HEALTH NOTES

Alternative Medicines

California State Board of Pharmacy

Dedicated to building bridges of communication with those Californians whose health depends on proper drug therapy, compliance with a treatment regimen and a healthier lifestyle.

Gray Davis, *Governor*

Aileen Adams, *Secretary, State and Consumer Services Agency*

Kathleen Hamilton, *Department of Consumer Affairs*

MEMBERS, California State Board of Pharmacy

Robert Elsner, Public Member, *President*

Steve Litsey, Pharm.D., *Vice President*

Caleb Zia, Public Member, *Treasurer*

Darlene Fujimoto, Pharm.D.

Donald W. Gubbins, Jr., Pharm.D.

John D. Jones, R.Ph.

Richard Mazzoni, R.Ph.

William Powers, Public Member

Holly Strom, R.Ph.

Andrea Zinder, Public Member

Patricia Harris, *Executive Officer*

A Note from the Editor

Alternative medicine, by definition, is anything but conventional. Nonetheless, consumers are pushing one component of alternative medicine, the dietary supplements, into the main stream. The focus on herbal products and nutritional supplements in this issue of HEALTH NOTES stems from their widespread use, the potential they have for interactions with prescription and non-prescription medication, and the confusion surrounding their safety and effectiveness.

The contributors to this issue are physicians, pharmacists and lawyers who have researched the literature and addressed the use of these products in their own practices. To enhance our understanding of the subject matter, the authors have taken an evidence-based approach to the evaluation of herbal and nutritional supplements and balanced the factual information with real cases to illustrate key concepts. I thank them for sharing their expertise.

While editing, I was struck by two observations 1) almost 20% of prescription drug users also take dietary supplements and 2) people who take dietary supplements are essentially medicating themselves. Both have huge implications for pharmacists. While many of us have not been formally trained in the use of these products, we are the health professionals who are responsible for identifying and preventing drug interactions or adverse effects resulting from their combined use with conventional medicines. Pharmacists are on the front lines and are in the best position to promote safe and responsible self-medication, whether that is with prescription, non-prescription or dietary supplement products. This issue of HEALTH NOTES is dedicated to helping pharmacists fulfill these important responsibilities. On behalf of the faculty of the Center for Consumer Self Care at the UCSF School of Pharmacy, I thank the State Board of Pharmacy for giving us this opportunity to develop a practical resource on dietary supplements for pharmacists and consumers.

Barbara Sauer

Barbara Sauer, Pharm.D.
Project Coordinator
Center for Consumer Self Care
UCSF School of Pharmacy

Introduction

HEALTH NOTES is a series of monographs published by the California State Board of Pharmacy's Communication and Public Education Committee to help California pharmacists and other healthcare providers become better informed on subjects of importance to their patients. The information will also be of value to the public.

Today, more than ever in the history of medicine, healthcare professionals are addressing the goals of integrated healthcare. They are providing patient care that focuses on physical wellness, service-satisfaction, and cost effectiveness. Patients themselves are looking for their own remedies and solutions to health problems and concerns.

Pharmacists, by virtue of their close relationship with patients, can quickly respond to patients' medication needs and can satisfy patients' desires to be informed about their treatment and the medications they are taking. They can also assist with information about herbal products and dietary supplements.

Access to information is an important component in attaining wellness. Pharmacists who develop programs that assist patients to better manage their medications and to meet their treatment objectives will help Californians reach higher levels of wellness.

As healthcare evolves into a system focused on integrated patient care, one fact becomes very clear: healthcare professionals who provide disease management programs and prescription information that increases medication compliance will help reduce hospital admissions and the need for follow-up care.

HEALTH NOTES is designed to be a reference source for pharmacists and other health care providers to use in helping patients better understand their illness, comply with prescribed treatment regimens and take greater responsibility for their health.

This issue of HEALTH NOTES addresses the area of alternative medicines and dietary supplements and the potential for interactions with prescription and non-prescription medication – in short, the problems that can be encountered with self-medicating.

Caleb K. Zia
Chair, Communication and
Public Education Committee
California State Board of Pharmacy

Learning Objectives

After reading the articles in this issue, you should be able to:

1. Describe the regulatory process for dietary supplements and explain how it differs from that for prescription and non-prescription medications.
2. List one or two common uses for frequently purchased dietary supplements and describe the scientific evidence to support each of these uses.
3. Recognize appropriate dosing regimens and common adverse effects of frequently used dietary supplements.
4. List five herbs or herbal products that are toxic to the liver.
5. List five dietary supplements that should be avoided when taking anticoagulants or anti-platelet medication.
6. Cite three additional examples of potentially harmful drug interactions reported with dietary supplements (other than those listed above).
7. List five medical conditions or diseases in which dietary supplements should be avoided.
8. List three alternative medicine resources that provide reliable information and are suitable for consumer use.
9. Identify five risk management strategies for pharmacists who sell or counsel consumers about dietary supplements.
10. Describe the pharmacist's role in promoting safe and appropriate use of dietary supplements.

References for this issue are available, upon written request, from the California State Board of Pharmacy.

Health Notes

Volume 1, Number 5

Alternative Medicines

TABLE OF CONTENTS

Introduction

4 Complementary and Alternative Medicine: Does It Work? Is It Safe? Why Are So Many People Using It?
Ellen Hughes, M.D.

Part One: Top Selling Dietary Supplements

7 Keeping Up With the Top Selling Herbs
Cathi Dennehy, Pharm.D.

16 Dietary Supplements: Sorting Through the Evidence
Candy Tsourounis, Pharm.D.

At-a-Glance

Garlic	8	Black Cohosh	14
Ginkgo	8	Melatonin	17
St. John's Wort	9	Glucosamine	17
Kava Kava	11	Chondroitin Sulfate	18
Saw Palmetto	12	Shark Cartilage	19
Ginseng	12	DHEA	19
Echinacea	13	Coenzyme Q 10	20

Part Two: Risks Associated With Use

23 Potential for Harm
Mary Chavez, Pharm.D.

29 Adverse Events Associated with Alternative Medicines – Recent Cases Reported to the California Poison Control Center
Christine A. Haller, M.D. and Thomas E. Kearney, Pharm.D. ABAT

Part Three: Information for Pharmacists

35 Inquiring Minds: Frequently Asked Consumer Questions About Herbs and Dietary Supplements
Mitra Assemi, Pharm.D.

39 Sources of Reliable Information on Alternative Medicine
Mary J. Ferrill, Pharm.D.

44 Legal Considerations Pertaining To Dietary Supplements
Richard R. Abood, R.Ph., J.D.

49 What's In a Claim?
Barbara Sauer, Pharm.D.

The views expressed by the individual authors are not necessarily the views of the Board of Pharmacy.

Does it work? Is it safe? Wh

Complementary and Alternative Medicine:

Ellen Hughes, M.D.
Associate Clinical Professor of Medicine
Interim Director, Osher Center for Integrative Medicine, School of Medicine
University of California, San Francisco

More than four out of ten Americans used some form of alternative medicine in 1997, paying an impressive $27 billion out-of-pocket for therapies such as herbal medicine, chiropractic, and acupuncture.[1] The same year, patients made a staggering 629 million visits/year to alternative practitioners, more than they made to all U.S. primary care providers. Who are these patients? Why do they discuss less than 40% of their alternative therapies with their medical doctors? Why are they willing to pay so much out-of-pocket for services that have rarely been scientifically validated?

Definition of Alternative Medicine

Various terms have been used to describe therapies that fall outside of mainstream medical practice, including "alternative," "non-traditional," "unconventional," "holistic," "complementary," and "complementary and alternative medicine" (CAM). Almost a decade ago, Eisenberg defined alternative medicine as "medical interventions not widely taught at U.S. medical schools or generally available at U.S. hospitals."[2] A more recent term, "integrative medicine," is gaining popularity as it emphasizes the growing trend to try to combine the best of both CAM and conventional care.

Who Seeks Alternative Care and Why?

Although the press initially portrayed most patients seeking CAM as terminally ill people hoping for miracle cures, the average person using CAM is actually a well educated health consumer with a chronic, but not life-threatening, condition who can afford CAM services. A higher level of education and living on the West Coast are two strong predictors of CAM use.[1]

CAM is attractive to many people because of its emphasis on treating the whole person, its promotion of good health (not just treatment of illness), its placement of value on prevention, and often a more personalized approach to patient concerns. A mail survey of more than 1000 Americans recently verified that 40% of adults used at least one type of CAM.[3] These consumers were asked why they sought out alternative therapies. Independent predictors of CAM use included: higher level of education, poorer health status, a "holistic" approach to health, and a world view that included an interest in personal growth and spirituality. People with conditions such as anxiety, back difficulties, chronic pain, and urinary problems were more likely to have used CAM in the previous year. Less than 5% of those who responded relied primarily on alternative medicine for their health care. Despite the popular belief that many patients seek out CAM because they are not happy with conventional medicine, dissatisfaction was NOT shown to predict greater use of alternative modalities.[3] The majority of CAM users appear to seek care for their chronic problems with BOTH alternative and conventional medicine, because CAM seems more congruent with their values and orientation towards health and is perceived to be as or more effective.

How is the Traditional Healthcare Community Responding?

Despite increasing public demand for CAM services, the lack of high quality data regarding safety and efficacy frustrates both patients and providers. In response to this lack of information, Congress established the Office of Alternative Medicine in 1992. It began as a very small division within the National Institutes of Health (NIH), but has recently been elevated to a full NIH Center (National Center for Complementary and Alternative Medicine, NCCAM). Part of their $70 million/year budget goes toward funding nine national research centers at universities such as Columbia, Maryland, Michigan, Oregon, and Arizona. These investigators are researching CAM's safety and efficacy in areas such as chronic disease, women's health, pediatrics, and chiropractic. High quality research is desperately needed to help patients and health care providers answer the crucial questions: Is CAM safe? Does it work? Is it cost-effective?

Health Insurance Coverage for CAM: Integration into Mainstream?

Virtually no third party payers were offering CAM services ten years ago, but a 1999 national survey of health maintenance organizations (HMOs) revealed that two-thirds are now offering at least one CAM modality - most commonly chiropractic (65%) followed by acupuncture (35%).[4] The top reasons given by the insurers for offering these services were "enrollees asked for them" or "they were

hy are so many people using it?

mandated." Half of all HMO enrollees reported that they were willing to pay a higher premium for CAM services.

The most common model of CAM insurance coverage is when enrollees pay a supplemental premium for access to independently contracted networks of CAM practitioners. Members receive coupons redeemable for a variety of discounted CAM and wellness services that they can often access without needing a referral from their primary care provider. Such plans are popular, offering enrollees independent access to a variety of CAM providers and services such as chiropractic, massage, acupuncture, and stress management. They do not, however, help bridge the communication gap that exists between patients and their primary care providers. Many patients are turning to pharmacists for first line advice about the fastest growing alternative medicine modality in the United States: herbal medicines and dietary supplements.

Epidemiology of Herbal Use

One out of three Americans purchased herbal medicines in 1997, spending more than $5 billion.[1] Fifteen million people in the United States (44% of all adults who regularly take prescription medications) took prescription medicines concurrently with one or more herbals, high dose vitamins, or both. This represented almost 20% of all prescription drug users.[1]

Can consumers trust what's on the market? Not always! The major reason that herbal medicines remain essentially unregulated in the United States is the passage of the Dietary Supplement Health and Education Act of 1994, DSHEA. In the early 1990's, consumers who were concerned that the FDA might begin to regulate the herbal industry wrote more letters to Congress than had been received since the Vietnam War! DSHEA was passed and all vitamins, minerals, herbs, and amino acids were classified as nutritional or dietary supplements. This means that they can be marketed without proof of efficacy, safety, or manufacturing standards, as long as they make no claim to diagnose, treat, cure, or prevent disease. In addition, before an herbal product can be taken off the market, the FDA must prove in court that it is unsafe, unlike OTC and prescription drugs that must be proven safe and effective by manufacturers before they are marketed.[5]

Economics: Big Pharmaceutical Firms Entering the Market

It is not surprising that until recently, proprietary drug manufacturers haven't been interested in producing herbal products, because plants cannot be patented. Within the last few years, however, large companies have entered the herbal market with brand name products. These often contain standardized extracts imported from European pharmaceutical firms. Some examples are:

- Warner Lambert: Quanterra® brands (ginkgo, saw palmetto, St. John's wort)
- Bayer Corporation: One-A-Day® products, Cold Season® (Echinacea, zinc, vitamin C) and Cholesterol Health® (garlic, soy extract, Vitamin E, lecithin)
- Whitehall-Robins Healthcare: six Centrum® Herbal Formulas
- Pharmaton® (Boeringer Ingelheim): Movana® (St. John's wort) and Ginkgoba®

Many feel that these large pharmaceutical companies will bring improved quality control, safety, and credibility to the herbal industry. (But, possibly with a higher price tag!)

Safety of Herbal Medicines: Buyer Beware!

A recent review of the risks associated with taking herbal medicines chronicles many examples of why the herbal consumer needs to beware.[6] There are often unanticipated or unwanted effects of the herb itself. For example, acute hepatitis has been associated with the Chinese herbal product Jin Bu Huan, a combination of germander and ma-huang. In another case, a combination of eight herbs (PC-SPEC) marketed to balance the immune system in patients with prostate cancer was found to contain potent estrogenic activity in vitro, in animals and in eight men with prostate cancer who developed breast tenderness, decreased libido, and deep venous thrombosis.[7] Other harmful effects have been described as a result of the herb interacting with prescription medication. St. John's wort has been reported to lower drug levels of indinavir in HIV patients[8] and it may affect the levels of other medicines metabolized by the cytochrome P-450 system.[9]

Consumers of herbal medicines have no guarantee that the plant was accurately identified in the field or that another less effective plant part or species wasn't substituted. There is also no assurance that the herb is pure (i.e., no microbial, pesticide or heavy metal contamination), safe, effective, or that the next bottle will have the same ingredients at the same dose.

Future of Alternative Medicine

A recent editorial in the prestigious *New England Journal of Medicine* stated the following: "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."[10] The demand for high quality research to make evidence-based decisions about health care is increasing in both conventional and alternative medicine. A lecturer at a recent CAM research conference said: "We should really just be aiming to be practicing 'best medicine,' no matter where it comes from and as long as its been proven safe and effective. In God we trust, all others must produce data!"

Part One: Top Selling Dieta

Keeping Up With The Top Selling Herbs

Cathi Dennehy, Pharm.D.
Assistant Clinical Professor
School of Pharmacy
University of California, San Francisco

A recent survey estimating that 42% of Americans used some form of alternative therapy studied 16 types of CAM.[1] The prevalence of herbal medicine use (12%) was second only to relaxation techniques (16%) and slightly ahead of massage (11%). In 1998, herbal sales increased 55% over the previous year. But, in the first eight months of 1999, sales increased only 11%, suggesting the trend is now leveling off.[2] Available primarily in health food stores in the past, herbs and other dietary supplements are now frequently stocked by retail pharmacies.

It is increasingly important for pharmacists to know what evidence supports the use of herbs, what potential they have for adverse effects, and what dosing is appropriate. This review will focus on the top selling herbs of 1999, in order of most to least frequently used.[2] Where possible, products available in the United States that are equivalent to those used in European trials are listed. Pharmacists and consumers, however, should be aware that product content is not guaranteed. Standardized markers, when listed on package labeling, can accurately reflect product content, but may also exceed or be drastically less than what is indicated.

Garlic – *Allium sativum*

An intact bulb of garlic contains many organosulfur compounds, but research into the activity of the herb has focused on allicin, the odiferous constituent.[3] Allicin is generated by a chemical reaction that brings its precursor, alliin, in contact with the enzyme allinase.[3] Disruption of a garlic bulb (e.g. chewing, chopping) causes this reaction. Allinase is highly unstable and is easily broken down by stomach acid and excessive heat.[4] Many commercial products are enteric-coated to prevent this breakdown and allow for maximal allicin formation. Clinical trials frequently used an enteric-coated powdered formulation called Kwai®, which is available in the United States. Garlic formulations that are properly freeze-dried and powdered can retain a high allicin-generating potential, while oil formulations are more likely to contain the breakdown products of allicin.[4]

The organosulfur constituents in garlic have a variety of properties that relate to its use in supporting cholesterol, blood pressure, and atherosclerosis. Garlic has been shown *in vitro* to inhibit hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol biosynthesis. It also enhances production of nitric oxide, a potent vasodilator. In animals, it reduces aortic smooth muscle proliferation. In humans, garlic reduces atherosclerotic plaque formation and has been shown to have antioxidant, antiplatelet, and fibrinolytic effects.[3, 5]

Clinical Trials

Garlic is most often studied for its effects on cholesterol. Older meta-analyses estimated a 9-12% reduction in total cholesterol, with 600-900 mg/day of powdered garlic taken for at least one month.[6, 7] Recent well-designed trials (randomized, double-blind, placebo-controlled) were inconsistent, demonstrating either a reduction in LDL cholesterol of 5-14% or no effect.[8-12] A meta-analysis of eight trials suggested that garlic may have a mild effect on blood pressure, lowering systolic pressure by 7.7 mm Hg and diastolic pressure by 5 mm Hg.[13] Only a few clinical trials evaluated the anti-atherosclerotic effects of garlic. Those that did reported reductions in carotid and femoral artery plaque volumes of 5-18% and less aortic stiffening with prolonged consumption for up to four years.[5,14,15]

Adverse Effects, Drug Interactions and Dosing

In clinical trials, body odor and stomach upset were the most commonly reported adverse effects.[3] A small percentage of patients (1%), reported lower blood pressure.[3] Individuals taking antihypertensive agents should monitor their blood pressure when initiating garlic therapy. Patients taking antiplatelet or blood-thinning medications (e.g., aspirin, ibuprofen, warfarin) may be at increased risk for bleeding, as garlic has been shown to have similar properties. Garlic should be avoided for 7 to 10 days pre- or post-operatively, to avoid potential bleeding complications. Garlic has not been shown to reduce blood sugar in patients with type 2 diabetes; thus, additional monitoring of blood sugar is unnecessary.[16,17] Consumers should be told to purchase a standardized formulation with 1.3% alliin or 0.6% allicin.[3] Powdered garlic should be enteric-coated and dosed at 600 to 900 mg/day in two to three divided doses.[3] An equivalent dose of raw garlic (i.e., one-half to one clove) may also be taken.[6]

Summary

Without further research, the benefits of garlic in supporting cholesterol, blood pressure and atherosclerosis are inconclusive. At best, garlic may have a mild effect on reducing LDL cholesterol, similar to that achieved with dietary modification. Effects on blood pressure are weakly established and are likely to be mild. The anti-atherosclerotic potential of garlic is promising, based on preliminary studies. The low potency of garlic precludes its use as a substitute for prescription drug therapy. However, it may be a useful adjuvant, given its favorable adverse effect profile.

Ginkgo – *Ginkgo biloba*

A concentrated extract of ginkgo can be prepared from the leaves of the tree. Extracts are typically standardized to contain 24% flavonoid glycosides and 6% terpenes.[3] Ginkgo is most often used for symptoms associated with vascular insufficiency to the brain

(cognitive insufficiency) and legs (peripheral arterial occlusive disease). Recent attention has focused on the use of ginkgo in dementia of the Alzheimer's type, which involves heightened levels of brain oxidation and changes in neurochemical transmission (e.g. low levels of acetylcholine).[18] Ginkgo and its constituents were shown to inhibit platelet-activating factor (PAF) and enhance nitric oxide production *in vitro*.[19,20] In animals, it enhances central nervous system levels of acetylcholine and norepinephrine and reduces corticosteroid secretion.[21-23] In humans, ginkgo enhances blood flow, reduces platelet aggregation and reduces markers of oxidative stress (i.e., has antioxidant and free radical scavenging properties).[20,24,25]

Clinical Trials

Two large clinical trials (randomized, double-blind, placebo-controlled) lasting 1 year and 6 months respectively, evaluated the effect of ginkgo extract, EGb 761, in patients with mild to moderate multi-infarct dementia or dementia of the Alzheimer's type.[26,27] In the year-long trial, patients receiving 120 mg/day of ginkgo showed significant improvements in tests assessing activities of daily living and cognition, but not in one assessing the clinician's perception of patient improvement.[26] This study had a high patient drop out rate (almost 50%), and used an analysis that compared data from the point of patient withdrawal to data from patients who completed the one-year observation period. The latter is problematic, since dementia typically worsens over time. In the second trial, clinicians perceived a significant benefit for patients receiving 240 mg/day of ginkgo extract.[27] Assessment scales for cognition and the clinician's perception of patient improvement were both significantly improved, while a scale assessing activities of daily living was not. Two recent reviews confirmed the findings of these two trials, noting a small, but significant, advantage of ginkgo over placebo for improving cognition in patients with dementia.[28,29]

The use of ginkgo to improve pain-free walking distance requires additional study, but appears promising. Initial trials have shown a two-fold increase in walking distance in subjects receiving ginkgo, as compared to those receiving placebo.[30,31]

Adverse Effects, Drug Interactions and Dosing

Adverse effects from ginkgo are rare. They typically consist of stomach upset, headache, anxiety, insomnia, and allergy.[3] Ginkgo may interact with antiplatelet or blood thinning medications (e.g., aspirin, ibuprofen, warfarin) and should be avoided in individuals using these products. There are a few case reports of hemorrhage and hematoma in people using ginkgo as monotherapy or in combination with other blood-thinning medications.[32] Ginkgo should be avoided for 7 to 10 days pre- or post-operatively to avoid potential bleeding complications. The extract formulation used in many European trials, EGb 761, is manufactured in the U.S. as Ginkgold® (Nature's Way), Ginkoba® (Pharmaton), Gingko 5® (Pharmline) and Quanterra Mental Sharpness® (Warner-Lambert). The extract should be standardized by its flavonoid glycoside and terpene contents. The dose is 120 to 240 mg per day, in two to three divided doses.[3] A delay in onset of 4 to 6 weeks may occur.

Summary

Ginkgo is likely to have a mild, but potentially significant effect on supporting cognitive performance in individuals with mild to moderate dementia. Ginkgo may also be helpful in alleviating symptoms such as painful walking in individuals with vascular disease.

St. John's Wort – *Hypericum perforatum*

An extract prepared from the above-ground portions of the *Hypericum perforatum* plant has been studied for its effects on mild to moderate depression.[3] St. John's wort products are standardized by their content of hypericin, which originally was thought to be the primary antidepressant constituent.[3] Recent attention, however, has focused on hyperforin as the primary antidepressant constituent. Hyperforin inhibits the reuptake of norepinephrine, dopamine, and serotonin *in vitro*.[33,34] With chronic administration, it also influences the density of various receptor subtypes (i.e., down-regulating cortical B-receptors and up-regulating cortical 5HT-2 receptors) in animals. The actual mechanism of action of this herb in humans is complex and may involve a number of different biochemical reactions.

Clinical Trials

In a large meta-analysis of over 23 clinical trials, the efficacy of St. John's wort was found to be superior to placebo and equal to that of tricyclic antidepressants.[35] While these results may seem promising, none of the comparative trials in this review included a placebo-control group. This is noteworthy, because placebo response rates ranging from 30-50% have been reported for studies involving synthetic antidepressants.[36] Most of the trials lasted only eight weeks and some used less than the recommended dose of the prescription drug. In addition, almost all of them used a common depressive rating scale (Hamilton Scale for Depressive Symptoms, HAMD) that is not as comprehensive or sensitive as some of the others (e.g., Inventory of Depressive Symptom Scale, IDS; Montgomery Asberg Depression Rating Scale, MADRS). Despite these shortcomings, St. John's wort did exhibit a more favorable adverse effect profile. More recent reviews include trials conducted subsequent to this meta-analysis. They also report superior outcomes with St. John's wort as compared to placebo and response rates similar to those of tricyclic antidepressants.[37,38] In at least one of these reviews, tests for publication bias were significant, indicating possible over-estimation of the effects of St. John's wort.[38]

Several clinical trials compared St. John's wort to the more commonly used selective serotonin reuptake inhibitors (SSRIs).[39-41] All of these were randomized, double-blind trials that compared St. John's wort (500-900 mg/day) to either fluoxetine 20 mg/day (Prozac®) or sertraline 75 mg/day (Zoloft®) for six weeks. All three trials showed significant reductions in HAMD scores for all treatments (St. John's wort and the SSRIs) when compared to baseline, and these results were not statistically different from one another. Another NIH trial is now comparing St. John's wort, SSRI, and placebo and will likely provide more information about the efficacy of St. John's wort.

Adverse Effects, Drug Interactions and Dosing

The formulation of St. John's wort extract used in many European trials, LI 160 (Jarsin®), can be found in the U.S. as Kira® (Lichtwer Pharma) and Quanterra Emotional Balance® (Warner Lambert). The recommended dose of St. John's wort extract is 900 mg per day in two to three divided doses.[3] A delay in onset of 4 to 6 weeks may occur. Most extracts are still standardized to contain at least 0.3% hypericin, although this ingredient may not be responsible for the antidepressant effects.[33,34] Adverse effects have been reported rarely with recommended doses. They include stomach upset, sedation, headache, restlessness, dizziness, and confusion.[42] An increased sensitivity to sun exposure is primarily due to the hypericin constituent and is unlikely to occur at recommended doses.[3] Nevertheless, it is still advisable to suggest the use of a sunscreen with this product. St. John's wort should not be used in combination with other prescription antidepressant or psychiatric medications to avoid an additive effect known as "serotonin syndrome."[43] St. John's wort should also be used cautiously in patients with a history of mania or bipolar disorder, as hypomania and mania have been observed.[44]

St. John's wort may decrease the efficacy of other prescription agents such as digoxin, theophylline, cyclosporin, warfarin, indinivir, and ethinylestradiol/desogestrel.[45,46] It may induce cytochrome (CYP) P450 enzymes such as CYP2C9 (metabolizes warfarin), CYP1A2 (metabolizes theophylline), and CYP3A4 (metabolizes indinivir, ethinyl estradiol and cyclosporin).[47,48] In the case of digoxin, induction of the drug transporter P-glycoprotein may have reduced drug absorption and enhanced elimination.[47] Individuals taking any of these medications should consult with a physician prior to initiating therapy with St. John's wort. While the mechanism of action of St. John's wort is still under investigation, initial reports of monoamine oxidase inhibition have not been substantiated at recommended doses.[33,34] Thus, dietary restrictions are probably unnecessary when using this product.

Summary

St. John's wort may enhance mood in individuals with mild to moderate depression. Future clinical trials should focus on comparing St. John's wort to the more commonly used SSRIs such as fluoxetine (Prozac®), sertraline (Zoloft®), and paroxetine (Paxil®). The long-term benefits of St. John's wort remain unknown, since a majority of the clinical trials lasted only eight weeks. Individuals should not initiate therapy with St. John's wort if symptoms are worrisome or severe. Pharmacists should question anyone considering the use of St. John's wort about concurrent medications, to limit the potential for adverse drug interactions.

> "Although herbs are widely believed to be safe because they are 'Natural', evidence suggests they are not without risks."

Kava Kava - *Piper methysticum*

For centuries, Pacific Islanders have used kava for ceremonial purposes to encourage socialization and relaxation.[49] The root of the plant contains pharmacologically active fat-soluble constituents known as kavalactones. Commercial formulations are typically standardized to contain 30-70% kavalactones.[50] Kava is most commonly used for its calming properties by individuals who have mild to moderate anxiety. Muscle relaxant, anticonvulsant, analgesic, and anesthetic properties were observed in animals.[3,49] The mechanism of action of kava is not well understood. It may enhance GABA neurotransmission, inhibit sodium and calcium channels, inhibit norepinephrine reuptake in the brain, and affect dopamine neurotransmission.[51-55]

Clinical Trials

Kava does not appear to cause the same level of impairment in reaction time or in information processing as benzodiazepines.[56,57] One six-week trial reported equivalent reductions in the Hamilton Anxiety Scale (HAMA) for patients receiving kava extract 300 mg (WS 1490, Laitan®, which is standardized to contain 70% kavalactones), oxazepam 15mg, and bromazepam 9 mg.[3] This trial, however, did not include a placebo arm. In another six-month trial in patients with moderate to severe generalized anxiety, 300 mg of WS 1490 was significantly better than placebo in reducing HAMA from weeks 8 to 24.[50]

Adverse Effects, Drug Interactions and Dosing

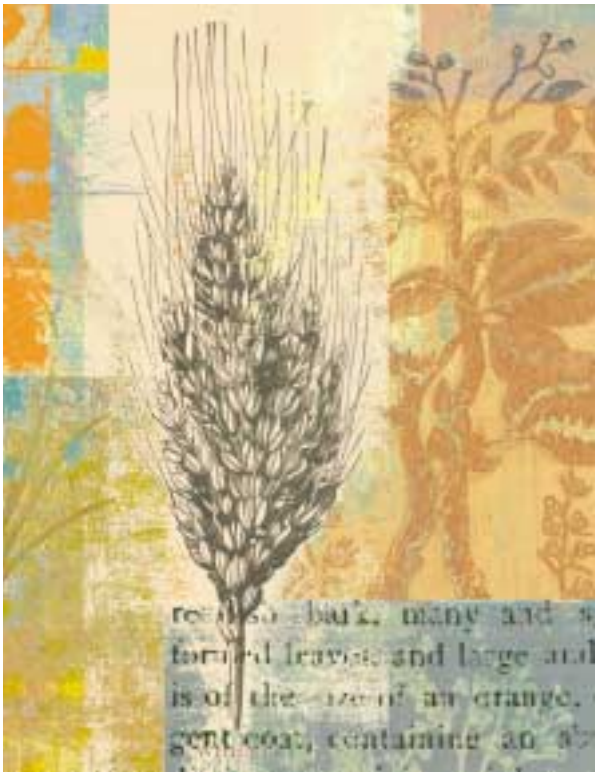
Laitan® is not imported into the United States. Consumers should therefore look for an extract with a similar kavalactone content. At recommended doses of 200 to 300 mg/day (150-210 mg kavalactones in a 70% formulation), kava does not appear to significantly impair motor function.[56,57] Kava withdrawal was not observed in the longest clinical trial, which lasted six months. Tolerance has been difficult to induce in animal models at high doses.[50,58] Kava, however, may accentuate the impairment observed with other sedative hypnotic agents when used in combination. Kava significantly enhances the impairment associated with alcohol as compared to alcohol alone.[59] There is also a case report of a consumer who became semi-comatose after combining kava with alprazolam (Xanax®).[60] Kava should be avoided in people who have Parkinson's disease or schizophrenia due to its potential effects on dopamine.[55] Four case reports of Parkinson-like symptoms have been reported in individuals using kava at recommended doses.[61] When high doses of kava are used for prolonged periods, a scaly yellow skin rash may develop.[49] At recommended doses, side effects are rare and typically consist of stomach upset and allergic skin reactions.[3]

Summary

Kava may promote a feeling of calmness that could be beneficial to individuals with mild to moderate anxiety. Kava has a favorable adverse effect profile at recommended doses. Unlike benzodiazepines, it has not been associated with dependence or tolerance. Kava may have a delayed onset of action of 4 to 8 weeks.[50] It should not be used for more than three months.[3]

Saw Palmetto - *Serenoa repens*

When extracted, the berries of the saw palmetto dwarf palm yield a fat-soluble substance comprised of fatty acids and sterols. The most common formulation used in Europe, Permixon®, is not available in the United States.[62] Standardized products that are available should contain at least 85-95% fatty acids and sterols.[62] Saw palmetto is most often used to alleviate symptoms associated with benign prostatic hyperplasia (BPH). BPH symptoms can improve even without treatment, as evidenced by a high placebo response rate of 40-60%.[62] For this reason, uncontrolled studies provide little proof of efficacy. The mechanism of saw palmetto is poorly understood, but a number of different possibilities have been suggested. These include inhibition of the enzyme that converts testosterone to dihydrotestosterone (DHT), direct antagonism of DHT binding to its receptor, blockade of alpha-1 receptors, antiinflammatory effects, and inhibition of prostate growth factors.[63-67] Saw palmetto does not affect prostate specific antigen (PSA) and therefore should not affect cancer screening.[63]



Clinical Trials

A recent review of 18 randomized controlled trials (16 of them double-blind), reported superior urologic symptom scores and urinary flow measures for patients receiving saw palmetto as compared to placebo.[67] These variables improved 24-28 %. Prostate size was not affected. Study participants had moderately severe BPH and received treatment for a mean of nine weeks. Two non-placebo controlled trials compared the efficacy of saw palmetto (320 mg) to an alpha-adrenergic blocker (either prazosin 4 mg or alfuzosin 7.5 mg.)[68] In both trials, improvements in symptom scores and flow measures favored the alpha-blocker. Saw palmetto 320 mg was as effective as finasteride 5 mg after six months of therapy in a randomized, double-blind trial involving patients with moderately severe BPH.[69] Both agents showed equivalent reductions in the International Prostate Symptom Score (IPSS), and increased quality of life and peak urinary flow. Only finasteride significantly reduced prostate volume and serum levels of PSA.

Adverse Effects, Drug Interactions and Dosing

Saw palmetto has rarely been reported to cause stomach upset and has no known drug interactions.[70] Products that are standardized to 85-95% fatty acid sterols should be selected. The recommended dose is 320 mg/day in two divided doses. The effects may be delayed 4 to 6 weeks.

Summary

Saw palmetto may alleviate certain symptoms associated with mild to moderate BPH. Its adverse effect profile is favorable and superior to that of alpha-blockers and finasteride. Long term benefits beyond six months have not been evaluated. Men wishing to initiate therapy with this product should have a baseline PSA to rule-out more serious disease. Pharmacists should be aware that the FDA discourages self-treatment of prostate problems. Under a new rule, manufacturers are not allowed to list "BPH" or "Helps to maintain urine flow in men over 50 years or age" on their product labels.[71]

Ginseng - *Panax species*

Of the various ginseng species, *Panax ginseng* (the Asian variety) and *Panax quinquefolius* (American ginseng), are most commonly found in the U.S.[72] There is also Siberian ginseng, which comes from the *Eleutherococcus senticosus* plant.[3] The latter is unrelated to the Panax species and has been studied less often in clinical trials. Nonetheless, European experts recommend both Siberian and Panax ginseng for similar conditions.[3] The root of the Panax species contains up to 28 different pharmacologically active ginsenosides.[73] The number and types of ginsenosides can vary between species, thus pharmacological activity may differ.[72] Mechanisms of action of ginseng observed *in vitro* and in animals are extensive and go beyond the scope of this review.

Clinical Trials

Panax ginseng is widely used for a variety of conditions including improved physical and mental performance, enhanced immune

function, and cancer prevention. There is no single, well-documented clinical use. *Panax ginseng* is typically reported to be adaptogenic, which means that it protects and normalizes the body against a variety of different stressors. Given this generalized claim, it is not surprising that many clinical trials have failed to find a reproducible effect. Most of the trials evaluating enhancement of aerobic exercise had small sample sizes and reported either beneficial results or no effect.[73, 74] Similarly, trials evaluating cognitive performance in healthy individuals only found improvement in a few out of a battery of cognitive tests.[75,76]

Other studies evaluated ginseng for its effect on quality of life and immune function.[77,78] A very low dose of *Panax ginseng* extract (40mg) given in a multivitamin complex significantly improved quality of life compared to patients receiving a multivitamin complex without ginseng.[77] Another trial suggested that the use of 100 mg of standardized *Panax ginseng* extract (G 115, Ginsana®) for 12 weeks at the time of flu vaccination significantly reduced the incidence of colds compared to vaccinated patients who received placebo.[78]

> "The majority of Complementary and Alternative Medicine users appear to seek care for their chronic problems with both alternative and conventional medicine."

Adverse Effects, Drug Interactions and Dosing

Ginsana®, a brand frequently used in European clinical trials, is available in the United States. The recommended dose of the Panax extract is 200 mg per day, standardized to contain at least 7% ginsenosides. Adverse effects are rare at recommended doses. High doses have been associated with a stimulatory response (insomnia, hypertension, nervousness) in some individuals.[79] However, these patients were also consuming undisclosed amounts of caffeine. Individuals who use prescription stimulants, should use ginseng cautiously or not at all. The herb may also have estrogenic properties and has been linked to case reports of breast pain and break-through vaginal bleeding in women.[80,81] Ginseng has been reported to cause manic behavior in patients, when used in combination with neuroleptics.[82,83] This combination should be avoided or closely supervised by a physician. Ginseng should be used cautiously in patients taking antiplatelet or blood thinning medications (e.g., aspirin, ibuprofen, warfarin), because of a possible interaction.[73] Pre- or post-operative patients should avoid taking ginseng for 7 to 10 days. Hypoglycemia has been reported following ginseng ingestion, so patients taking diabetic medications should monitor their blood sugar levels.[84] Other drug interactions suggesting increased digoxin levels and diuretic resistance have been challenged, based on the likelihood of product adulteration.[85-87]

Summary

Given the mixed clinical findings for *Panax ginseng* as a cognitive and performance-enhancing herb, and the small number of trials for other indications, there is no clear therapeutic recommendation for it at this time. With more well-designed clinical trials, a defined place in therapy may become apparent.

Echinacea - *Echinacea species*

Echinacea, also known as the purple coneflower, is commonly taken to alleviate symptoms of upper respiratory tract infection (URI). The primary species that are available in the U.S. are *E. pallida*, *E. angustifolia*, and *E. purpurea*. The German Commission E (Table 1.) only recommends the use of the above ground portions of *E. purpurea* and the root extract of *E. pallida*.[3] The most common formulations studied were *E. purpurea* fresh pressed juice (preserved in 22% alcohol by volume), Echinacin®, and *E. pallida* root extract. There has been no clinical research to support the use of the roots of *E. purpurea* or *E. angustifolia*. Investigators are now researching these particular formulations to determine if they have a place in therapy.

Echinacea products are not standardized by any specific constituent, but chicoric acid, alkamides, and the polysaccharide fractions are thought to have immune-modulating effects.[88] When used by itself, the polysaccharide fraction may have immuno-stimulant properties, increasing the production of various cytokines.[89]

However, when the entire extract is used in its marketed form, only enhanced phagocytic activity has been observed in humans.[89,90] One *in vitro* study did demonstrate enhanced cytokine production using *E. purpurea* fresh pressed juice.[91] Further research will likely identify the effects of echinacea *in vivo*.

Clinical Trials

Two recent randomized, double-blind, placebo-controlled trials evaluated the efficacy of echinacea in treating colds.[92,93] Both initiated treatment at the onset of symptoms. In the first trial, 120 people with symptoms of URI took *E. purpurea* fresh pressed juice preserved in 22% alcohol (Echinaguard®, the U.S. equivalent of Echinacin®) or placebo. The echinacea product significantly reduced time to recovery by 50%, from 8 to 4 days. A "full-blown" cold developed in significantly fewer patients receiving the echinacea product (40% versus 60%).[92] In the second trial, a dried ethanolic *E. purpurea* herb extract (Echinaforce®, prepared from 95% herb and 5% root), was significantly better than placebo or *E. purpurea* root extract at reducing cold symptoms.[93] This reaffirms the German Commission E recommendation that only the above ground portions of the *E. purpurea* plant should be used.

The use of echinacea to prevent the incidence of colds has also been studied in two clinical trials.[94,95] In both trials, echinacea or placebo was administered in a randomized, double-blind fashion for 8-12 weeks. One trial used *E. purpurea* fresh pressed juice and found no significant differences in cold incidence or severity.[94] The other trial compared *E. purpurea* root extract, *E. angustifolia* root extract, and placebo and found no significant differences in time to first upper respiratory infection.[95] The latter, however, used formulations of echinacea that are not recommended by the German Commission E.

TABLE 1.

German Commision E

- Formed in Germany
- Comprised of scientists and clinicians with various backgrounds
- Reviewed and wrote monographs for over 300 botanicals between 1982 and 1994
- Rated botanicals as "acceptable" if they displayed "absolute safety" and "reasonable certainty of efficacy"
- Published monographs in the German *Bundesanzeiger*, which is similar to the *U.S. Federal Register*
- Monographs were translated by the American Botanical Society

Adverse Effects, Drug Interactions and Dosing

Echinacea occasionally causes stomach upset, taste disturbances, headache, dizziness and tiredness.[89] Patients with asthma or allergic rhinitis may be at higher risk for allergic reactions, based on the results of skin testing.[96] There are no reported drug interactions. Given the high alcohol content of certain extracts, patients taking metronidazole (Flagyl®), chlorpropamide (Diabenese®), or cefotetan (Cefotan®) are likely to experience a disulfiram-like reaction (nausea, flushing) and should avoid these products. Until the mechanism is fully understood, patients with autoimmune disorders (e.g., rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus), those who are immune-compromised (e.g., AIDS, cancer), or those using immuno-suppressive agents (e.g., cyclosporine, corticosteroids) should not use this product.[3] The recommended dose is 900 mg/day of the *E. pallida* root extract or 6-9 mL/day of the *E. purpurea* fresh pressed juice prepared from the above the ground portions of the plant (e.g., Echinaguard® by Nature's Way) divided into two to five doses daily.[3] Products should not be used beyond 8 weeks.[3]

Summary

Echinacea may be beneficial in reducing symptoms associated with acute URI. Recent studies do not support its use for cold prevention. It should be taken at the first sign of a cold until symptoms resolve.

Black Cohosh - *Cimicifuga racemosa*

Among all herbs, sales of black cohosh increased the most (almost 500%) in

1999.[2] Black cohosh is commonly used for symptoms associated with menopause.[2] It is available both in Europe and in the United States under the commercial name Remifemin®. The root of the plant is rich in triterpene glycosides, which are considered to be the main active ingredients.9[7] An isopropanolic extract of Remifemin® is available as a 20 mg tablet that is standardized to contain 1 mg of 27-deoxyacetein (a triterpene glycoside).[85] An equivalent dose of the liquid ethanolic extract would be 20 mg or 20 drops. Commercially available isopropanolic and ethanolic extracts do not appear to contain isoflavones.[97,98]

Clinical Trials

Initial studies suggested that compounds in the root of the plant reduced secretion of leutinizing hormone (LH) in menopausal women and bound estrogen *in vitro*.[99,100] Subsequent research did not reveal estrogenic effects on vaginal or uterine tissue in rodents using the ethanolic extract.[101] A recent clinical trial found no effect of Remifemin® on LH secretion, follicle stimulating hormone (FSH) secretion, sex-hormone binding globulin (SHBG), prolactin, or estrogenic markers (hypertrophy of vaginal epithelium).[102] Effects of black cohosh on breast tissue in vivo are not known, but the isopropanolic extract was shown to inhibit growth of an estrogen-dependent breast cancer cell line in vitro.[97] Until further research is done, the mechanism of black cohosh remains unknown.

> "The average person using Complementary and Alternative Medicine is actually a well-educated health consumer with a chronic, but not life-threatening condition."

Two systematic reviews have detailed the results of eight studies published between 1982 and 1997.[97,103] The primary outcome measure in most of these trials was the Kupperman Index of Menopausal Symptoms, a standardized scale that encompasses a variety of menopausal symptoms. All eight trials reported significant benefits in symptom scores using 2 to 8 mg/day of 27-deoxyacetein, equivalent to 40 to 160 mg of Remifemin®, for up to 12 weeks. Of the eight studies, seven were published in the German language, seven had an open study design, two were randomized, and four had control groups. The only double-blind, placebo-controlled study randomized 80 patients to receive 4 mg of Remifemin®, 0.625 mg of conjugated estrogen, or placebo. At 12 weeks, the Kupperman score was significantly reduced for the Remifemin® group as compared to the estrogen and placebo groups. The vaginal epithelium of patients in the Remifemin® group was also notably increased. It should be noted that the manufacturers of Remifemin® now recommend a lower dose of 2 mg per day, based on research showing equivalent efficacy without deleterious effects on the vaginal epithelium.[104]

Adverse Effects, Drug Interactions and Dosing

The recommended dose of Remifemin® is 40 mg of the herb (i.e., one tablet containing 1 mg of 27-deoxyacetein twice daily or 20 drops of the liquid formulation twice daily.)[86] Onset of action may not occur for up to four weeks.[97,103] Benefits beyond 12 weeks have not been adequately studied, so consumers should continue to monitor for improvement.[97,103] Adverse effects are rare at recommended doses and typically involve stomach upset.[92] No drug interactions have been reported. Historically, this herb was used to induce labor and therefore should be avoided in pregnant women. Black cohosh has not been studied for other disorders associated with menopause, such as cardiovascular disease and osteoporosis.

Summary

Preliminary evidence indicates that black cohosh may be beneficial in reducing menopausal symptoms such as hot flashes, mood disturbances, and sleep disturbances. Long term benefits have not been adequately studied. The German Commission E recommends limiting product use to no more than six months.[104]

Dietary Supplements:

Sorting Through the Evidence

Candy Tsourounis, Pharm.D.
Assistant Clinical Professor
Acting Director, Drug Information Analysis Service
School of Pharmacy
University of California, San Francisco

Pharmacists today sell dietary supplements along with non-prescription products. Thus, they are likely to be approached by consumers with questions about supplement quality, efficacy, and safety. This article will focus on the scientific evidence supporting the use of some popular non-botanical, non-vitamin dietary supplements. The following products were selected because they are heavily promoted in the media and frequently considered for purchase by consumers.

Melatonin

Melatonin is a hormone produced by the pineal gland. The pineal gland is located in the base of the brain and is important in controlling normal sleep-wake cycles. Melatonin is released during periods of darkness, between 9 p.m. and 4 a.m. During the day, melatonin release is suppressed. With age, melatonin levels slowly decline such that levels in a 60-year old are much less than those in a 20-year old. For this reason, researchers have suspected that replacing low levels of melatonin may help correct age-associated problems such as insomnia. Insomnia has been estimated to occur in 13 to 33 percent of the U.S. adult population.[1] Young adults typically suffer from sleep onset insomnia (trouble falling asleep), while older adults commonly suffer from sleep maintenance insomnia (trouble staying asleep).[2]

Clinical Trials

Several clinical trials have studied melatonin for insomnia.[3-5] Improvements in the quality of sleep (onset and duration), were noted. However, these studies were poorly designed in that dosing, patient age, timing of drug administration, randomization of subjects, study duration, and type of monitoring varied greatly. According to the largest clinical trial, both immediate- and sustained-release melatonin appeared to help patients with sleep onset insomnia. Sustained-release melatonin did not help patients with sleep maintenance insomnia.[6] Further research is needed to determine the effect of patient age, melatonin dose, duration of therapy, and underlying etiology on melatonin efficacy.

Melatonin has also been studied for preventing jet lag. Jet lag occurs when the external time does not correspond with the internal time. This often occurs with air travel across multiple time zones. Typical symptoms of jet lag include daytime drowsiness, gastrointestinal distress, and frequent awakenings. Non-drug therapy for jet lag involves maximizing exposure to daylight and darkness according to the new time zone. Exogenous melatonin is used to reset peak melatonin levels. Older studies assessed the effects of melatonin in improving jet lag symptoms in passengers and flight crew traveling across multiple time zones.[7-11] These studies used varying melatonin doses (5 to 8 mg immediate release) at different times of administration. Subjective improvements in symptoms were reported, including decreased daytime fatigue, improved mood, and better recovery time. The most recent placebo-controlled clinical trial included 257 subjects traveling between New York City and Oslo, Norway.[12] Patients received placebo or three different doses of melatonin (0.5 mg at bedtime, 5 mg at bedtime, and 0.5 mg given an hour earlier each night). Upon arrival and for the next five days, all patients reported similar jet lag symptoms with no differences between groups. No improvements in napping, sleep onset, sleep duration, or other symptoms were observed.

Adverse Effects and Potential Interactions

The adverse effects of melatonin are mild, but may involve daytime drowsiness, headaches, rapid heart beat, and rarely, depressed mood.[7-11] A rare case of rash and one acute psychotic episode with melatonin overdose have been reported.[13,14] Although melatonin has been associated with daytime drowsiness, it is considered less sedating than over-the-counter antihistamines and other prescription sedatives. High doses of melatonin (75 mg to 300 mg) in combination with a progestin have been associated with partial inhibition of ovulation.[15] Therefore, women who are attempting to conceive, or who are currently pregnant, should avoid taking melatonin. Poorly manufactured melatonin formulations may be associated with adverse effects, as a result of releasing the melatonin all at once or not at all.[16]

Drug interactions with melatonin supplements have not been formally studied. However, combining melatonin with alcohol or other sedative hypnotics may cause excessive sedation or dizziness.

Dosing and Recommendation

Doses used to treat insomnia vary. Therefore, the lowest effective dose of melatonin should be used. Doses of 0.3 mg to 5 mg of the immediate-release formulation should be taken just prior to bedtime.[17] Reading lights should be turned off to help trigger natural melatonin release. Sleep onset should occur within 30 to 45 minutes. If sleep does not ensue, a repeat dose may be taken, up to a maximum of 20 mg. The safety of long-term melatonin use is not known, therefore it should only be used when necessary. As with any sedative-hypnotic, avoid using melatonin for prolonged periods of time (more than one to two weeks).

Melatonin appears to be useful for sleep onset insomnia. Its usefulness in maintenance insomnia and jet lag is less clear and requires further research.

Glucosamine

Glucosamine is an essential component for cartilage nutrition and is also incorporated into cartilage. Osteoarthritis (OA) is a degenerative disease that affects cartilage, bone and other tissues. Cartilage degeneration commonly occurs in the knee joints and spine. Cartilage is composed of cartilage cells and extracellular matrix. The matrix is a mesh of fibers that anchors cartilage cells, collagen, and other proteins. Together these proteins help to strengthen the joint and provide support. Cartilage does not receive blood supply; therefore, all necessary nutrients are supplied by the synovial fluid, bone, and other structures (perichondrium).[18]

Glucosamine incorporates into protein structures called glycosaminoglycans (GAGs). Multiple GAGs form proteoglycans (PGs), which resemble tree branches. When taken as the sulfate form, glucosamine gets incorporated into the GAGs allowing the sulfate structure to help keep the branches apart. Glucosamine also contributes to cartilage cell nutrition.

Clinical Trials

Investigators have studied glucosamine in OA, but many of these trials had serious design flaws.[19] Two adequately designed studies assessed the effects of glucosamine sulfate in patients with mild to moderate OA of the knee or in generalized OA.[20,21] Only one of these used oral glucosamine sulfate; the other used an injectable

form. After one week of oral glucosamine therapy (1,500 mg daily), patients displayed statistically significant improvements in pain scores as compared to placebo.[21] By the second week, patients receiving glucosamine sulfate experienced less joint tenderness and swelling than did those receiving placebo. Both of these studies were short and did not disclose concomitant medications. A recent meta-analysis had similar results, but noted that the published studies tended to overestimate the benefits of glucosamine.[19] These authors concluded that glucosamine may improve OA symptoms about 30%.

Glucosamine HCl has also been studied for OA knee pain. In a three-month study, patients received glucosamine HCl (500 mg three times daily) or placebo.[22] After two months, there were no differences in mobility and joint function. The only statistically significant improvements were in pain relief and objective knee improvements on X-ray. Another study assessed the role of a combination product of glucosamine HCl, chondroitin, and manganese ascorbate (Cosamin DS®) in treating knee and cervical spine OA.[23] While the authors concluded that it improved knee OA, this study was limited by the sample size and a cross-over design that could have resulted in carry-over of effect. Furthermore, the addition of chondroitin may have contributed to this product's effectiveness.

Other salt forms of glucosamine are available, such as glucosamine hydroiodide and N-acetyl-glucosamine. Glucosamine hydroiodide should be avoided because it can interfere with undiagnosed thyroid disease. There are no clinical trials assessing the effectiveness of the hydroiodide salt on knee OA. N-acetyl-glucosamine is thought to increase the incorporation of glucosamine into cartilage, but laboratory studies suggest that it is not incorporated into cartilage cells.[24] There are no clinical trials assessing the value of these or any other additional ingredients.

Adverse Effects and Potential for Interactions

Since glucosamine products are aminosaccharides, the most commonly reported problems are gastrointestinal (nausea, vomiting, diarrhea). One study suggested that glucosamine sulfate may contribute to insulin resistance.[25] While this study demonstrated an increase in fasting insulin concentrations, blood glucose levels were not affected. Patients with diabetes who want to take glucosamine should monitor their blood sugars as usual.

There are no known interactions between glucosamine and other drugs. However, the ingredients that are added to glucosamine products may interact with other drugs or diseases. These include sodium, potassium, manganese, and ascorbic acid. Sodium and potassium are added to increase the stability of glucosamine sulfate and are usually present in small amounts. Manganese and ascorbate are cofactors that are indirectly involved in strengthening cartilage. Ascorbate is added to products to help strengthen collagen fibers. Manganese deficiencies have been associated with abnormal bone and cartilage formation; therefore, manufacturers add manganese to increase glucosamine incorporation into cartilage. The recommended daily intake (RDI) for manganese is 2 mg to 5 mg. Many glucosamine products exceed the RDI and provide nearly 228 mg of manganese daily. While the effects of high dose manganese from glucosamine are unknown, there is potential for manganese-induced headache, confusion and other adverse central nervous system effects with excessive use.

Dosing and Recommendation

Currently, only glucosamine sulfate appears effective in improving the pain associated with OA. Combination products are more costly and require further study. With usual doses of 500 mg three times daily, OA pain relief with glucosamine sulfate typically takes about one week, but may be delayed up to one month.[26] Anti-inflammatory drugs (e.g. ibuprofen) have a faster onset and a shorter duration of action. People who wish to use ibuprofen in combination with glucosamine may do so, especially during the first week of therapy or for an acute flare of OA pain.

Chondroitin Sulfate

Chondroitin sulfate is one type of glycosaminoglycan and consists of repeating glucosamine units. It is often combined with glucosamine to improve the symptoms of OA. Dietary supplement manufacturers claim that chondroitin sulfate inhibits the breakdown of cartilage by blocking cartilage destroying enzymes. While this remains to be proven, there is evidence that chondroitin helps to prevent cartilage breakdown.[27] Early research suggested chondroitin sulfate was not absorbed;[28] however, other studies now suggest that it is, since it is broken down in the stomach to individual glucosamine units.[29,30]

Clinical Trials

A few randomized, double-blind, placebo-controlled trials (three months to one year) have assessed the effects of chondroitin sulfate in improving OA knee pain.[31-33] In one of these, chondroitin sulfate was dosed as either 400 mg three times daily or 1200 mg once daily. Patients had statistically significant improvements in joint pain and function with either regimen as compared to placebo.[31] Only one study compared chondroitin sulfate to a nonsteroidal anti-inflammatory agent, diclofenac sodium.[33] Patients with knee OA were given chondroitin sulfate (400 mg three times daily) for three months followed by placebo for three months. The other group of patients received diclofenac sodium (50 mg three times daily) for one month and then placebo for five months. Patients in the chondroitin group experienced gradual improvements in joint function and pain. These improvements were sustained for up to one month after discontinuation of chondroitin sulfate. Patients who received diclofenac experienced a gradual worsening of symptoms after discontinuation of the drug. While these results were statistically significant, the authors did not take into account the analgesic properties, faster onset and longer duration of action of diclofenac. A recent meta-analysis found that chondroitin sulfate can improve symptoms of OA to a similar degree as glucosamine, usually reducing them by about 30 percent.[19]

Adverse Effects and Potential Interactions

Chondroitin sulfate is well tolerated and has mild gastrointestinal side effects, similar to those of glucosamine. Its effects on glucose and insulin release are not known. Drug interactions have not been formally studied.

Dosing and Recommendation

Chondroitin sulfate has a very slow onset of action and the effects on joint function last longer than those of diclofenac. It can be dosed as either 400mg three times a day or 1200 mg once daily. Improvements may be noted in one week, but may take up to one or two months.

Clinical trials suggest that both glucosamine and chondroitin are effective in relieving symptoms of OA. The value of a combination of both of these products has not been compared to either one alone in clinical trials. The value of ingredients like manganese and ascorbate is unknown and their addition appears unnecessary.

Shark Cartilage

The manufacturers of shark cartilage have claimed for years that sharks do not get cancer and therefore must possess cancer protective substances. Sharks have an abundance of cartilage. Shark cartilage is primarily composed of the protein, chondroitin sulfate.[34] Researchers recently found that sharks do, in fact, get cancer, a form of cartilage cancer known as chondroma.[35] The exact components within shark cartilage that are thought to afford protective anticancer properties are not yet known. Manufacturers of shark cartilage contend that it contains angiogenesis inhibitors and would therefore be of benefit to people with solid tumors. Angiogenesis inhibitors block the formation of new blood vessels and subsequently block the delivery of nutrients tumor cells need for growth. Angiogenesis inhibitors are thought to target tumor cells directly, thereby preventing systemic side effects.

Clinical Trials

The role of shark cartilage in cancer is based on a 1977 *in vitro* study. Two shark extracts, sphyrnastatin 1 and 2, were purified from the hammerhead shark.[36] These extracts were thought to have angiogenesis inhibitor properties, but that still remains to be proven. Few clinical trials are available to support the use of shark cartilage in treating cancer. Only one published clinical trial assessed the effects of shark cartilage in 58 adult patients with advanced cancers, who were unresponsive to conventional chemotherapy. [37] All patients received 1 gm/kg/day in three divided doses. At the end of three months, no patients experienced a complete or partial response to therapy and there were no improvements in quality of life scores.

Adverse Effects and Potential Interactions

Since shark cartilage is composed of chondroitin sulfate, it has the same gastrointestinal side effects. There is one report of hepatotoxicity with shark cartilage; however, the product in question was never analyzed for contaminants.[38] Shark cartilage has not been studied for drug interactions.

Recommendation

Patients who wish to use shark cartilage should know that there is no clinical evidence supporting its use for cancer or solid tumors.

Dihydroepiandrosterone (DHEA)

DHEA is a precursor hormone produced predominantly by the adrenal glands.[39] DHEA is also called the mother hormone, because it is ultimately converted to both estrogen and testosterone. DHEA circulates in the blood as DHEA-S, the sulfate ester form. DHEA-S levels are more commonly measured, since there is less variation in these levels as compared to DHEA levels. DHEA and DHEA-S levels peak between 20-30 years of age[39] and then decline progressively until death. Dietary supplement manufacturers promote DHEA-S supplementation to prevent and slow age-associated disorders.

DHEA, when ingested as a supplement, is converted to both estrogen and testosterone.[40] Initially, this conversion depends upon gender. In non-menopausal women DHEA is predominantly converted to testosterone since levels of estrogen are abundant. In menopausal women and in men, DHEA appears to be converted to both estrogen and testosterone.[41,42] This has been the basis for researching DHEA in a number of disorders.

Clinical Trials

DHEA has been studied for its effects on weight loss, depression, prevention of cardiovascular disease, reduction of cholesterol, and improving the immune system.[43-46] However, these studies enrolled too few patients to adequately evaluate the suspected effects. Until more information is available, DHEA should not be used to treat any of these conditions in place of traditional agents.

DHEA has been studied in Alzheimer's disease, since low endogenous DHEA-S levels have been shown to correspond to dementia. The effects of DHEA supplementation are unknown; however, research is ongoing in this area. The use of DHEA in Systemic Lupus Erythematosus (SLE) appears promising. A few clinical trials found that DHEA doses of 50 mg to 200 mg daily for one year resulted in statistically significant improvements in disease activity measurements.[47-49] Some patients were able to decrease their prednisone dose, although the number was not statistically significant. Nearly 60% of women discontinued DHEA therapy before the study was completed, due to lack of effectiveness and androgenic side effects. Some women reported menstrual irregularities, acne, and emotional changes.[44,45] DHEA may not be effective in all women with SLE, but it may improve the quality of life for some. It has shown enough promise to receive orphan drug status for the treatment of SLE and to reduce steroid doses in steroid-dependent SLE.[50]

Men often wish to supplement declining DHEA-S levels with DHEA, but the effects of supplementation have not been adequately studied. Recent evidence suggests that DHEA may be useful in adult males with impotence.[51,52] Supplementation increases free testosterone

levels by about 5 to 10 percent for six weeks. Whether testosterone levels remain elevated or return to normal with use beyond six weeks is unknown.

In healthy adults, DHEA is most often used to increase testosterone and build muscle mass in athletes and those who are weight training. In these cases, high DHEA doses are used to increase testosterone production. Studies have shown men may experience a small increase in testosterone levels with a more pronounced increase in estrogen.[53] Others use DHEA for its euphoria-like effects and to increase their sense of well-being. These effects wear off with continued use.

During menopause, women may use DHEA to replace their natural levels of estrogen. While DHEA is converted to estrogen in postmenopausal women, there is no evidence to suggest that it can help prevent osteoporosis, cardiovascular disease or improve the symptoms of menopause.[41,54] DHEA is not recommended during menopause because it can decrease HDL cholesterol levels[55] and its effect on breast cancer risk is unknown. The amount of DHEA needed to replace endogenous estrogen levels also needs further study.

Adverse Effects and Potential Interactions

Most adverse effects of DHEA are related to dose. Women may experience mild side effects when taking 25-50 mg once daily.[56] At higher doses (> 50 mg daily), women may experience masculinizing side effects such as deepening of the voice, increased facial hair growth, acne, menstrual irregularities, and others.[41,56] In contrast, men who use more than 100 mg daily may experience estrogenic effects such as breast enlargement and tenderness. Rarely, adverse effects have occurred at replacement doses. One case of cardiac arrhythmia, which occurred with re-challenge, was reported in a person taking 25 to 50 mg of DHEA daily.[57] The product was not analyzed for content or contaminants. At high doses (200-300mg daily for three months) symptoms of mania have been reported.[58]

Since DHEA is converted to estrogen and testosterone, it may possibly contribute to undiagnosed prostate enlargement or prostate cancer in men. Men who wish to start therapy should have baseline DHEA-S levels measured. Men over 45 years of age should undergo yearly digital rectal examinations and a baseline Prostate Specific Antigen (PSA) level should be measured.

There are no reported drug interactions with DHEA. However, it may contribute to the adverse effects associated with drugs sharing a similar pharmacology. DHEA should not be combined with estrogen or testosterone.

Dosing and Recommendation

DHEA has no real clinical value for healthy adults. Its role in SLE is promising, but requires further research. Replacement doses have few adverse effects, depending upon the patient's gender and menopausal status. Doses of 50 mg to 100 mg daily are adequate to replace endogenous DHEA-S levels to those of young adulthood. The hormonal protective effects of DHEA have not been clearly defined or compared to standard pharmaceuticals. Since it is a precursor hormone, women should avoid taking DHEA during pregnancy and lactation. Individuals who choose to replace low levels of DHEA should take the lowest possible dose (25-50 mg once daily). Long term safety and efficacy have not been systematically studied. With long term supplementation, regulation of endogenous DHEA may be altered. The antioxidant properties of DHEA have not been tested, and it is not known if DHEA improves longevity or well being. There is no evidence that DHEA supplementation reverses age-related disease including cancer, cardiovascular disease, or Alzheimer's disease.

Coenzyme Q 10 (Ubiquinone)

Coenzyme Q 10 is also known as ubiquinone. Ubiquinone is naturally found in the body and in the mitochondria of many organ tissues such as the heart, kidney, and liver.[59] It is also found in foods such as spinach, soybeans, walnuts, and almonds. Ubiquinone circulates in the blood in the reduced form called ubiquinol. Ubiquinol is involved in many cell processes and in the generation of cell energy or ATP. Ubiquinol also serves as a natural antioxidant by blocking free radical scavengers. Free radicals contribute to heart disease and other disorders. Ubiquinone levels decline with age and therefore have been associated with an increased risk for heart disease.[59] The dietary supplement, Coenzyme Q10, is used primarily for its protective effects on the heart.

Clinical Trials

Coenzyme Q 10 has been studied as an adjunct for reducing high blood pressure.[60-63] In most studies, patients were allowed to continue their antihypertensive therapy during the administration of coenzyme Q10. Most of these clinical trials were not blinded and lacked a placebo comparison group. Despite these shortcomings, coenzyme Q10 reduced systolic and diastolic blood pressure an average 10 mm Hg after ten weeks of therapy at doses ranging from 100 mg to 225 mg daily. Only one controlled trial compared Coenzyme Q10 to placebo in reducing blood pressure.[63] After ten weeks of therapy, coenzyme Q10 reduced both systolic (SBP) and diastolic blood pressure (DBP) an average of 10 mm Hg and 7 mm Hg respectively. These reductions were statistically significant and were first observed at three to four weeks into treatment.

Numerous clinical trials have studied coenzyme Q10 in people with cardiomyopathy and heart failure. Cardiomyopathy is a general term referring to heart muscle dysfunction. There are many types of cardiomyopathy with various underlying causes, but prolonged cardiomyopathy can lead to heart failure. Most studies of cardiomyopathy and heart failure were poorly designed (e.g. small sample sizes, lack of blinding, lack of placebo control).

Two recent double-blind, crossover trials assessed the effects of coenzyme Q 10 (100 mg/daily) on moderate to severe

cardiomyopathy.[64,65] Patients were classified as having New York Heart Association (NYHA) functional classification stages II, III and IV and were assessed at four and three months respectively. In the first trial, no statistically significant differences were observed in ventricular function, ejection fraction, or calculated cardiac output at the end of four months.[64] No improvements in exercise tolerance or electrocardiogram (ECG) were observed. The second study measured baseline ubiquinone levels. Patients enrolled had ubiquinone levels that were considered low for patients with heart disease (less than 1.2 mcg/mL). Investigators observed statistically significant improvements in stroke volume and ejection fraction at three months. In addition, these patients had ubiquinone levels that were greater than 2 mcg/mL. This suggests that supplementation may help correct low ubiquinone levels and improve symptoms.[65]

One placebo-controlled study assessed the effects of coenzyme Q10 on congestive heart failure.[66] Six patients received placebo or 150 mg of coenzyme Q10 daily for four weeks. No statistically significant increases in exercise tolerance were observed, but patients receiving coenzyme Q10 had statistically significant improvements in ejection fraction and stroke volume. Another placebo-controlled trial found that patients receiving 2 mg/kg coenzyme Q10 were less likely to be hospitalized for worsening of heart failure, as compared to placebo.[67] These effects were statistically significant.

Many of these trials used crude estimates of left ventricular function. Only one clinical trial used Swan-Ganz measurements and echocardiography to assess ventricular heart function.[68] This trial enrolled 27 patients with left heart failure of at least three months duration. Patients received coenzyme Q10 (100 mg daily) or placebo for twelve weeks. There was no difference in cardiac output or any other objective cardiac parameters. There were no differences in well being or quality of life between patients receiving placebo or coenzyme Q10. A recent randomized, double-blind, placebo-controlled study also found no benefit from coenzyme Q10.[69] This trial assigned 55 patients with NYHA class II, III and IV symptoms (ejection fraction less than 40 percent) to receive either coenzyme Q10 (200 mg/day) or placebo. After six months, coenzyme Q10 had no effect on ejection fraction or symptoms. There was no relationship between coenzyme Q10 levels and supplementation.

Two randomized, double-blind, placebo-controlled studies assessed the efficacy of coenzyme Q 10 (120 mg daily for 28 days) in patients with coronary artery disease.[70,71] In the first, patients displayed statistically significant improvements in lipoprotein-a concentrations (a marker for atherosclerosis) and increases in HDL cholesterol levels.[70] In the second trial of patients with acute myocardial infarction, cardiac deaths and rate of re-infarction were significantly reduced, as compared to the placebo group.[71]

Coenzyme Q10 has also been evaluated as to its ability to improve exercise tolerance in patients with chronic stable angina.[72] Twelve patients were given either 150 mg coenzyme Q10 daily or placebo. After four weeks, patients receiving the dietary supplement displayed statistically significant improvements in exercise tolerance and a delay in the time it took to develop ischemic changes on ECG. These trials all suggest marked improvements in patients with angina. However, long-term trials beyond one month are needed to evaluate any protective effects.

Adverse Effects and Potential Interactions

Coenzyme Q10 is well tolerated. Most of the clinical trials report nausea and gastrointestinal distress (nausea, diarrhea, heartburn). Some patients have also experienced maculopapular rash and thrombocytopenia.[73,74] Other reported side effects include irritability, headache, and dizziness.[75-77] One *in vitro* study suggested coenzyme Q10 interferes with glucose regulation.[78] A study in patients with diabetes, however, did not show any effect on blood glucose regulation.[79]

One case report describes an interaction between coenzyme Q10 and warfarin.[80] In that case, the addition of coenzyme Q10 to warfarin therapy decreased the effectiveness of warfarin. Theoretically, co-enzyme Q10 may benefit people taking cholesterol lowering therapy, because ubiquinone is the end product of cholesterol formation. Drugs that block cholesterol formation, such as the HMG-CoA reductase inhibitors, have long been suspected of decreasing ubiquinone levels. Early clinical studies suggested that pravastatin and simvastatin decreased ubiquinone levels and therefore could affect a patient's risk for cardiovascular disease.[81] One study measured the effect of statin therapy on ubiquinone levels in seventeen men taking simvastatin (20 mg to 40 mg) daily for 4.7 years.[75] Simvastatin therapy was stopped for four weeks. After four weeks, serum ubiquinone levels increased by 32%. These patients were then treated with lovastatin (20 to 40 mg daily) and displayed a 25% decrease in serum ubiquinone levels. Despite these changes, the average levels approximated normal ubiquinone levels in healthy adult males. Furthermore, the metabolic consequences of low ubiquinone levels are unknown. Patients who are beginning statin therapy should not require ubiquinone supplementation, because it is likely that the benefits of statin therapy outweigh any potential risk associated with low ubiquinone levels.

Dosing and Recommendation

In healthy adults, doses of 30-60 mg daily can provide antioxidant effects. Most clinical trials in heart disease used doses between 100 to 150 mg daily, administered in three divided doses. These doses increased baseline ubiquinone levels to 2-3 mcg/mL, which some claim to be cardioprotective. Patients who wish to supplement coenzyme Q10 should know that minimal benefits have been observed in people with heart failure or cardiomyopathy. Patients who feel they need coenzyme Q10 should be referred to a physician for evaluation, because they may have symptoms of a more serious condition.

Part Two: Risks Associated C

Potential for Harm

Mary L. Chavez, Pharm.D.
Professor of Pharmacy Practice
Director of Complementary Therapies Education and Research
The Center for Advancement of Pharmacy Practice
College of Pharmacy
Midwestern University - Glendale

During the last century, Americans witnessed the gradual disappearance of herbs and other natural products, which were often misbranded or adulterated, from pharmacy shelves. They were replaced by synthetic drugs produced by the pharmaceutical industry.[1] Interestingly, as the twentieth century drew to a close, there was a resurgence in the use of natural products. Once again, an increasing number of Americans are using herbal remedies.[2]

Although herbs are widely believed to be safe because they are "natural," evidence suggests that these products are not without risks.[3,4] Herbs and dietary supplements have significant pharmacological activity and can potentially cause adverse effects and drug interactions. Assessment of the safety of these remedies is of utmost importance, but ascertaining whether or not a specific product is associated with harmful effects is difficult. Evaluation of these products is more complex than for pharmaceuticals, because herbs and other dietary supplements are often heterogeneous in nature. Additionally, information about them is often limited or anecdotal.[5]

Dietary supplements, including herbal remedies, are not regulated like over-the-counter (OTC) and prescription medications. Prescription medications cannot be marketed without undergoing a multi-step approval process that is designed to provide proof of both efficacy and safety.[1,3] With the passage of DSHEA, the burden of proof shifted away from the manufacturer to the Food and Drug Administration (FDA). No pre-marketing clinical research on the efficacy of the product or ingredients is required before manufacturing dietary supplements.[3] Unlike OTCs and prescription medications, dietary supplements are also not subject to enforceable quality control standards.[6] Thus, there are documented reports of adulteration and contamination of herbal products.[1-6] In addition, dietary supplements can be sold with advocacy third-party literature that may be misleading or does not include information on potential adverse effects and drug interactions.[1,3]

In the past few years, the dietary supplement industry has attempted to improve quality control in the manufacturing of these preparations. Reputable manufacturers strive to assure that their products are authentic, contain the chemical constituents as stated on the label, and are free of contaminants and adulterants. Nevertheless, potential for harm still exists. This article will review some of the primary reasons why pharmacists and consumers should exercise caution in the use of dietary supplements.

Misidentification

It is very important that the manufacturer establishes the authenticity of the plant material before processing herbal remedies. Unless authenticity of a plant is established, there is no way of assuring the true identify of the plant material inside the package. This can result in mislabeling. Inexperienced collectors have mistaken the identity of wild plants. Herbal preparations may not contain the plant as stated on the label, which can cause serious toxicities.[7-9]

Plants can be named using several different methods, including by the common English name, by various translated synonyms, and by the Latin binomial name. It is important to identify plants by their binomial Latin name for genus and species. Mistakes can occur when common names are used.[5] Plants can be misidentified at the time of picking or at the time of bulk purchase by the manufacturer. Often mistakes are not detectable upon gross inspection of samples of the plant material.[5] The authenticity of the material should be verified microscopically and compared with a voucher specimen of the plant held in an herbarium.

Inadvertent substitution because of false authentication or deliberate plant substitution has occurred.[5] There are case reports of rapidly progressive interstitial nephritis in young women who consumed a Chinese slimming tea that contained the nephrotoxic compound aristolochic acid. *Aristolochia fangchi* was used in place of *Stephania tetrandra*.[10] The mistake was thought to be due to confusion between the Chinese names "Fang ji" (*S. tetrandra*) and "Guang fang ji" or "Fang chi" (*A. fanchi*)[4,11] As a consequence, 80 cases have been identified and more than half of these patients have developed end-stage renal failure.[12] Some of these patients have now developed urothelial carcinoma.[13]

Adulteration

There are recent reports of adverse effects associated with the deliberate addition of unreported pharmaceutical drugs by manufacturers of dietary supplements.[14-16] Acute interstitial nephritis, reversible renal failure, loss of blood pressure control, and peptic ulceration have been reported with the multi-component Chinese herbal remedy "Tung shueh" used for arthritis.[17] Chemical analysis of the product found that nonsteroidal anti-inflammatory and sedative drugs had been added to the herbal mixture.[14,16-18] The toxicity caused by this product was most probably due to the addition of the synthetic drugs.

Ayurvedic remedies and traditional Chinese medicines usually contain a complex mixture of various herbs, animal components and mineral substances.[19] Heavy metals such as arsenic, cadmium, lead, mercury, and thallium have been found in appreciable quantities in some of these preparations.[5,19] There are case reports of serious lead poisoning from herbal remedies imported from Asia and India.[20-22]

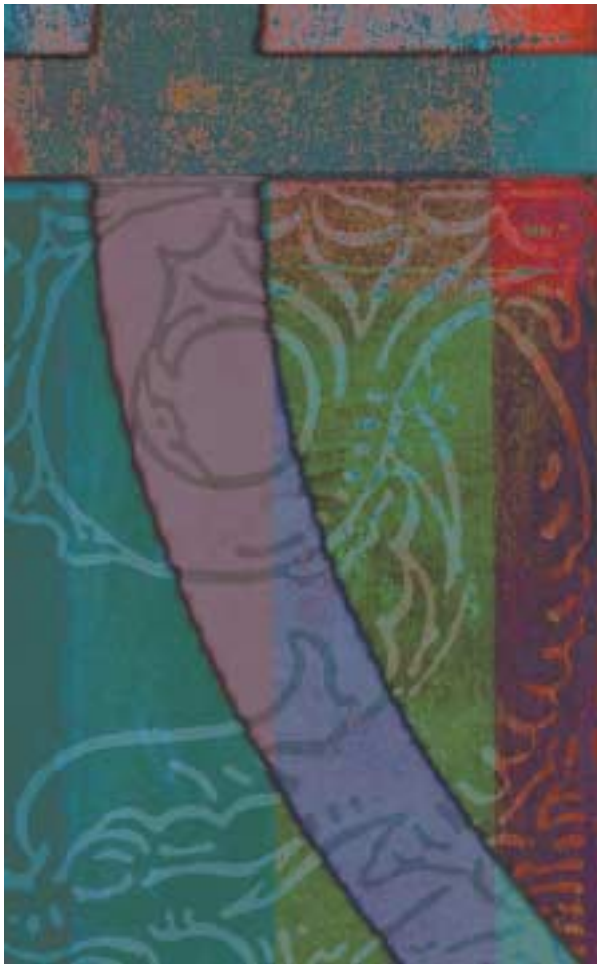
Contamination

Failure to adhere to Good Manufacturing Practices (GMPs) can result in contamination of dietary supplements.[4,5] During growth, plants can be contaminated with microorganisms or their by-products, pesticide residues, or radioactive materials. Bales or cloth sacks used for shipment of medicinal plants may be exposed to bird or rodent excrement, and animal excrement often contains pathogenic bacteria. In addition, plant material can contain the

fungi species, *Aspergillus*, which can produce the carcinogenic toxin, aflatoxin.[19]

Incorrect Preperation

Processing of crude plant material by the manufacturer can affect the pharmacological activity of the finished product.[5] The extraction procedure can vary depending on the type of solvent used, amount of fine plant material exposed to the solvent, degree of agitation, temperature, number of times the sample is extracted, age of the extract, and exposure to oxygen and light.[23] Preparation of concentrated extracts usually involves extraction with ethanol. But, hot water extraction is also used, as well as frozen and freeze-drying processes. Correct processing can affect the extent of adverse reactions and toxicity.[11] Depending on the processing, toxic plants can be made relatively safe if they are processed properly. For example, when the toxic aconite tuber is specially prepared with a heat and water extraction process, it is no longer toxic and appears to be a promising cardiotonic agent.[24]



Lack of Standardization

The chemical constituents of plants vary depending on which part of the plant is used, stages of harvesting, geographic location where the plant was grown, environmental factors such as temperature and rainfall, and drying and storage conditions.[5] Assuring that the herbal product contains the active chemical constituent(s) in the concentration associated with the reputed pharmacological activity is important. Therefore, many herbal preparations are sold as standardized extracts. Standardization is achieved by selecting a chemical constituent or group of constituents and monitoring concentrations of these in each batch of product to demonstrate consistency.[23] However, standardization does not assess the efficacy of the product, because it does not always measure the total active chemical composition.

Batch-to-batch and manufacturer-to-manufacturer variations in concentration of standardized ingredients have been reported.[5] Recent chemical analysis found variations from the labeled potency in some of the most popular herbal supplements including echinacea,[25] ginkgo biloba,[25,26] ginseng,[27] St. John's wort,[28] and saw palmetto,[29] as well as the dietary supplements melatonin[30] and glucosamine/chondroitin.[31]

Drug Interactions

With the increasing use of herbal remedies, there is an increased potential for adverse drug-herb interactions.[32-34] Drug interactions with herbal medicines are under-researched, so much of this information is based on plausibility.[19,33,34] There have been an increasing number of case reports of herb-drug interactions in the medical literature.[32-42] Incidents of bleeding involving anticoagulant therapy and herbs have recently been reported.[35] Bilberry, cayenne, danshen, dong quai, English chamomile, feverfew, garlic, ginkgo, and ginger can potentially increase the risk of bleeding in patients taking anticoagulants or antiplatelet drugs such as warfarin, aspirin, nonsteroidal anti-inflammatory drugs, and ticlopidine. The American Society of Anesthesiologists (ASA) has issued a warning about the use of herbs such as ginger, ginkgo, kava and St. John's wort in patients undergoing surgery.[36] These herbs may prevent blood clotting or prolong the sedative effect of anesthesia. The ASA recommends that patients undergoing surgery discontinue the use of herbal products at least two weeks prior to surgery. Surgical patients should also inform their physicians of any dietary supplements they are taking.

Researchers have found that grapefruit juice increases the serum concentration of antihistamines, benzodiazepines, selected calcium-channel blockers, cyclosporine, estrogens, and quinidine by altering the metabolism of these drugs by the liver.[37] Recent evidence suggests that St. John's wort interacts with drugs metabolized in the liver by the cytochrome P450 system.[38-40] Thus, St. John's wort can potentially decrease the serum concentration of cyclosporine, digoxin, non-nucleoside reverse transcriptase inhibitors, theophylline, oral contraceptives, and other drugs metabolized by this enzyme system.

Patients should not take St. John's wort with selective serotonin reuptake antidepressants, because the combination may cause mild serotonin syndrome, which can result in a number of serious problems.[34] Older reports suggest that St. John's wort should not be taken with monoamine oxidase inhibiting antidepressants (MAOIs).[32] This led to a recommendation that St. John's wort not be taken with decongestants, aged cheese and other foods that interact with MAOIs. More recent information suggests dietary precautions are probably unnecessary. Kava and valerian

Definition of A Dietary Supplement*

- A product (other than tobacco) intended to supplement the diet
- Contains one or more of the following ingredients: vitamin, mineral, herb or other botanical, amino acid, dietary substance used to supplement the diet by increasing total daily intake or a concentrate, metabolite, constituent, extract or combinations of these ingredients
- Is intended for ingestion in pill, capsule, tablet or liquid form
- Is not represented as a food or as the sole item of a meal or diet
- Is labeled as a "dietary supplement"
- Includes certain products that were previously marketed as dietary supplements, unless waived by the Secretary of Health and Human Services.

**U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Dietary Supplement Health and Education Act of 1994. December 1,1995. Accessed www.fda.gov August 3, 2000.*

can potentiate the central nervous system depressant effects of other sedatives, including alcohol.[41] *Aloe vera* juice taken orally may potentiate the effect of cardiac glycosides, antiarrhythmics, licorice, steroids, thiazides, and other potassium wasting drugs.[33]

Adverse Effects

A five-year study conducted by the National Poisons Unit in London demonstrated that herbal remedies and other dietary supplements can produce significant adverse effects, including allergic reactions and hepatotoxicity.[43] The risk and severity of adverse effects secondary to herbs is related to the patient's age, gender, genetic constitution, nutritional state, concomitant diseases and concurrent medications as well as the amount and length of consumption.[5]

Limited evidence suggests that adverse effects secondary to herbs are less common than with conventional medications. Investigators reviewed the charts of patients admitted to a community teaching hospital in Taiwan during a 10-month period and found that 4% of the admissions were drug-related and that herbal remedies ranked third among the categories of medications responsible for causing adverse effects.[44] However, many clinicians feel that under reporting of adverse effects associated with herbs is likely.[19]

Health care practitioners are often not aware that their patients are using herbal remedies and do not ask when taking drug histories.[4] Nor are practitioners and consumers actively encouraged to report adverse effects secondary to herbal remedies. Consumers often consider herbs "natural" remedies that are harmless and therefore do not suspect adverse drug reactions to be associated with these agents as they would with pharmaceuticals.[5]

Some Potentially Dangerous or Ineffective Herbal Remedies

Comfrey *(Symphytum officinale)* is used externally to aid in wound healing, and has been used internally as a tea for bronchitis, diarrhea, and pleuritis. Comfrey, borage (*Borago officinalis)*, and coltsfoot *(Tussilago farfara)* contain small amounts of pyrrolizidine alkaloids. Pyrrolizidine alkaloids have been found to be carcinogenic and hepatotoxic; the use of these herbs should be discouraged.[32]

Other herbs that can induce potentially irreversible liver injury, include chaparral *(Larrea tridentata)*, germander *(Teucrium chamaedrys)*, mistletoe *(Viscum album)*, pennyroyal *(Hedeoma pulegoides or Mentha pulegium)*, sassafras *(Sassafras albidum)*, senna *(Cassia angustifolia)*, skull cap *(Scutellaria)*, and certain traditional Chinese herbal medicines.[45]

Goldenseal (*Hydrastis canadensis)* has been used medicinally by native Americans as a topical anti-infective for inflamed eyes and

wounds. Internally, goldenseal is used for colds and flu and as a treatment for postpartum hemorrhage.[46] There is no clinical evidence supporting its use for any therapeutic application and large amounts can cause nausea, vomiting, diarrhea, hypertension, seizures, and paralysis. In recent years, goldenseal has been used in an attempt to mask urine drug screening tests by illicit-drug users.[47] There is little evidence that it masks drug screening tests, and now it is one of several adulterants commonly screened for in urinalysis samples.

Ma huang *(Ephedra sinica)* and other members of the genus *Ephedra* contain alkaloid mixtures of ephedrine and pseudoephedrine.[3] While these compounds have been commonly used in small doses to treat asthma since ancient times, they can cause vasoconstriction and CNS excitation in high doses. Ma huang is commonly used in weight loss products, but is potentially unsafe when used by patients with diabetes, hypertension, and hyperthyroidism. In addition, it is unsafe when taken in excessive doses or when used in combination with drugs such as caffeine, decongestants, monoamine oxidase inhibiting antidepressants (MAOIs) and theophylline. Since 1993, the FDA has received more than 800 reports of adverse events and more than 17 deaths secondary to the use of approximately 100 different products containing *Ephedra* alkaloids.[3,42] Most of these adverse events were cardiovascular or neurological in nature and occurred primarily in young healthy women who were asymptomatic prior to the events.

Other herbs that are frequently associated with adverse effects include aconite *(Aconitum napellus)*, which can produce palpitations, arrhythmias, nausea, and abdominal pain, and licorice root *(Glycyrrhiza glabra)*, which is associated with hypokalemia, hypertension, arrhythmias, and edema.[4]

Advice to Consumers

Even though herbal remedies and other dietary supplements are becoming increasingly popular, consumers should use these products cautiously. These remedies are not necessarily safe because they are "natural." Unlike prescription medicines, dietary supplements are not tested for proof of safety and efficacy. The efficacy of any dietary supplement or herb depends on its proper usage for the correct diagnosed medical condition. There is inherent danger when patients self-treat with dietary supplements, because of the potential for having a serious undiagnosed condition that requires conventional medical treatment. Consumers with health conditions such as blood clotting disorders, diabetes, heart disease, hypertension, Parkinson's disease, enlargement of the prostate gland, psychiatric disorders or other serious medical problems should not take dietary supplements without first consulting their health care provider.

New Labeling Requirements for Dietary Supplements*

- The words "dietary supplement" must appear on the product label
- Statement of identity of the product
- Net quantity of the contents
- Structure-function claim and the disclaimer statement "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease."
- Directions for use
- Supplement Facts panel (lists serving size, amount, active ingredient and part of the plant if a botanical)
- Other ingredients in descending order of prominence
- Name and place of business of the manufacturer, packer or distributor (i.e., the address to write for more information)

** Kurtzweil P. An FDA Guide to Dietary Supplements. FDA Consumer. September-October 1998; revised January 1999. www.fda.gov, accessed August 3, 2000.*

Adverse Events Associated with Alternative Medicines

Recent Cases Reported to California Poison Control

Christine A. Haller, M.D.
Toxicology Fellow
School of Medicine
University of California, San Francisco

Thomas E. Kearney, Pharm.D., DABAT
Clinical Professor and Managing Director,
California Poison Control System,
San Francisco Division
School of Pharmacy
University of California, San Francisco

Introduction

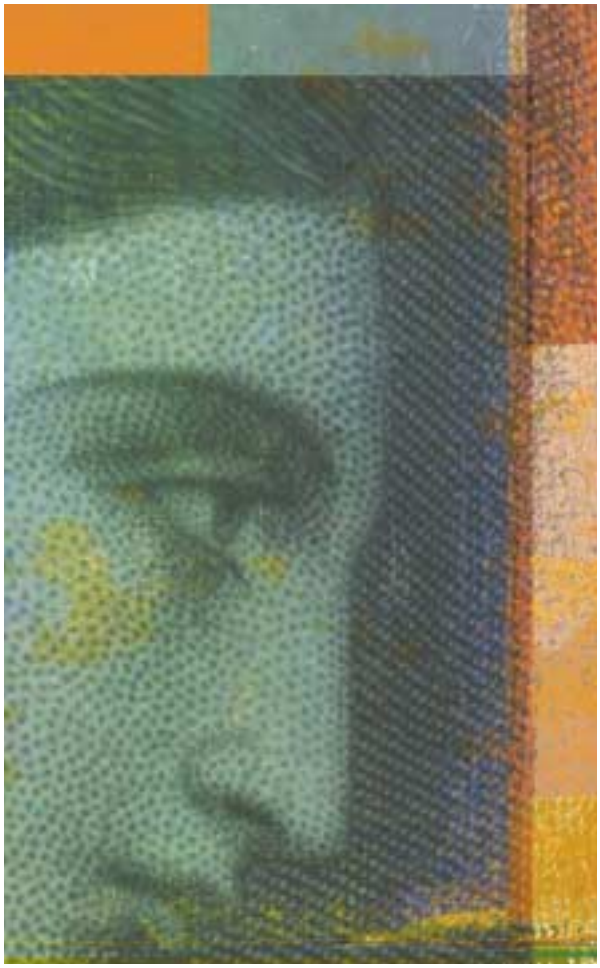
Adverse reactions associated with drugs have been described with herbal medicines[1-3] and have included allergic responses, organ system toxicity, autonomic dysfunction, and impaired levels of consciousness. Consumers may not be aware of the potential harm of alternative medicines, because botanical products are perceived to be more natural and better tolerated than synthetic drugs. However, many botanical products contain natural toxins, as well as toxic impurities or adulterants that may be added during extraction and processing of plant parts.

The extent or prevalence of adverse effects secondary to alternative medicine use in the U.S. is not known. Poison control centers provide a surveillance mechanism for reports of adverse events associated with the use of these products. In California, the San Francisco Division of the California Poison Control System receives approximately 1000 calls each year related to alternative medicines. About two-thirds of these calls are to report adverse symptoms. Symptoms range from minor complaints, such as nausea and headache, to severe reactions which include seizures, cardiac arrhythmias, coma, and death.

This article will present several recent cases of alternative medicine toxicity to illustrate the types and severity of adverse reactions that have been reported.

. . . . . Case 1

A previously healthy 42-year-old Caucasian female began taking three herbal medicines for insomnia on the advice of her homeopathic practitioner. The products were An Shu Ling *(Stephaniae sinica)*, Ignatia Amara, and Relaxed Wanderer. She took the products as directed for approximately ten weeks, then developed nausea, abdominal pain, and jaundice. She stopped using the herbal products and was seen by her primary care physician who diagnosed acute hepatitis. Her peak alanine aminotransferase (ALT) was 3386 U/L (reference range 0-45). Other laboratory parameters were within normal limits. Viral serologic markers for Hepatitis A, Hepatitis B, and Hepatitis C were negative.



The patient called the San Francisco Division of the California Poison Control System when the etiology of the hepatitis could not be identified. Her physician suspected the herbal products might be responsible. Ignatia Amara and Relaxed Wanderer were homepathic products that contained no suspected hepatotoxins. The Poisindex™ (Micromedex, Englewood CO) toxicology database listed the synonym Jin Bu Huan for *Stephaniae sinica*, the botanical name of An Shu Ling. Seven cases of hepatitis have been previously reported in adults using Jin Bu Huan.[4] The herbal products were sent to the California Department of Health Services (CDHS), Food and Drug Branch for laboratory analysis. Levo-tetrahydropalmatine, an active ingredient in Jin Bu Huan, was found in the product An Shu Ling. The product lot was confiscated from the importer/seller and a public health warning was issued by the CDHS.

The patient was presumed to have had a chemical-induced hepatitis due to the ingredient levo-tetrahydropalmatine in the herbal sedative An Shu Ling. Six weeks later the patient's aminotransferases had decreased significantly and she was completely asymptomatic. No additional cases of hepatitis associated with the use of this product were reported. Although Jin Bu Huan is prohibited from importation into the United States, this shipment of An Shu Ling reportedly cleared U.S. Customs because the shipping invoice only listed the Chinese botanical name.

Comment

The Poison Control Center may, as in this case, be presented with a patient that has specific end-organ damage or failure and a history of ingestion of an alternative remedy. The ability to determine an association between the use of these products and an adverse event depends on the recognition of herbs as possible causative agents for specific end-organ toxicity. For example, several herbal products can cause hepatitis and liver failure, including Jin Bu Huan, germander, comfrey, chaparral, and pennyroyal oil.[5] The intended use of the alternative remedy provides another clue. Pennyroyal oil has been used as an abortifacient and may be suspected in liver failure in a pregnant patient. In this case, the patient was attempting to treat insomnia and the hepatotoxic agent, Jin Bu Huan, was used as a sedative. When both patient and physician are aware of the potential for alternative remedies to cause toxicity, and appropriate agencies are notified when an adverse event occurs, prompt action can establish causality, improve patient care, and protect the public from dangerous herbal products.

. . . . . Case 2

A 46-year-old previously healthy Caucasian female was found unconscious in her apartment after suffering a massive right hemispheric stroke. She took no medications except for a weight loss product that contained ma huang, guarana, chromium picolinate, ginseng, bee pollen, and numerous other herbal ingredients. On admission, she was awake, but lethargic, with complete paralysis of her left side. She was unable to speak and her vision was impaired in her left eye. A CT scan of her head showed infarction in the area of the right middle cerebral artery, but no intracranial bleeding. Her medical evaluation revealed no risk factors for stroke. She reported taking the dieting aid as directed on the label for approximately one month before the event. She was not a smoker and did not take any drugs. She denied taking excessive quantities of the weight loss product. The product was lost by the treating hospital and could not be analyzed.

This patient required two weeks of acute hospitalization, three weeks of inpatient rehabilitation, and long-term physical therapy. Because of residual disability, she is unable to work or

live independently. Her caretakers describe emotional lability and poor judgment. She continues to have difficulty writing, walking and balancing. Her sense of taste is altered and her left vision remains impaired.

Comment

Dietary supplements containing ma huang (ephedrine) and guarana (caffeine) are widely promoted and used to boost energy, increase exercise tolerance, enhance athletic performance and promote weight loss. The stimulant actions of ephedrine and caffeine can cause nervousness, insomnia, rapid heart rate, hypertension, cardiac arrhythmias, and strokes. Adverse events have been reported with even modest doses of ephedrine (25 mg). The FDA has received more than 800 reports of adverse events associated with ma huang-containing supplements, raising serious concerns about the safety of these products for general use.[6] Regulatory changes regarding dose limits, label warnings and appropriate marketing are currently being debated by state and federal drug agencies. Pharmacists should be aware and caution consumers about the use of alternative remedies for dieting and enhancing energy. These agents are frequently used by teenagers and adults participating in sports and have been associated with cardiovascular catastrophes and sudden death.

. . . . . Case 3

A nine-year-old Asian male with a history of asthma treated with albuterol and beclomethasone was given a Chinese herbal tea to treat an episode of wheezing. Shortly after drinking the tea he became agitated and disoriented with flushed, dry skin and dilated pupils. In the emergency department, he was awake but uncooperative with the examination, responding only to touch. His heart rate was 150-160 beats minute with normal temperature and blood pressure. His lips and mouth were dry. His skin was hot, dry and flushed. His pupils were dilated and bowel sounds were absent. He was given intravenous fluids and admitted for observation. During the night, he appeared to have some hallucinations. His symptoms persisted for approximately 18 hours and then gradually resolved.

The child's family brought in the herbs used to make the tea and reported they had been steeped in water for one hour. Chemical analysis performed at the CDHS was negative for atropine, scopolamine or other pharmaceuticals. The active constituents of the herbs were thought to be sufficiently extracted during boiling as to be non-detectable by chemical analysis. The family reported prior use of the herbal remedy for the boy's asthma without adverse effects.

Comment

Traditional Chinese remedies can also cause significant adverse reactions. Mistaken identity, toxic contaminants, unapproved active ingredients, variability in dose/potency, and illegal importing have all been cited as reasons for toxicity associated with traditional Chinese medicines.[7] Imported herbal products pose a significant concern for state and federal regulatory agencies, because of limited resources to test them for quality and purity. The important diagnostic feature of this case was the recognition of a toxidrome or constellation of symptoms consistent with a particular toxin or group of toxins. This patient had a characteristic anticholinergic syndrome (dilated pupils, dry and flushed skin, tachycardia, absent bowel sounds, delirium, and hallucinations). Anticholinergics have been extensively used in Chinese medicine for the treatment of respiratory diseases. Abuse of another common plant in California, Jimson weed *(Datura stramonium)*, has also been associated with severe anticholinergic syndromes in teenagers.

. . . . . Case 4

A 13-year-old African American female ingested 8 to 10 tablets of kava 500 mg after an argument with her mother. Police brought her to a local emergency department after she stated that she had tried to hurt herself. On examination she was lethargic, but had normal vital signs. Her laboratory values were unremarkable. She became increasingly somnolent and was responsive only to painful stimuli. The medical staff consulted California Poison Control, San Francisco for advice on the expected clinical course of kava overdose. Poison specialists were not familiar with the toxicity of kava, since it had not been described in the medical literature. They recommended conservative management and she was admitted to the intensive care unit for observation. Overnight her mental status improved and she was discharged the next day for mental health evaluation.

Comment

Overdose management of alternative remedies can be difficult because of limited published data on the pharmacology and toxicology of ingredients. The kava plant *(Piper methysticum)* is indigenous to the South Pacific Islands, where it has been traditionally used as a ceremonial drink. It is now widely available in the U.S. and sold in many forms in health food stores, retail pharmacies, and grocery stores. Although it is considered to have mild anxiolytic and sedative properties, kava may adversely affect motor reflexes and judgment.[8] It also appears to have additive effects with ethanol, barbiturates, and benzodiazepines. There has been one report of an alprazolam and kava interaction causing lethargy and disorientation that necessitated hospitalization.[9] Co-ingestion of sedative hypnotic agents and excessive amounts of kava may cause significant central nervous system depression leading to loss of gag reflex or respiratory drive.

. . . . . Case 5

A 54-year-old Filipino-American male presented to the emergency department complaining of left chest and shoulder pain. His heart rate was 51 beats/minute and irregular. His blood pressure was 143/57 mm Hg and his temperature was normal. He had no murmurs and his chest was clear to auscultation. An electrocardiogram showed bradycardia with first degree AV block. He was admitted for cardiac monitoring and started on aspirin.

The patient had a history of hypertension, but no cardiac disease. He regularly took hydroxyurea (Hydrea®) for essential thrombocythemia. He also complained of migratory arthritis for the last two months affecting his feet, ankles and left shoulder. He had been taking Chinese herbs for several weeks for this. His medical work-up revealed an elevated sedimentation rate of 106 (reference range less than 50) and high platelet count, but was otherwise unrevealing.

By the fourth hospitalization day, the AV block had resolved and his heart was in a normal sinus rhythm. The etiology of his AV conduction defect was not determined, but the consulting cardiologist felt it might be attributable to the herbs. A digoxin level was not done during the hospital admission. Chemical analysis of the herb was negative for cardiac glycosides.

Comment

Cases of herb-induced toxicity can be missed if they are not considered in the differential diagnosis during the medical work-up. Although chemical analysis of herbal products is often possible, results may be negative if the sample deteriorates before analysis or concentrations of the active constituents are below detectable limits. Careful collection and storage of patient specimens, botanical products, dried herbs and liquid teas will reduce the frequency of false negative analyses. This patient's transient bradyarrhythmia and history of Chinese herbal use led to the suspicion of cardiac glycoside poisoning. There are several plants and herbs that contain cardiac glycosides including *Digitalis purpurea* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (Lily-of-the-valley), and *Urginea maritima* (squill). In addition, an aphrodisiac called Ch'an Su contains toad venom or bufotoxin (derived from secretions of the parotid and sebaceous glands), which has resulted in deaths from cardiac glycoside toxicity. Other cardiotoxic herbs have been used for arthritis, including aconite from monkshood or wolfsbane.

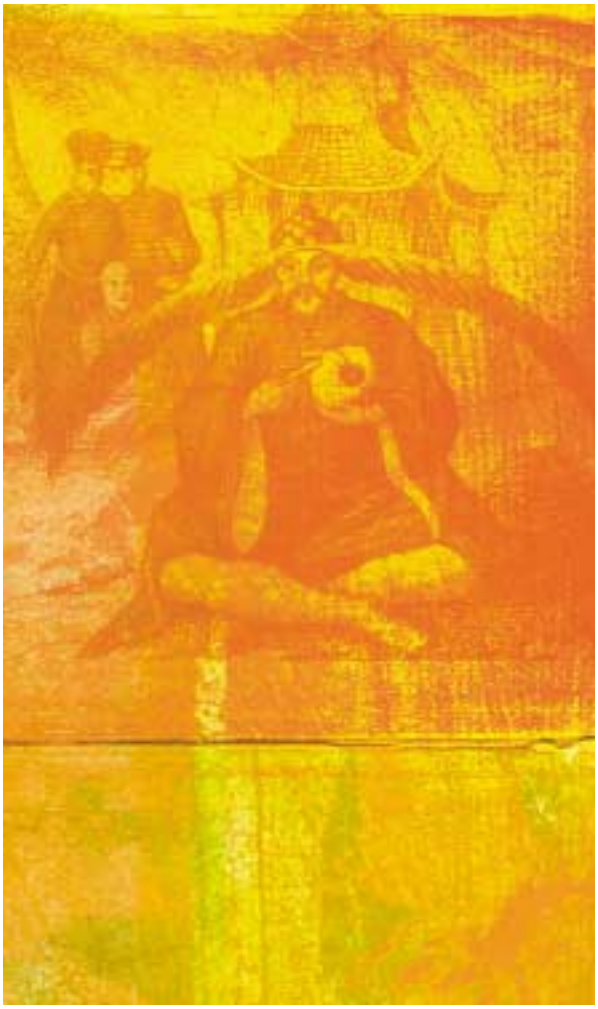
. . . . . Case 6

A 73-year-old male was on a golf course and complained of feeling hot. He took off his shirt and pants and then slumped over and vomited. In the emergency department, he was unconscious with severe hyperthermia (temperature of 108° F), and sinus tachycardia (heart rate 152 beats/min), with a blood pressure of 153/58 mm Hg. The patient was paralyzed with vecuronium and intubated. External evaporative cooling was started and the temperature fell to 103° F. When paralysis wore off after discontinuation of neuromuscular blocking agents, the patient began having tongue and mouth movements and myoclonic jerking.

The patient, a retired psychologist, had Parkinson's Disease and was taking a variety of medications to manage it. His physician reported that he had a habit of changing his drugs and doses on his own, in order to be able to participate in activities such as golf. The patient's medications included: selegiline, ropinirole, bromocriptine, tolcapone, levodopa and carbidopa (Sinemet®), tizanidine, amitriptyline, lorazepam, clonazepam, hydrochlorothiazide, potassium chloride, and multiple herbals including St. John's wort.

Comment

This patient had a life-threatening hyperthermia that most likely resulted from a neurotransmitter imbalance of an excess of dopamine and/or serotonin. Patients exhibit abnormal movements called dyskinesias from excessive dopamine effects. These movements are typically characterized as repetitive and involving small muscle groups (e.g. tongue darting) or may consist of generalized hyperkinetic activity. Excess of serotonin may lead to a serotonin syndrome. This is characterized by muscle rigidity, autonomic instability, and altered mental status, and may culminate in a life-threatening hyperthermia. This patient's hyperthermia may have been caused by a drug-herb interaction. St. John's wort *(Hypericum perforatum)* can inhibit the uptake of serotonin and dopamine in vitro.[10] It has been associated with serotonin syndrome when used in combination with selective serotonin reuptake inhibitors.[11,12] This patient's drug regimen had significant potential for inducing an imbalance of dopamine and serotonin. Ropinirol, bromocriptine and levodopa/carbidopa are dopaminergic agonists. Selegiline and tolcapone may increase dopamine and serotonin by inhibiting their enzymatic breakdown by monoamine oxidase (MAO) and catechol-o-methyltransferase (COMT), respectively. Amitriptyline and St. John's wort inhibit the uptake of dopamine and serotonin, contributing to a neurotransmitter imbalance. Of note, the potential for significant drug-herb interactions with St. John's wort has only recently been highlighted in the medical literature.[13] Two prominent therapeutic monographs *(American Herbal Pharmacopoeia and Therapeutic Compendium* and *The Medical Letter)* did not list any interactions in 1997.



. . . . . Case 7

A 69-year-old female presented in distress to the emergency department with an acute hypersensitivity reaction (generalized pruritis, urticaria, facial swelling) after using a Chinese herbal remedy for her diabetes. The herbal preparation was wafer-shaped and called Radix dioscoreae.

Poison specialists determined that this was the root of the plant *Dioscorea dumatorum*, which is used as a Chinese traditional medication. Fortunately, the patient's symptoms resolved with antihistamines. Epinephrine was avoided, since this patient had a past medical history of cardiovascular disease. This patient's past experience with use of this herbal product was unknown. The treating physician did not cooperate with the Poison Center to analyze the product.

Comment

Herbal medications have the potential for precipitating acute hypersensitivity reactions, including severe anaphylaxis. Causation may be difficult to establish because of the potential for misidentification, adulteration and contamination. It is possible that a patient may tolerate an herbal remedy for an extended period of time, then later develop an acute hypersensitivity reaction from contact with a new allergen from a contaminated lot. Patients may have cross-sensitivities to plant and animal materials or allergens as well. People with known plant sensitivities may need to avoid specific herbal remedies. Examples of known cross-sensitivities between herbal products and plants include: feverfew *(Tanacetum parthenium)* and plants in the daisy family *(Asteraceae)*; ginkgo *(Ginkgo biloba)* and poison oak or ivy *(Toxicodendron sp.)*; echinacea *(Echinacea purpurea)* and sun flowers and ragweed; and royal jelly (secretions from worker bees) and bee sting allergy (hymenoptera).[14,15,16]

. . . . . Conclusion

Alternative remedies may cause adverse effects in some people. Organ-specific toxicity, central nervous system and autonomic nervous system dysfunction, adverse drug-herb interactions and allergic reactions have all recently been described. Physicians and pharmacists should be aware of potentially harmful herbs and take action when a case of herbal toxicity is suspected. The implicated product should be held for future analysis. A regional Poison Control Center should be contacted for guidance on medical management of the poisoning. In California, the toll free number is 1-800-8 POISON. All adverse events related to alternative medicines should be reported to the FDA MedWatch Program. Forms are available online at the FDA website, www.fda.gov. The California Department of Health Services should be notified of adverse reactions to Chinese herbal products, since many of these are not under the jurisdiction of the FDA or are imported illegally.

Part Three: Information for

Inquiring Minds:

Frequently Asked Consumer Questions About Herbs and Dietary Supplements

Mitra Assemi, Pharm.D.
Assistant Clinical Professor
Coordinator, UCSF-Longs Drug Information Services
School of Pharmacy
University of California, San Francisco

Recent FDA changes in labeling requirements expand the allowable claims that dietary supplement manufacturers may place on their product labels. Although intended to clarify product labeling, the new rules may not diminish consumer confusion over indications for use, safety, and efficacy. Perhaps an indicator of the interest and confusion consumers' experience is the increasing numbers who seek information. Seventeen million of the 40 million people logging on to the Internet search it for health-care related information.[1] Pharmacists today have a unique opportunity to serve as trusted sources of information on herbs and dietary supplements. Pharmacists have traditionally been the "gatekeepers" of medication information and therapy. With expanding roles as health-care providers in ambulatory care settings and the proliferation of new pharmacies, pharmacists are more readily accessible than ever before.

The following cases reflect some of the questions most frequently asked by consumers regarding herbs and dietary supplements. These came from questions received in community pharmacies and an "Ask Your Pharmacist" web site.

. . . . . Case 1

Mrs. M approaches the counter with two Echinacea products in her hand. She wants to know the difference between a standardized extract tincture formulation and a capsule formulation.

Herbs come in a wide variety of formulations and dosage forms. For almost all herbs, the exact active ingredient(s) remain unknown. Different parts of the plant can also be used. For medicinal purposes, the active ingredient is either the herb itself or an extract of the herb.[2] Some solid dosage forms contain the crude, dried herb. Most herbal solid and liquid dosage forms, however, contain an extract of the herb.

Fluid extracts are made by chemically treating one part herb with one part solvent, usually water and/or ethanol.[2] Solid extracts are made by evaporating the solvent of the fluid extract. Extracts may be concentrated to contain higher amounts of active chemicals by increasing the ratio of crude herb to extracting solvent. Other formulations of herbs include volatile oils and fresh pressed juices.

A tincture is the liquid dosage form of an alcoholic extract.[2] Most of the clinical trials studying echinacea utilized a 1:5 tincture made from *Echinacea pallida* root and 50% ethanol.[2] The tincture formulation of echinacea may allow the active chemical moieties to reach their primary site of action: oropharnygeal lymphoid tissues.

Mrs. M's question provides an opportunity to educate her about the differences in dosage formulations of herbal products. The pharmacist should also ask Mrs. M about her interest in using echinacea. By doing so, the pharmacist can ensure that she is using the product for an appropriate indication. Appropriate indications include those for which there is some supporting data on efficacy and safety (e.g., treatment versus prophylaxis against the common cold). In addition, the pharmacist could help Mrs. M select a particular product. Reputable large manufacturers are more likely to take measures to ensure that their products contain properly identified plants and no adulterants. Some manufacturers also analyze their final products to ensure uniformity of formulation between different batches.

Mrs. M's question also provides an opportunity to screen for any contraindications to the use of echinacea (e.g., asthma, autoimmune disorders, pregnancy, breast-feeding, any reason to avoid alcohol). The pharmacist should remind Mrs. M to only use the product as directed on the label and not to exceed the manufacturer's dosing recommendations.

. . . . . Case 2

Mr. H came into clinic requesting refills of his d4T, indinavir, and nevirapine. He wants to know about any interactions between his prescription medications and the herbs and dietary supplements he recently started taking. These were ginseng, St. John's wort, and melatonin.

Recent evidence indicates that St. John's wort *(Hypericum perforatum)* induces CYP3A4.[3,4] St. John's wort decreased plasma levels of indinavir and digoxin in pharmacokinetic studies,[3,4] and it also decreases cyclosporin levels.[5] Both indinavir and cyclosporin are substrates for CYP3A4. Other substrates of CYP3A4 include other protease inhibitors, certain calcium channel blockers, HmG CoA reductase inhibitors, sex hormones, erythromycin, ketoconazole, rifampin, cisapride (now off the market), and warfarin.[6] Based on observed pharmacological effects of St. John's wort on a variety of neurotransmitters, it may potentially interact with other antidepressants, adrenergics, and amphetamines.[7,8,9]

To date, ginseng *(Panax ginseng, Panax quinquefolius)* has not been reported to interact with any antiretroviral agents or protease inhibitors. Formal pharmacokinetic studies, however, are lacking. One case report attributed a decreased INR to ginseng in a patient taking warfarin.[10] The mechanism of this interaction remains unknown. The effect of ginseng on the cytochrome P450 enzyme system is unclear.[11] Ginseng may cause insomnia, irritability, and mania in psychiatric patients taking phenelzine, neuroleptics, and lithium.[12-14] Due to observed pharmacological effects on platelet aggregation and observed varying effects on blood pressure, ginseng should be used with caution in patients taking aspirin, NSAIDs, antiplatelets, or antihypertensives.[15-17]

Mr. H should be advised to stop taking St. John's wort because of its potential interaction with indinivir. Decreased plasma levels of indinavir could result in decreased effects and, potentially, therapeutic failure. Mr. H should be encouraged to discuss any depressive or psychiatric symptoms or concerns with his primary care physician. Based upon information currently available, he may use ginseng and melatonin, but he should inform his physician that he is taking these products. The pharmacist should educate him about any potential side effects and other potential drug interactions with ginseng and melatonin.

. . . . . Case 3

Mrs. C is 10 weeks pregnant with her first child. She wants to know whether ginger is safe to take for nausea during pregnancy.

The FDA recently withdrew a new rule that would have allowed dietary supplements to be sold for common pregnancy-related conditions.[18] Birth defects experts had heavily criticized the proposed new rule. Almost all herbal products and dietary supplements lack safety data for use in pregnant or breast-feeding women and children.

Ginger root from *Zingiber officinale* is a common spice and flavoring agent. It is included in the FDA's list of substances "Generally Recognized as Safe" (GRAS).[19] A GRAS listing, however, is not synonymous with approval for therapeutic uses. Ginger is consumed in higher amounts when taken as an herbal supplement than when used as a flavoring agent. One study evaluated the use of ginger as an antiemetic for 26 pregnant women with hyperemesis gravidarum.[20] The results suggested some subjective benefits, but did not measure any significant objective outcomes. Children exposed to ginger in utero were not followed; therefore, the teratogenic risk of ginger when taken as an herbal supplement has not been evaluated.

The pharmacist should tell Mrs. C about the lack of data regarding the use of ginger during pregnancy. In addition, she should be advised that herbs and dietary supplements are not recommended for use during pregnancy and while breast-feeding.[18] She should be encouraged to discuss her symptoms and treatment options with her obstetrician or physician.

. . . . . Case 4

Ms. K is currently taking warfarin for a recent pulmonary embolism (PE). She took hormone replacement therapy for 5 months prior to her PE. During a visit to the anticoagulation clinic, she asks about using an herbal supplement to treat her hot flashes and vaginal dryness. She is especially interested in a combination preparation recommended by a friend. The product label indicates that it contains black cohosh, dong quai, chasteberry, and ginseng.

> "Consumer questions about herbs and dietary supplements present pharmacists with opportunities for patient screening and education."

Dong quai *(Angelica sinensis)* can increase the prothrombin time (INR) in patients taking warfarin.[21] The mechanism behind the interaction may involve interference with the metabolism or protein binding of warfarin.[21] Dong quai also contains several natural coumarins and other constituents with antithrombotic activity.[19,22] Ginseng has been reported to interact with warfarin to decrease the INR. There are no known drug interactions to date with black cohosh *(Cimicifuga racemosa)* or chasteberry *(Vitex agnuscastus)*. No pharmacokinetic studies in humans have been conducted with any of these herbs.

The pharmacist should advise Ms. K to avoid any products containing dong quai and ginseng while taking warfarin, because use of these products could make it difficult to maintain a therapeutic INR. The effects of black cohosh and chasteberry on warfarin remain unknown.

Ms. K's question presents the pharmacist with the opportunity to educate her about the potential risks associated with herbs having hormonal (e.g., estrogenic) activity. Black cohosh may relieve hot flashes and mood disturbances associated with menopause through its estrogenic effects.[23-25] Hormonal effects of dong quai may be derived from its use in combination with other herbs rather than as a single herb alone.[26] Ginseng may have weak estrogenic activity.[27] Chasteberry may exert hormonal effects by altering lutenizing hormone (LH) and prolactin levels.[28] The exact mechanism of hormonal action of all of these herbs has yet to be elucidated. Herbs with estrogenic activity could potentially increase the risks of adverse effects in patients with known contraindications to hormonal replacement therapy (e.g., history of thromboembolic disorder.) Until more information becomes available, Ms. K should be advised against using any herbal products containing herbs with known hormonal effects.

. . . . . Case 5

While picking up his Celebrex prescription, Mr.P asks about the use of SAMe for osteoarthritis.

SAMe, or S-adenosylmethionine, has gained recent notoriety as a dietary supplement in the U.S. Among its purported uses are depression, osteoarthritis, fibromyalgia, liver disease, and migraines.[29] SAMe is made in the body and plays a role in a variety of metabolic pathways.[30] *In vitro* data suggest that it enhances proteoglycan synthesis, which is important for cartilage formation.[31] Animal studies demonstrate that exogenously administered SAMe has anti-inflammatory and analgesic properties,[32] but these do not appear to be mediated by inhibition of prostaglandin synthesis.[33] Limited human trials suggest that SAMe (400 to 1600 mg/daily[29]) may be as effective as NSAIDs for relieving symptoms of osteoarthritis.[33] More research is needed to clarify the mechanism of action and efficacy of SAMe for osteoarthritis. Side effects of SAMe include mild gastrointestinal upset.[29] A few cases of agitation and mania in bipolar patients receiving SAMe have been reported.[29] There is one case report of serotonin syndrome in a patient taking clomipramine and SAMe.[34]

The pharmacist should tell Mr. P that there are limited data suggesting beneficial effects of SAMe for relieving osteoarthritic symptoms. Patients with bipolar disorder should not use it.[29] Patients with depression or depressive symptoms should not use SAMe without first consulting their physician. Based on its potential pharmacological effects on neurotransmitter levels, SAMe should not be used in patients receiving antidepressants.[29] Mr. P should tell his health-care providers if he begins using SAMe so that its efficacy and any adverse effects can be monitored.

. . . . . Conclusion

As the previous cases illustrate, consumer questions about herbs and dietary supplements present pharmacists with opportunities for patient screening and education. Pharmacists should not, however, limit their interventions to consumer questions. Because of their unique role and accessibility, they should proactively screen for use of herbs and dietary supplements. In doing so, they present themselves as trusted sources of information about these products. Proactive screening also allows pharmacists to identify side effects and drug interactions, document them, and report them to the patient's primary health care provider. This growing trend in use of dietary supplements provides pharmacists with a unique opportunity to help consumers.


www
@

Sources of Reliable Information on Alternative Medicine

Mary J. Ferrill, Pharm.D., FASHP, FCSHP
Associate Professor
Associate Director, Postgraduate Professional Education
School of Pharmacy and Health Sciences
University of the Pacific

Information concerning alternative medicine has exploded. Therefore, it is virtually impossible to cover and critique every reference available. Instead, this review will highlight some references that pharmacists should know about, and those that they might choose for their own personal use or recommend for patient use. The references that follow are listed in alphabetical order by title and not in order of importance.

Several key elements should be considered when evaluating information sources for alternative medicine. These include the reputation of the publisher and editors or authors, how often the reference is updated, and if the information is referenced. These key points should help pharmacists determine if the information is incorrect or biased, but will not ensure that the information is unbiased or totally correct. Readers will need to use their own judgment when encountering new references or information sources.

Readers need to be aware of some basic issues regarding alternative medicine literature. Manufacturers have limited incentive to conduct good, large clinical trials, due to lack of patent protection. To promote their own products, any manufacturer can use the results of any positive clinical trials. Although the trend is slowly changing, many alternative medicine studies are published in foreign languages. Often, those studies published in the English language are published in obscure journals that are usually not indexed in Medline. Many studies are older, and even recent studies often have poor study designs. In addition, studies often lack power (sufficient sample size) to detect a clinically significant difference.

Quality of alternative products can also be a concern, as mentioned in the previous articles.[1-6] Published studies often fail to document that the alternative medicine in question was actually the product tested or in the amount described. Lastly, there is a lack of consensus in the medical community regarding the use of alternative medicines. Considerations range from, but are not limited to, potential therapeutic uses, effectiveness, appropriate doses, monitoring parameters, adverse effects, and drug interactions. Therefore, it is important that multiple alternative medicine sources be examined to ensure that correct and up-to-date information is obtained.

Year & Edition	ISBN/ISSN or contact information	Available	Approximate cost ($)

Alternative Health and Medicine Encyclopedia: The Authoritative Guide to Holistic & Nontraditional Practices

1997	0-7876-007-33	Hardbound	$47.

Contents: *Discusses alternative health topics (e.g., biofeedback, yoga, visualization) and alternative "drugs." Written in textbook rather than monograph format. Good basic overview of CAM. Directed towards consumers. Resources listed at the end of each chapter rather than references.*

Alternative Medicine Alert: A Clinician's Guide to Alternative Therapies

2000 Monthly, yearly index	1096-942X	Newsletter & online	$219.

Contents: *Monthly newsletter on alternative topics directed towards physicians. Provides information on common and timely CAM. Information analyzed and highly referenced. Not as useful as a standard monograph "drug-type" reference.*

American Herbal Products Association's Botanical Safety Handbook: Guide for the Use and Labeling for Herbs in Commerce

1997	0-8493-1675-8	Hardbound	$45.

Contents: *Textbook with 600 commonly sold herbs in the U.S. listed alphabetically. Has information regarding international regulatory status and limited information on standard dosage, side effects and use. Referenced.*

Clinical Pharmacology

2000	1-885966-10-5 www.gsm.com (Registration Required)	CDROM & online	CDROM: $395. Online: Free

Contents: *Contains information on nutraceuticals when reliable clinical data exist. Monographs contain standard information. Referenced.*

Guide to Popular Natural Products

1999	1-57439-063-5	Handbook	$30.

Contents: *125 products abridged from Review of Natural Products. Introductory legal section. Helpful appendices such as therapeutic use index. Selected photographs. Referenced.*

Herb Contraindications and Drug Interactions

1998 2nd ed.	1-8884-8306-7	Handbook	$20.

Contents: *Listed in alphabetical order by common name. Only 95 references in entire text.*

Herbal Medicine: Expanded Commission E Monographs

2000	0-9670772-1-4	Hardbound	$50.

Contents: *107 of the most commonly used herbal monographs, expanded to provide more scientific information on efficacy. Listed alphabetically by common name. Often lacks critical analysis of clinical trials. Referenced.*

Herbal Medicinals: A Clinician's Guide

1998 1st ed.	0-7890-0467-4	Paperback & Hardbound	$40./$60.

Contents: *Information on herbs only. Listed by diseases or syndromes. Textbook-style format rather than monograph. Little on dosing, side effects, and drug interactions. More folklore and history than scientific information. Authors give recommendations on use. Lists cases at the beginning of each section. Referenced.*

IBIS Integrative Body Mind Information System

1999	www.teleport.com~ibis or 877-526-1972	CDROM & online	$200.

Contents: *Information on >2400 alternative medicines, 282 common medical conditions. Offers treatments for >12 systems (e.g., cardiovascular, nervous) of integrative medicine. Has note-taking and report-generating features. Personalized patient education materials possible. Directed towards physicians. Referenced.*

Year & Edition	ISBN/ISSN or contact information	Available	Approximate cost ($)
IBIS Interactions			
1999	www.teleport.com~ibis or 877-526-1972	CDROM & online	$100.
Contents: *Database contains information on drug-herb and drug-nutrient interactions. Referenced.*			
Martindale: The Complete Drug Reference			
1999 (32nd ed.) Updated every 2-3 years	0-85369-429-X	Hardbound & CDROM (Micromedx)	$299
Contents: *A British reference with a section on supplementary drugs. Limited information on physical and pharmaceutical properties. Does not have true monographs on alternative substances. Some "monographs" are longer than others. Referenced.*			
Micromedex			
2000 Updated quarterly	www.mdx.com or 303-486-6444	CDROM (online in beta form)	Varies
Contents: *Computer database with many sections. Sections with CAM topics: AltMedDex (alternative medicine evaluations), RPS (Royal Society's Herbal Medicines), DrugDex (drug evaluations), AltCareDex (pt. education information for CAM), and AltCare Consults (questions and answers related to alternative medicine). AltMedDex contains: summary of interactions, adverse effects, severity, onset, documentation, probable mechanism, and literature reports, if available. Referenced.*			
Natural Medicines Comprehensive Database			
2000 Text updated yearly, online continually	www.naturaldatabase.com or 209 472-2244	Paperback & Online	$85. for each or $132. for both
Contents: *Information on alternative "drugs." Monograph-type information: people use this for, effectiveness, comment, and interactions with herbs and other dietary supplements, drugs, foods, labs, diseases or conditions. States if no interactions known or predicted, insufficient information, or interactions with some expected outcomes or potential problems. Often cites textbooks and newsletters rather than primary literature. Referenced.*			
Natural Products Explorer			
1999 Updated annually	1-57439-069-4	CDROM	$180.
Contents: *Combines both The Review of Natural Products and The German Commission E Monographs.*			
Natural Therapeutics Pocket Guide			
Expected July 2000	0-916589-80-3	Handbook and CDROM	$32. to $40.
Contents: *Topics listed by conditions. Includes herbs, nutritional supplements, homeopathic remedies, and lifestyle modifications.*			
PDR for Herbal Medicines			
2000 2nd ed. Updated annually	1-5636-3292-6	Hardbound	$60.
Contents: *Over 700 monographs. Several indexes: common name, therapeutic use, side effects, manufacturers, Asian, homeopathic, and Indian index. Monographs contain actions, uses, precautions (with drug interactions), adverse drug reactions, & contraindications. Separate drug/herb interactions list and herb ID guide (pictures). Referenced.*			
Professional's Handbook of Complementary Medicine			
1999 1st ed.	0-87434-971-0	Handbook	$40.
Contents: *Monographs list actions, uses, dosage, side effects, drug interactions, special considerations, precautions, and analysis. Drug interaction section includes if combination should be given with caution, any monitoring required or if should be avoided. Appendices include table of therapeutic monitoring guidelines (e.g., labs to monitor), and herb information sheet (can be copied and individualized for patients). Referenced.*			

Year & Edition	ISBN/ISSN or contact information	Available	Approximate cost ($)

Rational Phytotherapy: A Physician's Guide to Herbal Medicine

1998 3rd ed.	3-540-62648-4	Hardbound	$50.

Contents: *Information on herbs only, listed by diseases or syndromes. Textbook-style format rather than monograph. Little on dosing, side effects, and drug interactions. More folklore, history than scientific information. Authors give recommendations on use. Referenced.*

Stedman's Alternative Medicine Words

2000 New edition	0-7817-2161-X	Paperback	$37.

Contents: *More than 40,000 terms, including medical acupuncture, homeopathy, herbs, and traditional Chinese medicine. Includes appendices with items such as illustrations and treatments by indication. No references.*

Textbook of Natural Medicine

1999 2nd ed.	0-443-05945-4	Hardbound 2 volume set	$200.

Contents: *Discusses CAM concepts. Written in textbook rather than monograph format. Several sections, including therapeutic modalities, syndrome & special topics, pharmacology of natural medicines and specific health problems. Referenced.*

The German Commission E Monographs: Therapeutic Guide to Herbal Medicines

1998 1st ed.	0-9655555-0-X	Hardbound & CDROM	Book- $99. CDROM- $165. $199. for both

Contents: *327 herbal monographs; 191 with a favorable listing. There are additional 108 unapproved herbs. Monographs include uses, side effects, drug interactions, dosage, and contraindications. There is a drug-herb interaction table. Very limited information on specific herbs. No references.*

The Pharmacist's Dietary Supplement Alert

2000 Monthly, indexed yearly	1527-7348	Newsletter & online	$229.

Contents: *Monthly newsletter on dietary supplements (vitamins, minerals, amino acids and herbs). Provides objective clinical information using evidence-based medicine. Information analyzed and highly referenced. Not as useful as a standard alternative medicine monograph "drug-type" reference.*

The Review of Natural Products

2000 Monthly updates	1089-5302	Newsletter & CDROM	Newsletter: $195. CDROM: $139. Yearly updates: $139.

Contents: *Newsletters alphabetized by common name. Contains chemistry, pharmacology, summary and patient information. No interactions listed in the monographs. Last drug-herb interaction table dated December 1998. Information more chemistry-based than clinical. Useful appendices such as therapeutic use index. Often references include textbooks and newsletters, rather than primary literature.*

Tyler's Herbs of Choice

1999 Updated every 1-2 years	0-7890-0160-8	Paperback & Hardbound	$20./$50.

Contents: *Information on herbs only. Listed by diseases or syndromes. Textbook-style format rather than monograph. Little on dosing, side effects, and drug interactions. More folklore and history than scientific information. Authors give recommendations on use. Written primarily for consumers, not health professionals. Referenced.*

Tyler's Honest Herbal

1999 Updated every 1-2 years	0-7890-0875-0	Paperback & Hardbound	$25./$50.

Contents: *Information on herbs only. Listed alphabetically by common name. Textbook-style format rather than monograph. Little on dosing, side effects, and drug interactions. More folklore and history rather than scientific information. Authors give recommendations on use. Referenced.*

Free Alternative Medicine Web Sites

Sponsoring Organizations	URL

Alternative Medicine Homepage — **www.pitt.edu/~cbw/altm.html**

Comments: Web site listing alternative Websites on the www. Links to databases, internet resources, newsgroups and mailing lists, and government resources. Covers all areas of CAM.

American Health Consultants — **www.ahcpub.com**

Comments: Commercial site that publishes several newsletters such as "Alternative Medicine Alert." Can search for write-ups on alternative medicine topics.

Health Care Information Resources — **www-hsl.mcmaster.ca/tomflem/altmed.html**

Comments: "Meta-Site" for alternative medicine, international scope. Provides a broad collection of Internet resources in the field of alternative medicine. Organized by treatment categories. Links are from education, organizations, government and commercial sponsors.

Mayo Clinic Health Oasis — **www.mayoclinic.com**

Comments: Information database where you can search for short write-ups. Some alternative medicine topics. Directed towards consumers.

MedlinePlus: Alternative Medicine — **www.nlm.nih.gov/medlineplus/alternativemedicine.html**

Comments: Sponsored by the National Library of Medicine. Directed towards consumers and primarily includes government resources. There is also a link to search Medline for articles on alternative medicine.

Medscape — **www.medscape.com/Home/Topics/specialties.html**

Comments: Information database that allows search for short write-ups. Some alternative medicine topics.

National Center for Complementary and Alternative Medicine — **nccam.nih.gov**

Comments: Allows search of 180,000 bibliographic citations from 1963-1999. Citations extracted from the NIH Medline Database. Some abstracts listed.

NIH Office of Dietary Supplements — **Dietary-supplements.info.nih.gov**

Comments: Allows search of the IBIDS database (International Bibliographic Information on Dietary Supplements.) Has international, scientific literature on dietary supplements, including vitamins, minerals, and botanicals. Currently contains > 300,000 citations and abstracts. Developed and will be maintained by the Office of Dietary Supplements at the NIH.

QuackWatch — **www.quackwatch.com**

Comments: Focuses on health-related frauds, myths, fads, and fallacies that are often propagated via the Internet and the media. An alternative medicine section has a variety of topics such as legal and specific misleading information. There is also a list of non-recommended references such as books, individuals, periodicals and web sites.

RxList - The Internet Drug Index — **www.rxlist.com**

Comments: Commercial site that lists alternative medicines (herbs, homeopathic, vitamins) from A to Z. Provides fairly detailed monograph-type information including dose and drug interactions. Referenced. Updated at an unknown frequency.

The Alternative and Complementary Medicine Center of Health World Online — **www.altmed.net**

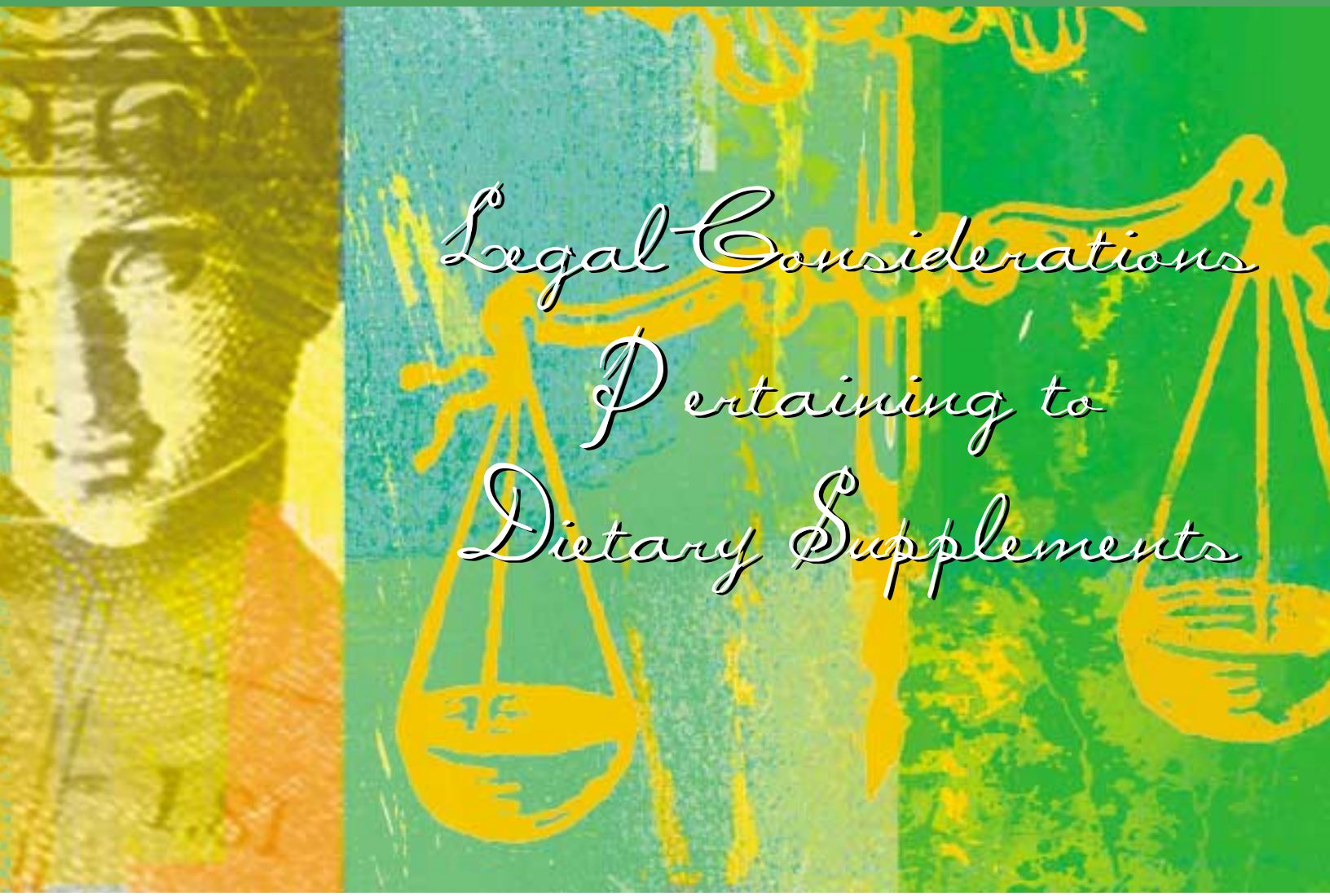
Comments: Site contains extensive resources for the most common types of alternative medicine. The Herbal Medicine link includes an online version of Materia Medica, containing monographs of many herbs used for treatment. Each monograph contains indications, doses, and many contain references.

The Natural Pharmacist — **www.tnp.com/home.asp**

Comments: Commercial site with alphabetical list of herbal remedies, drug-herb interactions, and herbal treatments for specific conditions.

Vitamins.com — **www.vitamins.com/encyclopedia/index/herbx.htm**

Comments: Commercial site with monographs on herbs, homeopathic and Chinese medicines. Referenced. Updated at an unknown frequency.



Legal Considerations Pertaining to Dietary Supplements

Richard R. Abood, R.Ph., J.D.
Professor
School of Pharmacy and Health Sciences
University of the Pacific

No one is in a more ideal position to recommend, sell, and advise patients about dietary supplements than pharmacists. Pharmacists, because of their position in society as drug experts, offer patients unmatched knowledge about dietary supplements. However, selling and providing information about dietary supplements does create legal concerns, as this article will demonstrate. But legal considerations should not be a determinate in whether to engage in the business of dietary supplements, but rather how best to practice that business.

Several potential legal issues may arise when selling and recommending dietary supplements, ranging from statutory violations to civil liability. In particular, this article will highlight liability concerns under the Federal Food Drug and Cosmetic Act (FD&C Act), the Federal Trade Commission (FTC) Act, negligence law and products liability law. Although not addressed directly, the reader should also be aware that many of the potential FD&C Act and FTC Act violations discussed in this article could also violate California law. Some pharmacists might be alarmed at the number of different applicable legal issues. However, the risk of liability becomes quite minimal when pharmacists insure that they are competent to perform the services they offer, understand the law, and follow the risk management suggestions in this article.

Federal Food Drug & Cosmetic Act

Dietary supplements are regulated under the FD&C Act, as amended by DSHEA.[1] As such, pharmacists should be aware of the law related to the following activities.

Making Disease Claims Rather Than Structure/Function Claims

Generally speaking, under the FD&C Act a product becomes a drug if the seller intends for the product to treat a disease or intends for it to affect the structure or function of the body.[2] DSHEA modified the drug definition allowing sellers of dietary supplements to make structure/function claims for their products, so long as the claims can be substantiated as truthful.[3] The FDA requires that disease (health) claims must be pre-approved and very few have been approved. Making disease claims for a dietary supplement product could subject the seller to charges of illegally marketing a new drug without approval and misbranding. (Misbranding occurs when a seller includes drug labeling information other than what was approved by the FDA.) For example, a patient who has had recurring urinary tract infections might ask a pharmacist for a dietary supplement. The pharmacist could recommend cranberry tablets and assert (as a structure/function claim) that the tablets should increase the acidity of the urine and help to maintain a healthy urinary tract. If the pharmacist asserted that the cranberry tablets prevent or treat urinary tract infections, this would be a disease claim. The manufacturer cannot legally make that claim on the product label. Whether the pharmacist has committed an illegal act is quite murky. Arguably, a pharmacist should be able to make a disease claim as part of his or her professional responsibility of providing patient information; and in this context, it would be highly unlikely that the FDA or any state regulatory authority would be concerned about the legality. On the other hand, a pharmacist who actively promotes and advertises a dietary supplement for disease purposes could be in violation of the law. The critical but blurry distinction then, is whether the disease claim was made within the context of patient education or product promotion. This issue becomes even less clear after a recent federal court of appeals decision finding that by requiring pre-market approval for health claims, the FDA violates the First Amendment rights of dietary supplement manufacturers.[4] The court held that the manufacturers should be permitted to make health claims so long as they include a disclaimer stating that the evidence is inconclusive that the product is effective for the claim.

Posting Signs

Signs posted in pharmacies that make disease claims for dietary supplements sold in the store could subject the pharmacy to misbranding violations. The FD&C Act defines labeling as labels and other written, printed or graphic matter either on the article, its container, or "accompanying" the article.[5] The courts have interpreted the word "accompanying" broadly to include literature supplied separately from the product[6] and to include literature displayed by retailers in connection with the sale of a product.[7] The sign could constitute labeling because it accompanies the products. Since the signs make disease claims, the product could be considered a drug and therefore misbranded.

Displaying Publications About Dietary Supplements

Some pharmacies place copies of published articles about dietary supplements in the dietary supplement section of the store. Prior to DSHEA, the act of displaying articles about a product would likely have constituted labeling, subjecting the pharmacy to misbranding. DSHEA, however, excludes certain publications, such as articles, book chapters, and official abstracts of peer-reviewed scientific publications when used in connection with the sale of dietary supplements to consumers. These publications may only be excluded from consideration as labeling provided all of the following conditions are met :

(1) They are reprinted in their entirety.
(2) They are not false or misleading.
(3) They are displayed or presented with other such publications so as to present a balanced view of the available scientific information.
(4) If displayed in an establishment, they are physically separate from the dietary supplements.
(5) They do not have appended to them any information by sticker or any other method.

These stated conditions create several unanswerable questions. How far apart must the articles be from the product? How many articles on each side of the issue constitute a balanced view? Even if a pharmacy complies with DSHEA by separating the publications and providing balance, there is always the danger that the publications might be considered false or misleading by the FDA. The burden of proof, however, falls on the FDA to establish that fact.

Risk Management Suggestions

Pharmacists should not fear violating the FD&C Act when counseling patients and providing educational information to patients. Pharmacists should, however, recognize the difference (where possible) between a structure/function claim and a disease claim. Even when counseling, pharmacists should be cautious about asserting disease claims for a product, especially without including at least a disclaimer that the product has not been proven safe and effective for the treatment of the disease. Pharmacists should not engage in

in-store promotion of dietary supplement products for the treatment of diseases, because this would most likely violate the FD&C Act. Literature about various dietary supplement products should be displayed in a section physically separate from the products themselves; and, if one article advocates a product's safety and efficacy, another, if available, should be displayed that offers another view.

Federal Trade Commision Act: Product Promotion and Advertising Issues

If a claim or statement about a dietary supplement is not labeling, it has to be advertising. While the FDA regulates dietary supplement labeling, the Federal Trade Commission (FTC) regulates dietary supplement advertising.

Deceptive Advertising

The FTC Act, which applies to retailers as well as manufacturers, prohibits "unfair or deceptive acts or practices" and in the case of food products, prohibits "any false advertisement" that "is misleading in a material respect."[8] Historically, the agency devoted priority attention to advertisements in which the accuracy of the claims was difficult for consumers to verify and where adverse health consequences and economic loss could result. Since 1990, the FTC has taken action against several dietary supplement companies including General Nutrition Corporation (GNC), the largest U.S. retailer of dietary supplements.[9]

The FTC cannot require product sellers to submit advertising to it for pre-market approval, but rather must act after the fact. Under the Act, an advertisement is deceptive or misleading when it is likely to mislead reasonable consumers to their detriment. Thus, the FTC need not prove that consumers were actually misled, only that they are likely to be misled. Advertising claims must have a reasonable basis, or in other words, must be substantiated. For example, if the advertisement states that the product reduces inflammation of the joints, the FTC will expect the advertiser to produce scientific evidence supporting that statement.

Perhaps the most significant legal advertising danger to pharmacies occurs when they engage in joint promotional activities with dietary supplement manufacturers. The FTC Act establishes a strict liability standard on all those who participate in false or deceptive advertising. Thus, if a dietary supplement manufacturer mentions a pharmacy in the advertisement and that advertisement is deceptive, the pharmacy is as liable as the manufacturer, regardless of whether or not the pharmacy even had knowledge of the ad's contents.[10]

Risk Management Suggestions

Pharmacies must ensure that safety and efficacy claims made in dietary supplement advertisements can be substantiated. When engaging in joint advertising activities with manufacturers, pharmacies must make it a point to review the advertisements before they are published. Advertisements that simply mention the product's name and price would not normally be a concern under the FTC Act.

Negligence

Under negligence law, pharmacists are expected to exercise that degree of competence expected of a reasonable, prudent pharmacist. Negligence issues can arise when counseling patients about dietary supplement products, as the following scenario provides.

Don is a regular patient of XYZ Pharmacy and has filled all of his prescriptions there, including warfarin. One day Don asks the pharmacist, Sue, if ginkgo is really effective for short-term memory loss. Sue replies that she knows many patients who think that it is effective and some of the literature indicates that it might be helpful. Don purchases the ginkgo and a few weeks later is admitted to the hospital with an abdominal hematoma and nearly dies. An investigation indicates that the ginkgo, which inhibits platelet aggregation, may have potentiated the effect of the warfarin, thereby causing the hematoma. Don files a negligence suit against Sue and XYZ Pharmacy contending that Sue should have warned him of the dangers of taking ginkgo with the warfarin. Are Sue and XYZ Pharmacy liable?

Analysis of Case

For Don to be successful in a negligence lawsuit he must prove four elements: (1) that Sue owed him a duty to exercise a particular standard of care; (2) that Sue breached that duty by acting substandardly; (3) that the substandard act caused his injury; and finally (4) the amount of injury and damages sustained. Starting with the issue of duty, under normal circumstances when a patient purchases a dietary supplement, a pharmacist would not likely owe the patient a legal duty to provide professional advice. In this case, however, Don asked Sue for advice, Sue provided the advice and Don relied upon it. In doing so, Sue has created a legal duty, which must then be exercised to the standard of care of a reasonable, prudent pharmacist.

If Don had asked Sue for advice and Sue refused to comment, Sue might still be negligent on the basis that since Don is a patient of XYZ and Sue, having knowledge of Don's medication history, could have prevented foreseeable harm to Don. The legal duty would be even more likely if XYZ advertised its dietary supplement department and promoted its pharmacists as dietary supplement experts. For example in a Michigan case, a pharmacy advertised that it maintained

a computer software program which would screen prescriptions for potential problems, including drug-drug interactions.[11] A patient suffered a drug-drug interaction from two prescription drugs received from the pharmacy. The pharmacy contended that Michigan law did not establish a duty upon pharmacists other than to fill the prescriptions accurately as written by the prescriber. The court, however, found that the pharmacy created a legal duty to the patient by advertising that its software program would protect the patient from drug-drug interactions, thus inducing the patient to rely upon that advertising.

Under the second element of negligence, the question becomes did Sue breach the legal duty she owed Don? The standard of care of a pharmacist is usually determined through expert witnesses. Don's attorney will introduce one or more pharmacists to testify that a pharmacist who provides advice on ginkgo should know that it inhibits platelet aggregation (especially if XYZ promoted the dietary supplement expertise of its pharmacists). These expert witnesses would also likely testify that since Don is a patient of the pharmacy, the pharmacist should have known that Don was taking warfarin. Therefore, the witnesses would conclude that a reasonable pharmacist would have warned the patient of the potential danger of taking the two products together and have urged the patient to discuss the issue with his physician.

The question then arises: Does Sue still have a duty to know that Don is taking warfarin if he is a patient of another pharmacy and his warfarin prescription was dispensed there? Although less clear, it could certainly be determined that Sue had a legal duty to discover Don's warfarin use by asking Don whether he is taking any prescription medications. If Don does not tell Sue about the warfarin, Sue could not be expected to know and should not be liable.

Pharmacists will not be legally responsible for knowing or warning about all the potential adverse effects or interactions regarding a dietary supplement, since this would not be reasonable. Pharmacists will, however, likely be expected to know and to warn of adverse effects that might be common or severe. This is especially true as software programs capable of detecting potential interactions and adverse effects of dietary supplements become more prevalent and widely used in pharmacies.

Even if Don establishes that Sue is negligent, he still faces a difficult hurdle in order to win the lawsuit. Don must still show that it was more likely than not that the ginkgo actually caused the hematoma. Sue's lawyer will argue that the hematoma occurred for other reasons, not related to the ginkgo. Both sides would have expert witnesses testify as to what caused the hematoma and a jury would evaluate their testimony. The scant availability of science regarding the safety and efficacy of many dietary supplements would likely place the plaintiff at a significant disadvantage in attempting to show causation in many cases.

Risk Management Suggestions

Pharmacists should educate themselves and become knowledgeable about the dietary supplement products they sell. The pharmacy's library should have one or more current dietary supplement reference books and the pharmacy should utilize computer software. Pharmacies should not promote their staff as experts in dietary supplement products unless they truly do have expertise. When counseling or advising patients about dietary supplements, the pharmacist should consider the following actions, depending upon the situation.

1) Emphasize that the product has not been proven safe and effective.
2) Obtain as much patient history as possible, especially any prescription and OTC medications the patient is taking, Elicit use of any other dietary supplements, disease and diet information.
3) Screen for any contraindications.
4) Warn the patient about any common and/or severe side effects or interactions that could occur.
5) Suggest that the patient inform his or her physician of the intended use.
6) Suggest that the patient contact either the pharmacist or physician if any problems arise during the product's use.

Product Liability

As the sellers of retail products in California, pharmacists face not only the possibility of liability for their actions, but liability for the products themselves when those products cause injury. Under a product liability lawsuit, a seller could be liable even when not at fault. Two theories of product liability will be discussed here, warranty and strict tort liability.

Breach of Warranty

When a pharmacy sells a dietary supplement product, a contract is formed between the pharmacy and the purchaser. That contract attaches certain warranties. Failure by the pharmacy to meet these warranties could result in a breach of contract action. Two types of warranties exist, express warranties and implied warranties.

An express warranty occurs when the seller makes an affirmation of fact or a promise, which becomes a part of the basis for the contract. For example, assume in the previous case study that Don asks Sue whether the use of ginkgo is safe when taken in conjunction with warfarin and Sue replies: "Yes. There are no safety problems." Sue's reply could be construed as an express warranty. If Don can establish that he relied on Sue's promise and that ginkgo is not safe when

taken with warfarin, then Sue could be liable for a breach of express warranty.

In addition to express warranties, the law imposes implied (or silent) warranties, which may exist with a contract unless disclaimed by the seller. One type of implied warranty, implied warranty of merchantability, gives buyers recourse when the products are not fit for the ordinary purposes for which they are used, because they are impure or mislabeled. For example, if the ginkgo product Sue sold Don contained much higher doses of ginkgo than labeled, and it can be established that this dose was the cause of Don's injury, Sue and XYZ Pharmacy might be liable because the product was not fit.

Another type of implied warranty, implied warranty of fitness for a particular purpose, would be particularly applicable to this situation. Under this theory, liability can occur when a seller exercises his or her professional judgment in the selection of a dietary supplement, the patient relies on the seller's judgment and then is injured. Unlike with merchantability, this warranty can exist even if the product is perfectly made. Don could argue that Sue breached this warranty by recommending ginkgo to him and that it was not fit for his particular purpose since he was taking warfarin.

Strict Tort Liability

Many jurisdictions, including California, also recognize strict tort liability as a cause of action against product retailers. Under strict tort liability the plaintiff does not have to establish fault by the seller or the existence of a contract, only that the product was in a defective condition, that the defect made the product unreasonably dangerous to the user, and that the defect caused the harm. Under this theory, Don would argue that the ginkgo was defective since no warnings were provided that it might interact with warfarin and that this warning defect made the ginkgo unreasonably dangerous to use, causing his injury. Under strict tort liability, a pharmacy could also be held liable for selling adulterated or misbranded dietary supplements even though it has no knowledge of this fact. This could be significant considering that the dosages of some dietary supplement products, especially herbs, can deviate significantly from bottle to bottle and even tablet to tablet.

Risk Management Suggestions

To protect against product liability actions, pharmacists should avoid making guarantees or promises about product safety and efficacy. Pharmacies should inventory only products that they are confident are pure, labeled properly and manufactured by reputable companies. Ideally and when possible, USP labeled herbs should be purchased.

Dispensing Prescriptions for Dietary Supplements

Many of the same issues previously discussed apply when dispensing dietary supplements pursuant to a prescription. If the product is prescribed for the purpose of treating a disease, the product could become a drug, in particular an unapproved drug prescribed for an unlabeled purpose.[12] In general, this would not violate the FD&C Act or state law, since this is an acceptable practice within the scope of medicine and pharmacy. Technically, a legal problem could exist when the product is compounded.[13] The FD&C Act provides that the ingredients used in compounding must either meet USP standards or be approved by the FDA. In the case of dietary supplements, except for a few herbals, these requirements could not be met. Dispensing dietary supplements might actually present an additional dimension of liability compared to prescription drugs, since the dietary supplement might be prescribed in lieu of conventional therapy. If the dietary supplement is ineffective, leading to further harm to the patient from the disease, the patient could contend that the prescriber was negligent in prescribing the dietary supplement. The pharmacist might be included in the lawsuit for not intervening. When faced with a dietary supplement prescription, pharmacists must determine if in the particular situation foregoing conventional therapy might be harmful to the patient. If the potential for risk warrants it, the pharmacist should contact the prescriber to confirm the accuracy of the prescription and justify it. If dispensed, the patient must be informed of the situation and allowed to consent to the treatment.

Conclusions

Although the sale of dietary supplements can trigger several potentially applicable legal theories, there have been relatively few lawsuits against the manufacturers and sellers of these products. There are several reasons for this. First, aside from contamination or adulteration, most dietary supplement products are relatively safe. Second, the widespread use of these products is relatively recent. Third, the deregulation of dietary supplements is relatively recent. And fourth, most consumers and health care providers do not know or realize that the dietary supplement may be the cause of an adverse effect. Most likely the number of lawsuits will increase with increasing consumer use and increasing consumer expectations resulting from product advertising. Further research will help to reveal more about the safety (or lack thereof) of these products. Although any consumer can be at risk of injury from taking dietary supplements, those most at risk include prescription drug users and those with chronic diseases. They are also the consumers most likely to seek advice from pharmacists. Nonetheless, pharmacists can minimize the risk of liability by following the suggestions in this article.

What's in a Claim?

Barbara Sauer, Pharm.D.
Clinical Professor, Vice Chair,
Department of Clinical Pharmacy
School of Pharmacy, UCSF
Clerkship Program Director, UCDMC

Disease claims,[1] also called health claims or risk reduction claims, describe an association between a food or nutrient and a disease or health-related condition. The FDA approves disease (health) claims before a product is marketed. Manufacturers must notify the FDA of their intent to make a disease (health) claim in advance and be able to substantiate the claim with scientific evidence or authoritative statements (e.g., statements made by the National Academy of Sciences).[2] Examples of approved disease (health) claims are: "Folic acid during pregnancy decreases the risk of neural tube defects" and "Calcium can lower the risk of osteoporosis." The FDA has generally allowed disease (health) claims for dietary supplements that prevent a disease or reduce the risk of developing a disease.[3]

The FDA recently denied the following disease (health) claim for Saw Palmetto: "Consumption of 320mg/day of Saw Palmetto extract may improve urine flow, reduce nocturia and reduce voiding urgency associated with mild benign prostatic hyperplasia (BPH)." The denial was based the FDA's position that BPH is an existing disease and the use of the product is intended to treat a disease, not prevent it, or reduce the risk of developing it.[3]

Nutrient-content claims[1] refer to the relative level of a specific nutrient in a product (e.g., "excellent source of Vitamin C" or "high in calcium"). These claims are allowed if one serving of the product meets the threshold amount established by the FDA for a specific nutrient (e.g. products containing 12 mg of Vitamin C or 200mg of calcium, respectively).

Nutrition support claims[1] describe a relationship between a nutrient and a disease or health condition that results from deficiency of that nutrient. An example is "Vitamin C prevents scurvy." Nutrition-support claims must also include the prevalence of the deficiency disease in the United States.

Structure-function claims[1] are a type of nutrition-support claim. They describe the effect of the nutrient on the body's structure or function, or overall effect on a person's well-being. Some examples are: "Calcium builds strong bones," "Antioxidants maintain cell integrity," and "Fiber maintains bowel regularity."

Manufacturers may make structure-function claims without prior FDA review, but must notify the FDA of the claim within 30 days of first marketing the product. The product label must also include the disclaimer "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." Manufacturers must be able to substantiate that the statements are truthful and not misleading, although they are not required to provide any proof of such to the FDA.

The final rule pertaining to structure-function claims (*Federal Register;* January 6, 2000) clarifies the distinction between a disease claim and a structure-function claim.[4] It permits health maintenance claims (e.g., "maintains a healthy circulatory system"), non-disease claims (e.g. "helps you relax"), and claims for common, minor symptoms associated with various life stages (e.g., "for hot flashes") for dietary supplement products. Express or implied claims to treat a disease are not allowed.

Strategies for Promoting Safe and Appropriate Use of Dietary Supplements

1. Learn about dietary supplement products and stay informed. Maintain an up-to-date library of dietary supplement references. Read what your patients are reading.
2. When counseling or advising anyone about dietary supplements:
   a. Determine who will be using the product and that person's age.
   b. Ask about the intended use.
   c. Obtain as much medical history as possible, especially any prescription or non-prescription medications or use of other dietary supplements. Ask about any dietary restrictions.
   d. Screen for any contraindications or reasons to avoid using the product.
   e. Warn about possible adverse effects or drug interactions.
   f. Encourage reporting of any dietary supplement use to the patient's health care provider.
   g. Emphasize that the product has not been proven to be safe or effective.
   h. Remind the patient to report any adverse effects to his or her physician or pharmacist.
3. Anyone with health conditions such as blood clotting disorders, diabetes, heart disease, hypertension, Parkinson's disease, prostate enlargement, psychiatric problems, autoimmune disease or other serious medical conditions should not take dietary supplements without first consulting their physician. Pregnant and breast-feeding women, children and the frail elderly should be discouraged from using these products.
4. Emphasize reading product labels. Consumers should know what the product contains, how much it contains and the suggested use. They should be told to follow the instructions for use.
5. Encourage the use of products manufactured by major companies. Look for expiration dates or other evidence of quality control.
6. Report adverse events to the FDA MedWatch Program (forms can be down-loaded from www.fda.gov).
7. Consult the California Poison Center for assistance in managing any adverse events associated with dietary supplements. The toll-free number is 1-800-8POISON.
8. Be alert to fraudulent products. Products that claim to be a "breakthrough," "miracle cure," or "new discovery" should raise suspicion. Vague medical claims, such as "detoxify," "purify," or "energize," are misleading and difficult to measure. Other possible indicators of fraud are products that claim to be effective against a wide range of unrelated conditions, have only health benefits and no adverse effects, or have claims supported by scientific studies that can not be traced or substantiated, according to Stephen Barrett, M.D. of the National Council of Health Fraud,*.

   ** Kurtzweil P. An FDA Guide to Dietary Supplements. FDA Consumer. September-October 1998; revised January 1999. www.fda.gov, accessed August 3, 2000.*

Suggested Reading

1. Angell M, Kassirer JP. Alternative medicine-the risks of untested and unregulated remedies. *N Engl J Med* 1998; 339:839-841. Editorial.
2. Astin JA. Why patients use alternative medicine: results of a national study. *JAMA* 1998; 279:1548-1553
3. Cirigliano M, Sun A. Advising patients about herbal therapies. *JAMA* 1998; 280:1565-1566. Letter to Editor.
4. Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med* 1997; 127:61-69.
5. Eisenberg DM, Davis RB, Ettner SL et al. Trends in alternative medicine use in the United States, 1990-1997. Results of a follow-up national survey. *JAMA* 1998; 280:1569-1575.
6. Eisenberg DM, Kessler RC, Foster C et al. Unconventional medicine in the United States: prevalence, costs, and patterns of use. *N Engl J Med* 1993; 328(Jan. 28):246-252.
7. Ernst E. Harmless Herbs? A review of the recent literature. *Am J Med* 1998; 104;170-178.
8. Fontanarosa PB, Lundberg GD. Alternative medicine meets science. *JAMA* 1998; 280:1618-1619. Editorial.
9. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000; 355:134-138.
10. Jonas WB. Alternative medicine-learning from the past, examining the present, advancing to the future. *JAMA* 1998; 280:1616-1617. Editorial.
11. Kurtzweil P. An FDA guide to dietary supplements. U.S. Food and Drug Administration, *FDA Consumer*. Sept-Oct 1998; Revised Jan 1999. www.fda.cfsan.gov/~dms/supplmnt.html
12. Lemley B. Why so many doctors hate Andrew Weil. *Discover* 1999 (August); 56-63.
13. Palmer ME. Dietary supplements: "Natural" is not always safe. *Emer Med* 1998; 30:52-74
14. Editor. Herbal Rx: the promise and pitfalls. *Consumer Reports* 1999 (March); 44-48.
15. Editor. The mainstreaming of alternative medicine. *Consumer Reports* 2000 (May); 17-25.

"Alternative Medicines"

A Continuing Education Program for California Pharmacists

Universal Program # 113 - 126 - 00 - 034 - H01 • 3 Contact Hours (0.3 CEU)

Co-sponsored by the California Pharmacists Association
and the California Society of Health-System Pharmacists

LEARNING OBJECTIVES:

After reading these articles, you should be able to:

1. Describe the regulatory process for dietary supplements and explain how it differs from that for prescription and non-prescription medications.
2. List one or two common uses for frequently purchased dietary supplements and describe the scientific evidence to support each of these uses.
3. Recognize appropriate dosing regimens and common adverse effects of frequently used dietary supplements.
4. List five herbs or herbal products that are toxic to the liver.
5. List five dietary supplements that should be avoided when taking anticoagulants or anti-platelet medication.
6. Cite three additional examples of potentially harmful drug interactions reported with dietary supplements (other than those listed above).
7. List five medical conditions or diseases in which dietary supplements should be avoided.
8. List three alternative medicine resources that provide reliable information and are suitable for consumer use.
9. Identify five risk management strategies for pharmacists who sell or counsel consumers about dietary supplements.
10. Describe the pharmacist's role in promoting safe and appropriate use of dietary supplements.

DIRECTIONS FOR OBTAINING CE:

- Read the articles and take the test to receive three (3) hours of continuing education credit. Return the entire test page and include a self-addressed, stamped envelope. Please note that the passing grade is 70%. If necessary, one test will be readministered.
- Type or print your name, address, and license number in the space provided on the form below.
- This continuing education monograph is jointly sponsored by CSHP and CPhA, and you may return your answer sheet to EITHER:

California Pharmacists Association
CE Exam
1112 I Street, Suite 300
Sacramento, CA 95814

California Society of Health-System Pharmacists
CE Exam
725 30th Street, Suite 208
Sacramento, CA 95816

PLEASE NOTE: It is not necessary to send the exam to both organizations. Select one. Remember to enclose a self-addressed, stamped envelope.

If returning test to CPhA:
☐ I am a CPhA member. Enclosed is a check for $10 payable to CPhA.
☐ I am not a CPhA member. Enclosed is a check for $25 payable to CPhA.

If returning test to CSHP:
☐ I am a CSHP member. Enclosed is a check for $10 payable to CSHP.
☐ I am not a CSHP member. Enclosed is a check for $25 payable to CSHP.

Please type or print neatly:

How do you rate this course: (Excellent) 7 6 5 4 3 2 1 (Poor) How well did this article meet its stated objective? (Excellent) 5 4 3 2 1 (Poor)

How long did it take you to complete the reading and the test? _____ minutes

Additional comments are appreciated: _____

Name: _____

CA license #: _____

CONTINUING EDUCATION CERTIFICATE OF COMPLETION

Date: _____ Course Name: Alternative Medicines. ACPE Universal Program #113-126-00-034-HO1.

This is to certify that the above-mentioned continuing education course was completed by:

Name: _____

Address: _____

City, State, ZIP: _____

The California Pharmacists Association Educational Foundation and the California Society of Health-System Pharmacists are approved by the American Council on Pharmaceutical Education as providers of continuing pharmaceutical education. This course provides three hours of credit, Universal Program #113-126-00-034-HO1. Pharmacists completing this course prior to April 1, 2004 may receive credit.

FOR OFFICE USE ONLY

You successfully passed with a score of: _____ %

CE Administrator: _____

Date Issued: _____

Not valid unless signed by the CE Administrator

Please enter your answer to each test question below:

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____
13. _____
14. _____
15. _____
16. _____
17. _____
18. _____
19. _____
20. _____
21. _____
22. _____
23. _____
24. _____
25. _____

TEST QUESTIONS

1. The number of U.S. adults who take one or more dietary supplements concurrently with prescription medication has been estimated to be:
a. 1 in 3
b. 1 in 4
c. 1 in 5
d. 1 in 10

2. Which of the following statements is NOT true:
a. Dietary supplements can be marketed without proof of safety and efficacy.
b. The FDA does not regulate dietary supplements.
c. Manufacturers of dietary supplements have responsibility for ensuring that their products are safe and properly labeled.
d. Manufacturers of dietary supplements must be able to substantiate any structure or function claims as truthful and not misleading.
e. For structure/function claims, the product label must also bear the statement "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

3. The intended use of a product determines whether it is a food or a drug.
a. True
b. False

4. Which of the following is NOT a dietary supplement:
a. Herbal products
b. Multiple vitamins
c. Glandular products
d. Beverages containing ginseng
e. All of the above are dietary supplements

5. The following information is required on the dietary supplement product label, except:
a. Name of active and inert ingredients
b. Directions for use
c. Supplement Facts panel
d. German Commission E rating, if a botanical
e. Name, place and business of the manufacturer, packer or distributor.

6. The majority of people who use alternative medicines are dissatisfied with the traditional health care system.
a. True
b. False

7. Dietary supplements should be avoided in pregnant or breast-feeding women:
a. True
b. False

8. Glucosamine HCl appears to be effective for relieving symptoms associated with osteoarthritis.
a. True
b. False

9. Garlic lowers LDL cholesterol about the same as dietary restriction.
a. True
b. False

10. Melatonin is effective for which of the following indications:
a. Jet lag
b. Sleep-onset insomnia
c. Sleep maintenance insomnia

11. St. John's wort enhances mood in mild to moderate depression.
a. True
b. False

12. Ginseng is effective in improving physical and mental performance.
a. True
b. False

13. Echinacea is effective in preventing the common cold.
a. True
b. False

14. Saw palmetto can interfere with measurement of prostate specific antigen (PSA).
a. True
b. False

15. Which of the following echinacea products has been shown to be effective in relieving cold symptoms:
a. *E. purpurea* fresh pressed juice preserved in 22% alcohol
b. *E. purpurea* root extract
c. *E. pallida* fresh pressed juice preserved in 22% alcohol
d. *E. angustifolia* root extract
e. All of the above

16. The primary antidepressant constituent in St. John's wort is hypericin.
a. True
b. False

17. Which of the following dietary supplements have been reported to cause liver disease:
a. Ma huang
b. Aconite
c. Germander
d. Jimson weed
e. None of the above

18. Adverse drug interactions may occur with St. John's wort and all of the following except:
a. Simvastatin
b. Paroxetine
c. Indinavir
d. Cyclosporin
e. Warfarin

19. Patients taking anticoagulants or anti-platelet medications should avoid the following dietary supplements, except:
a. Dong quai
b. Ginkgo
c. Garlic
d. Ginseng
e. Black cohosh

20. The following doses are appropriate for the dietary supplement listed, except:
a. Melatonin 100mg
b. Chondroitin sulfate 1200 daily, in one or three divided doses
c. St. John's wort 900mg daily, in two to three divided doses
d. Coenzyme Q10 30-60 mg daily
e. Black cohosh 40mg of the herb twice daily

21. All of the following are sound risk management strategies, except:
a. Suggesting that the patient inform his or her physician of any dietary supplement use
b. Cautioning patients that dietary supplement products have not been proven safe and effective for the stated claims
c. Obtaining as much patient history as possible, including prescription, OTC and other dietary supplement use
d. Relying on manufacturers of dietary supplement products to provide all the literature and advertising for in-store promotions
e. Maintaining a library of reliable references and information resources

22. Dietary supplements differ from OTC products in the following ways, except:
a. Manufacturers must follow GMP
b. They may not claim to diagnose, treat, cure or prevent a disease
c. They can be marketed without proof of safety and efficacy
d. They are regulated by the FDA
e. Product labels must include directions for use

23. All of the following have produced adverse reactions to herbal products, except:
a. Using the wrong plant or plant part during processing
b. Contaminating the plant material with microorganisms, heavy metals, pesticide residues or radioactive materials
c. Inadvertently or intentionally adding prescription drugs during processing
d. Drug interactions with prescription medication
e. Using standardized extracts of the plant material

24. Chinese herbal medicines have been associated with toxic reactions similar to those produced by:
a. Anticholinergic agents
b. Cardiac glycosides
c. Stimulants
d. Sedative hypnotics
e. Both a. and b.
f. None of the above

25. In a case of suspected toxicity from a dietary supplement, the pharmacist should:
a. Obtain the product or a sample of the product
b. Call the California Poison Control Center for guidance on management
c. Report the suspected adverse reaction to the FDA MedWatch Program
d. Notify the California Department of Health Services if the product is imported from China
e. All of the above

HEALTH NOTES
Alternative Medicines

Making a Difference

This issue of HEALTH NOTES is a collaborative effort of the California State Board of Pharmacy and the School of Pharmacy, University of California, San Francisco.

Sponsored by

The UCSF School of Pharmacy
Center for Consumer Self Care
"Helping People Help Themselves"

The Center for Consumer Self Care is an emerging collaborative center whose mission is to ensure optimal and responsible use of medication and dietary supplements by individuals and the public at large. The Center will accomplish its mission through the following program cores: Consumer Education, Research, Professional Education and Public Policy.

Planning Committee

Cathi Dennehy, Pharm.D.
Assistant Clinical Professor
UCSF School of Pharmacy

Lorie Rice, M.P.H.
Associate Dean
UCSF School of Pharmacy

Barbara Sauer, Pharm.D., FCSHP
Project Coordinator
Clinical Professor
UCSF School of Pharmacy

Candy Tsourounis, Pharm.D.
Assistant Clinical Professor
UCSF School of Pharmacy

Expert Review

Cathi Dennehy, Pharm.D.
Assistant Clinical Professor
UCSF School of Pharmacy

Mary Ferrill, Pharm.D., FASHP, FCSHP
Associate Professor
Associate Director, Postgraduate Professional Education
University of the Pacific
School of Pharmacy and Health Sciences

Candy Tsourounis, Pharm.D.
Assistant Clinical Professor
UCSF School of Pharmacy

Editorial Review

Elizabeth Johnson, Pharm.D.
Senior Vice-President
California Pharmacists Association

Mary Anne Koda-Kimble, Pharm.D.
Professor and Dean
T.J. Long Chair in Chain Pharmacy Practice
School of Pharmacy
University of California, San Francisco

Continuing Education

Special thanks to the following individuals for their collaborative support of this project and for providing continuing education credit for pharmacists:

Carlo Michelotti, Pharm.D., Chief Executive Officer, CPhA
Elizabeth Johnson, Pharm.D., Senior Vice President, CPhA
Teresa Miller, Pharm.D., Executive Vice President, CSHP

Design

Tim Davis Advertising and Design,
Sacramento, CA

PRSRT STD
U.S. Postage
PAID
Permit No. 424
Sacramento, CA

State Board of Pharmacy
Department of Consumer Affairs
400 R Street, Suite 4070
Sacramento, CA 95814

(916) 445-5014