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Herbal Experts Say CSPI Petition for St. John's Wort Warning Inaccurate

In early November, the nonprofit Center for Science in the Public Interest (CSPI) urged the US Food and Drug Administration (FDA) to require detailed warning language on all St. John's wort products.¹ In its citizen [petition](#), CSPI asserts that "St. John's wort and many commonly prescribed drugs simply don't mix," but some experts on St. John's wort herb-drug interactions say the group's science is inadequate and inaccurate.

St. John's wort (SJW; *Hypericum perforatum*) is used to treat mild-to-moderate depression, anxiety, some sleep disorders, and other conditions.^{2,3} Hippocrates first recorded its properties in ancient Greece, and a great deal of modern clinical research on SJW has been conducted. In his chapter on SJW in the 2010 edition of the *Encyclopedia of Dietary Supplements*, FDA psychopharmacologist Jerry Cott, PhD, wrote that it is "one of the best known and well researched of the western herbals."³ The American Botanical Council's 2010 Herb Market Report documented SJW as being the ninth best-selling herbal dietary supplement in the US food, drug, and mass market channel—bringing in almost \$9 million in sales.⁴ (This statistic does not include additional sales of SJW in other channels of trade.)

It is well known that many SJW preparations can interact with some prescription drugs by reducing blood plasma levels, most likely by inducing the important drug-metabolizing enzyme (cytochrome P450 3A4 [CYP3A4] and drug efflux transporter P-glycoprotein [Pgp]).³ In its petition, CSPI urges FDA to require dietary supplement manufacturers to include the following information on all SJW dietary supplement product labels in a "prominent" black box: "CAUTION: St. John's wort interacts with some commonly used prescription and over-the-counter drugs. DO NOT USE this supplement if you are taking contraceptives, antidepressants, immunosuppressants (such as cyclosporine), anticoagulants, Digoxin, HIV medicine, blood thinners, seizure-control medicine, cancer medicine, or any other medications."¹ Black box warnings, as being suggested by CSPI, are usually reserved for the most potentially dangerous pharmaceutical drugs. The *Los Angeles Times* reported that a black box warning is "the strongest the FDA issues short of taking a drug off the market."⁵

The Hyperforin Issue

According to Francis Brinker, ND, a clinical assistant professor at the University of Arizona's College of Medicine, "[CSPI] made several serious errors in judgment" (e-mail, November 12-22, 2011). Dr. Brinker wrote the exhaustively researched *Herbal Contraindications and Drug Interactions plus Herbal Adjuncts with Medicines* (4th ed., 2010), which includes a detailed chapter on SJW drug interactions. He noted the organization's failure to distinguish between SJW products that are high in the component hyperforin and those that are low in hyperforin content. "I don't have a problem with reasonable and appropriate warning labels for high-hyperforin products used orally for greater than a week, but that needs to be specified."

Hyperforin is one of SJW's active constituents and is often referred to as the plant's major antidepressant ingredient, though the complete chemistry and mechanisms behind SJW antidepressant efficacy remain undetermined.^{3,6} Hyperforin has been found to be the main cause of the herb's impact on drug metabolism, absorption, and bioavailability. As stated by Australian and German researchers in their 2011 letter to the editor of *Pharmacological Research*, "St. John's wort extracts with a low hyperforin content (less than 1 mg daily) have not demonstrated any clinically relevant interactions so far."⁶ Additionally, the SJW formulation, Ze 117TM (manufactured by the Swiss company Max Zeller Söhne AG), contains virtually no hyperforin (<0.2%) and has been shown to pose no risk of herb-drug interactions, while also resulting in antidepressant efficacy.⁷

Chief Science Officer of the American Herbal Products Association (AHPA)—Steven Dentali, PhD—also pointed out CSPI's omission in a recent article in *Natural Products INSIDER*: "It should be kept in mind that formulations are available that don't affect drug metabolizing enzymes," Dr. Dentali was quoted as saying in the article. "Not all SJW extracts are equivalent, in other words."⁸

When asked about CSPI's failure to differentiate between low- and high-hyperforin SJW products, CSPI's Litigation Director Stephen Gardner told the American Botanical Council: "It's not clear whether low-hyperforin SJW products are sold in the US (drugstore.com doesn't list any that claims "low-hyperforin"); there's no official definition of low- and high-hyperforin; labels may not provide enough information; and it may be difficult for consumers to know for sure if the labeled amount of hyperforin is accurate" (e-mail, November 22, 2011).

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"The current American commercial availability of low-hyperforin products is beside the point," Dr. Brinker responded. "If there are none now, there may (and should and likely will) be tomorrow, simply because of this very issue, if it is addressed correctly."

Drug Interaction Evidence

The evidence behind SJW herb-drug interactions is significant and the clinical implications are real, but these are not quite as alarming as CSPI's petition would indicate. The *Encyclopedia of Dietary Supplements*—which has been extensively peer-reviewed by numerous experts in medicine—states: "Tolerability of SJW has been found to be very good with few adverse drug reactions reported. Extensive use in Germany has not resulted in reports of serious drug interactions or overdose toxicity."³ While concern is appropriate for medications (like cyclosporine and indinavir) that are acted upon by *both* CYP3A4 and Pgp systems, drugs that interact with only *one* of these "are not generally clinically relevant." Additionally, the significance of data from case reports is uncertain for various reasons.

Importantly, said Dr. Brinker, CSPI omitted information on internal versus external preparations and uses, as well as internal dosage. For example, in a 14-day study with 96 participants assessing the impact on Pgp for the cardiac drug digoxin from co-medication with 7 different oral SJW preparations (standardized extract, 2 powdered herb products, oil extract, tea, fresh juice, and Ze 117) at 10 different daily hyperforin doses, the latter 5 preparations providing less than 5.4 mg hyperforin per day had no significant effect.⁹

"Not only are the SJW preparations variable," said Brinker, "but so are the protocols and techniques for measuring effects of reduced drug bioavailability. To adequately assess the actual effects and risks requires in-depth analysis of each study's parameters. Each combination of different SJW products and/or a different drug and/or a different person is different. What I most take issue with in the CSPI label warning is that SJW (even those with standardized high-hyperforin content) does not affect all medications, nor does it affect the different listed ones equally. Thus, there is a need to acknowledge relative risk based on the specific drug."

While CSPI wrote in press release discussing its petition, "Women taking St. John's wort and oral contraceptives may have unplanned pregnancies," the evidence of associated unwanted pregnancies are, necessarily for humans, all case reports, of which the one published in detail documented the woman as taking an unusually high dose of SJW (daily doses up to 1700 mg).¹⁰ Additionally, a study of Ze 117 resulted in no unplanned pregnancies in women who were taking a low-dose oral contraceptive.⁶ Dr. Brinker continued, "Regarding this particular category of drug, the probability is unconfirmed. Birth control fails a lot of times for a lot of reasons."

In its petition, CSPI discusses the alleged risk of taking SJW while also taking prescription antidepressants. "St. John's wort can interfere with the action of various classes of anti-depressants and other drugs used in the treatment of psychiatric disorders," CSPI wrote.¹

"The vast majority of evidence is based on case reports," said Dr. Brinker of this allegation, "which by their nature are incomplete, inadequate, and/or unreliable for making definitive judgments." According to Dr. Cott's chapter on SJW in the *Encyclopedia of Dietary Supplements*, "the concern about interactions of SJW with other antidepressants are hypothetical," as the data fall in the category of within the normal variation.³

Quality of Sources

The CSPI petition relies heavily on information published by the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health—a seemingly authoritative source. But, the main document CSPI used is NCCAM's consumer publication, *Herbs at a Glance: a Quick Guide to Herbal Supplements*, which provides only a "basic understanding" and "is not designed to be a comprehensive source of information about these specific herbs."¹¹ Additionally, almost all of the references for the petition's SJW-related scientific information are at least 10 years old.¹ The only one with a more recent date—2009—is a review of previous research and case reports.

CSPI also cited an article by former FDA director Jane Henney, MD, published in 2000 in the *Journal of the American Medicinal Association (JAMA)*.¹ CSPI wrote that in this article, Dr. Henney "warned that 'health care providers should alert patients about these potential drug interactions' because St. John's wort interacts with many drugs that are used to treat heart disease, depression, seizures, certain cancers, as well as drugs that prevent transplant rejection and pregnancy."

Noting that most of what Dr. Henney wrote in the article is true, Dr. Brinker said: "I don't know why [CSPI] goes all the way back to 2000 to get a statement on SJW that is a decade out-of-date, aside from claiming institutional authority."

In addition, a peer reviewer of this HerbalEGram article noted that the NCCAM and *JAMA* references are not reliable sources of scientific information on herbs due to poorly documented case reports and research, as well as "wild speculation."

Legal and Regulatory Implications

The legal grounds on which CSPI based its petition to FDA consist of the misbranding provisions of the Federal Food, Drug, and Cosmetic Act. CSPI wrote: "Under the Act, a food is 'misbranded' if its labeling is 'false or misleading in any particular.' Both Congress and FDA have clarified that labeling is misleading if it 'fails to reveal facts... material with respect to consequences which may result from the use of the article...' FDA has further clarified in its regulations that '[a]ffirmative disclosure of material facts... may be required' by regulation or court enforcement action."¹

In 2002—almost a decade ago—ABC's publication *HerbalGram* reported on the legal and regulatory environment surrounding "failure to warn" allegations upon manufacturers.¹² Author of the article, Paul D. Rubin, Esq.—a partner in the food and drug practice group of Patton Boggs LLP, in Washington DC—wrote that the decision to include a drug interaction warning on dietary supplement labeling depends upon a wide range of factors, including: "(1) the likelihood of a potential interaction; (2) the potential severity of a potential interaction; (3) whether the interaction is well known by the general population or scientific community; (4) whether drug product labeling already warns against ingestion of the herb or dietary supplement; and (5) the level of the herb present in the dietary supplement."

Rakesh Amin of the Chicago law firm Amin Talati, LLC, who is both an attorney and a pharmacist, agreed with CSPI that FDA has the authority to require warning labels on herbal dietary supplements—which, under federal law, are regulated as foods—though he noted that he is not aware of such labels existing for any other herbal dietary supplements (e-mail, November 29, 2011). AHPA's Dr. Dentali pointed out that some natural foods like grapefruit juice and leafy greens have significant interactions with some drugs, but are not required by FDA to feature warning labels. As noted by a peer reviewer of this article, many pharmaceutical drugs that are known to interact with natural substances like foods and herbs are required by federal drug regulations to feature warning statements within their informational leaflets.

Similarly, in the aforementioned *HerbalGram* article, Rubin also indicated that if prescription drug companies already include interaction warnings on their drug labels, requiring dietary supplements to include identical interaction warnings could be viewed in many cases as being "redundant, unnecessary, and contrary to industry custom." He continued, "Except in a few situations, such as iron-containing dietary supplements and foods and supplements containing psyllium, the FDA does not mandate the content or format of warnings that must be included on foods or dietary supplements." Rubin stressed that the decision to include herb-drug interaction warning labels on dietary supplements is a complex one that all dietary supplement manufacturers should consider carefully based upon a thorough evaluation of related scientific developments, industry custom, and legal advice.

A press release discussing the petition quotes CSPI's Gardner as saying, "Companies have taken a minimalist approach designed to protect themselves from litigation, rather than actually protecting consumers' health." Amin said this statement is not entirely accurate. "Some companies do provide specific material risks and some do use boilerplate warnings," he said. "A caution or warning statement asking consumers to consult with their doctor if they are taking any medication is sometimes preferred because [it] would provide an argument that an adequate warning was given. We don't think there is any correlation between boilerplate warnings and specific warnings in terms of liability."

Manufacturer Reactions

Since July of 2000, AHPA has recommended that its members include the following statement on their SJW product labels: "Notice: Do not use this product while taking any prescription drug(s) without the advice of your prescribing physician. Avoid excessive exposure to UV [ultraviolet] irradiation (e.g., sunlight; tanning) when using this product."¹³

"CSPI has not discovered any new information, but is only acknowledging what AHPA has known for many years with regard to the possibility for some St. John's wort ingredients to interact with certain drugs," said AHPA President Michael McGuffin in a press release. "But this information is already disclosed through the broad use in the herbal trade of AHPA's labeling policy for St. John's wort, and we do not agree that a black box warning—generally limited to only the most dangerous drugs—is warranted."¹⁴ AHPA's press release called the CSPI petition "redundant to established industry policy."

As noted in CSPI's petition, some SJW products currently available to American consumers do warn against herb-drug interactions, but some do not.¹ In a table appended to the petition, CSPI listed the warning information of 11 different commercial brands of SJW products available in the United States. Nine of these products feature some sort of precaution and/or herb-drug interaction language, most often by suggesting that customers consult with their physicians if taking any prescription medications.

The situation in Europe is somewhat different, with many countries regulating SJW products as drugs and requiring specific warning labeling.

Dr. Willmar Schwabe Pharmaceuticals, a leading German developer of plant-based medicines and other healthcare products, markets SJW products in several European countries. Dr. Cott wrote in the *Encyclopedia* that "SJW preparations have become increasingly popular in Germany where they are approved for use in the treatment of mild-to-moderate depression and have remained a first-line treatment for many years."³

According to Ulrich Mathes, PhD, head of International Regulatory and Scientific Affairs for Schwabe, most

EU countries require SJW products to be sold as drugs, while others allow them to also be sold as dietary supplements. "The dietary supplement products have no warning statements regarding interactions on their labels in contrast to the drug products," he said (e-mail, November 23, 2011). SJW products classified as drugs in the European Union must feature warning labels discussing possible drug interactions according to information published by the Herbal Medicinal Products Committee (HMPC) of the European Medicines Agency.¹⁵

In 1993, the Swiss herbal medicine manufacturer Zeller developed its over-the-counter, low-hyperforin SJW extract Ze 117 (brand name Remotiv®). Ze 117 contains less than 1% hyperforin, which corresponds to less than 5 mg hyperforin when taking a daily dosage of 500 mg extract. According to Catherine Zahner, PhD, medical director at Zeller, because Ze 117 was shown in clinical trials to have an improved safety margin concerning drug interactions, Switzerland's drug agency gave it a Class D designation, allowing it to be sold in drugstores and pharmacies (whereas it previously could only be sold in pharmacies as Class C). Remotiv, however, is not currently available in the United States. (Note: In Switzerland, as well as in Germany, there is a distinction between a pharmacy (where prescription drugs are sold) and a drugstore, where only nonprescription items are available.)

Despite its significantly decreased chance of producing drug interactions, Remotiv's informational package leaflet contains this "important information" statement: "St. John's wort preparations can influence the effect of many other drugs in a negative way. If you are already taking other medication, especially prescription drugs, you should take Remotiv® 250 only after consultation and approval by your doctor." The leaflet—which serves as a reference document available for patients—also discusses SJW's connection with photosensitivity and weakening the effect of medications. It states: "For preparations with a low hyperforin content such as Remotiv® 250, it has been shown that such changes in effect are unlikely over a limited treatment period. Even so, you are not recommended to take Remotiv® 250 if you are using the following medicines," and goes on to list 12 different medicines and medicine categories, including oral contraceptives, certain antidepressants, anti-retroviral agents, anti-blood-clotting agents, and certain anti-cancer agents.

"All SJW products in Switzerland carry such labels," said Zahner. "The same applies to [the rest of] Europe. The recently published HMPC monograph for St. John's wort indicates similar labeling for contraindication and interactions sections.

"We basically agree with [the CSPI] petition's content," Zahner continued. "However, we would like to emphasize the need for discussion about the interaction potential based more on the content of hyperforin in SJW products. Based on literature data, hyperforin is the most important constituent of SJW responsible for drug-drug-interactions. The content of hyperforin should, therefore, be restricted, as it is in Switzerland" (e-mail, November 25, 2011).

Conclusion

In response to ABC's inquiry on its intended response to CSPI's petition, FDA wrote that it has received the document and will give it "careful consideration" (S. Cianci, e-mail, November 30, 2011). Despite issues raised about alleged scientific inadequacies and inaccuracies—especially those concerning the hyperforin issue—CSPI told ABC that it does not plan to amend any part of its petition.

As Rubin noted in *HerbalGram* in 2002, "Even if an herbal ingredient is capable of interacting with a drug, it should be determined whether the ingredient could cause such an interaction at the level included within the food or dietary supplement. Many foods and dietary supplements contain very low levels of certain herbal ingredients, and assuming the background science supports the conclusion that interactions do not occur at such levels (taking into consideration daily consumption patterns), an interaction warning might not be necessary."¹² However, the issue is distinctively exceptional for relatively high-hyperforin SJW products, as the level of consumption of SJW extracts (usually 300 mg, 3 times per day) has been associated with several types of documented interactions.

"The main issue here is that the complete scientific database of human studies needs to be used, not ignored," said Dr. Brinker. "The CSPI petition asking for a warning for all SJW preparations equally for all drugs listed and for all medications in general is not a good application of pharmacological understanding. If they choose to ignore those studies and preparations that were negative for specific interactions, it is equivalent to others' ignoring the studies that were positive for interactions."

Dr. Brinker, continued, "The fact that CSPI states that this is the first herb for which they hope to require a (falsely exaggerated) warning label indicates that they must be held accountable for accuracy in this case so that it will be expected in future requests as well. If they are allowed to cherry-pick data now, they will do so again and again. The issue here is independent of current products on the market. A precedent is being set. The future is at stake."

—Lindsay Stafford

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