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Chemical compound and Therapeutic effects of *Hypericum perforatum*

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ABSTRACT

Hypericum perforatum is native to parts of Europe and Asia but has spread worldwide as a cosmopolitan invasive weed, including to temperate regions of India, China, Canada, Africa, and the United States. The aim of this study was to overview its therapeutic effects. This review article was carried out by searching studies in PubMed, Medline, Web of Science, and Iran Medex databases .The initial search strategy identified about 98 references. In this study, 42 studies was accepted for further screening and met all our inclusion criteria [in English, full text, therapeutic effects of Hypericum perforatum and dated mainly from the year 1987 to 2016.The search terms were "Hypericum perforatum", lemon balm, "therapeutic properties", "pharmacological effects". It is commonly used for antimicrobial effect, neuroprotective effect, anti-depressive effect, antioxidant effect, menopause, dental practice, anti-inflammatory, wound healing effect, anti-cancer effect, anti-herpes effect, phototoxicological effect. Hypericum perforatum is widely used for therapeutic and non-therapeutic purposes that trigger its significant value. Various combinations and numerous medicinal properties of its extract, oil, and leaves demand further and more studies about the other useful and unknown properties of this multipurpose plant.

Keywords: *Hypericum perforatum*, Phytochemicals, Therapeutic effects, Pharmacognosy, Alternative and complementary medicine.

INTRODUCTION

Hypericum perforatum is native to parts of Europe and Asia [1] but has spread worldwide as a cosmopolitan invasive weed [2, 3], including to temperate regions of India, China, Canada, Africa, and the United States [4]. Perforate St John's wort is an herbaceous perennial plant with extensive, creeping rhizomes. Its stems are erect, branched in the upper section, and can grow to 1 m high. It has opposite, stalkless, narrow, oblong leaves that are 1–2 cm long [5]. The leaves are yellow-green in color, with scattered translucent dots of glandular tissue. The dots are conspicuous when held up to the light, giving the leaves the 'perforated' appearance to which the plant's Latin name refers. The flowers measure up to 2.5 cm across, have five petals, and are colored bright yellow with conspicuous black dots [6, 7]. The flowers appear in broad cymes at the ends of the upper branches, between late spring and early to mid-summer. The sepals are pointed, with black glandular dots. There are many stamens, which are united at the base into three bundles. The pollen grains are ellipsoidal. Studies have supported the efficacy of St John's wort as a treatment for depression in humans [8]. It has superior efficacy to placebo in treating depression; is as effective as standard antidepressant pharmaceuticals for treating depression; and has fewer adverse effects than other antidepressants. St. John's wort (*Hypericum perforatum*) has antioxidant, anti-inflammatory, anticancer, and antimicrobial activities[9].

Chemical compound
Hypericin, pseudohypericin, and hyperforin may be quantitated in plasma as confirmation of usage and to estimate the dosage [10]. These three active substituents have plasma elimination half-lives within a range of 15–60 hours in humans. None of the three has been detected in urine specimens [11].

Antimicrobial effect
the antimicrobial activity of the ethanol extract (HP-EtOH) of *H. perforatum* and its sub-extracts, was investigated, against Streptococcus mutans, S. sobrinus, Lactobacillus plantarum, and Enterococcus faecalis. results found that HP-H2O sub-extract displayed strong antibacterial activity (MIC values 8 μg/mL) against S. sobrinus and L. plantarum, and exerted moderate activity against S. mutans and E. faecalis at 32 and 16 μg/mL concentrations, respectively. According to the results, we suggest that *H. perforatum* could be employed as a natural antibacterial agent in oral care products[12].

Neuroprotective effect
The effect of *H. perforatum* extract against unilateral striatal 6-hydroxydopamine (6-OHDA) toxicity was evaluated. The findings reveal the beneficial effect of *H. perforatum* via attenuation of DNA fragmentation, astrogliosis, inflammation, and oxidative stress [13].

Anti-Depressive effect
The relationship between clinical improvement and physician belief about assigned therapy was determined.it showed that Doctors tended to guess placebo more easily than Hypericum or sertraline, and their guesses tended to favor active therapies when improvement was more robust. Results show association but not causation, and merit more careful investigation [14].

The results of a study showed adhyperforin could reduce the immobility time of mice in the forced swimming test and tail suspension assay, antagonize the behaviors induced by reserpine, and have no effect on locomotor activity. Furthermore, following establishment of a chronic unpredictable mild stress model, adhyperforin increased the number of crossings and rearings in rats in the open field test and increased the sucrose consumption [15].

The effect *Hypericum perforatum* (HP), on behavioral changes, corticosterone, TNF-α levels and tryptophan metabolism and disposition in bilateral ovariectomized rats compared to 17α –ethinylestradiol was investigated. Results that the observed attenuating effect of HP on TNF-α and corticosterone could contribute in its antidepressant effect in this animal model by other ways than their effects on tryptophan-kynurenine metabolism pathway [16].

The synergistic antidepressant effect of quercetin and hyperforin (HF, extracted from *Hypericum perforatum*) was explored. The combination of quercetin and *Hypericum perforatum* extract in certain ratio has significant synergistic antidepressant effect in ICR mice [17].

Anti-depression effect of *Hypericum perforatum* was examined and it was found that there is a significant difference between sertraline and placebo with some statistical-methods used. It is important to conduct an analysis that takes account of missing data using valid statistically principled methods. The assumptions about the missing data process could influence the results [18].

H. perfortum extract in animal models of depression compared to clinically used antidepressants was Evaluated. *H. perforatum* has antidepressant properties similar to standard antidepressants. The antidepressant profile of *H. perforatum* is closely related to the selective serotonin reuptake inhibitors class of antidepressants [19].

The potential cytotoxic, mutagenic and antimutagenic action of *H. perforatum* was evaluated. The results suggest that the administration of *H. perforatum*, especially by gavage similar to oral consumption used by humans, is safe and with beneficial antimutagenic potential [20].

The effects of *Hypericum perforatum* extracts have been compared with those of conventional antidepressants in different in vitro and in vivo biochemical studies of antidepressant-like activity and in behavioral pharmacology studies using animal models of depression. the majority of findings in preclinical studies have been obtained with

high doses of pure compounds and extracts that are not comparable to the concentrations of single active constituents after oral administration in humans[21].

A model to assess the cost-effectiveness of St. John's wort based on this evidence was developed. This plant was shown to be a cost-effective alternative to generic antidepressants. Patients are more likely to receive treatment for a duration consistent with professional guidelines for treatment of major depression due to reduced incidence of adverse effects, improving outcomes. This represents an important option in the treatment of Major Depressive Disorder [22].

Longer-term efficacy of *Hypericum perforatum* as an antidepressant was investigated and it was revealed that an equivocal outcome between treatments at week 26, both SJW and sertraline were still therapeutically effective, with a pronounced "placebo-effect" impeding a significant result at week 26[23].

The available evidence for the effectiveness of pharmacological, psychological, and combined treatments for patients with depressive disorders in primary care was compared. A multiple treatment of primary-care based randomized controlled trials on the most important therapies against depression is timely and necessary [24].

Antioxidant effect
Adventitious root cultures in large-scale bioreactors for the production of useful phytochemicals was developed. Findings demonstrate the possibilities of using *H. perforatum* adventitious root cultures for the production of useful phytochemicals to meet the demand of pharmaceutical and food industry [25].

The phototoxicity of hypericin in HaCaT keratinocytes by *H. perforatum* extracts and constituents was determined. Alpha-tocopherol, a known antioxidant also did not influence the amount of lipid peroxidation induced in this system. These observations indicate that hypericin combined with *H. perforatum* extracts or constituents may exert less phototoxicity than pure hypericin, but possibly not through a reduction in arachidonic acid peroxidation [26].

Menopause effect
the efficacy and adverse events of *Hypericum perforatum* L. or its combinations, and placebo for menopausal women was examined. Extracts of *Hypericum perforatum* L. have possibly fewer side-effects than placebo for the treatment of menopausal women[27].

the effects of two herbal medications, *Hypericum perforatum* and Passion Flower, on menopause symptoms was examined and it showed that it can be used as an alternative treatment for individuals who cannot, whatsoever, use hormone therapy [28].

Dental practice effect
Although case reports suggest therapeutic potential of Hypericum for pain conditions in dental care, this effect is not currently supported by clinical studies. Further clinical controlled trials of Hypericum alone in dental practice should be performed [29, 30].

Anti-inflammatory effect
Ethanol extracts of different Hypericum species were compared for their inhibitory effect on LPS-induced prostaglandin E2 (PGE2) and nitric oxide (NO) production in RAW 264.7 mouse macrophages. Finally. It showed that a different group of major anti-inflammatory constituents were present in H. gentianoides, while showing that the previously identified 4 compound combination was important for *H. perforatum*'s anti-inflammatory potential [31,32].

Wound healing effect
In an animal study, the healing effects of *Hypericum perforatum* (HP) on full-thickness diabetic skin wounds was evaluated by using stereological methods. Numerical density of fibroblasts, volume density of collagen bundles, and mean diameter and volume densities of the vessels in HP group were significantly higher than control and vehicle groups. The results showed that HP has the ability to improve tissue regeneration by enhancing fibroblast proliferation, collagen bundle synthesis, and revascularization [33].

HP treatment in experimental thermal burns and compare it with silver sulfadiazine (SS) treatment was investigated. The results was shown that Administration of HP four times a day within the first 24 hours is clearly effective in wound healing in the experimental thermal second degree burn modality and is significantly superior to SS treatment[34].

Inan in vivo study, the healing properties of the ointment was investigated in wound models of linear incision, circular excision and thermal burn on Wistar rats. Topical treatment was achieved daily, for 21 days. Clinical and macroscopic evaluation, determination of wound contraction rate, period of re-epithelialization, and histopathological examination were achieved, along with the determination of the particle diameter and particle size distribution of the ointment. The results demonstrate that the tested novel ointment has significant wound healing effect in skin injuries and reveals to be safe for use [35].

The wound healing potential of this new formulation by using in vivo and in vitro models as well as histopathological methods were assessed. The experimental studies revealed that HPP crème mitRotöl formulation displays remarkable wound healing activity. To be acting on the different stages of wound healing process could be considered as a beneficial effect of the formulation for the treatment of wounds [36].

the wound healing activity of microcurrent application alone or in combination with topical *Hypericum perforatum* L. and Arnica montana L. on skin surgical incision surgically induced on the back of Wistar rats was evaluated. application of *H. perforatum* or A. montana was effective on experimental wound healing when compared to control, but significant differences in the parameters studied were only observed when these treatments were combined with microcurrent application [37].

Anti-cancer effect

the role of *Hypericum perforatum* and neem oil in the treatment of acute skin toxicity for patients undergoing radiotherapy or chemo-radiotherapy for head and neck cancer was evaluated. This oil proved to be a safe and active option in the management of acute skin toxicity in head and neck cancer patients submitted to RT or chemo-radiotherapy. A prophylactic effect in the prevention of moist desquamation may be hypothesized for hypericum and neem oil and need to be tested within a prospective controlled study [38].

The response mechanisms of melanoma cells to hypericin-PDT in an in vitro tissue culture model was Investigated. This treatment resulted in extrinsic (A375) and intrinsic (UCT Mel-1) caspase-dependent apoptotic modes of cell death, as well as a caspase-independent apoptotic mode that did not involve apoptosis-inducing factor (501 mel). Further research is needed to shed more light on these mechanisms [39].

The efficacy of photodynamic therapy with topical application of an extract of *H. perforatum* in actinic keratosis, basal cell carcinoma (BCC) and morbus Bowen (carcinoma in situ) was studied. Better preparation of the lesions, enhancement of hypericin delivery and other types of light exposure procedures could significantly improve the clinical outcomes of this relatively inexpensive treatment modality [40).

Anti-herpes effect

The comparative efficacy and tolerability of a single use, topical formulation containing copper sulfate pentahydrate was assessed .The Dynamiclear formulation was well tolerated, and efficacy was demonstrated in a number of measured parameters, which are helpful in the symptomatic management of HSV-1 and HSV-2 lesions in adult patients. Remarkably, the effects seen from this product came from a single application [41].

Phototoxicological effect

Photobiochemical properties of SJW extract and 19 known constituents were characterized with focus on generation of reactive oxygen species (ROS), lipid peroxidation, and DNA photocleavage, which are indicative of photosensitive, photoirritant, and photogenotoxic potentials, respectively. Results suggested that hypericin, pseudohypericin, and hyperforin might be responsible for the in vitro phototoxic effects of SJW extract [42].

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