

HYPERFORIN: A POTENT ANTI-DEPRESSANT NATURAL DRUG

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ABSTRACT

St. John's wort (SJW) extracts, prepared from the aerial parts of *Hypericum perforatum*, contain numerous pharmacologically active ingredients, including aphyllanthrones (e.g., hypericin and its derivatives) and phloroglucinols derivatives (e.g., hyperforin)[5]. Hyperforin is a structurally novel anti-depressant isolated from *Hypericum perforatum* commonly known as St. John's Wort. Hyperforin used as antidepressants by blocking the reuptake of the neurotransmitters norepinephrine, serotonin, and dopamine. Recent study found that hyperforin, in high daily doses, is superior to paroxetine[40] as a treatment for even severe depression. Hyperforin is photo and oxygen labile compound that is highly unstable and difficult to isolate in pure form. The standardization of *Hypericum perforatum* is based on presence of both Hyperforin and Hypericin. It is designated in percentile, meaning that if a 100mg dose of St. John's Wort is extracted at a standardized 5%, we will get 5 mg of hyperforin from that dose. However, relevant and, in some cases, life-threatening interactions have been reported, particularly with drugs which are substrate of cytochrome P450 and/or P-glycoprotein.

Keywords: SJW, cytochrome P450, P-glycoprotein, Standardized.

INTRODUCTION

Hyperforin flower has been historically used as a treatment for a wide variety of superstitions and nervous disorders. Its name, *Hypericum*, comes from the Greek word meaning 'over an apparition,' a link to the belief that St. John's Wort was such a powerful plant that it could ward off evil apparitions or spirits. Hyperforin is a structurally novel anti-depressant isolated from *Hypericum perforatum* commonly known as St. John's Wort [1]. The chemical hyperforin was first identified in 1975 by the Institute of Bio-organic Chemistry in the former Soviet Union while researching the active ingredients in St. John's wort. Hyperforin belongs to group of compound known as acylphloroglucinols. The hyperforin has also proved to be difficult to synthesize, making St. John's wort, the only plant containing high concentrations of the chemical, its only commercially viable source.

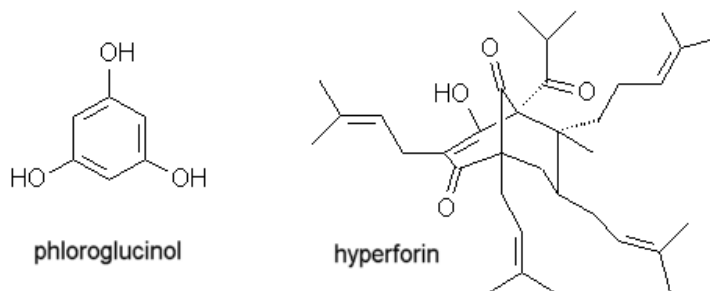
The peculiarity of Hyperforin is that it is chemically unrelated to synthetic antidepressants. Hyperforin is photo and oxygen labile compound that is highly unstable and difficult to isolate in pure form. Initially Hypericin a naphodianthrone compound was considered to be the anti depressant principle of the herb, but now it is better known as marker compound in *Hypericum perforatum* extract and is used as identification standard in *Hypericum* samples. The standardization of *Hypericum perforatum* is based on presence

of both Hyperforin and Hypericin. Generally, it is designated in percentile, meaning that if a 100mg dose of St. John's Wort is extracted at a standardized 5%, we will get 5 mg of hyperforin from that dose.

The name of plant derives from its flowering around the time of St. John's Day, June 24. In recent years St. John's wort has been studied extensively as a treatment for depression. Most studies show that St. John's wort may help treat mild-to-moderate depression, and has fewer side effects than most other prescription antidepressants. But it interacts with a number of medications, so it should be taken only under the guidance of a health care provider.



Active principles in St. John's Wort



(1R,5S,7R,8S)-4-hydroxy-8-methyl-3,5,7-tris(3-methylbut-2-enyl)-8-(4-methylpent-3-enyl)-1-(2-methylpropanoyl)bicyclo[3.3.1]non-3-ene-2,9-dione

The quantity and quality of active principles in Hypericin vary according to geographical locale, climate, time of day and time of year. St. John's wort contains dianthrone derivatives, mainly in the form of hypericin and pseudo-hypericin as well as flavonoids. Small

amounts of coumarins, phenolic carboxylic compounds, phloroglucinol derivatives, monoterpenes, sesquiterpenes, n-alkanes, n-alkanols, carotenoids and beta-sitosterol are present. The roots contain xanthenes.

Mechanism of action

Hyperforin acts as an antidepressant by blocking the reuptake of the neurotransmitters norepinephrine, serotonin, and dopamine. An imbalance of serotonin, norepinephrine, and/or dopamine may cause depression, anxiety or fatigue. By reducing the activity of reuptake transporters, hyperforin increases the levels of these neurotransmitters in the brain, which may improve mood and restore emotional balance. Hyperforin also inhibits the reuptake of GABA, a neurotransmitter that increases relaxation and reduces anxiety.

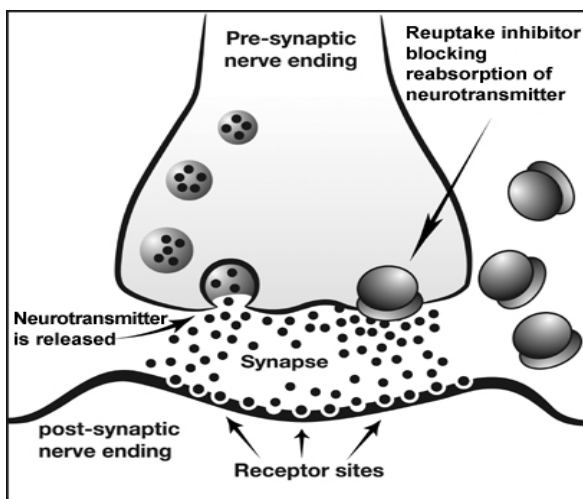


Fig. 1: neurotransmitter reuptake blocking activity of hyperforin

As a natural reuptake inhibitor, hyperforin is effective for treating many conditions (such as depression and anxiety) that are treated with reuptake inhibitor drugs. Unlike reuptake inhibitor drugs (including SSRI antidepressants), hyperforin is a non-competitive reuptake inhibitor. This means hyperforin does not actually bind to and block the reuptake transporters. Rather, it affects the pre-synaptic sodium channels that control reuptake transporter activity. Due to this novel mechanism hyperforin not cause many of the side effects associated with prescription SSRI drugs[6].

Pharmacokinetics of hyperforin

After administration of a 400mg tablet of St. John's wort extract containing 14.8mg hyperforin, a maximum plasma level of approximately 150ng/mL (280nM) hyperforin was reached after 3.5 hours. The oral bioavailability of Hyperforin in doses up to 30mg (i.e. 600mg St. John's wort extract) was high. The half-life of Hyperforin was 9 hours and the mean residence time 12 hours. No accumulation of Hyperforin occurred with repeated dosing. Estimated steady state plasma concentrations with 3x300mg extract per day were approximately 100ng/mL or 180nM. These data show that the oral bioavailability of Hyperforin is high and that steady-state plasma concentrations can easily be achieved and maintained with a three times daily dosing schedule.

Comparative study

More Effective than Paroxetine

Table 1: Comparative treatment study between Hyperforin and paroxetine[2]

Hyperforin	vs.	paroxetine	
71%	vs.	60%	Patients responds to treatment
50%	vs.	35%	Patients show complete remission
57%	vs.	45%	Reduction in symptoms

A study on hyperforin (from SJW extract with minimum 3% hyperforin) to paroxetine (Paxil®) in 251 patients with moderate-severe depression. The patients in this randomized, controlled,

double-blind trial took either paroxetine (Paxil®) or SJW extract for a total of six weeks, starting with a daily dose of 20 mg paroxetine or 900 mg SJW extract. For patients who failed to respond after two weeks (about 50% of each group), the doses were doubled to 40 mg paroxetine or 1800 mg SJW extract.

At the end of the trial, the results showed the clear superiority of hyperforin over paroxetine (Paxil®) as a treatment for severe depression after six weeks of treatment, symptoms of depression were reduced by 57% in the group taking hyperforin versus 45% in the paroxetine group, a statistically significant difference. A greater percentage of people taking hyperforin (71% vs. 60%) experienced a positive response to treatment (defined as at least a 50% reduction in symptoms of depression) and fifty percent (50%) of the patients taking hyperforin showed remission (i.e. complete recovery) compared to just 35% of those taking paroxetine. Moreover, the incidence of side effects was 42% lower for people taking hyperforin.

Significantly More Effective than Fluoxetine[3]

On comparing hyperforin rich *Hypericum* (St. John's wort) extract to the antidepressant drug fluoxetine (Prozac®) and placebo again confirmed the effectiveness of high-quality *Hypericum* extract for depression. In this randomized, controlled, double-blind trial, the 135 patients with major depressive disorder were given either fluoxetine 20mg/day, *Hypericum* extract 900mg/day, or placebo for twelve weeks. By the end of the twelve weeks, the patients taking *Hypericum* experienced a 48% greater reduction in symptoms of depression than those taking fluoxetine (Symptoms were measured using the HAM-D, the standard scale to measure depression. From an average HAM-D score of 19.7 at the beginning of the study, HAM-D scores dropped to an average of 10.2 in the *Hypericum* group and 13.3 in the fluoxetine group.). Moreover, a larger portion of those taking *Hypericum* experienced complete remission of depression than patients taking fluoxetine (38% vs. 30%). The researchers concluded that "Overall St John's wort appeared to be safe and well tolerated and significantly more effective than fluoxetine".

Equally Effective to Sertraline[4]

A double-blind multi-center German study from 2005 found *Hypericum* extract (612mg/day) to be equally effective to sertraline (Zoloft®) (50mg/day) after 12 weeks and possibly more effective after 24 weeks for the treatment of moderate depression. The number of patients responding and the average reduction in symptoms were nearly identical between the two groups after twelve weeks and during week's 13-24 symptoms in the patients taking *Hypericum* actually dropped 160% more than in those taking sertraline. Furthermore, the number of patients reporting adverse events (side effects) was 28% lower in the *hypericum* group versus the sertraline group.

Uses

1. *Hypericum* extract has been used to improve sleep, because it increases the brain's output of melatonin at night.
2. Topically hyperforin has anti-inflammatory properties. It is used in the treatment of wounds, burns, combat ulcers and hemorrhoids. It also helps in the treatment of vitiligo.
3. St. John's Wort used in the treatment of diarrhoea due to high tannin contents. It is also used for rheumatic pains, especially gout and to deter bed-wetting.
4. An early study suggests that St. John's wort may help relieve physical and emotional symptoms of Premenstrual syndrome (PMS) in some women, including cramps, irritability, food cravings, and breast tenderness.
5. Studies suggest that St. John's wort, combined with black cohosh, helps improve mood and anxiety during menopause.
6. St. John's wort has improved mood in people with Seasonal affective disorder (SAD), a type of depression that occurs during the winter months because of lack of sunlight. SAD is usually treated with light therapy, and there is some evidence that using St. John's wort together with phototherapy works even better.

7. St. John's wort 450 mg two times a day for 12 weeks improved Obsessive compulsive disorder (OCD) and social phobia symptoms.

Available Forms

St. John's wort can be obtained in many forms: capsules, tablets, tinctures, tea, and oil-based skin lotions. Chopped or powdered forms of the dried herb are also available. Most products are standardized to contain 0.3% hypericin. The brand names are Kira, Movana, Perika and Amoryn.

Patient medication

Pediatric

St. John's wort may be a safe and effective way of treating mild-to-moderate symptoms of depression in children. St. John's wort should not be given without medical supervision. Children being treated with St. John's wort should be carefully monitored for side effects, such as allergic reactions or upset stomach. You should not try to treat depression in a child without a doctor's help, because depression can be a serious illness.

Adult

- Dry herb (in capsules or tablets): The usual dose for mild depression and mood disorders is 300 mg (standardized to 0.3% hypericin extract), 3 times per day with meals. St. John's wort is available in time-release capsules.
- St. John's Wort is also available as a liquid extract or a tea.

Adverse effects

Side effects from St. John's wort are generally mild and include stomach upset, hives or other skin rashes, fatigue, restlessness, headache, dry mouth, and feelings of dizziness or mental confusion. St. John's wort can also make the skin overly sensitive to sunlight called photo dermatitis.

Precautions

On sudden discontinuing St. John's wort therapy, that may cause unpleasant side effects. Gradually lower the dose before stopping. If you have light skin and are taking St. John's wort, wear long sleeves and a hat when in the sun, and use a sunscreen with at least SPF 15 or higher. Avoid sunlamps, tanning booths, and tanning beds. Since St. John's wort can interact with medications used during surgery, you should stop taking it at least 5 days or more before surgery. Make sure your doctor and surgeon know you are taking St. John's wort. Do not take St. John's wort if you have bipolar disorder. There is concern that people with major depression taking St. John's wort may be at a higher risk for mania. Women who are pregnant, trying to become pregnant, or breastfeeding should not take St. John's wort.

Drug interactions

Cytochrome P450 (CYP) enzymes are common sites of drug interactions in human. Drugs may act as inhibitors or inducers of CYPs, leading to altered clearance of a second drug[32]. Strong evidence from animal studies as well as preclinical and clinical studies suggests that SJW may modulate CYP activity. Using well-established probe drugs (e.g., alprazolam and midazolam[38] for CYP3A4, caffeine for CYP1A2, chlorzoxazone for CYP2E1, dextromethorphan[36,37] and debrisoquine for CYP2D6, tolbutamide for CYP2C9[17-23], and omeprazole for CYP2C19), a number of clinical trials have consistently shown that SJW induces CYP3A4, CYP2E1, and CYP2C19, with no effect on CYP1A2, CYP2D6, or CYP2C9.

Research has shown that taking St. John's wort can limit the effectiveness of some prescription medicines including:

Antidepressants

Antidepressant medicines SJW interacts with 5-HT reuptake inhibitors such as paroxetine, sertraline, venlafaxine, and

nefazodone resulting in symptoms of a central serotonin syndrome. Characteristic symptoms observed include mental status changes, tremor, autonomic instability, gastrointestinal upset, headache, myalgia and motor restlessness. SSRI do not appear to be metabolized by CYP enzymes or P-glycoprotein. In these cases, a pharmacodynamic mechanism is postulated to be involved since both SJW and SSRI inhibit 5-HT reuptake.

Immunosuppressants

A number of heart, renal, or liver transplant patients stabilized on cyclosporine showed decreased blood levels (associated in some cases with acute rejection episodes) after taking SJW at therapeutic dosage. Cyclosporine is a substrate of P-glycoprotein and it is also metabolized by CYP3A4.

Birth control pills

Both intermenstrual bleeding and reduced efficacy are believed to be due to the reduced plasma concentration of the components of oral contraceptive pills by SJW. It is well known that drugs inducing CYP3A4[39] such as rifampicin may cause reduced efficacy of oral contraceptives and breakthrough bleeding[[22,30].

Anticoagulants

The anticoagulant exists as a racemic mixture of R- and S-enantiomers, with R-warfarin being metabolized mainly by CYP1A2 and CYP3A4 and S-warfarin which is more potent, predominantly by CYP2C19A[26]. SJW significantly induced the apparent clearance of both S-warfarin and R-warfarin which in turn, resulted in a significant reduction in the pharmacological effect of racemic warfarin[27]. Similarly, another trial found that SJW decreased plasma levels of phenprocoumon (a coumarin anticoagulant chemically related to warfarin)[28].

Antihyperlipidemic Drugs

The statins simvastatin and atorvastatin are metabolized by CYP3A4 and are also substrates for P-glycoprotein. SJW decreased plasma levels of simvastatin (but not pravastatin[29], which is not a substrate for CYP3A4 or P-glycoprotein) and reduced the efficacy of atorvastatin in hypercholesterolemic patients. Specifically, SJW significantly increased the serum level of LDL cholesterol compared with control and increased the total cholesterol level.

Calcium Blockers

Nifedipine and verapamil, metabolized by CYP3A4 and the effect of SJW on verapamil bioavailability is caused by induction of first-pass CYP3A4 metabolism most likely in the gut[25].

Beta Adrenergic Blockers

SJW affected only renal and nonrenal clearance (CLNR), of i.v. talinolol. The effects of SJW on oral talinolol pharmacokinetics were associated with increased MDR1 messenger ribonucleic acid (mRNA) as well as P-glycoprotein levels in the duodenal mucosa.

Antianginal Drugs

Ivabradine a new class of antianginal drugs is extensively metabolized by intestinal and hepatic CYP3A4. SJW significantly decreased ivabradine maximal plasma concentration (33 vs 15 ng/mL) and AUC (144 vs 44 ng h/mL)[24].

Cardiac Inotropic Drugs

Digoxin is a substrate of P-glycoprotein decreased in plasma concentration of digoxin[34] by SJW administration.

Benzodiazepines

The benzodiazepines alprazolam and midazolam[[17,20,23]] are used experimentally as probe for CYP3A4 activity because they are entirely metabolized by intestinal and hepatic CYP3A4. SJW decreased plasma levels of alprazolam[19] and midazolam.

Anti-HIV Drugs

SJW may interact with antiretroviral drugs leading to drug failure.

Anticancer Drugs

Irinotecan (a known substrate for CYP3A4 employed in the treatment of colorectal cancer) in the presence of SJW the degree of myelosuppression was substantially worsen[15].

Antiepileptic Drugs

The antiepileptic agent mephenytoin is primarily metabolized by CYP2C19[35] to hydroxymephenytoin. SJW increased the urinary 4'-hydroxymephenytoin excretion.

Drugs Used in Addicted Patients

Methadone is used in the controlled withdrawal of addicts from heroin. Methadone is mainly metabolized by CYP3A4, which is induced by St John's wort[14].

Central Muscle Relaxant Agents

Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasms and the resulting pain or discomfort. An increase in hydroxychlorzoxazone/chlorzoxazone serum ratios due to SJW[17,18].

Drugs Acting on the Respiratory System

Theophylline is mainly metabolized by CYP1A2, CYP2E1, and CYP3A4. Plasma levels of theophylline decreased after taking SJW[12]. This resulted in an increased dosage of theophylline to achieve therapeutic concentration[13].

Hypoglycemic Drugs

SJW significantly altered gliclazide pharmacokinetics by a decreased gliclazide AUC, t_{1/2}, and apparent oral clearance. There were no significant changes in glucose or insulin AUC after SJW treatment and no significant differences according to CYP2C9 genotype. Thus, treatment with SJW significantly increases the apparent clearance of gliclazide which is independent of CYP2C9 genotype[11].

Drugs Acting on the Gastrointestinal Tract

In vivo, omeprazole is metabolized mainly by CYP3A4 and CYP2C19 to two major metabolites, 5-hydroxyomeprazole and omeprazole sulfate. CYP2C19 is the predominant enzyme involved in the 5-hydroxylation reaction, whereas CYP3A4 is the major enzyme-mediated sulfoxidation of omeprazole. SJW, substantial decreases in plasma concentrations of omeprazole. SJW induced both CYP3A4-catalyzed sulfoxidation and CYP2C19-dependent hydroxylation of omeprazole[9,10].

Antimicrobials

Voriconazole is a triazole antifungal developed for the treatment of life-threatening fungal infections in immunocompromised patients. The extensive metabolism of voriconazole is primarily mediated by CYP2C19 and CYP3A as well as by CYP2C9 to a lesser extent. SJW slightly increased (after 10-h SJW intake) and strongly reduced (after 15-day SJW intake) voriconazole AUC[8].

DISCUSSION

This plant has often been referred to as a kind of "wonder herb" for its uses in treating depression, mental anxiety and even addiction as well as aiding the immune system and helping to improve the body's healing capabilities. St. John's Wort has been proven to be effective against depression in clinical trials. The results seen with properly graded St. John's Wort when used with moderately severe depression is comparable to tricyclic antidepressants and SSRIs, but without the nasty side effects those prescription antidepressants are known for. It causes some of the same dizziness, fatigue and headache common to prescription antidepressants, but it's generally not as severe as that caused by harsher prescription drugs. This supplement can react badly with other medications and supplements including prescription antidepressants, birth control pills and more, so be sure to mention anything you are taking to your doctor when asking about St. John's Wort. While the efficacy data appear impressive, it should be emphasized that the methodological standards and sample sizes of published trials would

not satisfy the criteria for marketing approval required by government regulatory authorities such as the Therapeutic Goods Administration in Australia or F.D.A. in USA.

The medical profession must remain circumspect in its judgment of St. John's Wort until confirmatory data from large, methodologically strict trials become available.

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