ABSTRACT

Hyperforin is a structurally novel anti-depressant isolated from *Hypericum perforatum* commonly known as St.John’s wort. Hyperforin belongs to group of compound known as acylphloroglucinols. The peculiarity of Hyperforin is that it is chemically unrelated to synthetic antidepressants. Hyperforin is a photo and oxygen labile compound that is highly unstable and difficult to isolate in pure form. Initially, Hypericin, a napthodianthrone 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.

Keywords: Anti-depressant, Hyperforin, St.John’s wort, Hypericin.

INTRODUCTION

Hyperforin exhibits significant antidepressant activity.¹ Biochemical research demonstrates that hyperforin - like many prescription antidepressants - inhibits the reuptake of the neurotransmitters norepinephrine, serotonin, and dopamine.² All three of these compounds are naturally found in the brain and regulate mood and emotion. They are called “neurotransmitters” because they are chemical messengers that transmit information between nerve cells. An imbalance of serotonin, norepinephrine, and/or dopamine can cause depression. By acting as a “reuptake inhibitor”, hyperforin increases the levels of these neurotransmitters in the brain, which can improve mood and restore emotional balance.³, ⁴ Hyperforin also inhibits the reuptake of GABA, a neurotransmitter that increases relaxation and reduces anxiety.

Hyperforin is not a drug, but a natural compound extracted from the St. John’s wort (*Hypericum perforatum*) plant. Only in the past few years have researchers discovered that hyperforin is the primary compound responsible for the antidepressant effect of St. John’s Wort.⁵ The ability of any St. John’s wort extract to relieve depression depends mainly on its hyperforin content. In other words, only St. John’s wort extracts with significant amounts of hyperforin are effective. This fact was confirmed by a clinical trial, involving 147 patients with depression, which compared placebo to two different St. John’s wort extracts with varying amounts of hyperforin. One extract contained only 0.5% hyperforin, the concentration found in most brands sold in the United States. The other extract was standardized to provide 5% hyperforin, the clinically-proven potency found in AMORYN and pharmaceutical-grade European St. John’s wort. (Aside from hyperforin content, the two extracts were identical. Both extracts were standardized to contain 0.3% hypericin, the compound previously thought to be the active constituent in SJW.) The 5% extract was found to effectively relieve depression, but the 0.5% was ineffective and performed no better than placebo.⁶ This study demonstrates the importance of choosing a St. John’s Wort extract that, like AMORYN’s, is standardized to contain a high concentration of hyperforin.

An extensive body of research, consisting of over 30 controlled clinical trials, proves the effectiveness of hyperforin-rich St. John’s wort extract for relieving depression.²,⁷,⁸,⁹,¹⁰ Because most studies used extracts containing at least 3% hyperforin, this research does not apply to SJW extracts without a standardized quantity of hyperforin (such as those commonly sold “over-the-counter” in the United States). In fact, a recent study found that hyperforin, in high daily doses, is superior to the prescription drug paroxetine as a treatment for even severe depression.¹¹
Furthermore, clinical research suggests that adverse side effects occur less frequently with hyperforin than prescription antidepressants. For instance, although hyperforin was shown to relieve severe depression at least as well as Paxil®, patients taking hyperforin reported 42% fewer side effects. And hyperforin rarely causes weight gain or sexual dysfunction, side effects common with popular prescription drugs.

**ACTIVE PRINCIPLES IN ST. JOHN’S WORT**
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 contain 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-alkanols, carotenoids and beta-sitosterol are present. The roots contain xanthones.

**STABILITY**
Hyperforin is unstable in the presence of light and oxygen.

**PHARMACOLOGY**
Hyperforin is a prenylated phloroglucinol believed to be the main active constituent responsible for the antidepressant effects of extracts of St John’s wort. Hyperforin has been shown to inhibit the uptake of the neurotransmitters serotonin, dopamine, noradrenaline, GABA and glutamate. It was identified as a specific activator of the ion channel TRPC6 which is involved in neuronal axonal sprouting. The activation of TRPC6 causes entry of sodium and calcium ions in neuronal cells which can explain the inhibition of neurotransmitter uptake. Hyperforin is also thought to be responsible for the induction of the cytochrome P450 enzymes CYP3A4 and CYP2C9 by binding to the Pregnane X Receptor (PXR).

**MECHANISM OF ACTION**
From a number of in vivo, in vitro and clinical studies it has been shown that hyperforin not only inhibits the neuronal uptake of serotonin, norepinephrine and dopamine, but it also inhibits amino butyric acid (GABA) and L-glutamate uptake. Recently it has been proposed that there occur a physiochemical interaction of Hyperforin with specific membrane structures, which contribute to anti depressant activity.

**ANTIBIOTIC PROPERTIES**
Hyperforin’s antibiotic properties were described before its antidepressive effects were known. It is active against methicillin-resistant strains of Staphylococcus aureus (MRSA) with a minimal inhibitory concentration (MIC) value of 1.0 µg/ml, as well as other gram-positive bacteria.

**ASEJACULATORY CONTROL**
Hyperforin and other serotonin agonists significantly reduces the pelvic floor contractions elicited by 8-OH-DPAT. Thus, pharmacological modulation of the ejaculatory threshold using serotonin reuptake inhibitors and hyperforin may offer patients an option of achieving improved ejaculatory control.

**PHARMACOKINETICS**
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 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. Nothing appears to be known about the metabolism of Hyperforin as yet.

**SIDE EFFECTS AND RISKS**
The most common side effects of St. John’s wort include dry mouth, dizziness, diarrhea, nausea, increased sensitivity to sunlight, and fatigue.

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

- Antidepressant medicines
- Birth control pills
- Cyclosporine, a medicine that helps prevent the body from rejecting transplanted organs
- Digoxin, a medicine used to strengthen heart muscle contractions
- Indinavir and other medicines used to control HIV infection
- Irinotecan and other anticancer medicines
- Warfarin and related medicines used to thin the blood (known as anticoagulants)

When combined with certain antidepressants, St. John’s wort also may increase side effects such as nausea, anxiety, headache, and confusion.

**CONCLUSION:**
Now a days herbal drugs are too in demand and interaction of herbal medicine with synthetic drugs are like a particular area of interest for research. St. John’s wort an herbal drug also known as hyperforin, basically hyperforin is not a drug it is isolated from the flowering tops of the perennial plane hypericum perforatum which exhibits significant antidepressant activity by inhibiting the reuptake of the neurotransmitters norepinephrine, serotonin, and dopamine. All three of these compounds are naturally found in the brain and regulate mood and emotion. They are called “neurotransmitters” because they are chemical messengers that transmit information between nerve cells. An imbalance of serotonin, norepinephrine, and/or dopamine can cause depression. By acting as a “reuptake inhibitor”, hyperforin increases the levels of these neurotransmitters in the brain, which can improve mood and restore emotional balance.

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