

# Complementary & Alternative Medicine

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**Editor's Note:** The widespread use of complementary and alternative medicine (CAM) by patients in the United States makes it imperative for physicians to have a better understanding and knowledge about CAM modalities in order to provide best care for their patients.

The University of Washington School of Medicine (UW-SOM), in collaboration with Bastyr University, has been awarded a grant from the National Center for Complementary and Alternative Medicine (NCCAM) directed at developing educational materials and integrating CAM into the UW-SOM curriculum. One aim of the grant was to develop evidence-based monographs for the most important herbs and supplements for physicians to know about.

Made possible by funds from this NCCAM grant (AT00813-01), this insert to *Drug Therapy Topics* reviews one of these herbs.

(continued on reverse)



*Hypericum perforatum*

## St. John's Wort

St. John's wort (*Hypericum perforatum*) is a weed with a yellow flower that grows throughout the world including in the Pacific Northwest. It blooms primarily in June when the feast of John the Baptist was celebrated. "Wort" is the Old English word for plant. Extracts have been used for centuries to treat "nervous conditions," and St. John's wort continues to be the most commonly prescribed treatment for mild depression in Germany.

### Pharmacology

St. John's wort contains at least ten substances, including hypericin and hyperforin, which have been shown to have biological activity. Although extracts have traditionally been standardized to their hypericin content, it now appears that hyperforin may have even more pharmacologic activity.<sup>1</sup> *In vitro* studies have shown binding of constituents to neuroreceptors and the re-uptake inhibition of the neurotransmitters serotonin and norepinephrine.

### Clinical studies

Dozens of randomized controlled studies of St. John's wort have been published, although most have been small. Most have been well-controlled, using standard methodology, and have used widely accepted outcome measures commonly used in antidepressant trials.

For mild depression, almost all trials show better response rates for St. John's wort than for placebo.<sup>2</sup> In studies which enrolled patients with more severe depression, however, results have been more mixed. Two recent well-conducted trials, enrolling patients with more severe, long-standing depression, found St. John's wort to be no more effective than placebo, although in one of these trials the active comparator (sertraline) also performed no better than placebo.<sup>3,4</sup>

Several trials have shown no significant difference in efficacy between St. John's wort and standard antidepressants, although it is difficult to draw conclusions from these results given the small size of many of these trials and the variability in the results of antidepressant trials in general.<sup>2</sup>

### Adverse effects

The incidence of sexual dysfunction due to St. John's wort appears to be similar to that of selective serotonin reuptake inhibitors (SSRIs).<sup>3</sup> Otherwise, St. John's wort is generally well-tolerated, although some patients may report nausea, headache, or rash.<sup>5</sup> When compared in head-to-head trials, the incidence of side effects from St. John's wort has generally been less than that from tricyclic antidepressants (TCAs). Individual case reports raise the possibility of photosensitivity when St. John's wort is taken at high doses.

### Important drug/herb interactions

St. John's wort is a powerful inducer of cytochrome P450, isoform 3A4.<sup>6</sup> As such, other drugs metabolized by that pathway are cleared faster; their serum levels are reduced by 30-80%, and they become less effective. Hundreds of drugs are metabolized by this pathway and so carry risk of this interaction.<sup>7</sup> Table 1 lists some of the most commonly used of these drugs.

(continued on reverse)

## St. John's Wort (continued)

### References

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### Drug Therapy Topics Special Supplement

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Drugs with the narrowest therapeutic window are most likely to be seriously affected, with potentially serious clinical consequences. HIV protease inhibitors and cyclosporine are the most well known.<sup>8,9</sup> Numerous case reports describe organ transplant rejection after St. John's wort was added to cyclosporine. Interactions have also been reported between St. John's wort and warfarin, digoxin, and oral contraceptives, although these interactions are less well documented.

### Formulation and dosage

Almost all clinical trials of St. John's wort have tested a dose of 300mg given three times daily of an extract standardized to 0.3% hypericin. Most commercial extracts are still standardized to hypericin, despite evidence that hyperforin may play a more important role in St. John's wort's pharmacologic activity.<sup>1</sup>

Because the dietary supplement industry is still poorly regulated, the reliability of commercially available dietary supplements remains variable. In a recent analysis by ConsumerLab, however, 12 of 13 St. John's wort products had the amount of extract claimed on the label.<sup>10</sup>

Of greater concern, 3 out of 13 products tested were found to have heavy metal levels which, though still low, were above generally accepted guidelines. Three had cadmium levels above recommended amounts set by the World Health Organization for medicinal plants and one had lead levels above that set by the State of California for daily dietary intake.

**Table 1:  
Selected Drugs Metabolized by P450 (3A4)**

Amlodipine	Indinavir
Atorvastatin	Loratadine
Carbamazepine	Lovastatin
Clarithromycin	Nifedipine
Corticosteroids	Ritonavir
Cyclosporin	Simvastatin
Diltiazem	Verapamil
Efavirenz	Vincristine

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• *Please note that, as a dietary supplement, St. John's wort has not been approved for use by the FDA and is not on the UW Medicine formulary.*

### Summary of the Evidence

- There is fair evidence that St. John's wort is a safe and effective treatment for mild depression.
- St. John's wort is not recommended for use in major depression: St. John's wort product formulations may be less reliable than TCAs or SSRIs, and their efficacy in more serious depression is questionable.
- Serious drug interactions occur between St. John's wort and many other medications, making these other medications less effective.

(Continued from reverse)

More than twenty other similar monographs are available at [www.uwcam.org](http://www.uwcam.org) including: black cohosh, echinacea, feverfew, garlic, ginkgo biloba, glucosamine, kava, milk thistle, phytoestrogens, and saw palmetto. For more information on the UW-SOM CAM curriculum project, contact Ronald Schneeweiss, MBChB ([sron@famned.washington.edu](mailto:sron@famned.washington.edu)) or Barak Gaster, MD ([barakg@u.washington.edu](mailto:barakg@u.washington.edu)).