**Hypericum perforatum**: Nature’s mood stabilizer

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*Hypericum perforatum* (HP), better known as St. John’s Wort, has been used clinically for centuries. Modern usage is still quite diverse and includes kidney and lung ailments, insomnia and depression. Standardised extracts of HP are widely used in the treatment of psychovegetative disorders and especially for mild forms of depression. Several bioactive constituents of this plant may play important role in its well-known antidepressant activity, which are discussed in the present article. Furthermore, emphasis is also given on its botany, chemistry, pharmacology and clinical efficacy.

The name *Hypericum* is a derivation of two Greek words, _hyper_ and _eikon_ which translate “over” and “icon” as in “over an apparition,” alluding to its use in ancient times for protecting against demonic possession and its reported ability to protect one from “evil spirits.” The species name _perforatum_ is based on the perforated appearance of the leaves due to their translucent leaf glands which can be observed when held up to light. *Hypericum perforatum* (HP) is also known as St. John’s Wort because its flowers bloom around St. John’s Day (June 24) and red pigments which are exuded when the buds and flowers are squeezed were associated with the blood of St. John the Baptist.

HP is a perennial plant belonging to the Guttiferae family. Some taxonomists classify the genus *Hypericum* in a separate family, the Hypericaceae. The genus *Hypericum* encompasses approximately 400 species, of which ten morphologically and chemically distinct species grow in central Europe.

HP is distributed in Europe, Asia, North Africa and North America. Indian HP (HP) is a rhizomatous perennial herb growing up to a height of 3 feet distributed in the western Himalayas at altitudes of 3000-10,500 feet.

*Hypericum* species were already known to ancient communities as useful medicinal plants. HP has been known since Greek and Roman times. Closer to our times, Mattioli also wrote of *Hypericum* _in Discorsi_.

The use of HP in particular, as a remedy was described and recommended throughout the Middle Ages. The primary ancient medical herbalists, including Hippocrates, Pliny, Dioscorides, Theophrastus and Galen wrote about the medicinal properties of St. John’s wort, noting its use as a vulnerary (wound healing) and for treatment of neuralgic conditions such as sciatica and hip pain. Mattioli wrote of its use as an emmenagogue, diuretic and antimalarial. The most common use of *Hypericum* has been for the treatment of depression and various psychological and neuralgic disorders, as an anthelmintic for worms, a vulnerary for minor hemorrhages, for bedwetting in children, and as a diuretic. Besides it has been also used as balm for wounds, burns, ulcers and bites.

**Botanical description**

HP is glabrous throughout, green or sometimes glaucous; the stems are erect, branched at top and 30 to 100 cm long; the leaves are oval or elliptic, sucordate, or rather narrow, oblong-linear, subobtuse, revolute-marginated with numerous pellucid black glandular dots. The flowers are numerous, forming a broadly paniculate, almost corymbose inflorescence, 7-11 cm long and 5-11 cm broad. The bracts are lanceolate, 0.5 cm long and acute. The calyx is deeply parted, 5 mm long and about two to three times shorter than corolla; sepals are lanceolate 4-5 mm long, 1 mm broad, as long as ovary, acute or acuminate, with black glandular mostly oval dots. The petals are oblong to oblong elliptic, in equilateral, 1.2 to 1.5 cm long, 0.5 to 0.6 cm broad, with numerous black glandular dots and lines on margin of upper part, surface with numerous yellow glandular dots. The stamens are numerous, in 3

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bundles; the ovaries ovoid, 3-5 mm long; there are three styles. The seed is 1 mm long, cylindrical, brown, minutely pitted longitudinally.

**Chemistry**

Hypericum contains numerous compounds with documented biological activity. Most researchers consider its effects to be due to a variety of constituents rather than any single component. Constituents that have stimulated the most interest include the naphthodianthrone hypericin and pseudohypericin, a broad range of flavonoids, including quercetin, quercitrin, amentoflavone and hyperin, the phloroglucinols hyperforin and adhyperforin, essential oils and xanthones. Recently hypericin has been considered as an important antidepressant constituent of HP. The following major groups of bioactive constituents will summarise the constituents of HP:

**Naphthodianthrones**—The naphthodianthrones present in HP include hypericin (1.8%), pseudohypericin (relative abundance 3.9%), isohypericin and emodin-anthrone (precursor of hypericins). Protohypericin and protopseudohypericin were also detected and found to be less than 1%. Hypericin and pseudohypericin, and a broad spectrum of bioactive constituents will summarise the constituents of HP.

**Flavonoids**—Flavonoids present in the HP include, flavonol glycosides, viz., rutin (0.3%), quercetin (0.3-0.524%), isoquercitrin (0.3%)14,15, hyperin/hyperoside (0.7-1.1%)16, and aglycones, viz., kaempferol, luteolin, myricetin and quercetin (2%).

**Biflavones**—The following biflavones: 3,8'-bipigginin (0.1-0.5%)16,17, amentoflavone/3,8'-bipigginin (0.01-0.05% in flowers), were reported from the HP.

**Proanthocyanidins**—The proanthocyanidins, consisting of dimers, trimers, tetramers, and high polymers of catechin and epicatechin, represent approximately 12% of the dried weight of the aerial portion of the plant,3,18, the highest values were observed during the flowering stage.

**Phenyl propanes**—HP contain phenyl propanes in the form of esters of cinnamic acids, such as p-coumaric and caffeic acids (0.1%). Chlorogenic acids have been detected and found to be less than 1%. Ferulic, isoferulic and gentisic acids along with leucocyanidin have also been described15-21.

**Phloroglucinols**—Two closely related phloroglucinol derivatives; hyperforin and adhyperforin, were reported from the HP. The amount of hyperforin was found be 2% in flowers and 4.5% in the unripe fruits while the amount of adhyperforin was found to be 0.2% (flowers) and 1.6% (unripe fruits)23,24. These hyperforins were lipophilic, unstable toward heat and light either on storage or in solution. One of the products of degradation was 2-methyl-3-buten-2-ol, probably generated by oxidative cleavage of isoprenyl side chains of hyperforin and adhyperforin. Recently, an unusual compound with combined structure of cadinan sesquiterpene and hyperforin, hydroperoxy-cadinorne (0.0006%)15, and furhyperforin (ca. 5% of hyperforin concentration)26 were isolated and characterized from HP.

Xanthones—A xanthanolignoid, kielkorin (0.01% in roots)27, and 1,3,6,7-tetrahydroxy xanthone (in trace amounts in leaves and stems)28 were reported in HP.

**Essential oil**—The essential oil consists mostly of monoterpenes (pines) and sesquiterpenes29. Of these, the primary compounds include the saturated hydrocarbons, 2-methyl-octane (16.4% and a-pinene (10.6%). Also present were traces of 2-methyldecane, 2-methyl-butenol and undecane, b-pinene, a-tocopherol, geraniol, myrcine, linolene, caryophillene, humulene, C16 and C24 n-alkanes, and C24, C26 and C28 n-alkanols29-31.

Additional compounds include choline, carotenoids (lutein, luteoxanthin, violaxanthin, cis-throilxanthin, throbilichromone), b-sitosterol, pectin, phlobaphene and rhodan; isolaveralanic, lauric, myristic, nicotinic (0.12% in leaves, palmitic and stearic acids, amino acids; including cysteine, GABA (0.7 mg/g), glutamine, leucine, lysine, ornithine, proline, threonine, scopolin, umbelliferone, and vitamin C16,19,31-34.

The pharmacological activity of various constituents are summarised in Table 1.

**Biological properties**

Hypericum perforatum has been widely researched for its antidepressant effects. Recent interest has focused on its potential as an antiviral agent. There is some data confirming its traditional wound-healing effects. Hypericum contains several compounds of biological interest, including the naphthodianthrones, hypericin and pseudohypericin, and a broad spectrum...
of flavonoids. Although investigations continue, these are considered to be primarily responsible for HP’s activities.

**Antidepressant activity**

A commercial standardized extract of HP (Psychotinin) was tested in several animal models predictive of psychotropic activity. These activities included two, used for antidepressants, increased activity in water wheel test in mice and reduced aggressiveness in isolated male mice. The pharmacological models most commonly used to demonstrate a potential antidepressive activity of *Hypericum* extracts are the examination of the behaviour of mice in an unknown environment, forced swim test, and the measurement of biogenic amines metabolites in urine. A correlation can be established between the excretion in urine of 3-methoxy-4-hydroxy phenyl glycol (MHPG), the main metabolite of noradrenaline, and the initiation of the therapeutic activity of HP as an antidepressant agent.

Butterweck et al. compared the *Hypericum* extract, LI 60, with bupropion, a synthetic antidepressant. Results indicated similar effects of both the drugs in the tail suspension test (mice) and the forced swim test (rats). Since *Hypericum* treatment was antagonized by drugs known to reduce dopamine functional activity (haloperidol, sulpiride, a-methyltyrosine and g-butylrolactone) the authors concluded that *Hypericum* exerted its activity via dopaminergic activation. *Hypericum* extract, LI 160, subchronic treatment (250 mg/kg for two weeks) resulted in a 15% down regulation of β-adrenergic receptors in the rat frontal cortex. In the same study, a 25% down regulation was observed after the imipramine treatment.

Many questions exist about the composition, pharmacology and mechanisms of action of HP. In fact the active constituent is still unclear. While previous studies report that hypericin inhibits MAO at concentrations of 50 μg/mL, others have failed to confirm this effect. Some of the research work on the identification of the active antidepressant constituent has been performed using computer modelling. Out of the flavonoids, xanthones and hypericins compared best. Overlap was obtained with flavonoid derivatives and suggest flavonoids as the most likely MAO inhibitor fraction, due to structural similarity to toloxone and brofaromine, two known inhibitors of MAO-A. Bladt and Wagner reported that the *Hypericum* fractions with the greatest MAO inhibition contains the highest concentration of flavonoids. In another study, the xanthone fraction was particularly strong inhibitor of MAO-A in vitro. However, the MAO inhibition shown by *Hypericum* may not be pharmacologically relevant since it has not been confirmed in vivo. Bladt and Wagner reported that no MAO inhibition was seen in vivo after administration of 300 mg/kg *Hypericum* extracts to rats.

Other proposed mechanisms involve effects on serotonin. Muller and Rosso reported that *Hypericum* extract inhibits serotonin receptor expression at 50 μM (~25 μg/mL) and Perovic and Muller reported inhibition of serotonin uptake (IC50 = 6.2 μg/mL). The concentration required for the former effect could never be achieved in the whole animal and even the latter concentrations seem unlikely. As a reference comparison, Muller et al. reported an IC50 for the synthetic antidepressant, clomipramine, of 0.9 nM (~0.3 ng/mL) for serotonin uptake inhibition. In addition, an inhibition of both synaptosomal GABA uptake (IC50 = 1 μg/mL, LI 160) and GABAA-receptor binding (IC50 = 3 μg/mL) was noted.
Through an National Institute of Mental Health (NIMH, USA) screening contract (Novasecreen, Baltimore, Maryland) a commercially available crude extract from the fresh flowers and buds of HP was subjected to in vitro assays in a battery of 39 receptor types and two enzyme systems. The receptor assays showing 50% displacement of radioligand (or 50% inhibition of MAO) were considered “hits”. Concentration-response curves (IC50) were then performed for the hits. The crude extract of HP had significant receptor affinity for adenosine, GABA_A, GABA_B, serotonin, benzodiazepine, inositol triphosphate (IP3), and MAO_A. The inhibition of MAO by crude Hypericum extracts is consistent with previous reports. Unlike the crude extract, synthetic hypericin (95%) lacked significant MAO_A or MAO_B inhibition at concentrations up to 10 μM. Hypericin had affinity only for NMDA receptors (Ki=1 μM) and this may play a role in its reported antiviral activity since NMDA antagonists prevent gp 120-induced neurotoxicity. These data are consistent with the recent pharmacological evidence suggesting that other constituents of this plant may be more important for the reported psychotherapeutic activity.

More recently, hyperforin, a prenylated phloroglucinol present in this plant, has been focused as primarily responsible for the antidepressant activity of the HP extract. Many of the experimental and clinical studies have confirmed the antidepressant activity of hyperforin. Hyperforin was shown to inhibit uptake of serotonin (5-HT), dopamine (DA), noradrenaline (NA), GABA and L-glutamate with IC50 values of about 0.05-0.10 μg/ml (5-HT, NA, DA, GABA) and about 0.5 μg/ml (L-glutamate) in synaptosomal preparation. Recently, Indian Hypericum perforatum (IHp) extract standardised for hyperforin lacked MAO A and B inhibitory activity. Additionally, Ihp showed antidepressant, anxiolytic and nootropic activities.

Another novel proposal is that Hypericum extract reduces cytokine expression (interleukin-6). The hypothesis is that interleukins can induce depression in susceptible individuals. The link between depression and the immune system is well established. In addition to the antidepressant effects, Hypericum has historically been used for a wide variety of neurological conditions, including anxiety, insomnia due to restlessness, irritability, neuralgia, trigeminal neuralgia, neuroses, migraine headaches, fibrosis, dyspepsia (oil), and sciatica.

Wound healing properties

Hypericum has historically been one of the most relied upon botanicals for the treatment of wounds. Part of this activity is due to Hypericum's antimicrobial activity, which is attributed to the essential oil, phloroglucinols and flavonoids. The essential oil and the water-soluble fraction of an alcoholic extract exhibit minor antifungal and significant antibacterial activity. A resin fraction of the alcoholic extract has also been shown to be effective against gram-positive organisms. The tannins and flavonoids were reported to inactive Escherichia coli at dilution of 1:400 or 1:200. Hyperforin and adhyperforin have been reported to possess an chemotherapeutic effect greater than that of sulfanilamide.

An ointment prepared by extracting the fresh flowers (5 g) with olive oil (100 g) (for 10 days at 20°C) was used in the treatment of 1st, 2nd and 3rd degree burns. First degree burns healed in 48 hours. Second and third degree burns healed at least three times faster than burns treated with conventional methods and keloid formation was inhibited. A commercial preparation containing 0.412% quercitrin (Novoimamin) was found to be effective against Staphylococcus aureus infection and its effects have been reported to be greater than conventional treatment with sulfanilamide. An ointment (1:10) of Hypericum was studied for its wound healing properties and compared with calendula, another widely used wound healing herb. The effect of orally administered tincture of Hypericum was more pronounced than topical application of Calendula tincture in the healing of incision, excision and dead space wounds, as evidenced by an increase in epithelisation and wound-breaking strength.

Antiviral activity

Hypericum is currently in early clinical trial in the USA as an antiviral agent. In an open pilot study, 18 patients with acquired immune deficiency syndrome (AIDS classifications; 3 with CDC II, 8 with CDC IVB and 3 with CDC IVC) were treated with an i.v. Hypericum perforatum preparation (Hyperforat; 2×2ml weekly) plus additional Hypericum tablets of undefined dosage. Sixteen out of 18 patients with good study compliance showed...
increasing counts of absolute CD4 values over a 40-month period. Also observed were improvements in CD4/CD8 ratios in the majority of patients. In addition only 2 of the 16 patients experienced an opportunistic infection during the 40-month observation period. The other 14 of the 16 patients remained clinically stable.

Studies have shown that two of HP's primary components, hypericin and pseudohypericin, inhibit a variety of encapsulated viruses, including herpes simplex types 1 and 2, and the human immunodeficiency virus type 1 (HIV-1) virus associated with AIDS. While the later researchers have concluded that hypericin and pseudohypericin display a unique and effective antiviral activity, Weber et al. suggest that it may be due to non-specific association with cellular and viral membranes. In vitro antiviral activity has also been reported against murine cytomegalovirus, parainfluenza 3 virus, Sindbis virus, vesicular stomatitis virus, and equine infectious anemia virus.

The antiviral activity appears to involve a photoinactivation process, which forms singlet oxygen and inactivates viral fusion and syncytia formation. While hypericin does show antiviral activity in vivo (mice), these photodynamic properties may limit its potential usefulness as an antiretroviral agent. However, besides singlet oxygen production, hypericin can photoreduce oxygen to superoxide radicals and can form semiquinone radicals in the absence of light. These authors speculate that this ability to form semiquinones might account for the antiviral activity.

**Protein Kinase C inhibition**

Hypericin has been reported inhibit the growth of glioma cell lines in vitro and to be a potent inducer of glioma cell death due to inhibition of protein kinase C (PKC) as measured by [3H] thymidine uptake. The anti-PKC activity doses are reported to be below those with clinical hypericin.

Other researchers report a PKC-inhibiting activity with both hypericin and pseudohypericin (IC50 of 1.7 µg/ml and 15 µg/ml, respectively). Receptor tyrosine kinase activity of epidermal growth factor has also been reported to be inhibited hypericin. These effects have been linked to both the antiviral and antineoplastic activities. In addition, the PKC inhibition may also contribute to the anti-inflammatory effects historically associated with Hypericum as hypericin has been found to inhibit the release of arachidonic acid and leukotriene B4.

**Other effects**

Hypericum has been reported to have number of additional effects. In one study the procyanidin fraction of Hypericum was tested in an isolated guinea pig heart preparation and found to enhance coronary flow in the same way as the procyanidin from Crataegus (Hawthorn). The procyanidins fractions also antagonized histamine or prostaglandin F2α-induced atrial contractions in porcine isolated coronary arteries.

In another study, a significant increase in the production of nocturnal melatonin was observed after administration of 90 drops of the commercial preparation, Hyperforat. These effects were observed after a three week period. Other researchers report that Hypericum may be useful in the treatment of chronic tension headaches, while a hepatoprotective activity of a water/alcohol extract has also been reported in animals. Pain and inflammation of nerve origin may also respond to Hypericum which can be administered both topically and orally. Recent study with IHp in our lab confirms its anti-inflammatory and analgesic activity.

**Clinical studies**

Hypericum has become increasingly popular in Germany, where physicians routinely prescribe herbal medicines. In 1994, 66 million daily doses of HP were prescribed there for use in the treatment of depression. This phytotherapy has been tested in more than 3,000 patients against placebo and various active medications. German researchers recently published a meta-analysis of 23 randomized trials of Hypericum with a total of 1,757 outpatients with mild to moderately severe depressive disorders. They concluded that the herb was significantly superior to placebo and appeared comparably effective to standard antidepressants (maprotiline, imipramine and amitriptyline) while producing fewer side effects.

**Pharmacokinetic studies**

Detailed pharmacokinetic studies have been performed with the standardized Hypericum extract, LI 160 (Jarrow® 300), one of several officially recognized formulations (containing 300 mg of the dried extract of HP, yielding 0.24-0.32% total...
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detection method.

Conclusion

Hypericum is a clearly one of the leading
psychotherapeutic phytomedicines for the treatment
of mild to moderate depression. The shortcomings of
the current controlled clinical trials of Hypericum
have been pointed out in the review by Linde et al.6
and by Ernst. They include lack of well-
characterised severely depressed patients populations,
heterogeneity of diagnoses, lack of intent-to-treat
analyses, lack of long term studies, lack of control
over compliance, and low dosages of comparison
medications.

Despite the extensive use of this plant extract as an
antidepressant, the chemical nature of its bioactive
principles still remains unclear. Earlier, in vitro
studies with hypericin and pseudohypericin as MAO
inhibitory agents suggested that hypericin may be
responsible for the antidepressant activity of this
plant. Consequently, the pharmaceutical preparations
were standardized on the basis of their hypericin
contents. However, in later studies, these earlier
results could not be confirmed. Flavonoids present in
the HP were also shown to inhibit MAO-A, but a
therapeutic efficacy of this class of compounds
appeared doubtful due to their low plasma levels after
oral administration13. Recently, hyperforin, a
prenylated phloroglucinol present in this plant, has
been focused as the major component responsible for
the antidepressant activity of HP. The lack of viable
pharmacological mechanism or the assurance of
which components within the plant are critical for
therapeutic effect (necessary in order to standardise
formulations) will continue to create skepticism among
psychopharmacologists and regulatory
authorities. However, continued research is needed to
identify the constituents most responsible for
Hypericum’s activity so that preparations can be
optimally standardised. While determining the
pharmacological profile of all major components of
Hypericum will be a difficult task, it will surely add
to the body of knowledge regarding the biochemistry
of depression. The presence of significant anxiolytic
activity of HP extract6, suggest that co-existence of
anxiolytic-antidepressant activity may help in its
clinical profile since anxiety and depression often co-
exist.

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