

Complementary, Holistic, and Integrative Medicine: St. John's Wort

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Introduction

St. John's wort, derived from the *Hypericaceae* family, has played a medicinal role for thousands of years. (1) Although it has been used empirically for a wide range of ailments in the past, including skin conditions, nerve problems, and muscle pain, the primary uses currently are for depression and nervous conditions, (2)(3)(4)(5)(6)(7) due to its ability to inhibit the reuptake of dopamine, serotonin, and norepinephrine within the brain. (2)

Although promising evidence is emerging for the clinical use of St. John's wort, data specific to pediatrics are still limited, warranting additional research.

Evidence of Efficacy in Pediatrics

Surveys in the United States and Britain of herbal use for the treatment of pediatric depression (8)(9) demonstrate that St. John's wort is used commonly by children (22% and 9% in the two surveys, respectively). Formal evaluation of efficacy in pediatric populations is preliminary but shows some promise. Presently, no systematic reviews or randomized, controlled trials have been published regarding the use of St. John's wort in children.

An open-label pilot study conducted by Findling and associates (10) analyzed the use of St. John's wort in children between the ages of 6 and 16 years for treatment of major depressive disorder. The starting dose was 150 mg 3 times daily for 4 weeks. Exclusion criteria included failure to respond to 4 weeks of antidepressant therapy. Patients considered clinically nonresponsive to St. John's wort (as per a priori criteria) after 4 weeks had their dosage increased to 300 mg 3 times daily. A total of 33 patients were enrolled in the study, with a mean age of 10.5 years (SD, 2.9 y). At the end of the 8-week trial, 25 patients met the criteria of clinical response (76%). Also, 93% of the study population decided to continue therapy at the end of the 8-week study. Statistically significant improvements were documented in the two primary outcome measures (Children's Depression Rating Scale-Revised and Children's Depression Inventory) from baseline to 8 weeks. The major limitations of this study are that it was open-label, had no control group, had a small sample size, and had limited follow-up (8 wk).

In a prospective, open-label, outpatient study, Simeon and associates (11) investigated the efficacy of St. John's wort in adolescents between 12 and 17 years of age (mean age, 14.8 y) who had major depressive disorders. Of the 26 patients enrolled, only 11 completed the 8-week study; the remaining 58% were either noncompliant or discontinued use due to continuing or worsening depression. Nine of the 11 compliant patients (82%) showed a significant clinical response, as indicated by the Clinical Global Improvement scores (either "very much improved" or "much improved") at the final visit. The limitations of this study include its lack of a control group, small sample size, short follow-up period (8 wk), and open-label design.

In an observational study involving pediatric patients taking St. John's wort for symptoms of depression, physicians and parents were asked to complete questionnaires about the efficacy and tolerability of the treatment. (12) Descriptive data were collected on 101 patients between the ages of 1 and 12 years (median age, 9 y). The median dose was 300 mg daily. Follow-up lasted 6 weeks, with physicians and parents reporting "excellent" efficacy in 55% of the patients. Although ratings of depressive symptoms improved over the course of the study, given the open-label, observational design, it is hard to interpret how clinically significant such improvements were. Physicians and parents did report high

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ratings of tolerability, but there were no descriptions of adverse events, and there was a high rate of losses to follow-up. Although 101 subjects were enrolled in the study, only 74 children were included in the final analysis. It is concerning that nine children dropped out during the trial, six of them because of inadequate therapeutic effects.

The data obtained from the previously cited studies show some promising results for the tolerability and potential efficacy of St. John's wort in the treatment of depression in children. Better-designed research involving blinded controls is required to strengthen the findings.

Formal evaluation of St. John's wort in the pediatric population includes its use in otitis media. (13) A randomized, controlled trial studying a combination product containing *Hypericum perforatum* in olive oil (as well as *Allium sativum*, *Verbascum thapsus*, and *Calendula flores*) found significant improvements in ear pain associated with otitis media in children between the ages of 6 and 18 years (n=103). This product was determined to be as effective as anesthetic ear drops in relieving ear pain.

Evidence of Safety

A systematic review analyzing the adverse effects associated with St. John's wort in patients of all ages concluded that the herb is well tolerated in most individuals, with adverse events occurring in approximately 1% to 3% of patients. (14) The rates of adverse events were similar compared with placebo and less compared with other commonly prescribed antidepressants. Clinical studies have found that healthy individuals can tolerate St. John's wort for up to 3 months. The adverse effects reported most commonly included gastrointestinal (GI) upset, fatigue, headache, restlessness, and dry mouth. Allergic skin reactions and increased photosensitization also have been identified, but evidence regarding the clinical relevance of these findings is conflicting. (1)(14) Fair- or sensitive-skinned individuals or those who have skin diseases should be cautioned about this possible risk. Potentially more serious adverse events, such as manic episodes, neuropathy, and serotonin syndrome, have been reported, but they were rare, and evidence is not clear whether St. John's wort was the only contributing factor. (1)(14)

Studies analyzing the effects of St. John's wort in the pediatric population found generally good tolerance for up to 8 weeks with appropriate doses. (10)(12) The most common adverse effects were dizziness, diarrhea, and change in appetite. (10)(12) Less commonly reported effects included constipation, headache, chills, GI dis-

comfort, rash, fatigue, and photosensitivity. Treatment with St. John's wort was found not to be associated with any clinically significant changes in weight, vital signs, or laboratory test results. (10) One case of worsening nervousness presented in the observational study, in which symptoms changed from "not present" at baseline to "mild" at 2 weeks. (12) Overall, the adverse events experienced in pediatric patients using St. John's wort were mild and short-lived. Additional research is needed to determine the long-term safety of St. John's wort use in children.

Pregnancy and Lactation

Sufficient evidence is lacking to recommend the use of St. John's wort in women who are pregnant or lactating, and the drug is rated as being risk category C in pregnant women. (15) In two cases of St. John's Wort use during human pregnancy, no immediate observable adverse effects were demonstrated. (16)

In terms of breastfeeding, one case report found that only hyperforin (not hypericin) was excreted in human milk after multiple sampling of both fore and hind milk. (17) Hypericin and hyperforin were immeasurable in the infant's plasma. An observational cohort study was conducted in 33 breastfeeding women receiving St. John's wort and 101 disease-matched controls as well as 33 age- and parity-matched nondisease controls. (18) The women were followed for 2 years, with no significant differences in adverse events. In the control infants, there was one case of colic; in the treatment group, there were two cases of colic, two cases of drowsiness, and one case of lethargy. No medical treatment was required for any of these reported events. No significant differences were found in relation to milk production or infant weight during the first postnatal year.

Drug Interactions

Numerous drug interactions are associated with St. John's wort, and caution is warranted during its concomitant use with certain medications (Table). The most significant interactions are the possible induction of serotonin syndrome when St. John's wort is combined with selective serotonin reuptake inhibitors and the induction of the CYP450 3A4 enzyme, which could reduce the plasma concentrations of drugs metabolized by this pathway. (14)(19)(20) Concomitant drugs of particular concern in a pediatric and adolescent population are cyclosporine, warfarin, oral contraceptives, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors. (14)(19)(20)(21)

Although several drug interactions associated with St.

Table. Summary of Drug Interactions With St. John's Wort

Drug	Mechanism	Management
Carbamazepine (11)(19)(20)	Decreased plasma concentrations due to the possible induction of CYP3A4 enzyme	Concurrent use should be avoided. Laboratory monitoring of carbamazepine concentrations should be increased upon the start and end of St. John's wort therapy.
Cyclosporine (14)(19)(20)	Decreased plasma concentrations due to the possible induction of CYP3A4 enzyme	Concurrent use should be avoided. If used concurrently, cyclosporine concentrations should be followed.
Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors (14)(19)(20)	Decreased plasma concentrations due to the possible induction of CYP3A4 enzyme and P-glycoprotein	Concurrent use should be avoided.
Oral Contraceptives (14)(19)(20)(21)	Increased metabolism of oral contraceptive	Patients should be counseled to monitor for breakthrough bleeding and advised to use an alternative method of birth control.
Selective Serotonin Reuptake Inhibitors (SSRIs) (14)(19)(20)	Increased risk of developing symptoms of central serotonin syndrome due to the possible additive effect on serotonin reuptake by hyperforin	Patients should be counseled on the potential signs/symptoms of serotonin syndrome (nausea, headache, agitation, confusion, fever, insomnia). The concomitant use of St. John's wort with SSRIs should be approached with caution.
Warfarin (14)(19)(21)	Reduced plasma concentrations of warfarin due to the possible induction of CYP2C9 enzyme and P-glycoprotein; increased risk of thromboembolic events	Patients using warfarin should be advised to avoid St. John's wort. If used concurrently, increased INR monitoring and follow-up is advised. Patients should be counseled on the signs and symptoms of thromboembolic events.

John's wort have been reported, no clinical reports of these interactions are available within the pediatric population. Encouraging parents to report the use of St. John's wort in their children is imperative to assess the safety of concomitant medication use.

Pharmacologic Action

The multiple constituents of St. John's wort identified as potential active ingredients include naphthodianthrones, flavonoids, and xanthenes. Most preparations are standardized to hypericin content (a naphthodianthrene), but recent data indicate other active ingredients, including hyperforin. (22)(23) The precise mechanisms of action are not known and are being debated. Irreversible monoamine oxidase inhibitory activity noted *in vitro* has not been observed *in vivo*. Other postulated mechanisms include selective inhibition of serotonin, gamma-aminobutyrate, norepinephrine, and dopamine reuptake in the central nervous system. (1)(24). Studies also have identified antibacterial, antiviral, and anti-inflammatory

actions in association with St. John's wort, although details are scarce on the exact mechanisms. (2)(4)

Administration/Dosage Forms

Commercially available extracts of St. John's wort are manufactured as capsules, tablets, or caplets. (2) Studies conducted with pediatric patients have found good tolerance with doses ranging from 300 to 900 mg/d in divided doses for up to 8 weeks. (10)(12)

Although most product labels state that the extract is standardized to 0.3% hypericin content, additional evaluation suggests that this concentration may vary considerably. (23) Patients should be cautioned to consider this variance when selecting an appropriate product.

Conclusion

Although preliminary data suggest efficacy and tolerability of St. John's wort for the treatment of depression in children, additional research with better study designs is needed to support using this agent as an antidepressant in

the pediatric population. Clinicians must inquire as to whether families are giving this agent to their depressed children.

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