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Pleiotropic activity of *Hypericum perforatum L*

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Abstract

Hypericum perforatum L. (St John's wort) is a medicinal plant since Hippocrates era, due to its anti-inflammatory and wound/burn healing properties. Its main constituents are flavonoid aglycones (quercetin, luteolin, kaempferol), biflavonoids (apigenin, skeleton) and glycosides (hyperoside, hypericin, hyperforin isoquercitrin and quercitrin). In addition to its wound healing properties, Hp extract reversed the arthritic symptoms in experimental Freund's adjuvant arthritis presenting its anti-inflammatory effect. *Hypericum perforatum* (Hp) extract exerts antidepressive and antiatherogenic activity. Furthermore, it possesses oestrogen-mimetic activity as it has been shown in a model of forced intensive swimming stress where Hp administration increased bone mass density. Moreover, lipid parameters were beneficially modified under Hp in the same experimental model of stress. Studies showed that Hp LI 160 treatment has a beneficial effect on most menopausal symptoms and potentially prevents obesity in a menopause experimental model in rats, where Hp treatment compared to estradiol administration seems to have similar activity.

Keywords: *Hypericum perforatum*, rats, ovariectomy, bone mass

Introduction

Hypericum genus (St John's wort), is a common perennial herb of bright yellow flowers originating in Europe, West Asia and North Africa and one of the oldest herbal remedies in various cultures. Different species of the genus *Hypericum* (*Hypericaceae*) have been used in traditional medicine to treat a variety of internal and external ailments. The use of this species as an herbal remedy dates back to the time of the ancient Greeks since Hippocrates era^[1].

St. John's wort name derives from the herb's tendency to flower around a 24 June feast of St. John's birthday (wort means plant in Old English.) The species name *perforatum* derives from the watermarking of translucent dots that can be seen when the leaf is held up to the sun.

Hypericum originated from the Greek name for the plant, *hyperikon*. Literally translated, the name is an amalgamation of the root words "hyper" (meaning over) and "eikon" (meaning image or apparition), referring to the plant's supposed ability to ward off evil spirits^[2]. Early Christians also believed, the greatest effect was obtained when the plant was harvested on Saint John's Day (June 24), which is often the time of peak blooming^[2] and that the plant released its blood-red oil on August 29, the day of St. John's beheading^[3].

The Greek physicians of the first century, Galen, Dioscorides, Pliny, and Hippocrates, recommended Hp as a diuretic, wound-healing herb, treatment for menstrual disorders, and cure for intestinal worms and snakebites^[2, 3]. Flowering tops placed in olive oil caused the oil to turn red after 3 weeks.

The plant enjoyed continued use as an herbal remedy in the Middle Ages. Sixteenth-century herbalists including Paracelsus, Gerard, and Culpeper all recommended Hp preparations to treat wounds and alleviate pain^[2, 3].

Pharmaceutical companies, particularly in Europe, prepare standard formulations of this herb that are taken by millions of people. *Hypericum perforatum* (Hp) has been administered for skin wounds treatment, eczema, gastrointestinal and psychological disorders^[4, 5, 6]. Moreover, other species as *Hypericum patulum*, seems to be more specific in accelerating the cutaneous wound healing process^[7, 8].

Hp (St John's Wort) is used in the treatment of minor depression, according to the ESCOP (European Scientific Cooperative on Phytotherapy) and the relative European Monography^[9, 10, 11].

The antidepressive activity of Hp is due to hyperforin and hypericin^[12] and has been proven superior to that of the synthetic antidepressants^[13]. Kotsiou *et al.* investigated the

discrepancies of femur mass density in Wistar rats submitted to different stress procedures and treated with Hp which ameliorated the bone mass status, despite the fact that the widely used SSRI'S decrease bone mass. The antioxidant activities of Hp are attributed to its content in flavonoids^[14, 15, 16]. Hp extract exerts substantial antiatherogenic activity. Furthermore through its hypericin, hyperforin, hyperoside, quecirtin and flavonoids exerts also oestrogen-mimetic activity as it has been shown in a model of forced intensive swimming stress where Hp administration influenced bone mass positively. Moreover, lipid parameters were beneficially modified under Hp in the same experimental model of stress^[17]. It has been reported that patients with rheumatoid arthritis are prone to ulceration of soft tissues^[18]. Freund's adjuvant arthritis of rats is a widely used experimental model that mimics human chronic arthritis immune disorders^[19, 20, 21]. In such a model Sapounakis *et al.*^[22] found that in dorsal and skin trauma, Hp induced a more rapid formation of granulomatous tissue, and wound shrinkage and healing compared to controls. In addition a tendency to the arthritis profile amelioration was observed under the influence of Hp^[22].

It must be mentioned that oil extracts of *Hypericum perforatum* (Oleum Hyperici) healing effect is independent of lesion origin since it is reported to exert gastroprotective, healing and palliative activity on gastric mucosa ulcers induced by NSAIDs such as indomethacin^[23].

Furthermore, in an evaluation study of *Hypericum patulum* leaf extract skin wound healing activity in rats compared with nitrofurazone ointment it was documented that leaf extract ointments lead to more effective tissue regeneration than the antibacterial agent^[24].

There are data demonstrating analgesic and anti-inflammatory effects of various *Hypericum* species in mice models acute inflammations either with tetradecanoylphorbol acetate (TPA) induced ear inflammation^[25, 26], or zymosan induced organ dysfunction syndrome or of carrageenan induced pleuritis^{[26,}

27, 28]

The anti-inflammatory effect of Hp is attributed by Bezakova *et al.*^[29] to its isolated constituents anthrone, anthraquinone, emodin hypericin and pseudohypericin while its analgesic effect may be attributed to the presence of flavonoids, tannins and saponins^[26, 29]. Moreover, the *Hypericum* anti-inflammatory effect is ascribed to the lipoxygenase activity inhibition and to the decrease of prostaglandine E^[29, 30].

In fields regarding female health issues, applications of Hp are reported in cesarean wound healing^[31] and in premenstrual, climacteric and menopausal syndromes^[32-35].

Materials and Methods

Twenty four (24) female Wistar rats were divided into four groups (A,B,C,D). A was used as control, while B,C,D were ovariectomized. Six weeks after surgery, group C was treated with LI 160 (Lichtwer Pharma AG, Berlin, Germany 80% methanolic dry extract of flowers and buds of *Hypericum perforatum* L., containing 0.17% hypericin and 4.3% hyperforin by HPLC analysis) 200mg/kg and group D with Menorest (Novartis[®]) 50 µg/kg/day, both per os for 4 weeks. Animals were weighed, sacrificed, uterus and femur were isolated and weighed. Femur bone mass density was estimated by DEXA (dual energy X-Ray absorptiometry).

The animals were cared in accordance with the principles of the "Guide for the Care and Use of Experimental animals^[36].

Data are expressed as the mean ± SE.

Results

Ovariectomized animals' body weight and adiposity increased, while femur bone mass decreased due to estrogen deficiency. Exogenous estradiol seems to attenuate this increment. Hp administration reduced body weight and abdominal fat (oestrogen-like activity) and femur bone density seems to be improved. (Table 1)

Table 1

	Control A	Ovariectomi B	Ovariectomi C	Ovariectomi D
Body weight g	256.67±25.0	303.57±51.37	276.67±47.08	261.11±65.28
Uterus weight g	3,2189±0.6634	2.7714±1.245	2.8083±1.054	2.855±0.8174
Uterus weight / body weight	0.0137±0.0044	0.0096±0.0051	0.0112±0.0037	0.0101±0.0048
Femur bone density BMD g/cm ²	0.195±0.09	0.158±0.010	0.178±0.003	0.180±0.006
Femur specific weight g/ cm ³	1.6486±0.3079*	1.126±0.1190	1.38±0.05	1.439±0.1052*

Discussion - Conclusion

Probably Hp treatment ameliorates menopausal symptoms through its antidepressive activity. Hp improves also physical and behavioral symptoms of pre and post menstrual symptoms^[32-35]. Moreover, menopause induces hyperlipidaemia which has been documented to be beneficially modified under Hp treatment^[17]. After menopause is established, estrogens are no longer secreted by the ovaries but produced via peripheral conversion from precursor androgens. Possibly Hp metabolic effects on CPY3A accelerate the elimination of the so produced estrogens. On the other hand flavonoids may be responsible for the bone density restoration.

It may be concluded that Hp may be proved a helpful tool in the treatment of menopausal symptoms and other disturbances as well.

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