OPIS PRZYPADKU / CASE REPORT
Otrzymano/Submitted: 11.01.2019 • Zaakceptowano/Accepted: 17.03.2019

The phototoxic properties of Hypericum perforatum – case report and review of the literature

Właściwości fototoksyczne dziurawca – opis przypadku i przegląd piśmiennictwa

Katarzyna Korzeniowska[1], Katarzyna Malesza[1], Mariola Pawlaczyk[2]

[1] Zakład Farmakologii Klinicznej, Katedra Kardiologii, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu

[2] Katedra Geriatrii i Gerontologii, Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu

Abstract

Background. *Hypericum perforatum* (St. John's wort) is a popular herb with many biological and medicinal properties, however, its aplication implies the risk of side effects, including photonsensitivity reactions. ***Material and methods.*** A 21-year-old woman had been using St. John's wort in a daily dose of 900 mg due to mild depression for three weeks. The patient had not been applying any other medicinal substances during that time. She had been gardening during sunny day and developed pruritic, elevated erythematous lesions on her face and dorsal surface of hands, imitating sunburn reaction. ***Results***. Symptoms subsided after administration of bilastine (20 mg per day) and application of mometasone 0.1% cream (once a day). ***Conclusion.*** During the therapy with St. John's Wort preparations, exposure to UVA radiation should be avoided. *(Farm Współ 2019; 12: 107-112)*

Keywords: Hypericum perforatum, St. John's wort, skin photosensitive reaction

Streszczenie

Wstęp. *Hypericum perforatum* (dziurawiec zwyczajny) jest popularnym ziołem o wielu właściwościach biologicznych i leczniczych, jednakże jego stosowanie pociąga za sobą ryzyko wystąpienia działań niepożądanych, w tym reakcji fotonadwrażliwości. ***Materiał i metody.*** Artykuł opisuje przypadek reakcji fotonadwrażliwości (swędzące, rumieniowate zmiany przypominające oparzenia słoneczne na skórze twarzy i dłoni wyeksponowanych na światło słoneczne) która wystąpiła u 21-letniej kobiety, stosującej wyłącznie preparat z wyciągiem z dziurawca z powodu łagodnej depresji przez trzy tygodnie w dziennej dawce 900 mg. ***Wyniki.*** Objawy ustąpiły po podaniu bilastyny (20 mg dziennie) i aplikacji kremu z 0,1% mometazonem (raz dziennie). ***Wnioski.*** Podczas terapii preparatami Dziurawca zwyczajnego należy unikać ekspozycji na promieniowanie UVA. *(Farm Współ 2019; 12: 107-112)*

Słowa kluczowe: dziurawiec zwyczajny, skórna reakcja fotonadwrażliwości

Introduction

Hypericum perforatum (*H. perforatum)* is an herb of many biological properties. It is a perennial flowering sprawling plant, growing in poor soils of meadows, fields and roadsides in the vast majority of Europe, but has also spread to regions of temperate climate in Asia, Africa, Australia, North and South America [1-3]. In ancient times there was a belief in the mystical properties of this herb, which were supposed to provide protection against evil spirits and demons. That is where the name "hypericum" comes from. It consists of two elements derived from the Greek – "Hyper" means "over, through", "eikon" – figure, image [3]. Commonly it is known as tipton weed, klamath weed, goat weed, and enola weed, but St. John's wort stands for the most prevalent name. This is a repercussion of a legend, according to which herb harvested on Saint John's Day – June 24, possessed the most valuable wealths (this period coincides with the flowering time). Another tale relates to the August 29, the day of St. John's beheading, when the herb released its blood-red oil [3-5]. *H. perforatum* is widely used for over 2000 years. The medicinal benefits of this plant have already been appreciated by Greek scholars, e.g., Dioscorides, Hippocrates, Pliny and Theophrastus

recommended this plant for its wound-healing and diuretic properties, to cure menstrual disorders and as a remedy for intestinal worms and snakebites [3,5,6]. In the Middle Ages, interest in St. John's wort has not declined. Its preparations were recommended for wound treatment and as a panacea for pain by sixteenth-century herbalists. During the eighteenth and nineteenth centuries knowledge about this medicinal herb spread in Europe and other continents. Teas and tinctures used to be recommended for water retention, gastritis, and such ailments as insomnia, anxiety and depression. The use of preparations from this herb to treat sores, abrasions, cuts and minor burns, has also been described [3,5,7,8]. Paracelsus claimed that there is no second, equally effective herb in the treatment of "crazy fantasies" – depression, melancholy, and overexcitation [9,10]. Currently, St. John's wort is a popular natural remedy for mood disorders, especially depression. Medicinal properties of *Hypericum* may also have a role in the treatment of other diseases and conditions counting bacterial and viral diseases, inflammation-related illnesses, and cancer. The herb is known to produce a multitude of different components and bioactive substances. Such multiplicity may contribute to difficulties in the interpretation of clinical trials. Two of the active constituents are of special medical importance- hypericin (naphthodianthrone) and hyperforin (lipophilic phloroglucinol). Apart from that, flavonoids (rutin, quercetin and kaempferol) present in the Hypericum extracts also appear to have medical activity. Hyperforin is especially valued as an antidepression agent and in this aspect, the mechanisms of action are fairly well understood. *H. perforatum* efficacy and safety in alleviating depressive symptoms is comparable to selective serotonin reuptake inhibitors (SSRIs) in patients with mild-to-moderate depression [12].

Various formulations containing *H. perforatum* extracts (derived from dried aerial parts typically) are commercially available on the European market, including dry extracts in the form of tablets or capsules, water-ethanol extracts and teas. Additionally, in many cases, widely available nonprescription preparations recommended for mood disorders, anxiety, and jet lag syndrome, in addition to St John's wort, contain also other phytotherapeutics (e.g. valerian) or melatonin [13]. Dosages ranging between 300-1800 mg/day are commonly used in clinical trials using various *H. perforatum* preparations [14]. Preparations of this herb, when taken alone at the recommended dosages, are rather well tolerated, but may have few adverse effects. These include symptoms such as allergic reactions, gastrointestinal irritations, abdominal discomfort or pain, restlessness, fatigue, headaches, nausea, which are generally mild and transient [15,16]. One of the known potential side effect of St. John`s wort is skin photosensitivity reaction.

Case report

A 21-year-old woman had been using St. John's wort in a daily dose of 900 mg due to mild depression for three weeks. The patient had not been applying any other medicinal substances during that time. She had been gardening during sunny day and developed pruritic, elevated erythematous lesions on her face and dorsal surface of hands, imitating sunburn reaction. As the skin lesions persisted for 7 days, she was consulted by dermatologist. The administration of bilastin (20 mg daily) and topical application of mometasone furoate 0,1% cream once a day together with soothing cream resulted in healing of the lesions after 14 days. She was advised to discontinue the herbal therapy. The interview excluded previous photonsensitive reactions, allergy, and drug induced adverse skin reactions.

Discussion

Drug-induced photosensitivity is an issue commonly occurring in clinical practice, causing about 8% of cutaneous adverse events from drugs. Photosensitization, also classified as photoallergic or phototoxic reactions, contributes to the development of a cutaneous disease, resulting from the exposure to a photosensitizing chemical agent- a systemic or topical drug, and ultraviolet (UV) or visible radiation [17]. Photosensitivity reactions can occur due to the intake of many medications, incorporating several classes of antimicrobials, nonsteroidal antiinflammatory drugs (NSAIDs), cardiovascular agents, and psychotropics [18]. However, the substances responsible for the photosensitization are also present in plants and herbs widely used at home. The example are furocoumarins and their derivatives, present among representatives of the Apiaceae and Rutaceae family, and the most potent natural photosensitizer known- hypericin present in *Hypericum* from Hypericaceae family [19].

Photosensitization by *H. perforatum*

St John's undeniably possesses beneficial medicinal properties, however, there is also a health-threatening

aspect related to the main active constituent of this herb. Hypericin absorbs UVA at 300 nm and visible light in the range from 550 to 590 nm and activation by solar radiation makes it a potent generator of singlet oxygen ($^1O_2$), superoxide anions and other reactive oxygen species (ROS) [20]. These molecules are able to induce skin photoaging and cell death in UVA light--exposed tissues. Hypericin appears to co-localize with the membranes of organelles such as endoplasmic reticulum, Golgi apparatus, lysosomes and mitochondria, which suggests that these might be the primary targets for this potent photocytotoxic chemical. The process of cell damage relies on the fact that hypericin generated ROS co-localize these cellular targets [21]. In the study of Onoue et al. [22], 19 constituents from *H. perforatum* supposed to exert phototoxic reactions were scrutinized, and it occurred that lots of them may produce ROS and be subjected to photochemical reactions. However, only hypericin, pseudohypericin, and hyperforin caused lipid peroxidation (none caused breaks in DNA strand). Nevertheless, oral doses of Hypericum extracts used as a remedy for mild to moderate depression do not induce clinically relevant photosensitization [23]. It has been indicated, that Hypericum supplementation may reduce the minimal erythemal dose (MED) in patients subjected to high dose UVA-1 phototherapy [24]. It is still questioned whether patients who receive phototherapy or are exposed to solar radiation for other reason and take oral supplementation or topical preparations of Hypericum extracts are more prone to develop skin cancers. When hypericin is ingested in an extract, combined with other herb's constituents, e.g., chlorogenic acid, flavonoids, or pyropheophorbide (which may occur photoprotective), phototoxic effects of hypericin on irradiated HaCaT keratinocytes are reduced by 25-50% [25]. Considering drug interactions, it has been noted that photosensitivity reactions may occur when *H. perforatum* is ingested with such medications as azithromycin, diphenhydramine, doxycycline, and ibuprofen [26].

However, phototoxicity induced by Hypericum extracts may have an application in photodynamic therapy (PDT) of skin cancer or, for example, psoriasis. Topically applied sensitizers are characterized by reduced risk for prolonged skin photosensitivity, which often appears after systemic administration. In a survey of Boiy et al, 0,1-1% hypericin (applied on mouse ears) generated limited phototoxicity, which was apparently due to restricted penetration into the epidermal layers. Hypericin acetate, a precursor molecule, has the ability to penetrate more readily, and respectively, may cause more severe phototoxic damages than methyl aminolevulinic acid, used in PTD so far. However, few days after application, hypericin acetate declined and induced wound healing within two weeks [27].

Photoactivated toxicity with *H. perforatum* has been reported in few cases. A 61-year-old woman with depression, who had been taking Hypericum extract for three years, acquired recurring elevated itching erythematous lesions in body parts exposed to light. Systemic oral photoprovocation test with *H. perforatum* and UVB radiation showed a decrease of MED, reversible after discontinuation of the herb administration [28]. Another report refers to a 35-year-old woman who developed neuropathy associated with Hypericum and exposure to sun. The patient took St. John's wort (ground whole herb, 500 mg/d) for mild depression. After a month of herb's intake, she acquired stinging pain on face and hands. The pain worsened after sun exposition. The herb's withdrawal resulted in the improvement in two weeks and symptoms disappeared over two months [29]. Another report is a case of a 65-year-old man who was subjected to locoregional radiotherapy (RT) after the resection of the squamous cell carcinoma of the epiglottis. He had been taking hypericin without informing the physician during and months after RT. In the course of the RT the patient developed unusual skin reactions, which diminished after few months. However, half a year later the patient presented erythema within the area of previously irradiated skin. Topically applied glicocorticosteroids alleviated the symptoms but they reappeared after discontinuation of the therapy. The skin symptoms subsided when the patient stopped taking hypericin, administered for depressive mood [30]. Schulz et al., scrutinized the effect of two different Hypericum extracts (STW 3, STW 3-VI) on photosensitivity in two identically designed, open, multiple-dose, one-phase trials. Twenty healthy men (15 of the 20 participants took part in both studies) received one tablet with Hypericum extract STW 3 (study 1) or STW 3-VI (study 2) per day. In each of the volunteers skin reactions (the development of an erythema after UV-light irradiation) were examined twice: before the treatment with Hypericum at the outset- to establish the baseline reaction, and after 14 days of treatment with particular *H. perforatum* extract- to observe the potential effects of herb extracts on skin photosensitivity. MED values were determined after

12, 24 and 48 hours and 7 days following irradiation. Before 14 day of a study (the day of the irradiation under treatment conditions), all patients reached steady-state of hypericin/pseudohypericin plasma concentrations. The results (mean MED) did not reveal significant differences between baseline conditions (without Hypericum preparation) and treatment conditions; there was no correlation between the individual plasma concentrations of hypericin, pseudohypericin or total hypericin and the effects on photosensitivity [31].

There were a lot of suggestions, that hypericin might be associated with cataractogenesis. In 2000, Schey et al carried an *in vitro* study, which in fact was a consequence of several reports from misinformed press stating, that people taking Hypericum may be at risk of developing cataracts after exposition to bright light. The team incubated alpha-crystallins (isolated from calf lenses) in 50 mmol hypericin (~1000 times therapeutic plasma concentrations) in the presence and absence of light. α-crystallin is a protein required for transparency of the lens. As there is no crystallin turnover, damage to these proteins can cumulate over the lens' lifetime and can results in cataracts [32]. The presence of light induced photo-polymerization of crystallins. Apart from the hypericin overdosage, and the fact that UV light itself is a risk factor for cataracts, this survey did not take into account the protective action of antioxidants, normally present in the serum. Therefore these results are rather ambiguous. However, Ehrenshaft et al. stated, that hypericin may accumulate in ocular tissues, including lenses, and can bind *in vitro* to α-crystallin. With the use of fluorescence confocal microscopy these researchers visualized hypericin and bovine α-crystallin binding in HLE (human lens epithelial) cell line. They also revealed that UVA irradiation of hypericin-treated HLE cells, eventuated in a significant decrease in α -crystallin detection simultaneous with a prominent accumulation of the N-formylkynurenine (tryptophan oxidation product) resulting from hypericin-mediated photosensitization. Moreover, wearing UV blocking sunglasses cannot sufficiently protect lenses of St. John's wort users, as filtration of wavelengths < 400 nm does not provide adequate protection against α-crystallin modifications and NFK accumulation [33].

Photosensitization in animals

Photosensitizing properties of St. John's wort were first observed in animals- an early report reffered to the German Blackface Sheep, which suffered from inflammatory skin conditions in the area of the eyes, ears and nose [34]. The consumption of *H. perforatum* can pose a threat to domestic livestock grazing on this plant. Ingestion of Hypericum increases the sensitivity of the animal's body to light wavelengths, which often leads to sunburns in the less hairy/wooly parts of the body (e.g. ears, nose) [35]. Photosensitizing effect displays with the classic signs- reddening and oedema of tissues of the muzzle, eyes and ears, and also increased rectal temperature [36]. In 2011 there was a case of severe sunburn in a mob of 350 adult Merino sheep with 200 lambs. The field where the sheep graze for about 4-5 months was covered in 40-50% with St. John's wort. The flock showed symptoms such as oedematous and swollen eyelids, ears or lips; severe alopecia around the eyes and muzzle was also present and the ears were frequently drooped with crusty blackened tips. Regarding the lambs, apart from the skin symptoms, they also manifested the signs from depression to extreme irritation with accompanying incessant head shaking. This mob was relocated to another grassland providing shade cover and lack of St. John's wort. After a month, there was a prominent improvement of skin condition of the sheep. The factor affecting sheep susceptibility to skin irritation after ingestion of this herb is the length of the wool. Four months (or more) of wool growth provided 3 to 4 times more tolerance to hypericin in comparison with recently shorn sheep. Skin protection presumably stands for the determining factor in the safety of Hypericum's ingestion by sheep. Nonetheless, regarding the concerns of photosensitizing effects of this herb to livestock, *H. perforatum* is considered as a noxious weed in seven western states in the United States; other locations (Canada, California, and Australia) have undertook the programs promoting herb's eradication [11].

Encapsulating all the information about *H. perforatum*, excepting its beneficial properties, especially in the treatment of mild to moderate depression, its usage may be a source of many complications, even life-threatening ones. The most fundamental and perilous is affecting the pharmacokinetics of various drugs (cardiovascular drugs, oral contraceptives, lipid lowering agents, immunosuppressants and anticancer agents) by induction of cytochrome P450 enzymes and P-glycoprotein transporter, caused by St. John's wort components- especially hyperforin [37]. Another remarkable nuisance of *H. perforatum* intake is an occurrence of

photosensitivity reaction as in medical case presented. These aspects are in majority an aftermath of insufficient knowledge and unawareness of patients about the threats, and subsequently, inappropriate application of Hypericum preparations. Therefore, to safely reap the medicinal benefits of *H. perforatum*, particular precaution is recommended while using this herb.

Conflict of interest
None

Correspondence address
Katarzyna Korzeniowska
Zakład Farmakologii Klinicznej
Katedra Kardiologii UM
1/2, Długa St.; 61-848 Poznań
☎ (+48 61) 853 31 61
katakorz@wp.pl

References

1. Klemow KM, Raynal DJ. Population biology of an annual plant in a temporally variable habitat. J Ecol. 1983;71:691-703.
2. Gleason HA, Cronquist A. Manual of Vascular Plants of Northeastern United States and Adjacent Canada. 2nd ed. Bronx, NY: The New York Botanical Garden; 1991.
3. Foster S. "St. John's Wort.". 2000. www.stevenfoster.com/education/monograph/hypericum.html (accessed November 18, 2010
4. Muenscher WC. Weeds. New York: The MacMillan Company; 1946.
5. Castleman M. The New Healing Herbs: The Classic Guide to Nature's Best Medicines Featuring the Top 100 Time-Tested Herbs. Emmaus, PA: Rodale Press; 2001.
6. Redvers A, Laugharne R, Kanagaratnam G, et al. How many patients self-medicate with St John's wort? Psychiatr Bull. 2001;25:254-6.
7. Blumenthal M, Busse W. R, Goldberg A, editors. The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. Boston: American Botanical Council; 1998.
8. Foster S, Duke JA. Eastern/Central Medicinal Plants and Herbs. New York: Houghton Mifflin Company; 2000. The Peterson Field Guides Series.
9. Nutt D. Management of patients with depression associated with anxiety symptoms. J. Clin. Psychiat. 1997, 58, 11.
10. Clement K, Covertson C, Johnson MJ, Dearing K. St. John's wort and the treatment of mild to moderate depression: A systematic review. Holist Nurs Pract. 2006;20(4):197-203.
11. Klemow KM, Bartlow A, Crawford J, et al. Medical Attributes of St. John's Wort (Hypericum perforatum). Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. Benzie IFF, Wachtel-Galor S, editors. Boca Raton (FL): CRC Press/Taylor & Francis; 2011.
12. Ng QX, Venkatanarayanan N, Ho CY. Clinical use of Hypericum perforatum (St John's wort) in depression: A meta-analysis. J Affect Disord. 2017 Mar 1;210:211-221
13. Ferrara M, Mungai F, Starace F. St John's wort (Hypericum perforatum)-induced psychosis: a case report. J Med Case Rep. 2017;11(1):137.
14. Barnes J, Anderson LA, Phillipson JD. St. John's wort (Hypericumperforatum L.): A review of its chemistry, pharmacology, and clinical properties. J Pharm Pharmacol. 2001;53:583-600.
15. "St. John's Wort". National Center for Complementary and Integrative Health, US National Institutes of Health. September 2016. Retrieved 1 February 2018.
16. Greeson JM, Sanford B, Monti DA. St. John's wort (Hypericum perforatum): a review of the current pharmacological, toxicological, and clinical literature". Psychopharmacology. 2001;153(4): 402-14.
17. Blakely KM, Drucker AM, Rosen CF. Drug-Induced Photosensitivity-An Update: Culprit Drugs, Prevention and Management. Drug Saf. 2019 Mar 19. doi: 10.1007/s40264-019-00806-5.).
18. Monteiro AF, Rato M, Martins C. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. Clin Dermatol. 2016;34(5): 571-81.
19. Fu PP, Xia Q, Zhao Y Wang S, et al. Phototoxicity of herbal plants and herbal products. J Environ Sci Health C Environ Carcinogen Ecotoxicol Rev. 2013;31(3):213-55.
20. Wölfle U, Seelinger G, Schempp CM. Topical application of St. John's wort (Hypericum perforatum). Planta Med. 2014;80(2-3):109-20.
21. Quinn JC, Kessell A, Weston LA. Secondary plant products causing photosensitization in grazing herbivores: their structure, activity and regulation. Int J Mol Sci. 2014 Jan 21;15(1):1441-65
22. Onoue S, Seto Y, Ochi M, et al. In vitro photochemical and phototoxicological characterization of major constituents in St. John's Wort (Hypericum perforatum) extracts. Phytochemistry 2011;72:1814-20.
23. Schempp CM, Müller K, Winghofer B, et al. Single-dose and steady-state administration of Hypericum perforatum extract (St John's Wort) does not influence skin sensitivity to UV radiation, visible light, and solar-simulated radiation. Arch Dermatol. 2001;137:512-3.
24. Traynor NJ, Beattie PE, Ibbotson SH, et al. Photogenotoxicity of hypericin in HaCaT keratinocytes: implications for St. John's Wort supplements and high dose UVA-1 therapy. Toxicol Lett. 2005;(15)158: 220-4.

25. Schmitt LA, Liu Y, Murphy PA, et al. Reduction in hypericin-induced phototoxicity by Hypericum perforatum extracts and pure compounds. J Photochem Photobiol B. 2006;85:118-30.
26. Patton LL. Medical History, Physical Evaluation and Risk Assesment. The ADA Practical Guide to Patients with Medical Conditions. Second Edition. 2015. Michael Glick DMD, FDS RCS (Edin).
27. Boiy A, Roelandts R, van den Oord J, et al. Photosensitizing activity of hypericin and hypericin acetate after topical application on normal mouse skin. Br J Dermatol. 2008;158:360-9.
28. Golsch S, Vocks E, Rakoski J, et al. Reversible increase in photosensitivity to UV-B caused by St. John's wort extract. Hautarzt. 1997 Apr;48(4):249-52.
29. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's Wort. Lancet. 1998 Oct 3;352(9134):1121-2.
30. Putnik K, Stadler P, Schäfer C, et al. Enhanced radiation sensitivity and radiation recall dermatitis (RRD) after hypericin therapy - case report and review of literature. Radiat Oncol. 2006;1:32. Published 2006 Sep 1. doi:10.1186/1748-717X-1-32.
31. Schulz HU, Schürer M, Bässler D, et al. Investigation of the effect on photosensitivity following multiple oral dosing of two different hypericum extracts in healthy men. Arzneimittelforschung. 2006;56(3):212-21.
32. Schey KL, Patat S, Chignell CF, et al. Photooxidation of lens α-crystallin by hypericin (active ingredient in St. John's wort). Photochem Photobiol. 2000;72:200-3.
33. Ehrenshaft M, Roberts JE, Mason RP. Hypericin-mediated photooxidative damage of α-crystallin in human lens epithelial cells. Free Radic Biol Med. 2013;60:347-54.
34. Cott JM. St. John's Wort and Photosensitivity. March 2001;3:20-3.
35. Walker E. A case of photosensitisation caused by St. John's wort. Posted flock & herd march 2012.
36. Bourke CA. Sunlight associated hyperthermia as a consistent and rapidly developing clinical sign in sheep intoxicated by St. John's wort (Hypericum perforatum) Aust Vet J. 2000;78:483-8.
37. Soleymani S, Bahramsoltani R, Rahimi R, et al. Clinical risks of St John's Wort (Hypericum perforatum) co-administration. Expert Opin Drug Metab Toxicol. 2017 Oct;13(10):1047-62.