

UCLA
Nutrition Bytes

Title

Saint John's wort might not be as safe as we thought

Permalink

<https://escholarship.org/uc/item/6fx487s1>

Journal

Nutrition Bytes, 6(2)

ISSN

1548-4327

Author

Moccia, Rob

Publication Date

2000

Peer reviewed

Introduction

Saint John's wort, also known as hypericum, has gained widespread popularity as a safe remedy for mild to moderate depression (1). It is available over-the-counter, and this ease of access may be at least partly responsible for its popularity (2). While there is still very little known about Saint John's wort, current data indicate it has similar efficacy and a better side effect profile than other commonly prescribed antidepressants (3).

Yet while several studies have concluded that Saint John's wort is safe, the truth is that very little is currently known about its pharmacology, particularly regarding potential drug interactions (1). This is a cause for concern, especially given evidence that over 18% of US adults are taking herbal remedies with their prescription medication and over 60% of them are not informing their physician (4).

If hypericum extracts were truly safe, then this would not be cause for much alarm. However, in the past six months documented cases of potentially deadly drug interactions involving Saint John's wort have been reported in the literature (5-9). While there is still too little evidence to make solid conclusions about product safety, the data currently available indicates a need for physicians to be more vigilant in monitoring their patient's hypericum use. As will be seen, this is particularly important for those whose health depends upon maintaining therapeutic plasma concentrations of certain drugs. To illustrate the need for better monitoring, current clinical and laboratory data will be presented, with particular consideration given to the effect of hypericum on plasma levels of cyclosporin and indinavir.

A potent inducer of hepatic enzyme activity?

While most studies have supported the safety of hypericum, newly emerging data indicates that it acts as a potent inducer of hepatic enzymes, specifically the cytochrome P-450 system (6). If so, this could lead to decreased bioavailability of prescription pharmaceuticals metabolized by this pathway. At least eight cases have recently been reported in peer-reviewed journals and at scientific meetings that support this idea. In vitro studies of the effects of hypericum on cytochrome P-450 have provided somewhat conflicting data, but most agreed that hypericum extracts increase the metabolic activity of cytochrome P-450 approximately two-fold (6).

There is also some indirect evidence that this enzyme induction occurs in vivo. In separate studies on healthy volunteers, it has been demonstrated that serum levels of phenprocoumon and digoxin are significantly reduced when taken concurrently with Saint John's wort as opposed to placebo (6,7). Similar reductions in plasma levels of theophylline, warfarin, indinavir, and cyclosporin have also been observed (6,8,9). A striking similarity is that all of these drugs are metabolized via the cytochrome P-450 system. It is therefore thought that this reduction in bioavailability is the result of increased metabolism of the prescription drugs owing to the enzyme inducing effect of Saint John's wort (6).

Currently, there appears to be only one paper claiming to directly assess the effects of hypericum on cytochrome P-450 activity in vivo. In an attempt to look specifically at the effect of hypericum on cytochrome P-450 2D6 and 3A4 activity, Markowitz and colleagues took the phenprocoumon and digoxin studies one step further by administering Saint John's wort together with drugs metabolized almost exclusively by either the 2D6 or the 3A4 pathway (10). They concluded that there was no statistically significant effect on enzyme activity, but there are severe limitations to this study. Only seven volunteers were included resulting in a very low power of detection; even a 25% difference in enzyme activity at the 0.05 significance level with a power of 0.80 would require at least 27 subjects (10). Moreover, dosing was only for three days and blood levels were only assayed out to 60 hours following final dosing. It is possible that longer-term use of hypericum is necessary to induce changes in hepatic enzyme activity levels or that changes will not be detected in the plasma until more than 60 hours have passed. In fact, it will be seen in the next two studies described that clinical observations of potential hypericum drug interactions were only observed following ten or more days of use (8,9). This illustrates the lack of information available and the general confusion that exists regarding the pharmacological effects of hypericum.

Reduced blood levels of a retroviral protease inhibitor

Of all the recent data addressing hypericum drug interactions, one of the most alarming comes from Piscitelli et al. who report significantly decreased plasma levels of the HIV-1 protease inhibitor indinavir when taken in conjunction with Saint John's wort. This preliminary study was performed on eight healthy volunteers who were screened to ensure they were not taking Saint John's wort or any other medication that may affect serum levels of indinavir. Subjects were brought to steady-state plasma levels of indinavir via three doses spaced eight hours apart. On the following day, blood samples were obtained both prior to a fourth administration of the drug, and serially out to five hours following administration to assay plasma levels. On the third day, patients began receiving the standard recommended antidepressant dosage of 300 milligrams of Saint John's wort standardized to 0.3% hypericin (an active ingredient in Saint John's wort) three times daily. After fourteen days of administering the Saint John's wort, the course of indinavir was repeated and plasma levels assayed exactly as before (8).

The results of this study indicate that co-administration of Saint John's wort reduced the plasma concentration of indinavir at eight hours following administration from a mean of 0.493 mg/ml for indinavir alone to 0.048 mg/ml with Saint John's wort ($p=0.027$). The range of reduction was from 49 to 99%. Similar statistically significant decreases were observed in other pharmacological parameters (maximum plasma concentration and total plasma levels for the first five hours). This reduction in plasma indinavir levels is enough to defeat the therapeutic effect of the drug. An even greater concern is that the presence of such low levels of an anti-retroviral drug, too weak to fight the full viral load, could induce drug-resistant viral strains in the patient (8).

It must be noted that there are severe limitations to this study. Only eight subjects were tested and all were healthy (i.e., not HIV infected). Additionally, six of the eight were male and seven of the eight were Caucasian (the other was Hispanic). It is therefore difficult to extrapolate the data to the population as a whole. Of course, one cannot rule out the possibility that the reduced bioavailability of indinavir was due to some contaminant in the hypericum preparation rather than the hypericum itself. Regardless, these preliminary data are alarming and certainly merit further investigation. Given the difficulty of treating HIV infection, as well as the severe consequences of treatment failure, it would be prudent to prohibit the use of Saint John's wort by patients taking indinavir or similar retroviral protease inhibitors.

As an interesting corollary to this story, hypericin has surprisingly been shown to have anti-retroviral effects and this resulted in a Phase I trial of hypericin as a treatment for HIV infection (11). In the published study, the authors note that many HIV-infected patients are taking Saint John's wort (quite worrisome given the effects described above). As it turns out, the trial failed. Severe cutaneous phototoxicity was observed in nearly half of the volunteers and no therapeutic effect was noted.

Heart transplant rejection

Published simultaneously with the article warning of the dangers of mixing Saint John's wort and indinavir, an independent study by Ruschitzka and colleagues documents two cases of heart transplant rejection temporally associated with the use of the hypericum (9). The mechanism appears to be similar, that is reduced bioavailability of a therapeutic prescription drug, although in this case it was plasma levels of the immunosuppressant drug cyclosporin that were affected. The two patients studied had gone 11 months and 20 months post-transplantation without any signs of rejection, both being maintained on a triple immunosuppressive regimen of cyclosporin, azathioprine, and corticosteroids. In each instance, the patient began taking Saint John's wort three weeks prior to presenting with acute heart transplant rejection. Laboratory tests confirmed that plasma levels of cyclosporin had been reduced below the therapeutic level in both patients. The rejection was treated by increasing the immunosuppressive therapy for ten days following presentation and discontinuing the use of Saint John's wort. No further episodes of rejection were noted.

As is the case with the study of indinavir, there are problems associated with this report. The evidence presented is anecdotal, and the association is based largely on a temporal relationship between hypericum use and transplant rejection. Furthermore, while the authors state "no further episodes of rejection

occurred," they do not mention for how long after rejection the patients have been followed. To their credit, however, they do document reduced plasma levels of cyclosporin, which supports one potential mechanism for the purported herb-drug interaction (increased cytochrome P-450 activity). Coupled with the very tight temporal relationship, the implication is difficult to ignore.

More data is required, to be certain. It may be that only a very small percentage of the population is at risk for this interaction, perhaps owing to some congenital alteration of cytochrome P-450 activity. Maybe it was even just some contaminated product that hit the market. Nevertheless, because the risk of transplant rejection outweighs the potential benefits of Saint John's wort administration, and it would be wise to avoid using this supplement in conjunction with cyclosporin until more is known.

Conclusion

The great increase in usage of dietary supplements such as Saint John's wort has not been mirrored by a great increase in knowledge about these products. While early studies indicated that Saint John's wort is safe with a more preferable side effect profile than commonly prescribed antidepressants, new data is emerging that clouds these perceptions. The pharmacology of hypericum remains largely a mystery and there is not much more to go on than anecdotal reports and clinical observations. When more data become available and the pharmacological properties of hypericum are better classified, it will be possible to make a more informed judgment regarding safety. In the meantime, it would be prudent to exercise caution.

Skeptics may argue that a few adverse reports are insignificant given the great number of people currently using Saint John's wort, and perhaps time will prove them correct. However, alternative explanations for the small number of complications that have been published include underreporting, small subsets of the population who are sensitive to hypericum, or confounding dietary factors that are working synergistically to bring about the observed effects. Until we know more, why take the chance? There is evidence for possible complications in the treatment of HIV infection and organ transplantation, situations where the risks certainly outweigh the benefits of Saint John's wort usage (8,9).

The bottom line is that there is some evidence of potential danger when Saint John's wort is used concurrently with certain prescription drugs. Therefore, doctors have a responsibility to their patients to inquire about the use of herbal supplements, particularly those taking digoxin, cyclosporin, theophylline, indinavir, or any other drugs whose bioavailability may be affected by hypericum induced changes in the P-450 cytochrome system. If these patients feel as though they need Saint John's wort to help treat mild to moderate depression, physicians could explain the situation and, if indicated, supply a prescription antidepressant with a better understood pharmacological profile instead. Indeed, we are fortunate that such alternatives are available rather than Saint John's wort being an irreplaceable and medically necessary therapeutic.

The current popularity of Saint John's wort as an herbal remedy for depression coupled with recent reports of harmful drug interactions should ensure that it will be studied increasingly in the coming years. As more is learned about the pharmacology of hypericum, the adverse effects that have been reported will become easier to understand. But until that day when we can better explain the drug interactions, and perhaps even identify which patients are most likely to experience problems, it is prudent to monitor patient usage and restrict if necessary.

REFERENCES

1. Deltito J, Beyer D. The scientific, quasi-scientific and popular literature on the use of St. John's wort in the treatment of depression. *Journal of Affective Disorders*. 1998;51:345-51.
2. Wagner PJ et al. Taking the edge off: why patients choose St. John's wort. *Journal of Family Practice*. 1999;48:615-9.
3. Ernst E, Rand JI, Barnes J, Stevinson C. Adverse effects profile of the herbal antidepressant St. John's wort (*Hypericum perforatum* L.). *European Journal of Clinical Pharmacology*. 1998;54:589-594.

4. Eisenberg DB, et al. Trends in alternative medicine use in the United States. *Journal of the American Medical Association*. 1998;280:1569-75.
5. Cupp MJ. Herbal remedies: adverse effects and drug interactions. *American Family Physician*. 1999;59:1239-45.
6. Ernst E. Second thoughts about the safety of St. John's wort. *The Lancet*. 1999;354:2014-5.
7. Johne A, et al. Pharmacokinetic interaction of digoxin with an herbal extract from Saint John's wort (*Hypericum perforatum*). *Clinical Pharmacology and Therapeutics*. 1999;66:338-45. (abstract).
8. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St. John's wort. *The Lancet*. 2000;355:547-8.
9. Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. *The Lancet*. 2000;355:548-9.
10. Markowitz JS, DeVane CL, Boulton DW, Carson SW, Nahas Z, Risch SC. Effect of St. John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. *Life Science*. 2000;66:PL133-9.
11. Gulick RM, et al. Phase I studies of hypericin, the active compound in St. John's wort, as an antiretroviral agent in HIV-infected adults. *AIDS Clinical Trials Group Protocols 150 and 258*. *Annals of Internal Medicine*. 1999;130:510-4.