St. John's Wort (*Hypericum perforatum*): Clinical Effects on Depression and Other Conditions.

by Alan L. Miller, N.D.

Abstract

St. John's Wort (*Hypericum perforatum*), a perennial flowering plant, has been used medicinally for thousands of years, and has most recently been identified as an effective treatment for mild to moderate depression. Clinical studies on the use of this plant for depression have utilized liquid tinctures and standardized solid extracts (0.3% hypericin—300 mg three times a day). Severe depression may also respond to this botanical, although it appears a larger dose is needed (600 mg solid extract three times a day). Hypericum has been favorably compared to numerous antidepressant drugs, the studies having revealed equivalent results and a much more favorable incidence of side effects. Studies have also demonstrated its efficacy in treating seasonal affective disorder. *In vitro* investigations of Hypericum show antiviral activity, although there is evidence these promising results might not occur *in vivo*. Traditional actions and uses include enhancement of wound healing, as well as anti-inflammatory and analgesic activity.

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Introduction

Hypericum perforatum, also know as St. John's Wort, Klamath weed, and goat weed, is a perennial weed which grows in sunny areas in well-drained, sandy soil, and is commonly seen growing by the roadside and along railroad beds. It is native to Europe and Asia, and was brought to the United States by European colonists. Its small, five-petaled, yellow flowers can turn a field into a sea of amber, a sight which, although beautiful, angers farmers who consider it a noxious weed. Hypericum's leaves contain tiny translucent excretory glands which look like perforations (hence, the Latin name) which are easily seen if held up to a bright light source. Small dark dots on the flowers contain a reddish-brown pigment, identified as hypericin. The Hypericum genus contains over 370 species; however, *H. perforatum* is unique in its appearance and chemical makeup. It is distinguished from other species in its appearance by a cylindrical stem with longitudinal, opposing ribs.[1]

The name St. John's Wort comes from the fact it flowers around St. John's Day (June 24). It is also said its red pigment symbolizes the blood of St. John. The word *wort* is an Old English term for plant. Hypericum is derived from the Greek words *hyper* (above) and *eikon*

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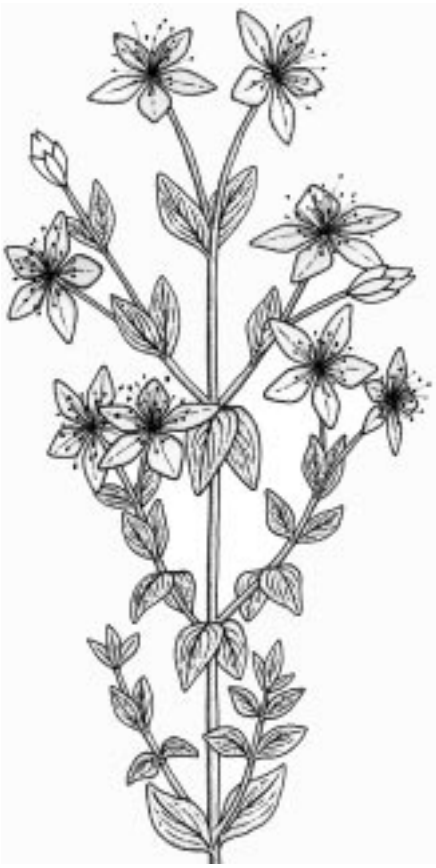
St. John's Wort (Hypericum)



(icon or image). Ancient Greeks and Romans placed sprigs of Hypericum above images or statues in their homes, as they believed this plant had mystical powers to protect them from evil spirits.[2] In the present day, Hypericum is used primarily to "ward off" depressive illness. In ancient times, "evil spirits" may have referred to just this indication, as depression can descend quietly and without any known reason.

For centuries Hypericum has been used orally and topically, as an anti-inflammatory, sedative, analgesic, diuretic, antimalarial, and as a vulnerary (a substance which enhances wound healing). Traditional indications have included trauma, burns, rheumatism, hemorrhoids, neuralgia, gastroenteritis, snakebite, ulcers, contusions, sprains, diarrhea, menorrhagia, hysteria, bedwetting, and depression.[1,2] The vast majority of the clinical research on St. John's Wort concerns its impact on depression. Public and practitioner response to this mostly-European research has caused a standardized extract of this plant to become the most utilized antidepressant treatment in Germany.[3] Investigations into the antiviral activity of Hypericum may also prove to be clinically useful in the future.

Depression affects more than 17 million adults in the United States each year, costing the nation $44 billion in treatment, disability, and lost productivity.[4] Cognitive therapy and other forms of non-pharmacological treatment bring about a resolution of symptoms in many individuals with depression. In addition, pharmacological or phytopharmacological methods are often helpful in releasing the grip of depression. Efficacy and safety are prime concerns when considering any therapeutic modality; however, pharmacological treatment of depression often results in unwanted effects of the drug, frequently resulting in non-compliance or discontinuation of treatment. In a recent comparative study of St. John's Wort versus the tricyclic antidepressant amitriptyline in the treatment of moderate depression, Hypericum was found to be similar in its efficacy to the drug, with significantly fewer side-effects.[5] Vorbach et al, found equivalent efficacy between St. John's Wort and imipramine in severely depressed patients. However, St. John's Wort patients exhibited a 0.7% drop-out rate due to adverse effects, compared to a 7.8% drop-out rate due to side-effects of imipramine treatment.[6]

Tricyclic and monoamine oxidase inhibitor (MAOI)-based antidepressants have been utilized clinically for more than 40 years. Their major drawbacks are the high frequency of side-effects and high toxicity. The newer antidepressants, the selective serotonin reuptake inhibitors (SSRIs), are better tolerated and less toxic than the first generation antidepressants,[3] although significant side-effects are still not unusual. This issue may be a significant component of Hypericum's recent popularity.

Hypericum contains numerous compounds with biological activity (see Table 1). It is not known at this time if one chemical or

Table 1. Identified Chemical Constituents of *Hypericum perforatum* [7,8,9]

Naphthodianthrones
hypericin
pseudohypericin
cyclopseudohypericin
isohypericin
protohypericin

Flavonoids
hyperoside
rutin
quercetin
quercetrin
isoquercetrin
campherol
luteolin
mangiferin

Proanthocyanidins
catechin
epicatechin
procyanidin B2

Biflavones
I3,II8-biapigenin
amentoflavone

Xanthones
1,3,6,7-tetrahydroxy-xanthone

Phloroglucinols
hyperforin
adhyperforin

Essential oils

Amino acid Derivatives
GABA
melatonin

Phenylpropanes
chlorogenic acid

a combination produces the antidepressant effects of St. John's Wort.

Mechanisms of Action in Depression

The biogenic amine theory of depression suggests it is caused by a deficiency of serotonin or norepinephrine. These neurotransmitters are actively secreted into synapses by neurons, then are taken up by receptors at the post-synaptic neuron. They are subsequently either stored or catabolized by monoamine oxidase. Therefore, substances having a positive effect on depression (drugs or phytomedicinals) should impact the levels of these neurotransmitters by: (1) increasing biogenic amine synthesis; (2) decreasing their catabolism by inhibiting monoamine oxidase; or (3) inhibiting their re-uptake.

Early *in vitro* studies of various components of St. John's Wort extract led to the establishment of MAO inhibition as the possible mechanism for Hypericum's antidepressant effects.[10,11] However, more recent investigation in this area suggests that, although MAO inhibition does occur with high concentrations of Hypericum constituents, it does not in the amounts found in commercial extracts.[12-14]

Testing by Perovic and Müller demonstrate a dose-dependent decrease of serotonin uptake by rat synaptosomes treated with Hypericum extract. The authors conclude the antidepressant activity of Hypericum extract is due to inhibition of serotonin uptake in post-synaptic receptors.[15]

In an attempt to elucidate the effects of Hypericum on serotonin receptors, Müller and Rossol incubated rat neuroblastoma cells with Hypericum solutions, and observed a decrease in serotonin receptor expression compared to a control solution without the extract. The researchers stated the reduction in serotonin receptors results in an impaired reuptake of serotonin, an effect similar to the selective serotonin reuptake inhibitors such as Prozac®.[16]

Müller et al, observed decreased synaptosomal uptake of serotonin, dopamine and norepinephrine by Hypericum, as well as weak inhibition of MAO-A and MAO-B activity *in vitro*. In light of this and other research which has suggested Hypericum may inhibit the reuptake of these neurotransmitters and enzymes, the authors conclude, "The fact that Hypericum shows affinity for three different neurotransmitter transporter systems might point to an unique and not yet known mechanism of inhibition of neurotransmitter uptake."[14]

A recent study found ß-adrenoreceptors down-regulated and 5-hydroxytryptophan (5-HT_2) receptors up-regulated by Hypericum.[14] ß-adrenoreceptor down-regulation is also seen with treatment by antidepressant drugs such as the tricyclic imipramine. 5-HT_2 receptors are usually down-regulated also, so the finding of up-regulation by Hypericum extract is atypical.

Hypericum extract was also found to decrease binding of a benzodiazepine drug to benzodiazepine-binding sites on $GABA_A$ receptors *in vitro*. Amentoflavone, a biflavone constituent of the extract, had the greatest inhibitory activity at these receptors. Hypericin, quercetin, rutin, and the biflavone 13,II8-biapigenin did not inhibit binding.[17]

A Hypericum tincture was recently investigated to determine if an alcohol/water extract has the same receptor-inhibiting activity as the standardized solid extracts. It was observed that the crude extract has an affinity for 5HT1, $GABA_A$ and $GABA_B$, benzodiazepine, and both MAO-A and MAO-B receptors,[18] which is similar to what has been noted for standardized solid extracts.

Another theory of depression which is gaining acceptance may provide a possible explanation for the antidepressant activity of St. John's Wort. Inflammatory cytokines, such as the interleukins and tumor necrosis factor, in addition to their effects on the immune system, may act as "messenger molecules" in the central nervous system. Interleukin(IL)-1 and IL-6 are potent activators of the hypothalamic-pituitary-adrenal (HPA) axis via stimulation of corticotropin-releasing hormone (CRH). Suppression of the normal HPA axis down-regulation is a frequent finding in endogenous depression,[19] and is characterized by hypersecretion of CRH, hypersensitivity of the adrenal cortex to ACTH, and increased cortisol levels.[20-22] It is hypothesized that cytokines such as IL-1 and IL-6, since they seem to be heavily involved in cell-to-cell communication both inside the immune system and within the nervous system, may act as neuromodulators involved in depression. Thiele et al reported Hypericum to be a powerful inhibitor of phytohemagglutinin-stimulated IL-6 release in an *in vitro* blood cell culture test. Controls and depressed patients showed marked inhibition of IL-6 release with Hypericum.[23] If this inhibition of IL-6 occurs *in vivo*, it could partially elucidate a mechanism for Hypericum in depression, as IL-6 inhibition might "re-set" the hyperactive hypothalamic-pituitary-adrenal axis.

One sequelae of prolonged cortisol increase is a reduction in serotonin synthesis. Excess cortisol activates the enzyme tryptophan pyrrolase, shunting the dietary amino acid precursor tryptophan away from the serotonin pathway and into the kynurenine-to-niacin pathway, resulting in inhibited serotonin production and reduced sensitivity of serotonin receptors.[24]

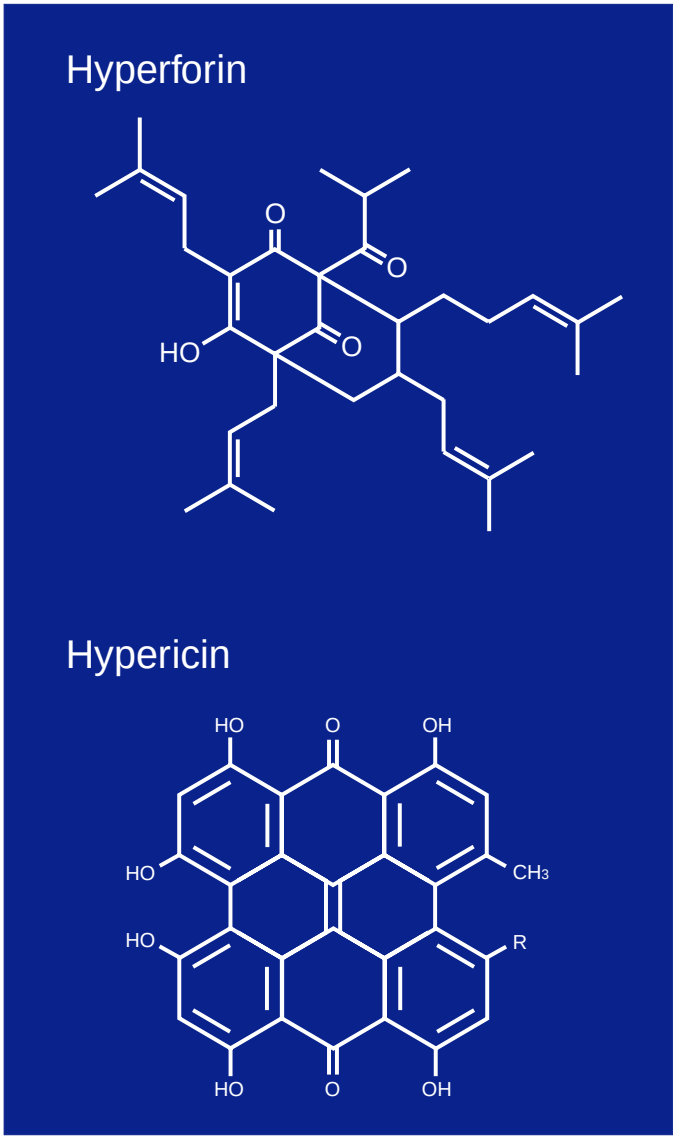
From these studies, it is noted that Hypericum may have an effect on serotonin, GABA, MAO, dopamine, norepinephrine, ß-adrenoreceptors, interleukins, and the HPA axis. With these illustrations of St. John's Wort's effects on these numerous biochemical models of depression, the clinical effectiveness of St. John's Wort is no surprise.

Clinical Trials Utilizing Hypericum in Depression

Regardless of the biochemical mechanism, Hypericum has been proven to be clinically beneficial in the treatment of depression. Numerous clinical trials have been conducted on Hypericum in the treatment of varying types and degrees of depression, including mild-to-moderate depression, severe depression, and seasonal affective disorder.

Linde et al, in their 1996 meta-analysis of clinical trials on Hypericum and depression,[24] investigated 23 randomized studies of liquid and solid St. John's Wort extracts. The

Figure 1. Structural composition of hypericin and hyperforin, two compounds in *H. perforatum.*



authors found most of the studies used reasonable to good methodology, although there was some criticism of diagnostic criteria, compliance control, and length of treatment (most were 4-6 weeks duration). Analysis of Hamilton depression scale scores before and after treatment indicated a significantly positive response in depression patients compared to placebo. In all, St. John's Wort extracts have been studied in over 1,500 individuals with depression.

In a double-blind, placebo-controlled, multi-center study of 105 mildly depressed patients, a standardized solid extract (300 mg t.i.d.) was given for four weeks, with examination at baseline, two, and four weeks. Using the Hamilton depression scale, significant improvements were noticed ($p<.01$), especially in "depressive mood," "psychological anxiety," and "difficulty initiating sleep."[25]

Hänsgen et al, studied 72 patients with major depression according to DSM-III in a randomized, placebo-controlled trial (300 mg t.i.d. standardized extract). The researchers noted a significant improvement in depressive symptoms using four standardized depressive scales. It is interesting to note that the placebo group was crossed over to the active medication at week four and experienced an improvement of symptoms similar to what the active group experienced in weeks one and two.[26]

A number of studies have been conducted comparing Hypericum with antidepressant drugs. These studies are of great interest, as the efficacy of these drugs has been studied extensively. Hypericum was noted to be equally effective as imipramine,[27] maprotiline,[28] and amitriptyline[29] in three diagnostically well-defined studies. These studies have been criticized for using drug doses which are less than that used in clinical practice.[24,30] However, a recent comparison of Hypericum and amitriptyline in moderately-depressed individuals used an often-prescribed dosage of 75 mg/day amitriptyline versus 900 mg/day Hypericum. Both groups showed statistically-significant improvements in the Hamilton depression scale, but a significant difference was noted in the mean Hamilton depression scale scores of the amitriptyline group compared to Hypericum at the six-week point, revealing that although both treatments were effective, amitriptyline was more effective. A significant difference was also noted in the number of adverse effects in the two groups, as St. John's Wort was virtually

non-sedating (3 percent), while amitriptyline was sedating in 24 percent of cases. The most common side-effect from amitriptyline was dry mouth (41percent).[5]

Until recently, no studies had been performed on Hypericum in severe depression. In the first such trial, 600 mg t.i.d. Hypericum was compared to 50 mg t.i.d. imipramine in 209 severely-depressed patients. St. John's Wort extract proved to be an equivalent treatment in severe depression to imipramine, with a significantly better adverse event profile (34.6% vs. 81.4%, respectively).[6]

Seasonal affective disorder (SAD), a subset of major depression occurring in fall/winter months and subsiding in the spring and summer, is usually treated with light therapy and antidepressants. A 1997 study of Hypericum treatment in SAD showed a significant decrease in depressive scores ($p<0.001$), and comparable results to a previous study of SAD and fluoxetine (Prozac®) by the same researchers.[31]

Hypericum flowers and leaves contain a "relatively high concentration" of melatonin,[32] the pineal gland hormone normally secreted in response to absence of light. As noted previously in this article, corticotropin-releasing hormone (CRH) stimulates the HPA axis and the hypercortisolemia of depression. CRH also inhibits melatonin secretion, and low levels of melatonin are noted in patients suffering from a major depressive episode.[32] It is possible further research in this area might point to St. John's Wort's melatonin content as an active participant in its antidepressive effects.

Since sleep disorders frequently accompany depression, a four-week investigation of Hypericum extract's (300 mg t.i.d.) effect on sleep was conducted. Older patients experienced an increase in slow-wave EEG activity, no sedation, and no increase in sleep time, all opposite of the typical response to tricyclic antidepressant drugs.[33]

Hypericum's Potential Antiviral Activity

St. John's Wort extract and purified hypericin have been studied for their antiviral activity, with promising results against human immunodeficiency virus (HIV) and other viruses *in vitro*.[34-37] However, this action might not occur *in vivo*. For hypericin to work as an antiviral, it needs to be exposed to visible light,[37-39] which will not happen to any great degree in the body. Further research in this area might solve this dilemma.

Vulnerary Effects

A vulnerary is typically a substance which enhances wound healing. Hypericum oil infusion has been used traditionally to speed healing of burns and wounds. Part of its effect might be due to its antibacterial activity.[1] To prepare an oil infusion, Hypericum flowers and leaves are packed into a jar and covered with olive or safflower oil. The jar is placed in the sun and shaken daily. The oil is poured off after 2-3 weeks and can be used in wound dressings and as a massage oil (caution: the red-pigmented oil can stain clothing).

Adverse Effects

Animals grazing on St. John's Wort have been known to develop phototoxic lesions. Hypericin has been identified as a photoactive substance which may cause photosensitization in fair-skinned individuals. A recent study utilizing 600 mg Hypericum extract orally t.i.d. showed a 21% reduction in the mean tanning dose, i.e., a person would get the same tanning effect in 21% less time.[40] Because of this possibility, patients should be advised to use caution when exposed to the sun, and wear appropriate clothing or sunscreen, especially if they burn easily. In a multicenter study of 3,250 patients, adverse effects occurred in 2.4% of patients, with the most common adverse effects being

gastrointestinal irritation, allergic reactions, tiredness, and restlessness.[41]

Discussion

Although St. John's Wort has been known for thousands of years, and has been used for a variety of medicinal purposes, understanding of its activity and mechanisms of action is relatively new and not well understood. While researchers originally thought the naphthodianthrone hypericin was responsible for Hypericum's antidepressant activity, it is now believed some other compound or a combination of constituents exert their antidepressant activity on the body. Hypericum is unique in that it seems to impact all known neurotransmitters at some level, directly, or indirectly through receptor sensitivity and regulation. This botanical also seems to have a beneficial impact on the HPA axis and cortisol production, which might be overstimulated in some people with depression, and on melatonin, which can be undersecreted in depressed individuals.

There has been a proliferation of European clinical studies on Hypericum in the last ten years, and even though some of these studies might be methodologically flawed, the preponderance of the evidence proves Hypericum to be beneficial in the treatment of mild-to-moderate depression. One recent study of severe depression treatment with Hypericum also noted its benefits, though more studies in this area are needed. St. John's Wort's popularity in the past few years in Europe, as well as the recent U.S. popularity, relates to this plant's efficacy as an antidepressant and its very favorable side effect profile.

A three-year study sponsored by the National Institutes of Health's Office of Complementary Alternative Medicine and the National Institute of Mental Health was recently announced, which will compare a standardized St. John's Wort extract with placebo and an SSRI antidepressant in 336 patients.[4] This will be the first U.S. study of Hypericum and major depression.

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