Complex Chemical Concoctions

James W. Jefferson, M.D.

We are all aware of the evils of misguided polypharmacy with the attendant risks of side effects, toxicity, drug interactions, and expense in the absence of an evidence base to support its use. Let us take this a step further and imagine that we are working with products that comprise numerous unknown chemicals of questionable purity in amounts of variable and inconsistent concentrations. Welcome to the world of herbal medicine.

Were you aware that the constituents of St. John's wort include phenylpropanes, flavonol glycosides, biflavones, proanthocyanidins, xanthones, phloroglucinols (including hyperforin), and naphthodianthrones (hypericin and pseudohypericin)[1] or that among the many chemicals in kava are yangonin, desmethoxyyangonin, dihydromethysticin, methysticin, kawain, and dihydrokawain?[2] Ergo, instant polypharmacy.

To top it all off, how much of what is within that single composite product often leaves much to be desired. For example, 8 commercial preparations of St. John's wort were analyzed for hyperforin, thought to be the ingredient most closely associated with antidepressant activity. The percentage of hyperforin ranged from 0.01 to 1.89, which translates to a 189-fold difference![3] Imagine if you wrote a prescription for olanzapine but could not be certain if it would contain 5 mg or 945 mg.

We can thank the U.S. Food and Drug Administration (FDA) and the pharmaceutical companies for their attentive and strict regulation of prescription medications. We can thank the American public, nutritional supplement purveyors, and Congress for the lax regulation of herbals. Believe it or not, the FDA was very much involved in the regulation of dietary supplements until Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994. Herbal products and other dietary supplements were, thereby, removed from close FDA scrutiny. Consequently, the FDA can no longer regulate an herbal product as it can a drug. There are no premarketing requirements to show efficacy and safety. The FDA can intervene if a marketed product is shown to be dangerous, but there is no requirement for reporting of adverse events.

In effect, Congress has handcuffed the FDA by placing the burden on the government to prove that a marketed product is unsafe.[4] Of course, these products are not allowed to be advertised for the diagnosis, treatment, cure, or prevention of disease, but they are marketed in ways that accomplish that by implication (e.g., for a healthy prostate; to promote leg vein health; to maintain proper bone and joint function; to induce relaxation, improve social interaction, and promote sleep).

As succinctly noted by Angell and Kassirer in referring to DSHEA, ". . . these products have flooded the market, subject only to the scruples of their manufacturers."[5(p840)] "Flooded" may well be an understatement, for Gibson and Taylor noted in 2005, "According to the FDA, there are more than 29,000 different dietary supplements available to consumers today."[6(p939)] Admittedly, many of these are rather benign vitamin and mineral preparations, but included at the other end of the spectrum are those "complex chemical concoctions" that can pose substantial risk to a generally unsuspecting public.

For example, because of a manufacturing error, a Chinese herbal weight-reducing pill contained *Aristolochia fangchi*, a nephrotoxin and carcinogen.[7] If we look into areas of interest to psychiatry, we find that *Ginkgo biloba*, a not very well established treatment for dementia[8] and sexual dysfunction[9] and an inhibitor of platelet activating factor, has been associated with a number of cases of bleeding into the brain and eye.[10,11] Kava, an herbal of controversial anxiolytic efficacy,[12,13] has been linked to hepatotoxicity, liver transplants, and deaths to the extent that it has been banned in many countries (but not in the United States).[14] St. John's wort, whose reputation as an antidepressant waxes and wanes from country to country and clinical trial to clinical trial,[15,16] was reported to cause severe phototoxicity in HIV-infected adults.[17]

On a much broader scale, St. John's wort's ability to induce cytochrome P450 (CYP) enzymes (particularly CYP3A4, but also 1A2, 2E1, and others) as well as the transmembrane efflux pump, P-glycoprotein, portends great potential for mischief.[18] Examples include induction of ethinyl estradiol metabolism resulting in breakthrough bleeding and reports of pregnancy in women taking oral contraceptives[19]; dramatic reduction in methadone (a CYP3A4 substrate) levels[20]; decrease in simvastatin levels of 50%[21]; marked reduction in blood cyclosporine levels that threatens transplant patients with organ rejection[22]; and so on and so forth.

To further complicate matters, the lack of standardization of contents adds additional chaos to efforts to understand an already complicated area. For example, in a study of 10 renal transplant patients, St. John's wort with high hyperforin content reduced cyclosporine area under the curve (AUC) by 52%, while St. John's wort with low hyperforin content caused no change at all.[23]

With so much known about the pharmacokinetic interactive effects of St. John's wort, it is somewhat surprising that so little is known about the effects of other herbal products. Valerian, an alleged hypnotic for which there are conflicting reports of efficacy,[24] was found in a study of 12 healthy volunteers to have no clinically meaningful effect on CYP1A2, 2D6, 2E1, and 3A4.[25] *Ginkgo biloba*, in small, in vivo studies in humans, induced CYP2C19 but had little effect on 1A2, 2D6, 2E1, and 3A4.[26,27] Two studies of kava in humans involving very small sample sizes found no effects on CYP2D6 and 3A4 but disagreed as to whether CYP1A2 and 2E1 were inhibited.[28,29] All in all, there is much to be learned about how herbal products affect the enzyme systems involved in drug metabolism.[30] Studies in animals and in vitro studies utilizing human liver microsomes often conflict with in vivo findings in human volunteers.

Given the rather limited pool of efficacy and safety information available for herbal products, what is one to do? On a national level, one can support the regulatory initiatives being promoted by the FDA to allow it to function to its fullest within the limitations of DSHEA. Beyond that, one can encourage even greater regulatory control over these herbal products that for all intents and purposes are currently being promoted for their medicinal value. On a more individual level, one can discourage the intermixing of herbal products and prescription drugs, although the rationale for doing so will often be merely the absence of information that assures safety of the mix. More research is clearly needed.

On the other hand, recall how much is known about that old nutritional standby, grapefruit juice. Because it is a rather potent inhibitor of CYP3A4, 1A2, 2A6, 2B6, P-glycoprotein, and organic anion-transporting polypeptide, it has the ability to interact in clinically meaningful ways with many of our proprietary medications.[31] For example, grapefruit juice in-

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creased the bioavailability of cyclosporine by 62%, more than doubled the bioavailability of felodipine, increased the bioavailability of lovastatin 15-fold, and increased buspirone AUC about 9-fold.[32] Of course, nothing may be absolutely safe, since there is recent evidence that orange juice decreases atenolol blood levels by close to 50%,[33] and pomegranate juice, in rats and human liver micromes, inhibits CYP3A4.[34]

While suggesting that the FDA regulate our juice intake would be folly, suggesting that we educate ourselves and our patients about what is known of the potential risks of even the most ordinary ingestibles makes very good sense.

Dr. Jefferson is Distinguished Senior Scientist at the Madison Institute of Medicine, and Clinical Professor of Psychiatry at the University of Wisconsin Medical School, Madison (e-mail: jjefferson@healthtechsys.com). He reports no financial or other relationship relevant to the subject of this column.

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