective and memory-enhancing activities of this herb [6].

Concerning the dosage, the standardized *Centella* extract contains up to 100% total triterpenoids and can be taken in the amount of 60 mg once or twice per day. The herb may be consumed in the portion of 600 mg of dried leaves or infusion, in the form of capsules (300 mg to 680 mg, thrice a day) or concentrated extract (10-mg, also in capsules). *C. asiatica* dried leaves can be used to prepare an infusion- 5-10 g per 150 ml of boiling water (10-15 min of brewing) in the suggested amount of 750 ml per day. In case of fluid extracts, the recommended dose is 3-5 ml or 10-20 ml of a tincture per day. Other available medicines include orally administered tablets (10 mg 3 times daily, tincture 1 ml), and ointment (twice a day) [1].

Adverse effects

Our knowledge of scientific approaches on clinical trials regarding health benefits, mechanisms of action and toxicity of *C. asiatica* remains limited and hence we are still lacking crucial information required for the

development of new drug prototypes. *In vitro* studies revealed that *C. asiatica* compounds' nutritional and medicinal values might be affected by the method of processing of this plant [6]. Also, various biotic and abiotic factors may influence the composition of *Centella's* compounds.

When it comes to adverse effects or toxicity, *C. asiatica* in recommended doses hardly induces any. Considering appropriate dosage of this herb, it is recommended not to use it for more than six weeks, as long-term treatment (especially with higher doses) may cause a delay in the metabolism of active compounds, which can induce toxicity. With regard to this fact, prolonged treatment should contain a 2-week break before re-use of the herb. In experimental animals, the standardized extracts of Asiatic pennywort were well tolerated and asiaticoside did not bare toxic effects (oral administration, the dose up to 1 mg/kg). Toxicity of asiaticoside was reported for mice and rabbits in case of intramuscular application of 40-50 mg/kg [1]. Rare adverse effects are connected to some skin irritations such as allergy, contact dermatitis and burning sensations, when (especially fresh) plant preparations are used externally. The way of administration is apparently strongly related to the occurrence of adverse effects, as they ensue less frequently when intramuscular injections are provided, compared to the subcutaneous injections, that may induce allergic reactions, and cause pain or discoloration at the injection site. Other symptoms may include stomach discomfort, nausea, dizziness, headache, excess drowsiness, and even unconsciousness when the herb is overdosed by oral consumption [7].

C. asiatica intake during pregnancy is a matter of controversy. This herb is alleged to modify the menstrual cycle (emmenagogue action) and to be abortifacient (prevents women from becoming pregnant by inducing spontaneous abortion). Triterpene compounds did not reveal teratological effects in rabbits, but regarding poor safety and toxicity data, it is advisable to avoid *Centella* consumption during pregnancy and lactation [8, 9].

There are few cases of conditions resulting from *C. asiatica* treatment. It has been noted that Gotu kola caused hyperglycaemia and hypercholesterolemia (a single trial from 1969 [10]). Another case was the development of jaundice in three women (aged 61, 52 and 49) after taking *C. asiatica* for 30, 20 and 60 days. These patients suffered from granulomatous hepatitis

with marked necrosis and apoptosis; chronic hepatitis with cirrhotic transformation and intense necroinflammatory activity, and granulomatous hepatitis respectively. After *C. asiatica* intake discontinuation (and additional treatment with ursodeoxycholic acid 10 mg/kg/day) all the patients improved (the first patient decided to take the herb again what resulted in recurrence of the symptoms). A hypothesis emerged, that herb's terpenic active principles are responsible for apoptosis prompting and altering of cell membranes, which lead to hepatic injury. The first patient case was characterized by the presence of granulomas and autoantibodies. Moreover, relatively short time between re-take of *C. asiatica* and symptoms development (in patients 1 and 2) promoted the possibility of an immune mechanism as a factor of hepatotoxicity [11]. There was also a report of acute liver failure following the use of a medication containing Gotu kola in a 15-year-old child as an anti-acne therapy. This patient used this medication (20 mg per day for six weeks), which resulted in the hepatotoxicity manifestation. Any other cause of liver injury was not detected as anti-acne antibiotics' adverse effects were excluded [12]. Cholestasis was not present here, although tetracyclines are known to cause acute hepatitis and/or cholestasis [13]. No reports referring to the hepatotoxicity induced by lymecycline in children have been published, but in this case, this medicines did not contribute to hepatotoxicity due to the time frames involved and cholestasis absence. The symptoms subsided after discontinuation of the medication by the child [12]. *Centella's* triterpene fractions, administered per os both in pharmacological and clinical studies, were well tolerated, very rarely with slight symptoms of gastric disorders. Majority of randomized placebo-controlled trials, where the daily dose of triterpene fraction was 60-180 mg and was administered for up to 12 months, did not reveal adverse effects. In one survey 139 patients were given *C. asiatica* extract at doses of 60 to 150 mg daily for 2-18 months and the only adverse effects were three cases of allergic reactions [14].

Interactions

Several herbal drugs, when co-administered with other medicines (e.g., allopathy) are prone to cause serious herb-drug interactions. In a study of Kar et al., *C. asiatica* (along with two other Indian medicinal plants- *A. paniculata*, *B. monnieri*), and thus its chemical constituents, was scrutinized for affecting the inhibitory potential on CYP450 enzymes and its

isozymes. The inhibition of human CYP3A4, 2C9, 2D6 and 1A2 by *C. asiatica* was slight, so it can be concluded that it is unlikely to cause drug interactions with the substrates of CYP450 enzymes that are clinically relevant [15]. However, other survey [16], in which *in vitro* (using human liver microsomes) inhibition potential of *C. asiatica* with CYP450 1A2 and 2C9 enzyme was assessed, revealed, that with respect to the crude extract, *Centella's* ethanolic extract significantly inhibited CYP1A2 and 2C9 enzyme in a competitive manner. Asiatic acid and asiaticoside did not display considerable inhibition up to 50 μM concentration; nevertheless, quercetin and kaempferol (flavonoids) exposed potent inhibition of only CYP1A2 enzyme. Therefore, *C. asiatica* ethanolic extract co-administered with medications, which are CYP1A2 and 2C9 enzyme substrates may lead to adverse pharmacokinetic herb-drug interactions.

Conclusion

Centella asiatica is one of the most valued herbs of the Far East. It is characterized by a wide range of therapeutic properties, including antioxidant, antimicrobial, wound-healing, neuroprotective and memory-enhancing activities. All these valuable traits and its therapeutic potential may indeed seem very promising, however there are some limitations considering the intake of *C. asiatica* herb and its preparations. The activity (and composition), health-related and nutritional

values of *Centella's* active compounds are affected by the method of processing as well as diverse biotic and abiotic determinants. The scientific support concerning appropriate herb preparation, standardization, product variation and posology is still insufficient. Particular attention should be paid to possible adverse effects, such as previously mentioned skin irritations, hyperglycaemia, hypercholesterolemia or jaundice cases. We can constantly observe the increasing number of various herbal medicines on the market. This entails the elevated risk of appearing complications connected with incorrect product usage (including interactions resulting from simultaneous use of other herbs and/or drugs) and poor medical supervision. Summing up, in order to take full advantage of this herb's therapeutic potential with minimum adverse reactions, further research and clinical trials ought to be performed.

Konflikt interesów / Conflict of interest

Brak /None

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