Title
St. John's Wort: What You Don't Know Could Hurt You.

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Introduction

St. John's Wort (hypericum perforatum) has been in use in Europe for over 2,000 years as a remedy for multiple ailments, including depression, bacterial infection, insomnia, and loss of libido (1). Recent evidence suggests that one component of the plant does appear to function as an antibiotic, while another element promotes the nocturnal production of melatonin (1,2,3). However, SJW is most extensively used as an antidepressant, in the form of an over-the-counter herbal remedy in North America, and as a prescription medication in Germany, indicated for anxiety, sleep disorders, and depression (SJW is, in fact, the most prescribed antidepressant in Germany) (3). Two recent randomized control trials conducted in Germany reported equal efficacy between SJW and Fluoxetine (Prozac), with fewer adverse effects identified with SJW use (4,5). And in the United States, a 1997 article published in The New York Times is thought to be primarily responsible for SJW's now widespread popularity as an over-the-counter cure for mild to moderate depression and/or mild anxiety (1). the U.S. revenue generated by the sale of SJW was estimated at $200 million for 1998 (6).

Given the popularity of SJW as a self-medicated answer to depression, the elucidation of any adverse effects or drug interactions is a current concern of the scientific and medical community. However, this is a rather daunting task, considering the high variability connected with SJW. For example, there exist 300 species of the genus hypericum; while SJW is typically a member of the specie perforatum, it can contain other species (1). Other variables that can significantly affect the biological activity of this herbal supplement include the time of harvest, the part of the plant that is used, the drying method employed, the means of storage, and the process of extracting the active ingredients (1). Additionally, to date, all randomized clinical trials have examined only the short-term affects of SJW compared to placebos or other prescribed anti-depressants; therefore, there is no current data on the long-term affects of the regular use of SJW (6,7). It is interesting that only such relatively short trials were conducted despite the commonly-accepted knowledge that SJW, like most other prescription medications for depression, exhibit a delayed therapeutic onset of several weeks (1). Since the Dietary Supplements Health and Education Act of 1994 deregulated the herbal supplement industry - placing herbal remedies in the same category as food - it is difficult to identify who is taking SJW, and precisely what constituents are to be found in a bottle of SJW (1,8). Most studies that considered herbal-induced interactions have failed to establish positive correlations with SJW, because these studies did not exclude the possible effects of contaminants (9). Some of the adverse effects and drug interactions seen could be caused by impurities present, or by the high degree of variability from one batch of SJW to the next (10,11). However, several more recent studies have obtained purified extracts of the chemical components of SJW - such as hypericin - and have shown in vitro the affects these components have on the metabolism of certain drugs (12,13).

The basic pharmacological mechanisms of action of SJW have yet to be confirmed. In fact, it is still debated exactly which chemical component of SJW functions as the antidepressant. Some studies have implicated hypericin (a naphthodianthrone) as the antidepressant component of SJW, while others suggest it is hyperforin (an

acylphloroglucinol). An additional SJW extract, s-adenosylmethione (SAM-e), has also been shown to relieve some types of depressions (1,8,11,13). Does SJW, through hypericin, function as a monoamine oxidase inhibitor (an enzyme that metabolizes monoamines in the presynaptic nerve terminal), or does SJW, through hyperforin, act as an inhibitor of the re-uptake transporter for monoamines? (6,10) Or does SJW work via both these mechanisms? Still other possibilities have been proposed. For example, SJW has also been shown to be an agonist for ?-aminobutyric acid (GABA) receptors (main inhibitory neurotransmitter of the (14). which might account for SJW's use as an anti-anxiety medication, considering that benzodiazepines (such as Valium, the most commonly prescribed anti-anxiety drug) are also GABA receptor agonists.

Despite all the uncertainty surrounding the nature and efficacy of SJW, recent research has brought to light the potential health risks to consumers of this herbal supplement. The Food and Drug Administration issued a warning in February 2001 about the possibility of SJW decreasing the effectiveness of numerous prescription drugs; recent reports show that the concomitant use of SJW lowers the plasma concentrations of some drugs (15). Hence, the purpose of this paper is to provide a systematic review of medications currently identified as having interactions with SJW, to discuss the two mechanisms currently implicated for these interactions, and to speculate on the possible impact such information will have upon the regulation of SJW.

Potential Mechanisms of SJW Associated with Drug Interactions

There are currently two mechanisms of action of SJW that have been implicated in reducing the efficacy of other prescription medications. The first mechanism is the activation of the human cytochrome P450 (CPY) enzymes, a large family of enzymes that metabolize many medications (6,12,16). More specifically, a study by Roby et al. showed a doubling of the activity of the CYP3A4 enzyme that is known to be involved in the metabolism of many common drugs (17). Such a high rate of metabolism can greatly reduce the efficacy of these drugs. Additionally, a sudden withdrawal of SJW could potentially induce toxicity from the resulting increase in the blood levels of a particular drug, caused by the body having lowered its inherent metabolic rate during SJW use (6,16). A recent study by Scott Obach actually suggests the reverse scenario, finding that hyperforin instead inhibits a few of the cytochrome P450 enzymes in an invitro study (13). One could therefore reasonably infer that individuals might experience toxic interactions between their medications and SJW. (This study did utilize doses of hyperforin that were far above what would be found in the blood system from a standardized dosage (900 mg) of SJW (2). Another study demonstrated that hyperforin activates the Steroid X Receptor (SXR) responsible for turning on the gene expression of the cytochrome P450 gene (12). The findings of this study support many current reports of drug interactions with SJW; these reports indicate that, when taken simultaneously with SJW, there is a reduction of the efficacy of drugs known to be active in a pre-metabolic state. (It should be noted here that many foods have been shown to induce cytochrome P450 enzymes, such as broccoli, cabbage, brussel sprouts, and charcoal-grilled beef (6).

The second potential mechanism of SJW that is associated with drug interactions is the induction of the drug transporter P-glycoprotein. This transporter is active in the intestinal absorption of many drugs, which leads to their excretion (6). The flavonoid component of SJW is thought to be responsible for the increased activation of this (6). Grapefruit juice has been shown to be an inducer of the P-glycoprotein transporter as well, and grapefruit juice and SJW are thought to have comparable levels of activation of the P-gylcoprotein transporter (6,18). The P-gylcoprotein transporter is found on cells throughout the body, and is known to actively pump drugs- such as HIV protease inhibitors - out of the cytoplasm of cells, thus reducing their bioavalibility. This ATP fueled transporter has been considered a major mechanism for drug resistance. It is believed to be normally involved in the transport and metabolism of lipids and steroids, and is thought to modulate the expression of the CYP3A enzyme (19). Therefore, SJW could be affecting the Cytochrome P450 enzymes indirectly through the P-glycoprotein transporter and/or through the steroid X receptor, or could be directly promoting its expression. In all likelihood, SJW works to varying degrees through all of these mechanisms.

Adverse Drug Interactions Associated with SJW

Through the two potential mechanisms described above, SJW has recently been shown to interact with a host of other drugs, ultimately leading to their reduction in the blood stream. A recent study produced by the National Institute of Health has shown a significant drug interaction between SJW and Indinavir, a protease inhibitor used to treat HIV: when SJW and Indinavir are taken concurrently, SJW greatly reduces blood plasma levels of the drug (20). Hence, people who are currently taking HIV medications are warned not to take SJW.

Anti-viral drugs, including Indinavir, are metabolized via the cytochrome P450 enzymes. Other drugs that use this metabolic pathway are also at risk of losing their optimal therapeutic affects by concomitant use of SJW. These include cyclosporin (an immunosuppressant taken by transplant patients), Warfarin (an anticoagulant), seizure medications (such as carbamzapine,) certain cancer medications (like taxol or tamoxifen indicated for breast cancer), and oral contraceptives (20,21). Several recent clinical cases support these claims. One study indicated rejection by two transplant patients that were taking SJW (6,21), while another reported break-through bleeding with loss of oral contraceptive effectiveness in eight women taking SJW (6). The latter study also reported that, since 1998, there are seven reported cases of a reduced anticoagulant effect of Warfarin, to a level that was considered significant (6). The activation of the P-glycoprotein transporter by SJW has been associated with the reduced efficacy of such drugs as digoxin, calcium channel blockers, and beta blockers, medications that are typically used to treat high blood pressure and heart disease. Activation of the P-glycoprotein causes an efflux of these drugs into the intestinal lumen (18). The drug Theophylline, a bronchodilator used for asthma, is also thought to be eliminated through this mechanism (16). Additionally, several of the drugs mentioned above that are metabolized by cytochrome P450 enzymes may also be partly removed by P-glycoprotein

(such as cyclosporine and some cancer medications), so SJW might reduce efficacy on two fronts (18).

In addition to the above interactions, preparations containing SJW can also interact with drugs that affect neurotransmitters in the brain. SJW has been shown to cause "Serotonin Syndrome" when taken concurrently with serotonin selective re-uptake inhibitors (SSRI), such as Fluoxetine (2,6). Such a condition is characterized by confusion, hyperthermia, headache, tremors, diaphoresis (profuse perspiration), gastrointestinal upset, and restlessness (2). This activity seems rather intuitive, as SJW has been shown to be a re-uptake inhibitor of monoamines: the concomitant use of SJW with SSRI would be the functional equivalent of a double dose of an anti-depressant. (It is indicated that the elderly are particularly susceptible to the "Serotonin Syndrome" (16). SJW may additionally interact with medications used to treat migraine, especially the triptans (16).

Discussion

There currently exists considerable room for the misidentification, adulteration, and contamination of SJW, despite reports such as that from the December 2000 issue of Consumer Reports that indicated that of 13 tested brands of SJW, all accurately labeled their bottles with the correct amount of dianthrones present per pill (8). The recommended antidepressant dose of SJW is 900 mg/day of the extract standardized to .3% of hypericin, the ingredient that has classically been considered the main active component of SJW (1,2). However, such a narrow active ingredient identification is problematic since, as stated above, other components of SJW (such as hyperforin) have been shown to have antidepressant mechanisms, in addition to other biological activities. Yet these other components are not regulated in the standardized dose of SJW, and this becomes problematic when physicians are treating patients for the numerous medical issues discussed above. One form of SJW might cause adverse drug interactions, while another might not. Furthermore, since there is variation in the potency of SJW based upon the time of year the plant is harvested, any one brand of SJW could potentially exhibit significant variation from one bottle to the (1). The level of concern regarding such issues is now sufficiently high that in 2000, Ireland reclassified SJW (as well as several other herbal remedies) as prescription only drugs (6).

Another issue regarding the unregulated nature of SJW is the fact that many individuals self-medicate themselves with SJW in an effort to treat depression and anxiety, without first seeking medical advice from their physicians (2,3). A recent study by Beckman, et al. surveyed 43 long- term users of SJW, and discovered that 74% of these individuals were taking SJW for depression without seeking any medical counsel, and only 14% said that they reported SJW use to their physician (2). This might be due to the fact that there still exists a considerable stigmatism associated with mental disorders such as depression. And, there is a general public perception that the "natural" nature of herbal supplements can only be beneficial, not harmful (1,2,14). So, with the use of SJW largely hidden from the medical community, it is quite difficult to obtain information on possible side effects and adverse reactions. But, more importantly, depression can be a very serious illness,

and it can be quite dangerous to have the condition misdiagnosed or inappropriately medicated (2,3).

Physicians should be aware of their patients taking SJW, not only because of the possibility of drug interactions, but also to help identify and better manage the underlying disease of depression. Physicians ought to inquire of their patients regarding the use of SJW, and do so in a non-judgmental manner, not discouraging its use unless other medical factors warrant it. A significant barrier to the research of herbal treatments has been the fact that such treatment cannot be patented, and therefore there is little financial incentive for the pharmaceutical industry to invest in such research (1). However, the N.I.H.'s National Center for Complementary and Alternative Medicine, now in its eighth year, is funding $36 million in research grants in the area of herbal remedies. The N.I.H. is also funding the opening of eleven new alternative medicine research centers, two of which are already operating in Los Angeles (1,8). In addition to the N.I.H.'s efforts, the FDA is currently working with herbal supplement manufacturers to ensure that the labeling of SJW is being revised to include the potential for herb-drug interactions (6). All of this should help fill the current knowledge void regarding the efficacy and adverse reactions associated with SJW, and may eventually lead to an entirely new spectrum of affordable and effective healthcare.

There appears to be a great deal of promise associated with SJW, a potent multi-purpose remedy that has been in use for many centuries. It would be a pity if the present controversy eventually hinders the public's access to SJW. Rather, a balance should be struck between ready availability, high-quality consumer information, and physician involvement. What is needed is more long-term and comprehensive research, better regulation of SJW's contents, labeling that clearly indicates SJW's possible drug interactions and its adverse affects, and a community of healthcare providers that are much more rigorous in inquiring about their patients' use of herbs. Once such controls are in place, and once a better understanding of SJW achieved, the public will have the opportunity to maximize the significant benefits of this ancient time-tested remedy while minimizing its very real hazards.

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