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### St John's wort (*Hypericum perforatum L.*): A Review of its Chemistry, Pharmacology and Clinical properties

AR. Mullaicharam\* and Nirmala Halligudi

Oman Medical College, Bowsher campus, Muscat, Oman.

#### ABSTRACT

St John's wort (also known as hypericum, millepertuis) is *Hypericum perforatum L.*, Hypericaceae, an herbaceous perennial plant native to Europe and Asia, and which has been introduced into the United States where it has naturalized. The chemical composition of St. John's wort has been well-studied. Documented pharmacological activities, including antidepressant, antiviral, and antibacterial effects, provide supporting evidence for several of the traditional uses stated for St John's wort. Many pharmacological activities appear to be attributable to hypericin and to the flavanoid constituents; hypericin is also reported to be responsible for the photosensitive reactions that have been documented for St. John's wort. This systematic review overviews the literature on the use of St. John's Wort for chemistry, pharmacology and clinical properties.

**Keywords:** *Hypericum perforatum*; pharmacological activities; hypericin.

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#### Corresponding Author

Name: AR. Mullaicharam  
Email: [mullai@omc.edu.om](mailto:mullai@omc.edu.om)

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#### INTRODUCTION

*Hypericum perforatum L.* (St. John's wort) is a five-petaled, yellow-flowered perennial weed common to the western United States, Europe, and Asia. [1] There are several explanations as to the origins of the names hypericum and St John's wort. Commonly, the name hypericum is believed to be derived from the Greek word *hyper* (over) and *eikon* (image), and the name St John's wort may have arisen as the flowers bloom around St John's Day (June 24). *Hypericum perforatum* is native to parts of Europe and Asia [2] but has spread worldwide as a cosmopolitan invasive

weed [3, 4], including to temperate regions of India, China, Canada, Africa, and the United States [5].

*Hypericum perforatum* is a five-petal perennial flowering plant notable for its ability to treat mild to moderate depression. [6,7] Historically, hypericum was used in patients with feelings of isolation who lacked community and felt separated from the rest of the world. It has been described as a "wound healer" for nervous individuals [8,9]. The flowers measure up to 2.5 cm across, has five petals, and are colored bright yellow with conspicuous black dots [10, 11]. 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 [12]. 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 [13].

#### Monograph

Common name: St John's wort

Other names: Hypericum, amber, goat weed, john-wort, Klamath weed, tipton weed, hardhay, prikbladett perikon, hartheu, herb de millepertuis, hyperici herba, iperico, johanniskraut, sonnenwendkraut [14].



**Figure 1: Hypericum perforatum**

Family: Clusiaceae

Parts used: above ground parts

### Active Constituents

St. John's wort has a complex and diverse chemical makeup. Constituents include volatile oils (0.05 to 0.3%, including  $\alpha$ -pinene, and cineole), anthraquinones, carotenoids, coumarin, flavonoids (0.5- 1.0%, including hyperoside, quercetin, and rutin), naphthodianthrones (0.1-0.3% of which 80-90% are hypericin and pseudohypericin), carboxylic acids, phloroglucins (up to 3% hyperforin), xanthenes, and proanthocyanidins.<sup>[15]</sup> The naphthodianthrones hypericin and pseudohypericin previously received most of the attention in pharmacological studies. This is based on their contributions to the antiviral properties of the plant as well as speculation (based on early *in vitro* data) that they may also contribute to the plant's antidepressant actions.<sup>[16]</sup> This may partially explain why many extracts continue to be standardized to contain measured amounts of hypericin. Recent research, however, indicates that other constituents such as hyperforin,<sup>[17,18]</sup> and possibly flavonoid compounds, may also contribute to the antidepressant actions of the plant.

### Historical use

St John's wort has a long history of usage, being used in antiquity for the treatment of burns, snake bites, fever and wounds. During the medieval period, St. John's wort was ascribed almost magical powers of protection against evil spirits because of its association with St. John the Baptist. The yellow petals when bruised show a reddish mark that symbolized the bloodshed by the saint. Hung in the house or rubbed over the lintels, the herb would prevent witches and death from entering during the year. Wort is from the old English wyrt, meaning a plant or herb, especially one used in medicine. Paracelsus, the Swiss physician, chemist and natural philosopher who lived in the 16<sup>th</sup> century, wrote of the superior healing powers of St. John's Wort as menopausal neurosis, other indications listed are excitability, neuralgia, fibrositis and sciatica.<sup>[14]</sup>

### Mechanism of action

A number of proposed mechanisms exist for St. John's wort's antidepressant effect, involving several neurotransmitters and hormones. Initially, inhibition of monoamine oxidase (MAO) was believed to be the

primary mode of action,<sup>[19]</sup> and was thought to be due primarily to hypericin.<sup>[20]</sup>

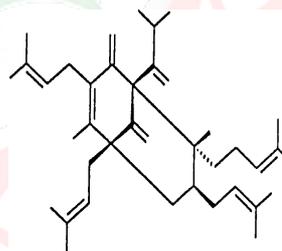
Hypericin and hypericin-like constituents may possibly act on acetyl cholinesterase by reducing the degradation rate of acetylcholine.<sup>[21]</sup> Sedative actions come from the hypericins, bioflavones, and hyperphoria. Other reports demonstrate a serotonergic activity<sup>[22]</sup> that causes hypericum to act like a weak serotonin reuptake inhibitor (SSRI), but with fewer side effects than its pharmaceutical counterpart.<sup>[23]</sup>

Hypericum may encourage production of thyroid-stimulating hormone, though a clear link has not been established.<sup>[24]</sup>

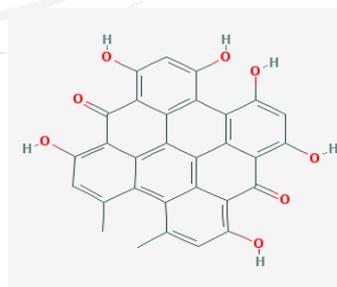
Hyperforin has also been shown to have antimicrobial activity against gram-positive bacteria and numerous viruses. This property is likely attributed to the essential oils, phloroglucinol, and flavonoid constituents, and may involve a photo activation process that disrupts certain components of the organism's cell membrane.<sup>[25,26]</sup> The antitumor properties of St. John's wort are attributed to hypericin, which is a powerful photo sensitizer. Once taken up by tumor cells, hypericin reacts in the presence of oxygen and activates multiple apoptosis pathways that results in malignant cell death.<sup>[27,28]</sup>

### Chemistry

The major active constituents are considered to be hyperforin (a prenylated phloroglucinol; Figure 1) and hypericin (a naphthodianthrone; Figure 2), although other biologically active constituents, eg flavonoids, tannins, are also present.<sup>[29]</sup> The constituents of St John's wort (*Hypericum perforatum* L.), compiled from several sources (Bisset 1994) Bombardelli & Morazzoni 1995;<sup>[30-31]</sup>



**Figure 2: Chemical structure of hyperforin**



**Figure 3: Chemical structure of hypericin**

**Table 1: Phytoconstituents of *Hypericum perforatum***

S.No	Constituents	
1	Flavanoids	Flavonols (e.g. kaempferol, quercetin), flavones (e.g. luteolin) and glycosides (e.g. hyperoside, isoquercitrin, quercitrin, rutin), biflavonoids including biapigenin (a flavone) and amentoflavone (a biapigenin derivative) <sup>[32]</sup>
2	Tannins	Proanthocyanidins (condensed type) have been reported <sup>[31]</sup>
3	<i>Anthraquinone derivatives (naphthodianthrones)</i>	Hypericin, pseudohypericin, and isohypericin; protohypericin, and protopseudohypericin (biosynthetic precursors of hypericin and pseudohypericin, respectively) Cyclopseudohypericin, Hypericin pseudohypericin <sup>[33]</sup> .
4	<i>Prenylated phloroglucinols</i>	Hyperforin adhyperforin <sup>[34]</sup>
5	Other phenols	Caffeic, chlorogenic, <i>p</i> -coumaric, ferulic, <i>p</i> -hydroxybenzoic and vanillic acids.
6	Volatile oils (0.05±0.9%)	methyl-2-octane (saturated hydrocarbon); others include nonane and traces of methyl-2-decane and <i>n</i> -undecane (saturated hydrocarbons; Brondz et al 1983), $\alpha$ - and $\beta$ -pinene, $\alpha$ -terpineol, geraniol, and traces of myrcene and limonene (monoterpenes), caryophyllene and humulene (sesquiterpenes) <sup>[35]</sup>
7	Other constituents	Acids (isovaleric, nicotinic, myristic, palmitic, stearic), carotenoids, choline, nicotinamide, pectin, $\beta$ -sitosterol, straight chain saturated hydrocarbons (C16, C30) and alcohols (C24, C26, C28) <sup>[36]</sup>

### Pharmacology

Several pharmacological activities, including antidepressant, antiviral, and antibacterial effects, have been documented for extracts of St John's wort and/or its constituents<sup>[37]</sup>

### Anticancer effect

Hyperforin has also been investigated in animals and *in vitro* studies for its antitumor effects. Schrempp et al found hyperforin dose dependently inhibited the growth *in vitro* of rat and human mammary cancer, as well as squamous cell carcinoma, malignant melanoma, and lymphoma better than or equal to other cytostatic drugs tested, including camptothecin, paclitaxel, and vincristine. The data revealed hyperforin appears to induce tumor cell apoptosis via activation of mitochondria, release of cytochrome c, and caspase activation, which all in turn trigger cell death pathways. Further research in this area is indicated.<sup>[39]</sup>

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<sup>[40]</sup>.

The Hypericum constituent, hypericin, is a powerful photosensitizing agent and its use in photodynamic

therapy for cancer patients has gained the attention of researchers for over a dozen

years. Numerous *in vitro* studies<sup>[41-44]</sup> have investigated its effect on various cell lines. These studies all demonstrate hypericin's cytotoxic effect on tumor cells after photosensitization.

### Antidepressant activity

The precise mechanism of action for the antidepressant effect of St John's wort is unclear. Initially, attention was focused on hypericin as the constituent of St John's wort believed to be responsible for the herb's antidepressant effects. However, experimental has now emerged to indicate that hyperforin is one of the major constituents required for antidepressant activity.<sup>[45-46]</sup>

### Wound healing

St. John's wort has long been used successfully as a remedy for wound healing, and research in

humans supports its effectiveness in this arena. All patients were treated twice daily for 16 days and Surface Perimeter Area (SPA) of the surgical wound was measured before and after treatment. Patients treated with the Hypericum/Calendula mixture exhibited a significant decrease (approximately 38%) in the SPA of the surgical wound compared to patients in the placebo group (approximately 16%).<sup>[50]</sup>

### Hypericum in Pregnancy

Despite considerable scientific investigation, relatively little information has been garnered regarding

the use of hypericum for depression during pregnancy. A few animal studies have investigated its effect on pregnancy and progeny. A study in rats using doses up to 25 times the equivalent recommended human dose throughout gestation was unable to show any neurobehavioral or developmental effects on the offspring. Maternal weight gain or length of gestation, likewise, was not affected [51]. Other murine studies showed no significant impact on cognition or behavioral tasks.

In 1998, there were reports on 2 women who took hypericum in their pregnancies to avoid the use of conventional synthetic medications. Both cases seemed to reveal no concerns. One of these cases was of a 38-year-old woman who started hypericum at 24 weeks gestation. The pregnancy was unremarkable, with the exception of late onset of thrombocytopenia, which the author did not attribute to hypericum. The offspring was born healthy, had a normal birth weight, normal APGAR scores, and physical examination and laboratory results were normal. Infant behavioral assessment at 4 and 23 days was normal. [52]

#### Antiviral activity

Hypericin has also been reported to inactivate murine cytomegalovirus (MCMV) and Sindbis virus [47]. The antiviral activity of hypericin appears to involve a photo activation process

Flavonoid- and catechin-containing fractions of St John's wort have exhibited activity against influenza virus [48]. Hypericin and pseudo hypericin have been reported to inhibit several encapsulated viruses in vitro, including herpes simplex virus types 1 and 2. [49]

Hypericin is a well known photosensitizing agent used in the photodynamic therapy of cancer and viral infections. The photodynamic therapy involves the combination of photosensitizing agent and visible light at the absorption wavelength of the compound. Lavie et al demonstrated [53] the inhibitory effect of hypericin and pseudohypericin against vesicular stomatitis, influenza virus and herpes simplex virus type II and I. Both hypericin and pseudohypericin prevents the viral fusion by the generation of singlet oxygen up on illumination [54].

#### Antimicrobial activity

Hyperforin is reported to have antibacterial activity against *Staphylococcus aureus* [55]. Antibacterial activity of hyperforin against multidrug-resistant *S. aureus* and Gram-positive bacteria, including *Streptococcus pyogenes* and *Corynebacterium diphtheriae*, has been reported [56]. However, it has been emphasised that the antibacterial effects of hyperforin are only observed at high concentrations [57-58]

#### Hypericum Interactions

Although now not considered a concern regarding interaction with monoamine oxidase (MAO)-inhibiting

drugs or tyramine containing foods, hypericum has been shown to have the ability to either enhance or reduce the circulating levels of certain drugs: [59-61] Hypericum is known to induce enzymes of the cytochrome P450 system (3A4 and 1A2) as well as P-glycoprotein from the intestinal wall. Hypericum interacts with and lowers the effectiveness of oral contraceptives. If a patient is taking specific or multiple medications, hypericum should be used with caution or avoided altogether, and other options should be considered.

#### Medications Known to Interact with Hypericum

Alprazolam, Amitriptyline, Cyclosporine, Digoxin, Indinavir, Irinotecan, Methadone, Nevirapine, Oral contraceptives, Phenprocoumon, Simvastatin, Tacrolimus, Theophylline, Topo II-poisoning chemotherapy regimens, Verapamil, Warfarin.

#### CONCLUSION

The review describes chemical profile, pharmacology with special reference to hypericin. The vast body of research, as well as historical use, suggests that hypericum is a useful as part of a broader treatment plan for adults with minor to moderate depression. Emergent studies suggest that hypericum may be helpful and does not cause any birth defects, may be useful in adolescents with depression, and has a favorable side effect profile. However, hypericum is known to have interactions and modulate the pharmacokinetics of many medications. As a result, caution is recommended with patients on medication(s).

Concerns have been raised over interactions between St John's wort and certain prescribed medicines (including warfarin, cyclosporine, theophylline, digoxin, HIV protease inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, triptans, oral contraceptives); advice is that patients taking these medicines should stop taking St John's wort, generally after seeking

professional advice as dose adjustment of conventional treatment may be necessary.

Some studies in basic research however do report on anti-inflammatory and analgesic effects of *H. perforatum*. We therefore encourage further studies with homeopathic Hypericum in both basic research and randomized controlled clinical trials in dental practice

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