

# Dietary Supplements and Botanical Medicines: A Commonsense Approach



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## Introduction

**Dr Low Dog:** That was excellent, Dr Wallace. You provided a great lead-in, because I'm also going to discuss the FDA. However, I want to focus primarily on two areas that are growing in popularity: dietary supplements and my area of expertise, botanical medicines.

For some cultures in the United States, herbs never went out of style. They remained, especially in culturally intact communities. I am from New Mexico, where many people use herbal medicines, although they use them in the context of their own cultural background and history. We have done research in those groups and found that they learned about herbal medicines from their parents, their grandparents, their aunts and uncles; and that they use herbs such as chamomile, lavender, and spearmint—benign herbs that are quite safe.

My main concern today is not with these groups of people; instead, my concern is primarily directed toward the folks who do not have a culturally intact memory, if you will, for how to appropriately use herbs. They've read about it in a magazine or book, they've heard about it on the news, and, of course, many—like my mother, for example—think that if they read it, then it's true, especially if it's in *Prevention* magazine.

I will be covering just a couple of topics, including regulatory status; quality control issues; herb-drug interactions; our current state of science regarding several herbs; and the issue of selling these products in your office.

## The Saga of Regulatory Oversight

Starting around 1991, a government movement—led in part by Dr David Kessler of the FDA—attempted to regulate dietary supplements more strictly. Well, as you know, the American public does not like being told that they're not going to have access to things that they want. Driven in part by a lot of misinformation that instilled fear, people wrote letters to their representatives in Congress; and the only topic in the history of our country that prompted more letters from the public to the government was the Vietnam War. That was how upset the American public was about losing their potential right to freely buy herbs and vitamins! All of this led to enactment of the Dietary Supplement Health Education Act (DSHEA), which basically guaranteed Ameri-

cans access to dietary supplements. In my opinion, however, the legislation did little to address the issue of public safety; what it did was maintain that dietary supplements will be regulated as food under food regulations.

The problem with this step is that we accept a certain level of safety regarding food as long as it is prepared and handled correctly. *By regulating these substances as food, we took away the FDA's ability to demand safety data before these substances are released into the marketplace.* Because of this Act, manufacturers of products introduced into the marketplace after 1994 are not required to give the FDA any information about their safety. Now, as Dr Wallace stated, the FDA is asked only to prove that something is unsafe. That sounds easy, but it's not: Chasing the horse after it has already left the barn is actually quite difficult and very inefficient.

## Foods and Plants are Not Always Safe!

We are the only country in the world that has chosen to regulate botanicals and dietary supplements as food. Some herbs, such as garlic, oregano, and basil, are foods as well as spices; however, other plants—goldenseal root, poke root, and blood root, for example—are not foods: They were never consumed as foods but were used as medicine. These plants are pharmacologically active and really have no place in a "food" category. Categorizing dietary supplements as foods that do not require any safety data prior to release into the marketplace has led to problems such as encountered with combining ephedra and guarana for weight loss and potential liver toxicity associated with kava. In my opinion, these problems will continue until this issue has been addressed.

## What's Really in the Packet? Problems of Mislabeling and Underlabeling

Mislabeling and underlabeling are very real problems. I am currently the Chair for the United States Pharmacopoeia (USP) Dietary Supplements/Botanicals Information Expert Panel. The USP is a standard-setting body for drugs and is now also setting standards for dietary supplements. This situation is interesting because most entries in the old US pharmacopoeias from the 1850s and 1870s were botanicals. Why were pharmacopoeias

created in the first place, and what problems originally necessitated development of standards? Hundreds of years ago, our drugs were botanicals; but even then, consumers had to contend with problems such as adulteration, contamination, and substitution of cheaper herbs for more expensive herbs.

A number of products coming from Asia (especially products used in traditional Chinese medicine) have been noted to be contaminated or adulterated. A study in Taiwan<sup>1</sup> found that of 2609 traditional Chinese medicine products collected from the pharmacies of eight hospitals, 23.7% were adulterated with undeclared pharmaceutical medication; and more than half of the adulterated products contained two or more adulterants. The most common additives included nonsteroidal anti-inflammatory drugs (NSAIDs), diazepam, corticosteroid agents, and anticonvulsant agents. This problem is real. In addition, concern is growing about presence of toxic heavy metals (such as arsenic, lead, and mercury) in traditional Chinese medicines.<sup>2</sup>

Botanicals are not the only problem; other dietary supplements also have failed to meet their label claims. A University of California Los Angeles (UCLA) study<sup>3</sup> assessed 12 products that were said to contain androstenedione and concluded that only one of these products contained what it claimed on the label. One product had twice the amount of androstenedione, one product didn't contain any, and one product provided 10 mg per day of testosterone—a clinically significant amount, especially given that it was not declared on the label.<sup>3</sup> The point I want to make here is that, of 12 products, only one contained what it said it contained!

The other area of concern in the marketplace is the widespread use and advertisement for products containing ephedra and guarana. Now, tell me how much sense it makes to market to athletes a product that increases heart rate, raises blood pressure, and is labeled with instructions to take the product 30 minutes before heavy exercise! We should not be surprised when adverse events are reported.

In addition to problems with manufacturing, some botanicals contain naturally occurring toxic constituents. Aristolochic acid poisoning received a great deal of attention after a tragic accident occurred at a Belgian weight loss clinic that had ordered the relatively safe herb *Stephania tetandra* from an herbal supplier. Instead of this herb, the clinic received *Aristolochia fangchi*, a botanical which contains aristolochic acid, a known nephrotoxin.<sup>4</sup> Seventy women treated with this

substance at the clinic were later diagnosed with progressive interstitial fibrosis of the kidney; in 30 of these women, terminal renal failure developed.<sup>5</sup> The FDA has banned products containing aristolochic acid; however, a number can still be found on the shelves.

PC-SPES was a popular botanical product that had undergone clinical research indicating that the product may be effective for reducing prostate-specific antigen (PSA) levels both in androgen-dependent and in androgen-independent prostate cancer. Preliminary data were encouraging; however, questions of safety surfaced about men taking PC-SPES who had pulmonary embolism<sup>6</sup> and bleeding diathesis.<sup>7</sup> The California Department of Health tested several batches of the product and found that it contained warfarin. The FDA then removed the product from the market because of adulteration with a pharmaceutical agent. Unfortunately, more investigation indicates that products sold between 1996 and 1999 were adulterated with indomethacin, diethylstilbestrol, or both.<sup>8</sup>

The “bottom line” is that we have good reason to be cautious about the products available on our store shelves. You would have less of a problem if you lived in Europe, because these products are more tightly regulated there. In the United States, we do a good job of giving the public access to dietary supplements, but we have done little to ensure that what they're buying is actually what they think they are getting.



### Kava-Related Liver Damage

Kava is an herb with proven anxiolytic properties. This herb has been popular in the South Pacific as a mildly intoxicating beverage as well as a medicine. I always enjoyed it while traveling through the islands of Fiji and Samoa and found it useful for occasional neck and back pain, especially when traveling and not sleeping well. Kava is generally sold as a concentrated, standardized product, mostly from Germany.

In November 2000, German health authorities issued a warning alerting the scientific community that nine patients had been diagnosed with what seemed to be kava-related liver damage. The German authorities asked for feedback from the industry, requested manufacturers' safety data, and began networking with the other European drug-regulating agencies. By November 2001, 29 cases of possible kava-related hepatotoxicity were reported in Europe, and the FDA had received reports of as many as 62 adverse events associated with kava.

Germany has removed kava from both the over-the-counter and prescription markets; France, Switzerland, and Canada have followed. The United Kingdom and

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Ireland also will probably remove kava from the marketplace. The FDA is “investigating” the matter, and kava is still readily available in the United States; however, a number of lawsuits against the manufacturers of kava products are currently underway. Although people have argued that kava has been safely used for thousands of years, the substance was used in a very small, genetically isolated group of people who used a water-extracted preparation that was not concentrated to contain 70% kavalactones! Hepatotoxicity appears to be seen primarily when kava is taken in highly concentrated forms. In the United States, I will remind you, some adolescents use kava as an intoxicant at parties, sometimes taking as much as 20 times the recommended dose. People who take kava in concentrated form, take kava for a long period of time, combine kava with alcohol or acetaminophen, or choose more than one of these behaviors may just end up having liver failure.<sup>9</sup>

## Complexity of Botanicals, Attempts to Verify Quality

I want to point out that botanicals are complex and are therefore somewhat difficult to study. We do not have standardized, validated analytic methods for evaluating most of these plants, and developing USP standards is a long, tedious process. Although typical medicines contain one isolated chemical, plants contain hundreds of constituents in varying amounts. Constituents vary from plant to plant, depending on such factors as when the plant was harvested, how it was dried, and how much rain it received. Some active constituents in the plant may vary thirtyfold. However, although standards are difficult to determine, we are not excused from solving the quality control problem that currently exists in the United States.

I want to tell you about two initiatives currently being conducted in the United States to address quality control issues by developing quality verification programs. Existing in addition to the USP is another group, the National Sanitation Foundation (NSF), which certifies water filtration systems. If a company is willing to submit to a Good Manufacturing Practice (GMP) audit by having its manufacturing facility inspected and then having their products randomly tested four times a year, then the company may place a certification seal on the front of their product's label. This seal is not an endorsement of the efficacy of the product, but it does indicate that the bottle contains what is stated on the label. This certification will go a long way toward assuring American consumers that they are getting a quality product. For example, if one of the 20 ginkgo products on the market receives a certification seal for purity

and quality—meaning that it contains what it claims to contain and nothing else—certainly that will be a step forward for the consumer. But although I think it will help, the number of companies coming forward to participate in this certification process are few.

## Herb-Drug Interactions

Attending a talk yesterday, I listened to an acupuncturist describe the way in which practitioners learn the properties of an herb so that herb-drug interactions can be prevented. This description was his explanation for why we don't see many herb-drug interactions. Understanding the pharmacologic actions of an herb will certainly yield some insight into its potential “class” interactions; however, without appropriate pharmacodynamic and pharmacokinetic studies, we have no way to accurately predict which herbs might interact with a given drug. Nothing inherent in the known properties of St John's wort would have allowed us to predict that it interacts with two metabolic processes within the body: the P450 CYP3A4 system and P2 glycoprotein.<sup>10</sup>

Whether or not St John's wort interacts with oral contraceptives has not been explored until recently. A study presented in March 2002 found that more than half of the women receiving birth control pills (norethindrone) who then started taking St John's wort had a decrease in estrogen levels and had breakthrough bleeding.<sup>11</sup>

What about herbal interactions with warfarin? I tell medical residents: If a question on an exam ever asks which of the following drugs herb X interacts with and warfarin is listed as an option, check that one. In general, patients taking any drug with a narrow therapeutic window (eg, anticonvulsants, cardiac glycosides, warfarin) should be counseled to be cautious about using dietary supplements. My bottom line with patients in my own practice is that the more necessary that a drug is for life and the more narrow the therapeutic window, the fewer choices they have for exploring the use of dietary supplements and herbal medicines. We try to choose more noninvasive types of alternative therapy—including massage, meditation, biofeedback, and yoga—if that's what the patient is looking for. That way, at least the patients are not ingesting problematic substances and may improve their health without using substances that may alter the mechanism of response to necessary medications.

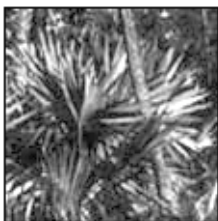
## The Danger of Observation Alone in Evaluating Efficacy

A growing body of research about plants supports what Dr Wallace said about the need to be very cautious about

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observation. For instance, I love reading the stories about digitalis. A book written in the 1860s or 1870s presented 32 diseases that should be treated with foxglove, a plant containing cardiac glycosides (digitalis). The list of diseases included typhoid, dysentery, and a range of other ailments. When viewed from a purely observational perspective, treating these ailments with foxglove made sense to early practitioners, as digitalis slows the heart rate. Because digitalis was observed to slow the rapid pulse that normally accompanies a high fever, digitalis was used commonly as a treatment for fever and infectious disease; however, it also killed people.

If you look back through history, you'll find that many of these plants in fact had some effect on the vast array of conditions we treated but that we had no explanation for these effects. There were probably a few ailments for which an herb was truly efficacious, but it is unlikely that a single herb could treat the hundreds of problems that were sometimes claimed.



### **Dietary Supplements Proven Effective: Saw Palmetto and Glucosamine, but not Chondroitin**

Because preparations of saw palmetto, glucosamine, or chondroitin cannot be patented, pharmaceutical companies have no incentive to produce them or to do the research needed to ensure their safety and efficacy. This lack of patent protection hinders research on botanicals and other dietary supplements in this country by preventing manufacturers from collecting a sufficient return on their research investment.

Despite this fact, some success stories have been reported. We are now able to state with some certainty that saw palmetto is more effective than placebo for treatment of mild benign prostatic hypertrophy (BPH). In addition to one meta-analysis<sup>12</sup> that was done, the Cochrane Review also has issued a favorable position.<sup>13</sup> Saw palmetto is indicated for patients who have mild symptoms, no sign of clinically significant obstruction, and normal creatinine level. I have to question why saw palmetto isn't available on more hospital formularies. It's not really a choice for many patients because a \$2.00 copayment is required for terazosin as compared with \$28.00 for saw palmetto at the local health food store. However, if I have an elderly, normotensive man with very mild symptoms of BPH and don't want to give him something that might make him orthostatic, recommending saw palmetto as initial therapy may be wiser.

The only good study that compared saw palmetto with

one of the alpha blockers was a three-week study—and, of course, you should know that saw palmetto doesn't work in three weeks. If you're looking for a rapid effect, you're not going to find it in saw palmetto: It really doesn't begin to take effect for six to eight weeks, and the effects are maximized at about three or four months—so a regimen of this substance must be started early. The USP has recognized the once-per-day (320 mg/day) and twice-per-day (160 mg twice daily) dose for saw palmetto.

Glucosamine is another dietary supplement that really prompts the question of whether it should be considered alternative or complementary medicine. I don't really like either term, because every treatment modality, dietary supplement, and botanical gets included in it. It doesn't matter if you're talking about homeopathy, massage, energy medicine, iridology, or botanicals; we just throw everything under this umbrella of "CAM." Sixteen trials on glucosamine now exist; however, all but one have shown benefit.<sup>14</sup> The Cochrane Review issued a positive recommendation, finding that glucosamine was more effective than placebo.<sup>14</sup> Actually, several studies showed that glucosamine was as effective as NSAIDs,<sup>14</sup> and the *Lancet* study<sup>15</sup> may have actually shown joint preservation by glucosamine in osteoarthritic patients. Patients obtained tremendous relief with glucosamine compared with placebo, and radiographic imaging showed greater joint preservation (in the knee) in patients who received glucosamine;<sup>15</sup> however, follow-up studies are needed to determine if glucosamine is actually our first disease-modifying agent for osteoarthritis. When I spoke recently to a group of rheumatologists, I asked how many of them would recommend glucosamine in an older patient who may not be a great candidate for treatment with NSAIDs. Most of them felt comfortable recommending glucosamine—a response very different from responses given three and four years ago. So, now I need to ask, why isn't glucosamine more available on a formulary? You still have to buy it from Sam's Club or Wal-Mart or the health food store, not with a copayment at the hospital pharmacy.

Although studies show that glucosamine is efficacious, studies on chondroitin are less impressive: The bioavailability of chondroitin taken orally is still unclear. Because chondroitin costs about twice as much as glucosamine and has unproven effectiveness, patients are probably better off in the long term to use glucosamine without chondroitin.

### **A Few Closing Comments**

In conclusion, I just want to comment again that I think this terminology of "complementary" and "alternative" is

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problematic. Medicine should really be about what works—the best choices that can be made from what we know at the time, and remedies and treatments that present the least harm. We need to be careful not to place something in the category of complementary and alternative and then add to it a lot of mysticism and pseudoscientific information and present it as something that it isn't. We do want to offer people choices and options for therapy—but only for options that are proven or that offer some reasonable hope of benefit.

I believe that further research will help us learn a lot more about the potential benefits and pitfalls of botanicals and dietary supplements. The Natural Medicines Comprehensive Database ([www.NaturalDatabase.com](http://www.NaturalDatabase.com)) is a good resource for health care professionals. People argue that it's a little conservative, but I think we should err on the side of conservatism, especially when we are not familiar with the subject.

All right, I think I'll stop there. I look forward to your questions during the panel question-and-answer session. Thank you. ❖

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## New Alternative Medicine Database — <http://pkc.kp.org/>

PKC (Permanente Knowledge Connection) has just added a new alternative medicine database called "Natural Standard" to its suite of products. To access this site, click on the URL: <http://pkc.kp.org/>, and you will find "Natural Standard" listed under the Drug, Lab & Formulary category.

Natural Standard is an international research collaboration that aggregates and synthesizes data on complementary and alternative therapies. Using a comprehensive methodology and reproducible grading scales, information is created that is evidence-based, consensus-based, and peer-reviewed, tapping into the collective expertise of a multidisciplinary Editorial Board. The aim of this collaboration is to provide objective, reliable information that aids clinicians, patients, and health care institutions to make more informed and safer therapeutic decisions.

For each therapy covered by Natural Standard, a research team systematically gathers scientific data and expert opinions. Validated rating scales are used to evaluate the quality of available evidence. Information is incorporated into comprehensive monographs which are designed to facilitate clinical decision making. All monographs undergo blinded editorial and peer review prior to inclusion in Natural Standard databases.

You may look up information either by the name of the herb or supplement or by using the "Condition Center," where you can focus your search on a specific disease or condition and find strong scientific evidence, unclear or conflicting scientific evidence, or traditional or theoretical uses that lack sufficient evidence. No password is needed for the site if you are connecting from an in-house terminal. For further questions or comments, please call Drug Information at 404-364-7076.