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Review

Hypericum's 90th Anniversary in the Laboratory

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ABSTRACT

Hypericum perforatum (HP) and its varieties are plants that have been attracting the attention of scientists since 1931. In almost every country, it is possible to encounter different HP varieties. Whereas in many countries HP is indicated as an antidepressant, its commonly used forms in our country are mainly oils for topical application due to its wound-healing properties. More than 50 substances in its composition have been well established and have been the subject of detailed scientific studies, such as those on antimicrobial, antineoplastic, and antioxidant effects. The most noteworthy point of its application in daily practice is the lack of standardization, which may lead to inadequate treatment and adverse drug interactions. Although HP's antidepressant and wound-healing properties have been traditionally accepted, its side effects and safety profile limit its use in clinical application; in addition, the HP exposure in pregnancy is an arising issue. Considering that new drug molecules are usually approved in clinical use after 10–15 years, the safety of HP application in clinics have not been established even after 90 years of rigorous studies.

Keywords: Depression, *Hypericum perforatum*, St. John's wort, wound-healing

INTRODUCTION

The development of laboratory conditions and improved knowledge in working methods have increased the synthesis of drug molecules in laboratories, and scientific studies have also accelerated the use of natural resources in drug research. *Hypericum perforatum* (HP) is a plant with approximately 400 varieties (1). It is also commonly known as St. John's wort. Its wound-healing effect was known in the 5th century, and its extract is the most consumed extract in the world today for medical purposes (2). Indeed, many of its varieties grow almost everywhere in the world, and it is well known among people. Thus, the plant was further examined in laboratories. One of the first articles on HP is, to the best of our knowledge, the one about the structure of the plant that was published in Science in 1931 (3). This shows that the plant has been right in front of us in modern science ever since.

In 1951, it was determined that the prominent active substance is hypericin (4). The new chemical substances have been found in studies over the last 60 years and are sometimes referred to the type of HP. It has also been reported that the active ingredients present in different parts of the plant, such as the root or leaves, are highly variable (2). The geographic region, methods of purification, humidity of the extract, and even exposure to light make it difficult to standardize the plant extract (5). For this reason, it can be seen that the amount of compounds in the commercial forms vary greatly. Indeed, lack of standardization of HP forms is the very important issue for human health. The components of extract are summarized below (6):

- Anthraquinone (naphthodianhrones) derivatives: *hypericin, pseudohypericin, protopseudohypericin, protopseudoacetic acid, isohypericin,* and *cyclopseudohypericin,*
- Flavonoids*:* flavonols (kaempferol*,* quercetin); flavones (luteolin); glycosides *(*hyperoside*,* isoquercitrin, quercirin, rutin); *biflavonoids* (biapigenin, amentoflavone)
- Prenylated phloro glucinols: hyperforin and adhyperforin,
- Tannins: proanthocyanidin,
- Other phenols: caffeic*,* chlorogenic, p-coumaric, ferulic, p-hydroxybenzoic, and vanillic acid,
- Essential oils: methyl-2-octane, n-nonane, methyl-2-decane, n-undecane, alpha and beta-pinene, alpha terpineol, geraniol, myrcene, limonene, caryophyllene, and humulene (sesquiterpene),
- Other ingredients: isovalerianic, nicotinic, myristic, palmitic, and stearic acid; carotenoids; choline; nicotinamide; pectin; beta-sitosterol; straight chain saturated hydrocarbons*;* and alcohols.

St. John's wort is presented in the British and European Pharmacopoeia as prepared from the dry HP tips collected at the time of flowering, and they have to contain hypericines not less than 0.08% (6).

Analyzing the results of 21 HP products sold in the United States determined that five products contained cadmium above the acceptable limits, seven of them did not fulfill even one of the quality criteria, and one product contained only 21.7% of the indicated amount of hyperphorin. In another study in the United States,

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it was reported that the content of hyperforin in eight samples varied between 0.01% and 1.89%, and only two products exceeded the recommended concentration of 1% for antidepressant activity. Similarly, when hypericin content was examined, it was found that according to the labels, the active ingredient percentage fluctuated between 57% and 130% (6). Indeed, the lack of standardization and contamination of the product with heavy metals can bring other problems into everyday practice.

Much of the work done is aimed at the treatment of depression. It is recommended to take 300 milligrams/3 times a day of standardized extract (0.3% hypericin), or 2-4 grams of dry plant, three times a day (as infusion in hot water) for antidepressant activity (6). In clinical studies on depression, the dose ranges from 240 to 1800 mg/day. In addition to the treatment of depression, the studies about anxiety, menopausal and premenstrual symptoms, and against bacterial and fungal infections are still ongoing (6).

Clinical Research Results

Depression Treatment

As of February 2017, more than 300 million people are fighting depression, and approximately 800 thousand people die from depression each year (7). The most commonly prescribed drug group in the world (with 160 million prescriptions) are antidepressants (8). Ever since the Swedish physician Paracelsus determined in 1525 that HP could be used in the treatment of psychiatric disorders, it has been used in the treatment of neuralgia, anxiety, neurosis, and depression in traditional Western medicine (9). Historically, hypericum has been used in patients who felt isolated from the community and the rest of the world. It is defined as the "wound-healing" for nerve diseases (10, 11). It is used in the short-term treatment of mild to moderate depression, and the number of studies on reliable availability in the treatment of depression is increasing. It was written in the 1800s that HP proved to be beneficial in hysteria and depressive neurological diseases (2). The extract was named LI 160 in Germany in 1990, and it is sometimes possible to see this name in the studies. A report from 1999 published that 131.5 million daily doses of HP were prescribed in 1996 for the treatment of mild to moderate depression in Germany (12).

To explain the underlying mechanisms of its antidepressant effect, many of the compounds of the extract have been subject of research. Three compounds, xanthones (1.5-dihydroxyxanthone, 5-hydroxy-1-methoxyxanthone, and 6-deoxyjacareubin), were identified by crystallography in 1994 as monoamine oxidase A and B inhibitors (MAO-A and B) (13). Hypericin 10 (-3) mol/L and hypericum total extract 10 (-4) mol/L were administered in pig liver cells, but the MAO and catechol-o-methyltransferase (COMT) inhibitory properties were not sufficient at these concentrations (14). This finding was supported by another report, which stated that the HP compound administered intraperitoneally 10 (-3) mol/L to the rats did not inhibit MAO in brain homogenates to explain depression treatment (15). On the other hand, the synthesis of serotonin receptors was found to be significantly reduced at 2, 4, 6, 8, and 10 hours after the LI 160 administration in neuroblastoma cell culture (16). In 1995, 6.2 µg/ml of LI 160 administration to neuronal cell culture showed 50% inhibition of serotonin reuptake and reported that this inhibition was responsible for its antidepressant activity (17). Another study about the astrocytic cell culture in 1999 showed that LI 160 inhibited both serotonin and norepinephrine reuptake, supporting the antidepressant activity mechanism (18). Rutin, an active ingredient of the plant, was also found have an antidepressant effect (2).

It has been suggested that daily HP use at 300-1200 mg is as active as tricyclic antidepressants or serotonin reuptake inhibitors, affects the neurotransmitter system, and activates GABA, NMDA, and serotonin receptors (19). HP was found to be significantly associated with receptor for adenosine, serotonin, GABA-A, GABA-B, benzodiazepine, inositol triphosphate, MAO-A, and MAO-B. It has been reported that the isolated pseudohypericin inhibits the enzyme of dopamine-β-hydroxylase. Flavonoids and xanthones also have a strong selective inhibitory effect on MAO-A. Flavonoid-containing fractions were found to inhibit COMT. It was determined that naftodiantronsalone generally had no effect, but only had an antidepressant effect when used in combination with flavonoids (9, 20). It is clear that the activity of each compound is different, and more studies have to be conducted for a successful stabilization and standardization of the extract.

Effects on Pathogenic Microorganisms

After the antidepressant activity, the most disputed issue was whether the plant components had a chemotherapeutic effect against microorganisms. The surgeon's wound cleaner, *oleum hyperici*, was accepted in the first official pharmacopoeia of London in 1944 (2). Sarothralen A and B (21) and saroaspidin A, B, and C were studied for antibiotic effect (22), chromene for antifungal effect (23), and hypericin and pseudohypericin (24, 25) for antiretroviral activity. In 1989, drummondins A, B, C, F compounds from *H. Drummondii* were reported to have stronger antimicrobial properties than streptomycin (26). Very effective results have been obtained against methicillin-resistant *Staphylococcus aureus* by hyperphorin. Today, clinical studies are also available. Hypericum preparations prescribed in Russia (rich in hyperphosphorins) were found to be effective against the *S. aureus* infections, additionally at three different concentrations of 30%, 40%, and 50%, has been shown to be effective against vaginal pathogenic bacteria without affecting the vaginal flora. As a result of intensive studies, the hypericum extract and its components have been found to be more effective on gram-positive bacteria than gram-negative. It should be mentioned that while the extracts prepared in July did not have an antimicrobial activity, the samples collected in August had antimicrobial properties, most probably due to the light-induced chemical reactions. Also, alcoholic extracts are more effective than water extracts (2). Additionally, 6 "-O-Acetyl Quercetin 3-O-β-D-alloside, Quercitrin, Quercetin compounds have been reported to be effective against *Plasmodium falsiparum* (2). Preclinical studies show that HP is a promising antimicrobial agent, and one of its components might be on the market after its standardization in the future. However, in a study, 30 patients with an HIV infection were applied hypericin in the Phase 1 study, and they did not show any improvement in virological markers and CD4 cell counts, developing serious phototoxicity in 1999 (6).

Wound-Healing and Immunomodulatory and Antioxidant Properties

After the 16th century, the most effective and widespread use of HP in Europe was the application of distilled oil on wounds. Experimental studies also support this well known feature of the HP varieties. The healing effect on the wounds and burns can be attributed to its antibacterial effect, increased polygonal formation of fibroblasts, and increased production of collagen. It should be emphasized that the wound-healing time is not sufficient for deciding HP; the quality of wound collagen has to be questioned for this property as well.

In a study of 24 female patients who underwent cesarean section, a calendula-hypericum oil mixture (30:70) was used, and the improvement was observed in 38% of patients, while in the control group, it was only 16% (2). Hypericin has been described as an immunomodulator due to a decreasing power of induction of NF-Kappa B by phorbol 12-myristate 13-acetate and tumor necrosis factor-alpha (TNF-alpha) in HeLa and TC10 cells (27). In addition, HP's immunomodulatory properties were observed in 18 patients with atopic dermatitis in 2003; a hypericum cream, standardized to contain 1.5% of hyperphorin and a drug-free vehicle cream were applied twice a day to the right and left side of the same patient for 4 weeks, and it was proved that hypericum was effective (28). When polymorphonuclear leukocytes were stimulated by Ca-ionophore, hyperphorin 90 nanoM concentration prevented the formation of 5-lipoxygenase (5-LO) products, and this effect was found to be nearly equivalent to zileuton; also in the same study, when platelets were stimulated by thrombin and ionophore, 0.3 and 3 μM concentrations of hyperphorin inhibited cyclooxygenase (COX)-1, and this inhibition was 3 and 18 times more potent than aspirin, respectively, but the interaction with COX-2, 12-LO, and 15-LO could not be detected (29). Alveolar A549/8 and colon DLD-1 cell lines' release of inducible nitric oxide synthase (iNOS) were inhibited due to the concentration of HP extract. Therefore, it became a promising agent in chronic inflammation (30). Glutamate-induced cell death of hippocampal HT22 cells was examined in an experimental model for neuronal diseases, and it has been reported that the administration of standardized HP extract at a concentration of 0.05% results in a reduction of calcium uptake into the cell and thus a cytoprotective effect (31). It has been shown that HP has anti-inflammatory activity by suppressing the nitric oxide release and, depending on the dose, attenuating the production and release of TNF-alpha into lipopolysaccharide-induced human monocytic cell lines (THP-1) (32). In addition to previous studies, the peroxide damage was induced for 4 hours in the PC12 pheochromocytoma cell line, whereas cells pretreated with HP were protected against the stress, and the release of lactate dehydrogenize was reduced; therefore, it has been suggested that HP may be useful in diseases with oxidative stress (33). On the other hand, beside the beneficial reports on HP, it was reported that hyperforin collapsed the mitochondrial membrane potential of cortical neurons and the released Ca and Zn from the cell, and at this point, it safety is questionable (34). The immune-modulator effects of HP require more clinical studies.

Cytotoxic and Antineoplastic Studies

Hypericin is recommended to increase the sensitivity to radiation in the photodynamic treatment of cancer, and in addition, hyperforin is frequently encountered in the literature as another active substance that is intensively studied in cancer treatment (2, 35). When applied to the mouse tumor model P388, and when the vascular effect and tumor cytotoxicity were investigated, hypericin was found to be beneficial in the reduction of tumor angiogenesis and oxygenation, which is based on the photodynamic treatment (36). When different cancer cell lines are photosensitized with hypericin, the caspase pathway participates in the apoptotic effect, and the CNE2, CCL-220.1 (colon), and bladder SD cancer series are more susceptible than nasopharyngeal carcinoma TWO-1cells (37). Hypericin accumulates in the cell endoplasmic reticulum and Golgi, in many different cell groups, such as adenocarcinoma WiDr cells, NHIK 3025 cells, and D54Mg glioblastoma; while, 10 μM hypericin is not toxic to WiDr cells in dark, 1 μM is toxic under orange light, which shows the importance of light (38). The effects of pseudohypericin and hypericin on the Jurkat cells were compared, and it was found that they decrease the cell proliferation in a dose-dependent fashion, and the possible side effects of systemic treatment were emphasized because of an increased DNA fragmentation due to drug dose (39). It is known that in vitro studies of cancer treatment do not reflect the conditions at clinics; therefore, data have to be carefully interpreted as there have not been any clinical trials so far.

Teratogenicity and Effects on Reproduction

In 1990, a series of studies was carried out on Syrian hamster embryos and Chinese hamster bone marrow cells to determine the mutagenic properties of quercetin from HP, and it was reported that this substance was not genotoxic (40). However, in another study, it was reported that when hamster oocytes were incubated for 1 hour at a HP concentration of 0.06 mg/mL, the sperm penetration to oocyte was not disturbed, but if the dose was increased to 0.6 mg/mL, the sperm penetration stopped, and DNA denaturation of spermatozoa developed (41). When HP was applied in rats 2 weeks before gestation and continued 21 days postpartum at two different doses at 100 and 1000 mg/kg, liver and kidney damage in fetuses was found (42). The safety of hypericum in pregnancy has not been determined according to the Food and Drug Administration (6). An analysis of the Danish National Birth Cohort records about the safety of maternal use of HP during pregnancy and pregnancy outcomes indicated that the prevalence of malformations in the HP exposed group was slightly higher (8.1%) than observed in the control groups (3.3%; p=0.13) (43). These authors also mentioned that the agent use was not in the prescription database, and therefore, it was hard to evaluate the real issue. Further studies have to be done on the safety of HP in pregnancy and lactation.

Other HP Characteristics

Among the studies conducted to determine the properties of hypericum varieties, those on relaxant properties of the plant on the vascular smooth muscles should also be mentioned. Melzer et al. (44) showed that prostaglandin F2-alpha and histamine-induced swelling in isolated coronary arteries were antagonized by the procanidin HP compound. In another study, phenyleph-

rine and potassium chloride aortic smooth contractions were reduced by the *H. triquetrifolium tura* extract (45). Khan et al. (1) were investigating antispasmodic properties of HP on different tissues, such as rabbit jejunum, guinea pig trachea, rabbit aorta, and guinea pig atrium, and they indicated that the extract had significant calcium antagonistic properties.

It is known that cytokine-mediated beta-cell death is the main problem in diabetes, and 1-3 μM of HP extract or hyperphorin prevent the deterioration of glucose-induced insulin release and protect the INS-1E beta-cell lines against apoptosis. Furthermore, cytokine-induced STAT-1 and NF-kappa B levels have been reduced, and the functions and lifespan of the beta cells increased (46).

For the treatment of gastric ulcer, anti-gastric, and topical antibacterial properties as well as sedative and healing properties have been reported (47, 48).

Hypericum perforatum has been also reported to be able to prevent the polymerization of p-amyloid peptide, which is responsible for the onset of Alzheimer's disease (49).

Side Effects and Drug Interactions

Gastrointestinal system disorders such as diarrhea, constipation, nausea, or many different findings such as frequent urination, mouth instability, itching of the skin, edema, fatigue, headache, anorexia, manic episodes, and anxiety can be seen with the use of HP (6). Animal poisoning was defined, and photosensitization was reported (50, 51). By using human retinal pigment epithelium cells, 10 (-7) to 10 (-5) M hypericin or fluorescence light applied separately did not show phototoxicity; however, when applied together, they showed to be phototoxic to retina due to a decreased glutathione reductase activity and increased lipid peroxidation, and it has been noted that they may lead to early retinal and macular degeneration (52). In a similar study, when 0.1-10 μM hypericin and light were applied to human lens epithelial cells together, the cells became necrotic and apoptotic. For this reason, an exposure to intense light in HP users has been shown to have catarogenic effect (53).

Although work on phototoxicity is noteworthy, adverse drug interactions are the most commonly observed clinical issues. It has been published that hyperphorin increased the CYP3A4 and CYP2C9 activities, but hypericin did not interact with the CYP1A2, CYP2C9, CYP2D6, and CYP3A4 enzyme systems on human hepatocyte culture (54). One of the valuable studies to explain the drug interactions about P-glycoprotein is from 2005. The chronic effect of HP, hyperphorin, and hypericin on the LS 180 intestinal cell line and an acute effect of HP on the LLC-GA5-COL150 cells were investigated; it was determined that in case of a long-term application of hypericum P-glycoprotein substrates, the blood level significantly decreased due to increased P glycoproteins (55). Affected drug groups especially include immunosuppressants, anticancer agents, cardiovascular drugs, oral contraceptives, and lipid-lowering agents, which caused life-threatening events in several cases (56). For this reason, herbal teas used by the patients should be well questioned in the anamnesis before any treatment. The drug interactions can change the formal treatment of the patient, or any drug can become toxic. Biggs et al. (57) has also reported an alarming issue that HP can be abused by adolescents for believing of being healthy and feeling well.

A High Dose Exposure

A 1000 mg HP extract and 2.7 mg hypericin were reported to be well tolerated, but active charcoal application and blood pressure monitoring were recommended if those were taken at very high doses (6).

CONCLUSION

The number of studies on HP has increased dramatically in the past 10 years. The efforts to determine all the properties of the plant, for example in the treatment of depression, might offer us cheaper options. Identification of the compounds obtained and the determination of their stability are promising in infectious diseases, inflammatory diseases, and cancer treatment. However, it should not be forgotten that undesirable side effects in systemic use may occur in patients and that the plant extracts used by the patients with the current treatment should be properly questioned.

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