Current Issues Regarding Complementary and Alternative Medicine (CAM) in the United States

Part 2: Regulatory and Safety Concerns and Proposed Governmental Policy Changes with Respect to Dietary Supplements

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This is the second in a series of three articles about complementary and alternative medicine (CAM) in the U.S. Part 1, in the August issue of *P&T*, focused on the widespread use of CAM and dietary supplements and the need for better-informed health care professionals to provide patient counseling about these treatments. Part 3 will address health care facility policies and practices regarding CAM, dietary supplements, and integrative medicine.

Introduction

In the U.S., the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994 classified dietary supplements as foods, thereby preventing the FDA from regulating them as strictly as drugs with respect to their efficacy, safety, or marketing claims.[1–4] Although considered by many consumers to be safe because supplements are "natural," they can still be potentially harmful as a result of drug interactions, toxicities, contamination, and other dangers.[5–8] Because manufacturers are not required to submit clinical efficacy and safety data for their products to the FDA before obtaining marketing approval, the lack of this information presents a significant health risk to the public.[1,2,5,8,9]

The National Center for Complementary and Alternative Medicine (NCCAM) was established to sponsor research and disseminate scientific data regarding CAM therapies and dietary supplements to help fill this information gap.[7,10,11] Proposals have been made for governmental policy changes that will enhance the FDA's regulatory authority over dietary supplements, ensure that NCCAM-sponsored research meets quality standards comparable to those for the study of conventional medicines, and integrate those therapies found to be safe and effective into mainstream medicine as "standards of care."[7–9]

Regulation of CAM and Dietary Supplements

In the U.S., dietary supplements are not regulated nearly as strictly as drugs are, with respect to efficacy and safety testing or marketing claims.[1–4] This is because the DSHEA, enacted by Congress in 1994, classifies these products as foods, rather than as drugs, regardless of their historical uses.[4,12] Specifically, the DSHEA defines them as products "intended to supplement the diet" that contain vitamins, minerals, herbs, or other botanicals, amino acids or a "concentrate, metabolite, constituent, extract, or combinations of these ingredients."[8,12] The DSHEA eliminated the requirement that the FDA review efficacy and safety data for these products—providing that no claims are made to diagnose, treat, cure, or prevent disease.[1] This legislation also eased marketing restrictions for dietary supplements.[2,3]

According to the DSHEA, the regulatory classification of a natural product as either a drug or a dietary supplement is determined primarily by the intended use stated in its labeling.[2] Although the labeling of a supplement is not permitted to claim to treat a specific disease or condition, marketing statements that suggest an effect on the "structure or function of the body" are allowed.[2,8] For example, a dietary supplement containing *Echinacea* can be promoted as supporting immune health (as a function) but not as preventing or curing colds (treatment of a condition).[8] Similarly, the label for a glucosamine supplement can state that it improves joint function and mobility, but it cannot claim to relieve symptoms of osteoarthritis.[2]

Although such general claims are allowed by the DSHEA, there has been concern that they create confusion for consumers.[8] Nonetheless, the FDA's attempt to hold health claims for dietary supplements even to the same scientific standard required for conventional foods was rejected in *Pearson* v. *Shalala*.[8] The ruling in this court case stated that the FDA must allow such "qualified" health claims in labeling even if they are based on equivocal scientific evidence.[8] The FDA is therefore restricted from policing "truth-in-labeling" for dietary supplements, and manufacturers are permitted to use vague terms to suggest therapeutic effects for nonspecific health problems, which consumers tend to interpret inaccurately as efficacy.[4,18]

The DSHEA, however, does require that manufacturers submit a New Dietary Ingredient (NDI) application to the FDA for approval 75 days in advance of marketing a new product.[10] Products that met the definition of a dietary supplement and that existed before October 15, 1994, were allowed to remain on the market without submission of an NDI.[2] After the FDA receives an NDI, it reviews the proposed dietary supplement and its intended use and determines whether it is reasonably safe for marketing.[2]

Although the FDA reviews NDI applications for potential safety problems, under the DSHEA, manufacturers are not required to submit product efficacy or safety data with the NDI application.[2,8] Therefore, there is no burden on dietary supplement manufacturers to prove that their products are effective or safe.[13] Instead, the DSHEA places the burden on the FDA to prove that a dietary supplement product or ingredient

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is *unsafe*.[4] This is distinctly different from the FDA approval process for pharmaceuticals, in which manufacturers must demonstrate the safety and efficacy of a product before it is approved for sale in the U.S.[4] Because manufacturers of dietary supplements are not required to prove the safety of their products, unsafe products have made their way onto the market and fatal adverse reactions have been reported.[8] The DSHEA also allowed supplements that had previously been banned by the FDA because of safety concerns, such as sassafras tea and dehydroepiandrosterone (DHEA), to return to the U.S. market.[8,13]

National Center for Complementary and Alternative Medicine

An additional governmental office was founded in 1992 to evaluate and provide much needed scientific data on CAM and dietary supplements.[7,10,11] The Office for Unconventional Medical Practices, later renamed the Office of Alternative Medicine (OAM), was established by the National Institutes of Health (NIH) in response to an increasingly widespread use of CAM and dietary supplements, concern for public safety, and controversy over clinical trials evaluating CAM therapies.[7] The OAM was granted an initial budget of $2 million to be used to fund research on CAM and dietary supplements conducted by other NIH branches.[7] In 1998, the OAM was renamed the National Center for Complementary and Alternative Medicine (NCCAM), and because of the increasingly expanding scope of this office, its budget was increased from $50 million in 1999 to $121.4 million in 2007.[7,10]

The NCCAM defines CAM as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[10,14] It further classifies CAM therapies into five distinct categories:[11]

- alternative whole medical systems (homeopathic and naturopathic medicine, Chinese medicine, and Ayurveda)
- mind–body interventions (meditation, prayer, mental healing, art, music, and dance therapy)
- biologically based therapies (herbs, foods, vitamins, and other dietary supplements, including natural products such as shark cartilage)
- manipulative and body-based methods (chiropractic and osteopathic manipulation, massage)
- energy therapies (*qi gong*, Reiki, therapeutic touch, or electromagnetic exposures)

The mission of the NCCAM, as the federal government's lead agency on CAM, is to apply rigorous science to evaluate CAM practices, train CAM researchers, and inform health care professionals and the public about CAM-related research findings.[11] The agency's ultimate goal is to build an evidence base that facilitates the integration of CAM therapies that have proved to be efficacious and safe into mainstream medicine.[7] Although some CAM therapies and dietary supplements have been scientifically evaluated, important questions of safety and efficacy still remain for many others that have not yet been studied by the NCCAM or other investigators.[11]

Lack of Regulatory Oversight: Perception or Reality?

The increasingly widespread use of dietary supplements in the U.S. has been accompanied by growing concern about the limited ability of the government to regulate the sale of these products.[3] Surveys of pharmacists in the U.S. have consistently shown that they believe there is a lack of governmental oversight of these products, a perception that is likely a result of the regulatory shortfalls in the DSHEA.[13] A statement issued by the American Society of Health-System Pharmacists (ASHP)[8] similarly notes:

> ASHP recognizes that patients may choose to use legally available dietary supplements but believes that the decision to use substances that may be pharmacologically active should always be based on reliable information about their safety and efficacy. The current regulatory framework governing dietary supplements does not provide consumers or health care providers with sufficient information on safety and efficacy to make informed decisions.

However, there are conflicting opinions on this topic, as reflected by a statement issued by the House Committee on Government Reform in 2001, which declared that the FDA's alleged lack of regulatory authority over dietary supplements is frequently overstated.[10] The FDA does have power to regulate dietary supplements by:[10]

- enforcing good manufacturing practices (GMPs) with respect to the identity, potency, cleanliness, and stability of these products. However, it took the FDA 14 years after the DSHEA to finally establish the awaited GMPs in 2008.[6,7]
- referring parties responsible for the sale of toxic or unsanitary supplements for criminal action.
- obtaining injunctions that halt the sale of dietary supplements that make false claims.
- seizing products that present an unreasonable risk for illness and injury.
- suing companies that claim that their products cure or treat disease.
- halting the sale of a product class that is considered to pose imminent health hazards.
- blocking the marketing of products that the FDA does not consider to be generally recognized as safe (GRAS).

Despite the perception of insufficient governmental oversight, the FDA has had some impact in removing unsafe dietary supplements from the market.[3,5] In April 2004, the FDA succeeded in banning the sale of ephedra after reports of ephedra-related toxicity and deaths led to an increased review of its safety.[3] In 2009, the FDA also issued a warning against dietary supplements that were labeled as containing steroids or steroid alternatives and sold as body-building products because of a potential to cause serious adverse effects, including liver and kidney damage.[5]

Safety—Potential Drug Interactions, Toxicities, and Other Dangers

Although many consumers assume that CAM therapies and

dietary supplements are safe because they are often described as natural, they can cause harm both directly (through drug interactions) and indirectly (by delaying conventional care that has been proven to be effective).[5–7] Establishing the safety of dietary supplements has been complicated by a lack of systematically collected data on adverse reactions because the assessment of the efficacy and safety of these products has been largely anecdotal.[5,6,8,9] The FDA's MedWatch system does collect adverse-event reports on dietary supplements, drugs, vaccines, biologics, medical devices, and cosmetics, but it has been used only to a limited extent to report adverse events related to dietary supplements.[8] Despite the lack of data from controlled clinical studies regarding safety, case reports of drug interactions with dietary supplements are increasing.[8]

Some additional potential dangers that dietary supplements may present to public health include:[8]

- *toxicity:* Some products are inherently unsafe when orally ingested (e.g., chaparral, ephedra, comfrey, aristolochic acid, and colloidal silver).
- *adulterants:* There is a risk of contamination or adulteration of dietary supplements with harmful substances, including carcinogens, particularly in some imported products.
- *dosage variability:* Variations in the concentration of active ingredients in a dietary supplement may occur, particularly in some imported products.
- *risk to special populations:* Children, pregnant women, patients undergoing surgery, and patients with impaired organ or immunologic function are more susceptible to safety risks from dietary supplements, particularly because most of them have not been evaluated in these groups.
- *economic risks:* The amount of money Americans spend on dietary supplements ($14.8 billion in 2007[5]) represents an enormous health-related expenditure that is, for the most part, of unsubstantiated value.

Potential Drug Interactions with Dietary Supplements

Both pharmacokinetic and pharmacodynamic drug interactions are of significant clinical interest and concern.[2] Historically, people could ingest herbal and botanical remedies without having to consider society's current use of prescription and over-the-counter medications.[14] The contemporary overlap between dietary supplements and the use of conventional medicine increases the concern about unintended drug interactions.[1] Dietary supplements can affect a patient's response to conventional medications, anesthesia, surgery (by interfering with hemostasis or interacting with sedative or anesthetic agents), and healing.[6,9] In addition, dietary supplements can influence a patient's response to acute care, depending on the underlying pathology and the products or conventional therapies he or she is taking.[9] Potential problems from drug–supplement interactions are compounded by the fact that many patients don't tell their health care providers that they are using dietary supplements.[4,8,9,14]

The most prevalent drug–dietary supplement and drug–drug interactions involve cytochrome P450 (CYP 450) enzymes.[3] Dietary supplements that contain a combination of natural products compound this problem because each product can either inhibit or induce the CYP 450 system.[14] Evaluation of the interference of dietary supplements with CYP 450 and other metabolic enzymes is an example of the type of scientific research funded by the NCCAM.[14]

Most dietary supplement–drug interactions reported in the published literature involve St. John's wort, an herbal agent commonly used for the treatment of depression.[2,15] This herb is also used for the treatment of bronchitis, asthma, gastritis, gallbladder disease, gout, and rheumatoid arthritis.[15] Oral use of St. John's wort strongly induces CYP isoenzyme 3A, which is involved in the metabolism of approximately 50% of conventional medications.[2,15] Ingestion of the herb can reduce the plasma concentrations of protease inhibitors, cyclosporine, theophylline, and other common drugs (Table 1).[2,15] St. John's wort can also decrease prothrombin time when it is taken with warfarin (Coumadin, Bristol-Myers Squibb).[15] When taken with SSRI antidepressants, the herb can also lead to the sometimes fatal serotonin syndrome.[2,15] Agitation, hyperthermia, diaphoresis, tachycardia, and neuromuscular disturbances (including rigidity) characterize this syndrome, which occurs as the result of dangerously high levels of serotonin in the brain.[2,15] Although many of the reports of drug interactions with St. John's wort in the literature are anecdotal, they have been judged to be of sufficient clinical significance for the FDA to issue a public health advisory in 2000 against the concomitant use of this product with the antiviral agent indinavir (Crixivan, Merck) as well as with other medications that are

Table 1 **Effect of St. John's Wort on Reducing Plasma Levels of Common Drugs**

Medication	Enzyme/ Transporter	Decrease in Plasma Levels
Alprazolam	CYP 3A4	41%
Amitriptyline	CYP 2C19, 3A4	22%
Cyclosporin	CYP 3A4, Pgp	30%–60%
Digoxin	Pgp	25%
Fexofenadine	Pgp	20%–40%
Imatinib mesylate	CYP 3A4	30%
Indinavir	CYP 3A4	57%
Irinotecan	Pgp	42%
Methadone	CYP 3A4	47%
Oral contraceptives	CYP 3A4	13%–41%
Simvastatin	CYP 3A4	52%
Tacrolimus	CYP 3A4, Pgp	58%
Warfarin	CYP 2C9	Case reports

PgP = P-glycoprotein.

Adapted from Waldman SA, Terzic A. *Pharmacology and Therapeutics: Principles to Practice*. Philadelphia: Elsevier/WB Saunders; 2008:1536.[2]

metabolized by CYP 450.[2]

Some other possible interactions or toxicities to be alert for concern dietary supplements that:[16]

- are high-dose antioxidants, because of the concern that the efficacy of chemotherapy might rely on free radical production; however, this issue is controversial.
- have hormonal properties or can increase hormone levels in patients with breast cancer.
- have effects on coagulation, particularly in patients using warfarin.
- could either stimulate or depress the immune system; this could be a concern for some patients, such as those with multiple sclerosis who are taking immunosuppressants.
- are known to cause liver dysfunction or other safety problems (e.g., chaparral or pennyroyal oil).

Potential drug interactions that can occur with common dietary supplements, including garlic, *Gingko biloba*, ginseng, licorice, grapefruit juice, and traditional Chinese medicines, are shown in Table 2.[15]

Potential Dietary Supplement–Related Toxicities

Some dietary supplements are intrinsically toxic and therefore cause predictable adverse effects in exposed persons.[2] These products have inherent properties that can affect physiological functions, such as blood coagulation, glucose homeostasis, and immune response.[2] Fortunately, laboratory testing can rapidly identify herbal toxins and limit public exposure to harmful dietary supplement therapies.[2] However, because of the regulatory limitations imposed by the DSHEA, such adverse events may occur for months or years before laboratory testing or other appropriate action is taken to minimize the risks to consumers.[2] Of even more concern is the incidence of dietary supplement–related adverse events that are sporadic and unpredictable, such as idiosyncratic reactions in unknowingly susceptible people with underlying health problems or genetic variants in metabolizing enzymes or drug transporters.[2]

Adulteration of dietary supplements with toxic contaminants is also a serious safety issue.[13] A number of well-known toxins have been found in herbal preparations, sometimes resulting in significant human injury.[2] Progressive renal fibro-

Table 2 **Interactions Between Common Dietary Supplements and Pharmacological Agents**

Herb	Action	Adverse Effect	Drug Interaction
Chan Su	Anti-inflammatory Analgesic Cardiotonic	Eye irritation Teratogenesis	Increases unbound digoxin
Danshen (*Salvia* root)	Analgesic Tx of menorrhagia, postpartum bleeding, angina, and furunculosis		Increases INR when used with warfarin
Garlic	Antihypertensive Hypolipidemic Tx of bronchitis and gastritis	Platelet inhibition	Increases risk of bleeding with anticoagulants
Ginkgo biloba	Tx of memory loss, Alzheimer's disease, vertigo, tinnitus, and intermittent claudication	Increased bleeding	Spontaneous hyphema with aspirin Increases INR with warfarin Causes hypertension with thiazide Inhibits efficacy of insulin
Ginseng	Stress reducer Tx of anxiety, insomnia, impotency, loss of appetite	Nephrotoxicity	Causes resistance to loop diuretics Reduces effect of warfarin Causes headache, tremors with MAO inhibitors
Grapefruit juice			Increases plasma level of calcium-channel blockers
Licorice	Tx of bronchitis, cough, gastritis, constipation	Hypokalemia Edema Hypertension	Potentiates effect of corticosteroids
St. John's wort	Anti-inflammatory agent Tx of depression, anxiety		Decreases protease inhibitor activity Decreases cyclosporin and theophylline levels Decreases prothrombin time with warfarin Causes serotonin syndrome with SSRIs

INR = International Normalization Ratio; MAO = monoamine oxidase; SSRI = selective serotonin reuptake inhibitor; Tx = treatment.

From Saini A, et al. *P&T* 2001;26(12):616–621;[15] Lee DR. *J Am Board Fam Pract* 1998;11(2):140–144; and Ariga T, et al. Letter. *Lancet* 1981(8212): 150–151.

sis, associated with a Belgian herbal slimming formulation, was traced to the unfortunate misidentification and substitution of *Stephania tetranda* with *Aristolochia fangchi,* an herb that contains the cytotoxin aristolochic acid.[2] Contamination of kava preparations with the stem and aerial parts of the plant is also suspected of causing hepatotoxicity.[2]

Contamination may be an even more significant problem with imports from overseas, particularly China.[9] In at least one facility, a class of dietary supplements known as Asian patent medications has been banned.[4] These medications are thought to commonly contain adulterants such as heavy metals (including mercury, arsenic, and lead), pharmaceuticals (such as acetaminophen and diazepam), or substances that have been banned in the U.S. (such as phenylbutazone and phenformin).[4] Root extracts of *Aconitum* species (e.g., *Chuan-Wu* and *Cao-Wu*), have also been identified as adulterants in Chinese herbal medicines.[2] They can cause serious poisonings, including profound muscle weakness and cardiac dysrhythmias.[2]

Common uses and potential toxicities of some popular supplements are summarized in the following text and in Table 3. A listing of potential dietary supplement-induced toxicities according to body system is presented in Table 4 (see page 520).

Ephedra

Ephedra sinica contains six alkaloids that are sympathomimetic amines, with ephedrine and pseudoephedrine being the two primary constituents.[2] Ephedra was a popular ingredient in products marketed in the U.S. for weight loss until it was banned by the FDA in April 2004 because of reports of ephedra-related toxicity and death.[2] Reported adverse events included seizures, psychiatric disorders, cardiac dysrhythmias, myocardial infarction (MI), hemorrhagic and ischemic stroke, and sudden death.[2] The potential toxicity of these ephedra-containing products was further augmented by the sympathomimetic effects of caffeine-containing co-ingredients, including *Guaraná (Paullinia cupana,* Brazilian cocoa), *Yerba mate,* and kola nut.[2] Although ephedra has been banned as a dietary supplement in the U.S., it can still be obtained from traditional Chinese medicine practitioners as the herbal *ma huang*, which is used for the short-term treatment of wheezing and nasal congestion associated with asthma, allergies, and colds or flu.[2]

Kava

Kava is an herbal anxiolytic agent that has been traditionally used as a social and recreational beverage in South Pacific cultures.[2] Kava-related hepatitis is unknown in South Pacific nations, but more than 25 such cases have been reported in the U.S., Australia, and Europe, including eight involving liver-transplant recipients and several deaths.[2] These reported adverse events have caused several countries (including Germany, France, Switzerland, Canada, and Australia) to restrict or ban the sale of kava-containing products.[2] In 2002, the FDA issued an advisory about the potential risk of liver damage from kava products.[2]

The pathogenesis of kava-induced hepatotoxicity remains unknown; however, an idiosyncratic immune-mediated response is suspected.[2] Pipermethystine, an alkaloid found in the stem and aerial parts of the plant, is also believed to be a hepatotoxin.[2] Traditional formulations of kava found in Polynesian cultures use only the plant root, but some manufacturers of dietary supplements might not bother to isolate different kava plant parts in their raw materials.[2]

Yohimbine

Yohimbine is an indole alkaloid that occurs naturally in the bark of the West African *Pausinystalia yohimbe* tree.[2] It has selective antagonist activity at alpha$_2$-adrenergic receptors, resulting in increased central and peripheral sympathetic activity.[2] Dietary supplements containing yohimbine are promoted for their sympathomimetic and aphrodisiac properties.[2] Despite a lack of scientific data regarding the efficacy and safety of such combinations, yohimbine supplements also frequently include caffeine and other herbs, such as horny goat weed.[2] These products are marketed to increase energy, build lean body mass, and enhance sexual performance.[2] Case reports of yohimbine-associated toxicities (including hypertension, anxiety, headache, tachycardia, tremor, weakness, and mania) suggest that these products pose significant health risks.[2] Clinical studies have also shown that yohimbine induces a dose-dependent increase in plasma norepinephrine and blood pressure, with variable effects on heart rate.[2]

Yohimbine HCl is also an FDA-approved drug (Aphrodyne and Yocon), indicated for the treatment of xerostomia, impotence, and orthostatic hypotension secondary to antidepressant therapy.[2] It is also sometimes used to reverse adverse effects associated with clonidine (Catapres, Boehringer Ingelheim).[2]

The Need for Scientific Evaluation of CAM and Dietary Supplements

The dearth of scientific data concerning the majority of CAM therapies and dietary supplements is unrivaled in medicine.[2] Scientific evidence exists for some of these treatments, but for most, important questions regarding safety and efficacy remain because answers can be obtained only through well-designed clinical trials.[11] Experts state that the popularity of CAM and dietary supplements, consumed by millions of Americans, makes it that much more important to carefully conduct much needed efficacy and safety studies of these treatments.[2,5] They argue that CAM and dietary supplements should be subject to the same level of critical assessment, by organizations such as the NIH and FDA, that conventional therapies have undergone.[9] Without this scrutiny, experts caution that there is a risk of creating a health care system that is less efficient, less cost-effective, and less safe.[13]

Marcia Angell and Jerome Kassirer, former *New England Journal of Medicine* Editors-in-Chief, urged:[1]

> There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset. If it is found to be reasonably safe and effective, it will be accepted. But assertions, speculations, and testimonials do not substitute for evidence. Alternative treatments should be subjected to scientific testing no less rigorous than that required for conventional treatments.

Table 3 **Potential Benefits and Adverse Effects of Some Top-Selling Dietary Supplements in the U.S.**

	Scientific Name	Common Uses	Strength of Evidence of Benefit*	Adverse Effects
Garlic	*Allium sativum*	Hyperlipidemia, hypertension	+	Gastroenteritis; contact dermatitis; antiplatelet actions
Echinacea	*E. purpurea* *E. angustifolia*	Prevent and shorten cold and flu duration	–	Allergic reaction
Saw palmetto	*Serenoa repens*	Male urinary dysfunction	–	Headache; diarrhea; antiandrogenic
Ginkgo	*Ginkgo biloba*	Dementia, peripheral vascular disease; tinnitus	++	Antiplatelet effect; bleeding
Soy	*Glycine max*	Menopausal symptoms; high cholesterol	+	Phytoestrogens may increase breast cancer risk
Cranberry	*Vaccinium macrocarpon*	Urinary tract infections	+	None reported
Ginseng	*Panax* ginseng	Weakness, fatigue, boosts immune system	+	CNS/cardiac stimulation; hypoglycemia; bleeding
Black cohosh	*Cimicifuga racemosa*	Menopausal symptoms	+	Gastroenteritis; hepatitis
St. John's wort	*Hypericum perforatum*	Mild-to-moderate depression	++	Gastroenteritis; dizziness; sedation; photodermatitis
Milk thistle	*Silybum marianum*	Viral, alcoholic, and toxin-induced hepatitis	+	Gastroenteritis; possible allergic reaction
Evening primrose	*Oenothera biennis*	Rheumatoid arthritis; diabetes; PMS; hot flashes, mastalgia	+	Nausea, loose stools; headache; possible bleeding
Valerian	*Valerian officinale*	Insomnia; anxiety	++	Sedation; potentiation of alcohol effects
Green tea	*Camellia sinensis*	Lower cholesterol; weight loss; improve cognition; decrease cancer risk	++	Inhibits platelet function; GI upset; irritability, tremor palpitations, diarrhea
Bilberry	*Vaccinium myrtillus*	Improve visual acuity; diabetic and hypertensive retinopathy	+	None reported
Grape seed	*Vitis vinifera*	Venous insufficiency; hemorrhoids; atherosclerosis	+	Inhibits platelet function
Horny goat weed	*Epimedium sagittatum*	Erectile dysfunction	0	Dry mouth, dizziness; vomiting
Yohimbine	*Pausinystalia yohimbe*	Erectile dysfunction	0	Hypertension; anxiety; tremor; headache; insomnia; palpitations
Horse chestnut	*Aesculus hippocastaneum*	Hemorrhoids, varicose veins, phlebitis	+	GI irritation; nephropathy
Siberian ginseng	*Eleutherococcus senticosus*	Weakness, fatigue; boost immune system	+	None reported
Ginger	*Zingiber officinale*	Motion sickness; postanesthesia; chemotherapy, pregnancy-related nausea	++	Heartburn, diarrhea; bleeding; mouth/throat irritation; allergic dermatitis

CNS = central nervous system; GI = gastrointestinal; PMS = premenstrual syndrome.

Strength of evidence is based on: (–) = controlled clinical trials failed to demonstrate significant effect for major indications; (0) = no published clinical trial data; (+) = some evidence from clinical trials of a modest benefit or efficacy for limited indications but with conflicting data; (++) = controlled clinical trials demonstrating consistent, moderate benefit for major indications.

Adapted from Waldman SA, Terzic A. *Pharmacology and Therapeutics: Principles to Practice*. Philadelphia: Elsevier/WB Saunders; 2008:1536.[2]

To that end, increased funding by the NIH, as well as growing interest among alternative and traditional practitioners and medical researchers, has increased scientific inquiry into the safety, efficacy, and mechanism of CAM and dietary supplements.[6] However, even though more CAM therapies and dietary supplements are now being scientifically evaluated, the quality of these trials has been debated.[7] Applying rigorous randomized, double-blind, placebo-controlled trials to CAM research is difficult, because devising placebo controls for therapies such as *Tai Chi* and massage is problematic.[7] It can also be difficult to devise a study design that is accepted as valid by both conventional researchers and CAM practitioners.[7] Clinical epidemiology and biostatistics have played important roles in evaluating disease and conventional therapeutics, and the use of these methods is just as critical in examining the safety and efficacy of CAM and dietary supplements.[17] However, research methods that have been used over the years to study pharmaceuticals might need to be adapted for CAM and dietary supplement research because of the unique characteristics of some of these interventions.[17]

Despite the great lack of reliable scientific data regarding dietary supplements, health care professionals should be aware that reputable informational resources on the safety and efficacy of these products do exist.[14] A comprehensive listing of these resources is provided in Table 5.

Proposed Governmental Policy Changes

It has been recommended that the DSHEA be modified so that dietary supplements are subject to regulations similar to those for over-the-counter medications.[7] This change would ensure the collection and submission of efficacy and safety data by manufacturers of these products prior to FDA approval.[7]

Product registration would be required so that the FDA could instantly access an ingredient listing and distribute information, warnings, and recalls to the public when an adverse event is reported.[7] The FDA could also require dietary supplement manufacturers to provide warnings on product labeling about drug–dietary supplement interactions and other adverse events relating to these products.[7] The agency could provide an incentive to manufacturers to submit their products for independent laboratory certification by requiring uncertified supplements to prominently state, "Warning: This supplement has not been certified for its purity or consistency."[7] In addition, independent laboratories could be required to register with the FDA; to be inspected for good laboratory practices; and submit all results on product purity, ingredients, and levels of contamination to the agency.[7]

The ASHP has also recommended changes to governmental regulatory policy regarding dietary supplements in its "ASHP Statement on the Use of Dietary Supplements."[8] The ASHP recognizes concerns about the additional costs manufacturers would incur if dietary supplements were regulated as nonprescription drugs, especially because natural ingredients cannot be patented.[8] However, the ASHP still urges Congress to amend the Dietary Supplement Health and Education Act (DSHEA) to allow the FDA to develop regulations

Table 4 Toxicities Induced by Dietary Supplements, According to Body System

Central Nervous System
- ***Stimulation***
  - *Ephedra sinica*
  - *Guaraná/Yerba mate*
- ***Sedation***
  - Kava

Cardiovascular
- ***Vasopressive***
  - *Ephedra sinica*
  - *Guaraná*
  - Yohimbine
  - *Citrus aurantium*
- ***Electrophysiological***
  - *Ephedra sinica*
  - Hawthorn
- ***Hypertension***
  - Hawthorn
  - Ginseng

Dermatological
- ***Skin rash***
  - Kava
- ***Photodermatitis***
  - St. John's wort
  - Goldenseal

Immune
- ***Allergic reaction***
  - *Echinacea*
  - Bee pollen
  - Milk thistle

Hematological
- ***Antiplatelet/ anticoagulant***
  - Feverfew
  - *Ginkgo biloba*
  - Garlic
  - Ginseng
  - Willow bark

Hepatic
- ***Hepatitis***
  - Black cohosh
  - Chaparral
  - Comfrey
  - Kava
  - Pennyroyal
  - Lipokinetix (usinic acid)

Metabolic
- ***Hypokalemia***
  - Licorice
  - Aloe
  - Senna
  - Cascara
- ***Hyperglycemia***
  - Glucosamine
  - *Ephedra sinica*
  - Licorice
- ***Hypoglycemia***
  - Fenugreek
  - Garlic
  - Ginseng

Mutagenic/Carcinogenic
- ***Urothelial***
  - Aristolochic acid
- ***Hepatocellular***
  - Pyrrolizidine alkaloids

Renal
- ***Renal failure***
  - Aristolochic acid

Adapted from From Waldman SA, Terzic A. *Pharmacology and Therapeutics: Principles to Practice.* Philadelphia; Elsevier/WB Saunders; 2008: 1536.[2]

Table 5 **Informational Resources for Dietary Supplements**

U.S. Food and Drug Administration
Information about the regulation of dietary supplements by the FDA can be found at www.fda.gov/Food/DietarySupplements/default.htm. Adverse effects occurring with the use of dietary supplements should be reported to the FDA's MedWatch program, which collects and monitors this information (1-800-332-1088 or www.fda.gov/Safety/MedWatch).

National Center for Complementary and Alternative Medicine
The NCCAM Clearinghouse provides information on the center and CAM therapies, including free publications and free federal database searches of the scientific and medical literature. The NCCAM (www.nccam.nih.gov) can be reached at info@nccam.nih.gov or by telephone at 1-866-464-3615.

National Institutes of Health, Office of Dietary Supplements
The Office of Dietary Supplements (ODS) evaluates scientific information, supports research, shares data, and educates the public about dietary supplements. The resources offered include publications and international bibliographic information from databases about dietary supplements. The office can be reached at www.ods.od.nih.gov or by phone at (301) 435-2920.

The U.S. Pharmacopoeia
The USP is a nongovernmental public standards-setting authority for prescription, over-the-counter, and other health care products that are manufactured and sold in the U.S. The U.S. Pharmacopeia–National Formulary (USP–NF) describes quality standards for dietary supplements. The USP also offers a voluntary supplement-testing program as well as a listing of quality-tested supplements. More information is available at www.usp.org.

***Herbal Companion to the AHFS–DI* (American Hospital Formulary Service–Drug Information)**
AHFS–DI is a publication from the ASHP that includes monographs on uses, indications, dosage ranges, cautions, interactions, regulatory status, and references regarding herbal supplements. This science-based information was collected from more than 3,000 sources and has been reviewed by an advisory board of physicians, scientists, and other medical professionals who are recognized as experts in herbal therapies. More information can be found at www.ashp.org/import/news/pressreleases/pressrelease.aspx?id=107.

The Review of Natural Products: Facts and Comparisons
This comprehensive publication includes more than 350 peer-reviewed, evidence-based monographs. This reference provides detailed information about natural products, including their botany, history, chemistry, pharmacology, medicinal uses, toxicology, drug interactions, and patient information. More information can be found at www.factsandcomparisons.com/review-of-natural-products-bound.aspx.

PDR for Herbal Medicines (Physician's Desk Reference for Herbal Medicines)
This compendium of general and clinical knowledge of herbal medicine, published by Thomson Reuters, provides evidence-based identification, safety, efficacy, and therapeutics information cross-referenced to therapeutic category, indication, side effects, and drug interactions.

Natural Medicine Comprehensive Database
This comprehensive database (www.naturaldatabase.com) includes evidence-based information on herbs, vitamins, minerals, and other dietary supplements regarding their interactions, uses, safety, efficacy, special populations, and ingredients.

American Botanical Council
This nonprofit organization is dedicated to promoting the effective and safe use of medicinal plants and phytomedicines. The council publishes the journal *HerbalGram*, offers literature reviews, and provides access to continuing education materials on dietary supplements, including the *German Commission E Monographs*. These monographs describe more than 300 herbal products that have been evaluated by members of a German regulatory agency, including physicians, pharmacists, scientists, and toxicologists, by using case, clinical, and field studies as well as other scientific literature. More information can be found at www.herbalgram.org.

Natural Standard, The Authority on Integrative Medicine
An international research collaboration, Natural Standard collects and synthesizes data on CAM therapies and dietary supplements. This information is incorporated into fully referenced evidence-based monographs that have undergone a blinded editorial and peer-review process. Natural Standard also publishes reference books, research reports, and monthly newsletters that can be accessed at www.naturalstandard.com.

Journal of Natural Products
This publication focuses on the chemistry and biochemistry of naturally occurring compounds and the biology of the living systems from which they are derived. The journal (http://pubs.acs.org/journal/jnprdf) is co-published monthly by the American Chemical Society and the American Society of Pharmacognosy.

Data from *J Manag Care Pharm* 2005;11(3):252–258;[1] *Am J Health Syst Pharm* 2006;63(1):65–70;[3] NCCAM, December 2008;[11] and *J Manag Care Pharm* 2005;11(8):695–703.[14]

that ensure that dietary supplements are safe and effective.[8] The ASHP states that under the DSHEA, consumers and health care practitioners are not provided with the information they need to use these products safely.[8] The ASHP therefore recommends that in order to reduce the potential dangers associated with dietary supplements, Congress should amend the DSHEA to require that:[8]*

- dietary supplements undergo an FDA review of evidence for safety and efficacy prior to approval.
- dietary supplements display standardized FDA-approved labeling that clearly describes safe use, potential drug interactions, and cautions for special populations.
- the FDA enforce GMPs for these products.
- all dietary supplements meet FDA-established standards for identity, strength, purity, and quality.
- the FDA establish and maintain an adverse-event reporting system specifically for dietary supplements.

Several other governmental policy changes have been recommended to ensure that the results of NCCAM-funded research are used to facilitate the integration of safe and efficacious CAM and dietary supplements into conventional medicine.[7] Concern exists about the quality of the methods used to evaluate CAM and dietary supplements and whether or not they are consistent with those techniques used to assess conventional treatments.[9] The NCCAM must therefore commit to fund only studies that use methodology that matches accepted standards for expressing data and studying the efficacy and safety of conventional drugs.[7,9]

Finally, the results of NCCAM-funded clinical trials should then be used to modify both conventional and CAM practices.[7] Therapies that are unsafe and ineffective should be abandoned, and those that are both safe and effective should become standards of care for conventional medicine.[7] The continued use of therapies that are either safe or effective, but not both, should be determined by a risk–benefit evaluation.[7] The cost of CAM and dietary supplements should be a factor in risk–benefit assessments, especially when therapies with similar expectations are being considered as treatment options.[7]

Conclusion

The current regulatory environment for dietary supplements in the U.S. is insufficient and presents significant public safety risks.[1,2,5,8,9] While in recent years there has been an increased effort on the part of both the government and dietary supplement manufacturers to collect efficacy and safety data for these products, a wealth of information is still lacking.[2,7,10,11] Proposed changes to the DSHEA that would enhance the regulatory authority of the FDA over dietary supplements should be considered.[7,8] With increased regulation, supplements marketed in the U.S. would ideally include only nutritional products that enhance human health and well-being and that have been proven to be safe and effective.[2]

* The ASHP Statement also recommended that the FDA establish GMPs for dietary supplements and that manufacturers be required to submit reports of suspected adverse reactions. In 2008, the FDA did enact GMPs for dietary supplements and began to require the manufacturers to submit reports of serious adverse reactions.[8]

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