

NATURAL MEDICINES NEWSLETTER

Your source for unbiased, peer-reviewed answers to important patient care questions.

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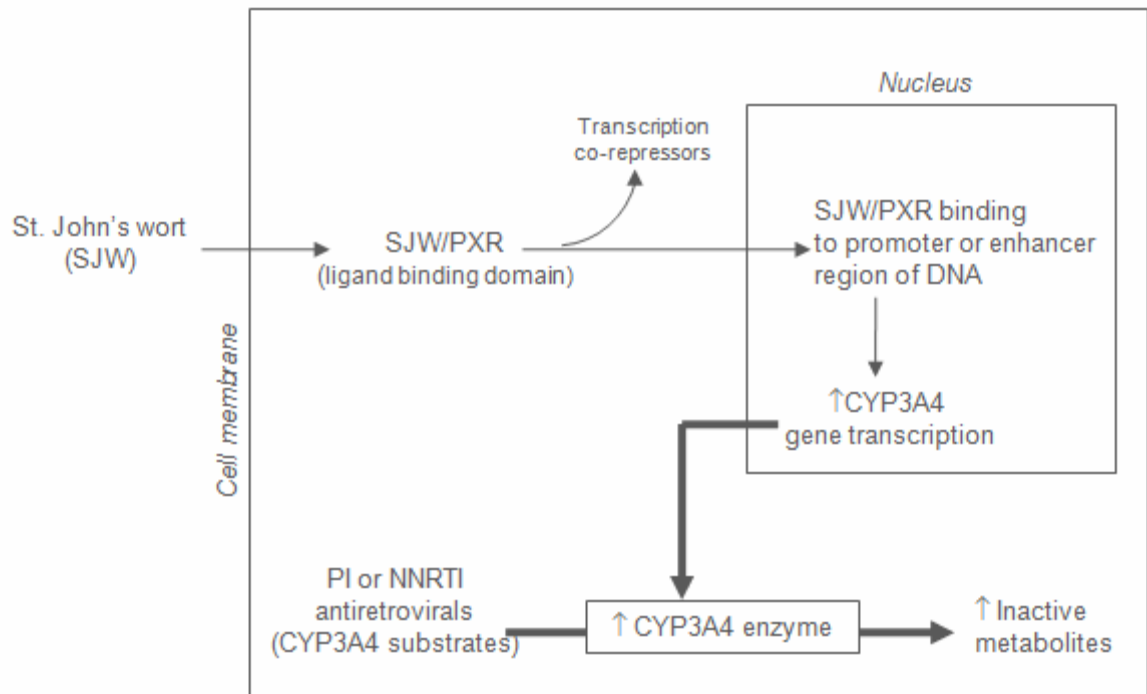
[Take CE](#)

Question: How does St. John's wort (*Hypericum perforatum L.*) decrease drug concentrations of antiretroviral medications thereby causing a loss of viral control in HIV patients?

Answer: St. John's wort (*Hypericum perforatum L.*) has been used for centuries to treat a number of common ailments (such as neuralgia, sleep disorders, wound healing, and hemorrhoids), but it is best known for its use in the treatment of mild to moderate depression.¹ Its use in clinical practice is very common in Germany and other areas throughout Europe and its use in the United States is increasing.² St. John's wort is an herb that is derived from the tops of the flowering parts of *Hypericum perforatum L.* and is known to have several active ingredients which include cyclopseudohypericin, hypericin, hyperforin, isohypericin, protohypericin, pseudohypericin and several other flavonoids.² The mechanisms of action for the above indications will be released in future newsletter issues.

Due to the life changing effects of being diagnosed and living with HIV infection, it is not uncommon for this patient population to experience depression, anxiety and related conditions. Due to a lack of medical care, insurance, social support or other reasons, many patients seek out natural remedies to treat themselves for these conditions. The problem arises when St. John's wort is taken by HIV patients who are also taking either protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based highly active antiretroviral therapy (HAART).³⁻⁶ Why is this combination a problem? Unfortunately, St. John's wort is known to reduce the concentrations of both PI's and NNRTI's, thereby resulting in a loss of viral control. In fact, one pharmacokinetic study showed that St. John's wort caused a 57% reduction in the mean area under the curve and an 82% reduction in indinavir (a PI) concentrations.⁵ These reductions are significant enough to induce the development of HIV resistance and/or the loss of viral control. So, what is the mechanism by which St. John's wort does this and why do I need to consider this as a clinician?

First, it is important to recognize that many antiretrovirals (HIV medications such as PIs and NNRTIs) are known substrates for the cytochrome P450 (CYP450) enzyme system for their metabolism and elimination from the body.³ Therefore, anything that affects CYP3A4 in particular, can impact drug concentrations of these antiretrovirals in the body. Second, St. John's wort is a substrate for the activation of the pregnane X receptor (PXR), which is a well known nuclear receptor found in the cytoplasm of various cells, including liver and gastrointestinal cells.⁷ The PXR is important because it is one of the transcription factors known to influence gene expression of CYP3A4 within the nucleus of hepatic and intestinal cells.⁸ So, any substrate that activates the PXR will increase the gene expression of CYP3A4, thus making more CYP3A4 enzyme available to metabolize more medications. This ultimately, results in an increased clearance of the known substrates of CYP3A4, such as PIs and NNRTIs medications. So how does St. John's wort actually do this?



The Details for Those That Want Them:

The ingredient, hyperforin, found in St. John's wort is a substrate, or activator, of PXR. As mentioned before, PXR is a nuclear receptor found in the cytoplasm of cells. It has 3 major domains that influence its function and level of activity on gene expression. The first domain, (activation function 1 (AF-1) domain) located at the amino terminus, is where recognition of other transcription factors and/or co-activators cause ligand-independent activation. The second domain (DNA-binding domain) is the part that directly binds to DNA to modulate gene transcription. The third domain (ligand-binding domain) on PXR is where substrates, like drugs, bind to "activate" the transcription of more genes. So, as St John's wort passes through the cell membrane, by diffusion or transport, it will bind to the ligand-binding domain of PXR in the cytoplasm. This causes a dissociation of the histone deacetylase-containing complex (transcriptions co-repressors) so that PXR can then enter the nucleus. Once in the nucleus of the cell, the ligand-receptor complex either recruits co-activators to form a homodimer or heterodimer with the retinoid X receptor (RXR), where it can now bind to response elements in the promoter and enhancer regions of the target gene. Once this occurs, gene transcription for CYP3A4 is turned on. The more CYP3A4 transcribed, the greater the ability to metabolize medications known to be a substrate for CYP3A4, accelerating their clearance from the body. While not the focus of this newsletter, it is also important to know that the PXR, and this entire process, can each be influenced by genetic polymorphisms causing the full impact of this drug interaction to vary from patient to patient (see future Pharmacogenetics Newsletter issue for more information).

Conclusion

In conclusion, the concern for this herb-drug interaction was so significant for this patient population that the FDA's Center for Drug Evaluation and Research put out a Public Health Advisory warning patients not to take St. John's wort with their antiretrovirals.⁶ If an HIV patient on HAART requires treatment for depression, it would be prudent to use an antidepressant without enzyme inducing properties.

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Take Home Points:

- St. John's wort (*Hypericum perforatum L.*) has been used for centuries to treat a number of ailments, including depression, which can be common in HIV infected patients.
- St. John's wort can significantly reduce the drug concentrations of both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), thereby resulting in the loss of viral control and/or the development of viral resistance.

- It does this be increasing the gene expression for the drug metabolizing enzyme CYP3A4, which is known to be used by PIs and NNRTIs for their metabolism and elimination from the body.
- The significance of this herb-drug interaction was so important that the FDA Center for Drug Information and Research put out a Public Health Advisory warning patients not to take St. John's wort if they are taking PI or NNRTI based HAART.

Considerations for Clinicians Based on Setting:

Outpatient:

If patients are seeking the use of St. John's wort, it is most likely to occur in the outpatient setting. It is important to investigate the patient's use of natural or herbal medicines since these patients may be self-treating and/or not consider St. John's wort to be a medication. This is especially important in an HIV infected patient with unexpected changes in viral control and reported adherence to all antiretrovirals.

Inpatient:

Given that St. John's wort can result in the loss of HIV viral control and a possible increased risk for opportunistic infections, it would be prudent to keep such drug interactions in the differential diagnosis, should a patient be admitted to the hospital for acute treatment and workup for infection. In addition, many institutions now require clinicians to document the use of any natural medicines as part of the admission assessment. Knowing this could impact discharge planning and counseling especially if HAART is initiated in the hospital.

Important Counseling Bullet Point(s):

- It is important to stress that the patient communicate with all of his or her healthcare providers about any new medications (synthetic, natural, or herbal) that are started by either themselves or other providers as soon as possible because of the number of known drug interactions with antiretrovirals. In particular, they should not take drugs or natural products, like St. John's wort, due to an increased risk of viral resistance and a loss of viral control.

Medical/Legal Consideration(s):

- There were no cases identified in the 2008 edition of LexisNexis' Drugs in Litigation regarding the nature of drug interaction of efavirenz, nevirapine, indinavir, or saquinavir with St. John's wort.⁹ Regardless, given that the problem associated with the coadministration of St. John's wort and various antiretroviral medications for the treatment of HIV infection is documented (and reported publically by the FDA as well as being listed specifically in product labeling for many of the antiretrovirals), and given that other antidepressant drugs are available with less potential to interact with antiretroviral therapy, it is conceivable that an adverse event-related use of the combination of St. John's wort and a PI or NNRTI might lead to legal action. For prescribers, it is important to note that the warning regarding the St. John's wort and PI or NNRTI interaction applies to ALL available PIs and NNRTI (until further evidence would suggest otherwise). For pharmacists, it is important to ask about and verify other medications a patient may be taking before selling or recommending any product containing St. John's wort (*Hypericum perforatum L.*)

Test Questions for CE:

St. John's wort is a natural medicine that is commonly used to treat which of the following conditions?

- Asthma
- Depression
- Pneumonia
- Cancer

St. John's wort is known to increase the activity of which CYP450 enzyme?

- 1A2
- 2C9
- 2D6
- 3A4

Which class of antiretrovirals used in the treatment of HIV infection can be negatively affected by the coadministration of St. John's wort?

- a. Beta lactams
- b. Fusion inhibitors
- c. Protease inhibitors
- d. None of the above

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