ST. JOHN'S WORT

(Hypericum perforatum)

An Overview of its Safety and Clinical Efficacy

Michael Traub, ND

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St. John's Wort: An Overview of its Safety and Clinical Efficacy

BACKGROUND AND USES

St. John's Wort (SJW) is a beautiful plant that grows on sun-exposed hills, grasslands and on the edge of pine forests.[i] It owes it name in the Western world to the fact that it begins to flower around the summer solstice, known as St. John's Tide. It's golden yellow flower buds have small black dots, which, when rubbed between the fingers, produce a red stain. The pigment is photosensitizing, which was discovered when cows developed inflamed skin after eating the plant while exposed to the sun. Other unique features of the plant are the leaves, which look like they have small perforations, hence the Latin name *peforatum,* and the stem, which has two raised lines making it appear flat, something unusual in the plant kingdom. Round or square are the common structure of stems. The genus name *Hypericum* is derived from the Greek words *hyper* (above) and *eikon* (picture), referring to the plant's historical use to ward off evil by hanging it over a religious icon on the feast day of St. John the Baptist (June 25).

Extracts of SJW have traditionally been used for a wide range of medical conditions.[ii] The treatment of mild to moderate depression is the most well known contemporary use of SJW. As numerous studies on this application published in the 1980s to 1990s attracted major media coverage, SJW rose from obscurity in the U.S. to become the second-best selling dietary supplement in mainstream retail stores in 2000.[iii] Subsequently adverse publicity regarding reports of interactions with various prescription drugs caused it to drop to fifth place a year later.

The pharmacology and clinical uses of SJW is the subject of substantial research. Relatively recent scientific reviews are somewhat dated due to the rapid accumulation of new data. This review includes clinically relevant published literature through the end of 2013.

MECHANISMS OF ACTION

The broad mechanisms of action of SJW remain to be fully elucidated. Biologically active constituents include hyperforin adhyperforin (phloroglucinols), hypericin, pseudohypericin (naphthodianthrones), flavonoids, xanthones, oligomeric procyanidins, and amino acids.[iv]

Antidepressant effects: mediated by serotonergic, noradrenergic, and dopaminergic systems, as well as glutamate and gamma-aminobutyric acid (GABA). Components of SJW extract bind to benzodiazepine, MAO-A and MAO-B receptors. Hyperforin may inhibit uptake of several neurotransmitters. SJW may inhibit 5-hydroxytryptamine (5HT, serotonin) receptor expression, resulting in inhibition of 5HT reuptake.[v] The limited data so far suggest that these components pass the blood-brain barrier poorly in animals. Concentrations in the brain of these compounds after pharmacologically

effective doses of SJW are far below those effective on neurotransmitter receptors and their mechanisms underlying the CNS effects of synthetic antidepressants.[vi]

Analgesic effects: hyperforin and hypericin exert prolonged analgesia through inhibition of protein kinase C epsion isoforms and their phosphorylation.[vii]

Anti-inflammatory effects: hyperforin induces expression of IL-8.[viii]

Antimicrobial effects: hypericin and hyperforin are responsible for inhibiting the growth of bacteria.[ix]

Antineoplastic effects: synthetic hypericin has demonstrated efficacy in reducing the size of gliomas in preliminary human trials.[x] Hyperforin induced apoptosis of chronic lymphoid leukemia cells and acute myeloid leukemia cells *in vitro.*[xi] Hypericin induces apoptosis in normal and malignant B and T lymphocytes.[xii]

Antiviral effects: demonstrated in a variety of *in vitro* studies, and in a randomized, controlled clinical trial of a single application for herpes simplex.[xiii] HIV inactivation by hypericin *in vitro* may be through a photodynamic mechanism that induces alterations of the retroviral capsid p24.[xiv]

Immunosuppressive effects: inhibition of T cell proliferation in response to SJW *in vitro* and *in vivo* (the effect of SJW ointment compared to the immunosuppressive effect of UV radiation) may explain the efficacy of hyperforin in treatment of inflammatory skin disorders.[xv]

CLINICAL TRIALS

Depression

For the short-term management of mild-to-moderate depression (1-3 months), SJW has been found to be equally effective as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), and more effective that placebo, in meta-analyses of studies published over the past 20 years,[xvi] including a Cochrane review,[xvii] and in recent randomized trials. Negative results published may be due to adherence issues. In the National Institutes of Health Hypericum Depression Trial, detectable plasma hyperforin could not be detected in 17% of patients taking SJW, and plasma hyperforin was detected in 17% of patients taking placebo.[xviii] The cumulative evidence in support of SJW as efficacious in mild-to-moderate depression is strong. The evidence for severe major depression and other depressive disorders (e.g., somatoform and seasonal affective disorder) is equivocal.[xix]

Irving Kirsch PhD. exposed the weakness inherent in placebo-controlled trials of antidepressants, based on the potent placebo response in these studies. Kirsch has convincingly stated in his book "*The Emperor's New Drugs: Exploding the Antidepressant Myth":* "Our analyses of the FDA data showed relatively little difference between the effects of antidepressants and the effects of placebos. Indeed, the effects were so small that they did not qualify as clinically significant. The drug companies knew how small the effect of their medications were compared to placebos, and so did the FDA and other regulatory agencies. The companies found various ways to make the data seem more favorable to their products, and the FDA helped them keep their negative data secret. In fact, in some instances, the FDA urged the companies to keep negative data hidden, even when the companies wanted to reveal them. My colleagues and I hadn't really discovered anything new. We had merely revealed their 'dirty little secret'."[xx]

Mood disorders *(supported by one or more lesser-quality clinical trials or case reports)*

- Obsessive-compulsive disorder: an open-label trial suggested possible benefit; a subsequent randomized clinical trial by the same researchers found no benefit over placebo.[xxi]

- Anxiety disorder: a systematic review of trials of SJW for anxiety found mixed results.[xxii]

- Psychological symptoms associated with perimenopause: a case series of 111 women taking SJW experienced significantly improved menopausal symptoms by self rating as well as physician rating.[xxiii] A combination of SJW and Black Cohosh versus placebo demonstrated significant benefit in psychological perimenopausal symptoms in a double-blinded, randomized controlled trial of 301 women.[xxiv]

Other health conditions *(supported by one or more lesser-quality clinical trials or case reports)*

- Glioma: the results of one study indicated that synthetic, oral hypericin is well tolerated in recurrent malignant glioma. The response results (26 weeks median survival) were comparable to those reported from other studies of salvage therapies for recurrent malignant brain tumors.[xxv]

- Neuropathic pain: two clinical trials of the efficacy of SJW in neuropathic pain provide mixed evidence. One trial showed a trend of lower total pain score with SJW compared to placebo.[xxvi]

- Osteomyelitis: in subjects with diabetic foot ulcers and osteomyelitis, a combination product containing SJW was efficacious in avoiding amputation and increasing bone healing.[xxvii]

- Perimenopausal symptoms: a randomized, double-blind, placebo controlled trial of SJW on quality of life and symptoms for perimenopausal women found significantly fewer sleep issues, and significantly improved quality of life scores.[xxviii] A controlled open-label observational study of 6,041 women at 1287 outpatient gynecologists in Germany found that the combination of Black Cohosh and SJW was significantly more effective than Black Cohosh alone in improving menopausal symptoms.[xxix]

- Premenstrual syndrome (PMS): a randomized crossover trial of SJW and placebo demonstrated statistically significant improvement in behavioral and physical symptoms of PMS in 36 women. A randomized, double-blinded, placebo-controlled trial of 170 women with moderate to severe PMS found significantly lower PMS scores in those on SJW compared to placebo. The largest benefit was seen in crying (71%) and depression (52%). [xxx] Premenstrual dysphoric disorder (PMDD) comprises the more severe and disabling end of the spectrum of PMS. SJW may be a useful adjunct in the treatment of PMDD, and may be effective when taken only during the luteal phase of the cycle as needed.[xxxi]

Skin Disease

- Atopic dermatitis: a double-blind, randomized, placebo controlled trial of a topical cream containing SJW showed significant superiority of the SJW cream compared to vehicle in mild-to-moderate subacute atopic dermatitis.[xxxii]

- Herpes: a clinical trial of a topical combination product containing copper sulfate pentahydrate and SJW showed an improvement in pain, erythema and vesiculation.[x]

- Cutaneous T-cell lymphoma and psoriasis: a placebo-controlled trial of topical hypericin was applied as a photodynamic agent to mycosis fungoides and plaque psoriasis, resulting in significant improvement of lesions among the majority of patients, whereas the placebo vehicle was ineffective. (11) SJW ointment and placebo vehicle were also used twice daily in a case series split-body study of 10 patients with plaque psoriasis in a single blinded manner for one month. Modified psoriasis area severity index (PASI) scores were significantly lower where the SJW ointment was applied.[xxxiii]

- Wound healing: topical application of SJW ointment significantly improved wound healing and scarring after Cesarean section in a randomized controlled trial.[xxxiv]

Negative studies

1. Attention-deficit hyperactivity disorder (ADHD)[xxxv]
2. Human immunodeficiency virus (HIV)[xxxvi]
3. Irritable bowel syndrome (IBS)[xxxvii]

PRECAUTIONS, CONTRAINDICATIONS, and INTERACTIONS

SJW is well tolerated at recommended doses for up to 1-3 months.[xxxviii] The most common adverse effects include gastrointestinal symptoms, skin reactions, fatigue or sedation, restlessness or anxiety, sexual dysfunction (including erectile dysfunction and anorgasmia), dizziness, headache, and dry mouth. Several recent meta-analyses and one clinical trial concluded that adverse event rates are comparable to placebo and less-than-standard antidepressant treatment. Allergic skin reactions are infrequent. Photosensitization is rare in typical doses up to 1,800 mg daily.[xl] Possible serotonin syndrome has been reported in only 3 cases. Only one case of withdrawal syndrome has been reported.

SJW affects the pharmacokinetics of many pharmaceutical agents by inducing cytochrome P450 isozymes, including CYP3A4, CYP2C19, CYP2C9 and the P-glycoprotein (P-gp) transporter.[xli] Hyperforin downregulates the expression of P-gp, a protein that is involved in the resistance of leukemia cells to chemotherapeutic agents. (10) Metabolic interactions between SJW and drugs are not invariably dangerous and may be beneficial (e.g., reduction of irinotecan toxicity and increase in response to clopidrogel). The precautions listed below suggest that SJW preparations with a low hyperforin content should be used with these drugs, with close monitoring. Women who use SJW concomitantly with oral contraceptives should also use another preventive method to avoid unintended pregnancy.

Avoid in patients with HIV/AIDS who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors, due to documented reductions in drug concentrations with concomitant SJW.

Avoid in transplant recipients taking immunosuppressants (particularly) cyclosporine due to significant reductions in drug levels and possible organ rejection with concomitant SJW.

Avoid in patients taking digoxin, anticoagulants (warfarin, clopidogrel), and photosensitizing drugs.

Use with caution with drugs metabolized by cytochrome P450 (particularly the CYP3A4 and CYP1A2 family), as increased or decreased drug levels may occur.

Use with caution with chemotherapeutic agents (etoposide, anthracyclines, imatinib, irinotecan, docetaxel), as concomitant use of SJW may modify the efficacy of chemotherapy. Radiosensitization of temozolomide has been increased by SJW.

Use with caution in patients taking MAO inhibitors, SSRIs, TCAs, or 5HT1 agonists (triptans), due to risk of serotonin syndrome. Use with caution with zolpidem.

Use with caution in women taking oral contraceptives or other estrogens; in patients with diabetes, in renal transplant patients, in patients with hepatic dysfunction, in patients with thyroid disorders, in patients with cataracts, in patients with hypertension, arrhythmia, and high cholesterol, in patients with edema, in patients taking analgesics, antibiotics, antifungals, antihistamines, CNS depressants or stimulants, omeprazole, and in patients with seizures.

Use with caution in pregnancy and lactation.

DOSAGE

St. John's wort products are often standardized to 0.3% hypericin extract, although there has been a movement within the manufacturing industry to standardize to hyperforin (usually 2-5%)[xlii]

ORAL – Adult dose:

- **Anxiety**: 900mg twice daily for several weeks
- **Cancer**: A dose of 0.05-0.50mg/kg of hypericin for a maximum of three months
- **Depression (mild-to-moderate)**: starting dose of 300mg of standardized 0.3% hypericin extract three times daily (may be standardized to 2-5% hyperforin as well) and a maintenance dose of 300-600mg daily.
- **Glioma:** hypericin 0.33 ± 0.070 mg/kg/d
- **Nerve pain**: Three tablets each containing 900mcg of total hypericin have been administered daily for two treatment periods of five weeks each
- **Obsessive-compulsive disorder (OCD)**: A flexible-dose schedule was used (600-1,800mg daily) for 12 weeks; 450mg, equaling 0.3% hypericin, has been used twice daily for 12 weeks
- **Pain (burning mouth syndrome)**: 300mg capsules containing *H. perforatum* extract (hypericin 0.31% and hyperforin 3.0%) have been taken three times daily for 12 weeks
- **Perimenopausal symptoms**: 900mg daily or 300mg of ethanol extract three times daily has been used for 12 weeks; drops containing 0.4mg of hypericin have been administered daily for 12 weeks

- **Premenstrual syndrome (PMS)**: 600mg (standardized to 1,800mcg of hypericin) for two menstrual cycles; 300mg (standardized to hypericin) for a two-cycle treatment period; 450mg of standardized to 3.38% hyperforin and 0.18% hypericin twice daily for two menstrual cycles; and two 680mg tablets of *H. perforatum* daily for two menstrual cycles
- **Social phobia**: 600-1,800mg has been taken daily for 12 weeks
- **Somatoform disorders**: 300mg of extract has been taken twice daily for six weeks

TOPICAL:

- **Atopic dermatitis**: Cream containing 1.5% hyperforin (verum) has been administered twice daily for four weeks
- **Psoriasis**: *Hypericum perforatum* ointment has been used two times daily for four weeks
- **Wound healing**: Topical application of *H. perforatum* (20% in petroleum jelly) has been used three times daily beginning 24 hours after Cesarean section and continued for 16 days

CHILDREN – Oral dose:

- **Depression (children)**: limited clinical information exists in pediatric populations: 300-1,800mg of St. John's wort extract

SUMMARY

SJW is one of the best known, well-researched, and best-selling herbal therapies for depression. Meta-analyses of randomized controlled trials of SJW indicate that it is superior to placebo in major depression, is comparable in efficacy to conventional antidepressants, and exhibits substantially lower incidence of adverse events than synthetic antidepressants. SJW has a broad spectrum of other proven indications as well, including psychological and other symptoms associated with perimenopause, premenstrual syndrome, gliomas, osteomyelitis, atopic dermatitis, herpes simplex, psoriasis, cutaneous T-cell lymphoma, and wound healing.

Although SJW is generally well tolerated, it has many important drug interactions. Some of the reported interactions are based on findings from *in vitro* studies, where clinical relevance remains to be seen. Some case reports reveal interactions that call for caution, and disclosure of potential interactions prior to informed use of SJW.

ABOUT THE AUTHOR

Michael Traub, ND, DHANP, CCH, FABNO attended the University of California, Irvine where he received a B.S. in biological sciences, and graduated from National College of Naturopathic Medicine (NCNM) in 1981. He completed a residency program in Family

Practice and Homeopathy at NCNM. Since 1986, Dr. Traub has been Medical Director of an integrative healthcare center (Lokahi Health Center) in Kailua Kona, Hawaii. He is board certified in naturopathic oncology as well as homeopathy.
Dr. Traub has conducted a wide range of research studies on homeopathic growth factors in HIV and AIDS, Attention Deficit and Hyperactivity Disorder, Paroxysmal Nocturnal Hemoglobinuria in Bone Marrow Failure Syndromes, Hypovitaminosis D, and Elderberry Extract for Prevention of Influenza.

He has been invited to make presentations at numerous medical conferences, including the 1999 International Conference on HIV/AIDS in Paris. He is the author of "Essentials of Dermatological Diagnosis and Natural Therapeutics" and "Essentials of Dermatological Diagnosis and Integrative Therapeutics." He has contributed to several textbooks including the Textbook of Natural Medicine. He serves on the editorial board of the Natural Medicine Journal, the International Journal of Naturopathic Medicine, and Holistic Primary Care. He is a member of the Board of Directors of the Integrated Healthcare Policy Consortium and was co-author of the "Final Report of the National Policy Dialogue to Advance Integrated Health Care: Finding Common Ground, 2001-2002, and co-editor of "The Affordable Care Act & Beyond: A Stakeholder Conference on Integrated Healthcare Reform," Sept. 2010.

He currently serves on the Scientific Advisory Boards for Gaia Herbs, Inc., Kamedis, and Nordic Naturals.

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