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Herbal Supplements—Drug Interactions

Scientific and Regulatory Perspectives

edited by
Y. W. Francis Lam
Shiew-Mei Huang
Stephen D. Hall

Herbal Supplements—Drug Interactions

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Scientific and Regulatory Perspectives

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Preface

Although the potential of an interaction between concurrently administered botanical and pharmaceutical products is not unexpected, this topic has received increased attention and scrutiny over the past several years. The widespread use of botanical products in Western societies and the potency of modern pharmaceuticals have led to numerous reports of interaction, sometimes with significant adverse effects.

While no one would argue for the need of another book related to drug interaction, this book differs from available books in several aspects. This book is not a standard book listing numerous reported botanical product-drug interactions organized by examples. Rather, the focus is to provide a timely discussion and perspective on the complex scientific and regulatory issues associated with investigating, reporting, and assessing these interactions in humans.

From the beginning, our goal has been to provide information that is not readily available in other books covering the same topic. In addition to regulatory and industry perspectives, we have included a chapter describing interactions involving the more commonly used traditional Chinese medicine, and discussion regarding specific issues unique to this group of medicinal products that needs to be taken into consideration when assessing the potential and significance of interaction. In contrast to single active components in modern pharmaceuticals, the presence of multiple active ingredients commonly present in botanical products underscores the importance of quality assurance and standardization in this emerging industry. The relevance and challenges of standardization for documentation and evaluation of botanical product-drug interactions are presented in depth in one chapter and, where applicable, discussed throughout the book.

We realize that the terms *herbs*, *herbal products*, *botanical products*, and *dietary supplements* are often used interchangeably in the literature

or sometimes even within the same context by consumer. While dietary supplements may be more easily recognized by consumers, the term includes vitamins, minerals, and other nutritional products that are not the focus of this book. On the other hand, it is generally accepted that herbs and botanical products also encompass different concentrated forms including extracts, powders, and formulated products containing a combination of different herbs. We used the term *botanical products* where applicable throughout the book because it denotes a more extensive scope than the more commonly used term *herbs* or *herbal products*, and it enables the inclusion of interaction involving citrus products as well.

The book chapters are organized into five major sections. Section 1 (Chapters 1 to 3) provides background information regarding botanical usage and discusses several of the mechanisms in which botanical products can interfere with drug disposition and effect. The complex nature of botanical product-drug interaction and the different variables associated with interpretation of the reported interaction are highlighted in this section as well. The second section (Chapters 4 to 7) focuses on botanical products that have been documented to interact with pharmaceutical products and, where applicable, their purported mechanism of interaction. Where possible, the contributors use specific examples in this section to illustrate the complexity of the issues in assessing the potential and significance of the interaction. The next section (Chapters 8 and 9) provides an overview of the pharmacokinetics of different botanical products, and discusses the importance of quality assurance and standardization. The fourth section on regulatory viewpoints (Chapters 10 to 13) outlines the Food and Drug Administration's approach to utilize the MedWatch program for documenting and evaluating reported botanical product-drug interactions. The last section (Chapters 14 and 15) provides industry and regulatory perspectives on developing botanical products as pharmaceutical agents.

This book is intended not only for scientists involved in the study of botanical product-drug interactions, but also for practitioners who advise patients on the safety concerns involved with using these products concurrently. It is our sincere hope that the use of this book will serve to improve understanding of the complex issues associated with evaluating botanical product-drug interactions, which is an essential component in further developing botanical products and obtaining regulatory approval as pharmaceutical agents.

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The Landscape of Botanical Medicine Utilization and Safety

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INTRODUCTION

Comprehending the use and safety of botanical dietary supplements is challenging largely owing to the lack of regulation and the paucity of data on their utilization, effectiveness, and safety. The literature describing the utilization of botanical products tends to be poorly documented and incomplete and evidence in the form of clinical trials is sparse; safety data are largely derived from anecdotal case reports. Medications from botanical sources have been described as far back as 60 millennia and most of the medications used throughout the world were derived from plants until the early 1900s (1). It is estimated that 35,000 to 70,000 plants have been used for medical purposes (2). For example, opium and willow bark have long been used for the treatment of pain (3). It was not uncommon for over-the-counter medications to contain opium without warnings or legal restrictions (4). Willow bark may still be purchased over the counter as an extract to relieve pain and many other prescriptions medications are currently derived from botanical sources.

Prescriptions Derived from Botanical Sources

Today, it is estimated that 25% of the Western pharmacopoeia contains chemical entities that were first isolated from plants and another 25% are

derived from chemical entities modified from plant sources (1,2). In 1999, 121 prescription medicines worldwide came directly from plant extracts and it is now a $10 billion-a-year industry (1). These medicines are not dietary supplements but rather are botanical products that have passed the more rigorous process of approval to be used as a prescription drug. The World Health Organization estimates that 75% to 80% of the developing world continues to rely heavily on botanicals for medication (1,5). However, most products available are considered dietary supplements in the United States.

Botanical Dietary Supplements

The use of botanicals in the industrialized world is growing. In the United States, it has been estimated that about 20,000 products are in use (6), with the top ten botanical products comprising 50% of the commercial botanical market (7). In China, approximately 80% of medications are obtained from between 5000 and 30,000 types of plants (2). In the era of increased globalization, many botanical products are available to people all over the world through the Internet, imported for sale by botanical shops catering to high-use ethnic populations, or imported (often illegally) by individuals returning from global travel (8). Utilization of these products has dramatically increased in the past decade (2,9–18). In 1991, the U.S. Congress passed legislation to establish the National Institutes of Health Office of Alternative Medicine, which later became the National Center for Complementary and Alternative Medicine, to better understand how Americans are embracing the use of unconventional therapies.

UTILIZATION OF BOTANICAL DIETARY SUPPLEMENTS IN THE UNITED STATES

Although physicians in the United States infrequently prescribe botanicals, they receive little formal training on the benefits and risks of these and other complementary and alternative medications (CAM) (19). This is disturbing because a significant proportion of patients take botanical dietary supplements. More than 37 million Americans utilize botanical remedies and some estimates put forth a much higher (20–23). Since the Dietary Supplement Health and Education Act (DSHEA) of 1994, growth of the botanical market has been dramatic. However, the industry is fragmented, with a few large corporations manufacturing the bulk of botanical products and many smaller companies targeting specific herbs. Market research organizations have traditionally avoided analyzing botanical products because the market was too small (24), but this has changed recently because botanicals are now profitable to analyze. As a result of DSHEA, the public now has many botanical dietary supplements from which to choose. With the increasing number of products competing against one another, corporations have taken action

to distinguish their products from one another. As such, dietary supplement manufacturers have taken a page from the pharmaceutical industry and have begun branding botanical products to develop a market following for their product (25–34). Many products also consist of combinations of dietary supplements and at least one of them also uses a nonprescription medication in combination with the botanical dietary supplement. At least one pharmaceutical manufacturer has also entered the branded botanical market (32).

Direct-to-consumer advertising of branded botanical dietary supplements appears to be quite effective, judging from the number of advertisements appearing in the print and electronic media. Many of these products claim to improve conditions that are refractory to conventional medical treatment or they are touted to be natural and, as such, purported to be safer than conventional pharmaceuticals and free of side effects. The public is well aware of dietary supplements, because many of these have appeared on late-night infomercials. Some examples of branded products touted for weight loss include Metabolife® (33), Leptoprin® (29), and Cortislim™ (30). Most weight loss products in the United States contained ephedra before the Food and Drug Administration (FDA) banned ephedra-containing dietary supplements. It appears that weight loss products are now being reformulated with other stimulants that have not received the intense scrutiny of the FDA, such as bitter orange (synephrine), green tea extract (caffeine), and guarana (methylxanthines: caffeine, theobromine, and theophylline). Other branded combination botanical products such as Enzyte® (25) and Avlimil® (26) are touted for treatment of sexual dysfunction and are advertised in a manner similar to sexual dysfunction pharmaceuticals. Still other formulations are advertised for breast enhancement—Bloussant™ (28), hair loss—Avacor™ (34), depression—Amoryn™ (27), nourishing the brain—Focus Factor™ (31), and sleep—Alluna™ Sleep (32). All of these contain one or more botanical constituents and are sold under the auspices of DSHEA, and therefore are not regulated by the FDA and the Federal Trade Commission as rigorously as prescription pharmaceuticals or food additives.

Sizing up the economics of the botanical dietary supplements market in the United States is challenging because the market is prodigiously dynamic. The market has been estimated to represent a demand between $0.6 and $5.1 billion (9,13,23,24,35–41). Estimated retail sales in the United States by year can be seen in Figure 1. It is important to note that each study sampled a different population. Growth in the market occurred rapidly between 1991 and 1998, but recent sales appear to have reached a plateau. Americans usually pay for botanical dietary supplements as well as other CAM therapies out of their own pockets because most health insurance programs do not cover CAM therapies (9,42). In 1997, total CAM out-of-pocket expenses exceeded $27 billion (43), with the expenditure on botanical products estimated at greater than $5 billion (9). Insurance coverage that covered CAM therapies would also likely result in

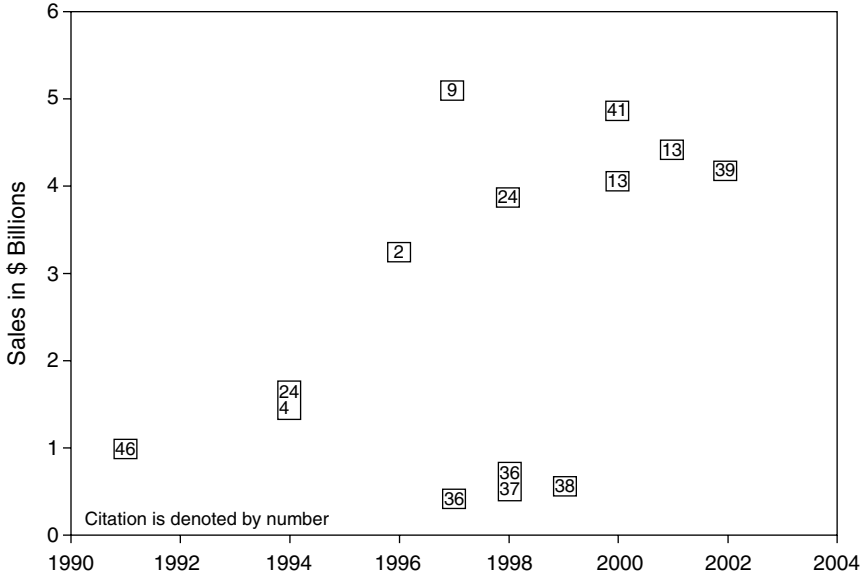

Figure 1 Estimates for U.S. retail botanical sales in billions of dollars by year from multiple citations.

growth in the botanical industry. One study found that full insurance coverage for botanical dietary supplements predicted an increase in usage of fivefold and partial insurance coverage predicted a threefold increase in botanical utilization (44).

Rapid growth in the botanical dietary supplement industry occurred within the first four years of DSHEA and there was also a concurrent growth spurt in the U.S. economy in the mid-1990s. DSHEA relaxed regulatory restrictions on dietary supplements, thus lowering the barrier to enter the market. As a result, growth in CAM likely is a result of deregulation by DSHEA and may reflect the disposable income available. This would explain the rapid growth in the mid-1990s and leveling of spending on botanical products at the turn of the century. Also, Eisenberg et al. found that the increase in botanical product utilization between 1990 and 1997 was likely due to an increase in the proportion of the population using botanicals rather than an increase in per patient utilization (9). In contrast to the growth of botanical products in the mid-1990s reported by Eisenberg et al., growth of the botanical market in early 2000 was reported to be from patients already using sundry botanical products according to the Natural Marketing Institute (NMI) (18). This indicates that botanical dietary supplement market expansion among new patients has moderated, which would explain the apparent stabilization of sale around the year 2000, as shown in Figure 1.

Market Analyses

Several major surveys of dietary supplement utilization have been conducted recently. The Saskatchewan Nutriceutical Network (SNN) (13), National Nutritional Food Association (NNFA) (14), Consumer Healthcare Products Association (CHPA) (11), Landmark Healthcare, Inc. (16), The NMI (18), individual investigators (9,12), Centers for Disease Control and Prevention (CDC) (15), and FDA (10) have all recently either conducted or contracted market analyses of CAM utilization in the United States, which included botanicals. Each survey is presented individually because the data are so heterogeneous among studies.

Saskatchewan Nutriceutical Network (13)

The SSN estimated U.S. botanical sales in 1999 to be $4 billion. The network further quantified where consumers buy their botanical products. Forty-seven percent are sold in retail stores, 30% are sold in multilevel distribution systems, 8% are sold by mail order or practitioners, 6% was sold by Asian herbal shops, and only 1% was purchased on the Internet (13). Notwithstanding these findings, it is important to note that the Internet was the fastest growing sales market for botanical products, at 150% per year (45).

National Nutritional Food Association (14)

The NNFA commissioned a telephone survey of 736 adults in October of 2001. The key finding was that women (25%) were more likely to take botanical products than men (15%). The survey emphasizes the importance of accurate labeling. Seventy percent agreed with the statement "Labels on supplements' bottles or packages are carefully read by most: they help the majority of older adults choose the right supplement and to determine the correct dosage." Only 22% disagreed with that statement. Fifty-five percent of respondents agreed with this statement: "Labels on dietary supplements help me understand if this is the right supplement for me," while 64% agreed with the following statement: "Labels on dietary supplements help me determine the dosage I need to take." The more educated patients were less likely to agree with this statement (14).

Consumer Healthcare Products Association (11)

The CHPA commissioned a study entitled "Self-Care in the New Millenium: American Attitudes Toward Maintaining Personal Health and Treatment." They conducted 1505 telephone interviews in January of 2001, using random telephone numbers. African-Americans and Hispanics were oversampled to conduct in-depth subgroup analysis. Of particular interest is the finding that 96% of respondents felt confident that they could take care of their own health. This might explain why so many people want access to pharmacologically active botanicals. These products do not require a prescription and thus allow patients to treat themselves.

Many of these products are being used for specific medical conditions. The top five conditions, in many cases are refractory to conventional medicine, namely menopausal symptoms, colds, allergies/sinus, muscle/joint/back pain, and premenstrual/menstrual symptoms.

The demographics of utilization in the past six months were reported. Thirty percent of women reported using a dietary supplement and 23% of men used a dietary supplement in the six-month period. Results for the effect of age on utilization have been mixed across studies. Patients who were between 50 and 64 years old had the highest reported use of dietary supplements, and 59% and those who were 18 to 34 years old had the lowest use at 48%. Income may be reflected in the utilization-by-age category. Utilization of dietary supplements by ethnicity was characteristic of other studies. Forty-four percent of African-Americans and 42% of Hispanics reportedly used dietary supplements, as compared to 53% of the general population. Although the study did not report Caucasian dietary supplement utilization rates, we can infer that Caucasians increased the overall utilization rate for the population. Health insurance status was associated with greater dietary supplement use, 56% versus 45%. This likely reflected the fact that patients who had health insurance also had more income. Those with some college education reported the highest utilization rate of 60%. People with college degrees used dietary supplements slightly less, 57%, but those with high school education or lesser educational qualification reported 48% utilization of dietary supplements in the past six months (11).

Landmark Healthcare Inc. (16)

In 1997, Landmark Healthcare Inc. commissioned a report entitled "The Landmark Report on Public Perceptions of Alternative Care." They conducted 1500 telephone interviews in November 1997, using random digit selection. The survey included a representative sample of minority patients—85% Caucasian, 8% African-Americans, and 3% Hispanic. The survey found that 17% of the U.S. population used botanical dietary supplements in the past year and even more striking, 75% of the U.S. population was most likely to use botanical products. Eighty-five percent of those reported to have taken a botanical supplement self-prescribed and self-administered the products. Three-fourths of patients who used alternative forms of care did so in conjunction with conventional medicine, yet 15% of patients replaced their conventional treatment with alternative care (16).

Natural Marketing Institute (18)

The NMI surveyed by mail 2002 households, July through August 2001. Only 53% of botanical supplement users were satisfied with botanical supplements. Despite the low satisfaction for botanical products, supplement users accounted for most of the increase in the previous year: 46% of botanical users increased utilization while only 10% of the general population

increased utilization of botanical dietary supplements. Consumers took botanical supplements primarily for general health benefits, 59% versus 40% for a specific condition. Only 6% took botanicals products for short-term benefits, whereas 80% took them for daily or long-term benefit. Many have recently started, with only 50% having used an herb for more than three years (18).

Independent Investigators (9,12)

Eisenberg et al. surveyed 1539 adults in 1990 and 2055 adults in 1997. Botanical use in the prior 12 months increased from 2.5% in 1990 to 12.1% in 1997—a 4.8-fold increase. They estimated, in 1997, that 15 million adults took a botanical product or high-dose vitamins with other medications, which represented approximately 18.4% of those taking medications in the United States. Growth in botanicals was found to be from an increase in the percentage of the population taking botanicals and not due to an increase in utilization per patient. More than 60% of patients did not discuss CAM use with their doctor. Patients spent an estimated $5.1 billion on botanical medications (9). Kaufman surveyed 2590 patients, February 1998 through December 1999. Fourteen percent of the U.S. population reported using botanical supplements. Concurrent use with medication was highest with patients on fluoxetine, 22%; overall, 16% of those taking medication reported using botanical medications (12).

Centers for Disease Control and Prevention (15)

The Division of Health Interview Statistics, National Center for Health Statistics, CDC conducted a survey entitled ''Utilization of Complementary and Alternative Medicine by United States Adults'' in 1999. The survey attempted to obtain a representative sample of minorities and also patients without telephones. This is important because these demographic groups tend to report lower utilization of botanicals products than Caucasians and those of higher socioeconomic status. The CDC found that 9.6% of the population took botanical medicines. Hispanics reported the lowest use of CAM followed by African-Americans, and then Caucasians: 19.9%, 24.1%, and 30.8%, respectively. The western part of the United States reported the highest use of CAM (15).

Food and Drug Administration (10)

FDA commissioned a study of dietary supplement sales in the United States in 1999. Samples of products were purchased from a representative sample of retail establishments, catalogs, and the Internet. The authors looked at the consistency of botanical products purchased. Forty percent to 46% of botanicals and botanical products were consistent with the ingredients listed on the label. Botanical extracts were even less consistent with the label, only 12% to 24% (depending on where purchased) were found to be consistent

with the label. They also gave the mean, minimum, and maximum price paid for dietary supplements by source of purchase. Interestingly, the mean purchased price on the Internet was the most expensive at $23.34, followed by the mean catalog price, $16.40. The mean retail price was less than half the cost of the mean Internet price, at $11.62 (10).

Utilization Summary

Patients who use botanicals tend to have attained higher education, be female, be older persons, have higher incomes, and have a recalcitrant chronic disease unresponsive to conventional medicine. There is also evidence that cultural differences have a strong impact on the use of botanicals. Certain subpopulations may defy these generalizations to the U.S. population. Asian-Americans have a long history of using botanicals as medication and often consider botanicals a conventional form of treatment (2). Southern rural poor are also reported to have a higher utilization profile of plant-derived products (46). Rural poor may treat illness with botanical products while the U.S. population as a whole tends to use botanical products for general health benefits rather than to treat a specific illness (18,46). Table 1 summarizes frequently used botanical products and what the patients are using them for.

SAFETY OF BOTANICAL PRODUCTS

As a result of DSHEA, the majority of botanical drug products are used in the United States without medical supervision. Only 8% of those who use botanicals do so under medical supervision (13) and 85% of those who treat themselves with herbs do not seek professional guidance or advice (16). Even if patients utilizing botanical dietary supplements were medically supervised, adulteration and misbranding are prevalent and so little is known about the supplements that many untoward events could not be prevented or recognized in a timely fashion (47,48). Despite the widespread acceptance of CAM by the lay public, clinicians possess little scientific information about the practices of CAM relative to conventional western medicine. This is particularly unsettling because it is estimated that 16% to 18% of prescription medication users took botanical and supplements coincidentally (9,12). Medication–botanical interactions are largely unknown (42). Even more alarming is a report that 14.5% of women used botanical products during pregnancy and 23.5% of children under 16 may be taking botanical products. Neonatal heart failure has been attributed to the use of Blue cohosh during pregnancy (47).

Up to 60% of patients using alternative therapies are reported to have never informed their physician of their botanical or CAM use (9,22,49,50). Furthermore, only 40% of physicians ask their patients about alternative therapy (22). The 60% of physicians who do not ask about the use of

Table 1 Estimates for Botanical Utilization, Sales Data in the United States, and Reasons for Patient Use of Botanical Products

Herbal product	United States herbal rank (7)	United States herbal rank (13)	United States sales in $ 1998 (36), 1998–1999 (13), 1999 (7,39), 1999–2000 (67), 2000 (38), 2000–2001 (68)	Possibly effective uses (66)	Ineffective uses (66)
Aloe Vera	10		49.37 million (7)	Burns, frostbite tissue survival, psoriasis	
Bilberry	8		97.21 (7)	Retinopathy	Night vision
Capsicum (cayenne)	16		36.29 million (7)	Pain, fibromyalgia, prurigo nodularis	HIV-associated peripheral neuropathy
Chinese herbs	18		33.57 million (7)		
Chondroitin		8		Eye surgery, osteoarthritis, dry eyes	
Cranberry	17		34.27 million (7)	Urinary odor, urinary tract infections	Diabetes
Creatine		9		Athletic performance, congestive heart failure, gyrate atrophy of the choroid and retina, McArdle's disease, muscular dystrophy	Amyotrophic lateral sclerosis, rheumatoid arthritis, athletic conditioning
Garlic	2	3	61.21 million (38), 84 million (36),	Atherosclerosis, colon cancer prevention, gastric	Breast cancer prevention, diabetes prevention and

(*Continued*)

Table 1 Estimates for Botanical Utilization, Sales Data in the United States, and Reasons for Patient Use of Botanical Products (*Continued*)

Herbal product	United States herbal rank (7)	United States herbal rank (13)	United States sales in $ 1998 (36), 1998–1999 (13), 1999 (7,39), 1999–2000 (67), 2000 (38), 2000–2001 (68)	Possibly effective uses (66)	Ineffective uses (66)
			280.85 million (7), 100 million (68)	cancer prevention, hyperlipidemia treatment, hypertension treatment, prostate cancer prevention, tick bite prevention, tinea corporis treatment, tinea cruris prevention, tinea pedis treatment	treatment, *Helicobacter pylori* treatment, familial hypercholesterolemia treatment, lung cancer prevention, peripheral artery disease treatment
Ginger	20		27.48 million (7)	Chemotherapy-induced nausea, morning sickness, postoperative nausea and vomiting, vertigo	Motion sickness
Ginkgo	1	2	151 million (36), 395.68 million (7)	Age-related macular degeneration treatment, age-related memory impairment, altitude sickness, cognitive performance, dementia, diabetic retinopathy,	Antidepressant-induced sexual dysfunction, seasonal affective disorder, tinnitus

				glaucoma, premenstrual syndrome, Raynaud's disease, vetigo	
Ginseng	6	1	96 million (36), 159.32 million (7), 56.27 million (66), 62.5 million (38)	Cognitive performance, diabetes, erectile dysfunction, premature ejaculation	Athletic performance, menopausal symptoms, quality of life
Glucosamine		4	871.8 million (39)	Osteoarthritis, temporomandibular joint arthritis	
Goldenseal	14		39.01 million (7)		Urine drug testing
Grape seed	7		122.41 million (7)	Chronic venous insufficiency, ocular stress	Allergic rhinitis
Green tea (extract)	15		37.68 million (7), 3.15 million (38)	Bladder cancer, esophageal cancer, pancreatic cancer, breast cancer, cervical dysplasia, cognitive performance, gastric cancer, hyperlipidemia, leukoplakia, ovarian cancer, Parkinson's disease	Colon cancer
Echinacea	5	6	70 million (36), 193.03 million (7), 58.42 million (38)	Common cold, vaginal candidiasis	Herpes simplex, influenza, leukopenia
Horse chestnut	11		49.24 million (7)	Chronic venous insufficiency	

(*Continued*)

Table 1 Estimates for Botanical Utilization, Sales Data in the United States, and Reasons for Patient Use of Botanical Products (*Continued*)

Herbal product	United States herbal rank (7)	United States herbal rank (13)	United States sales in $ 1998 (36), 1998–1999 (13), 1999 (7,39), 1999–2000 (67), 2000 (38), 2000–2001 (68)	Possibly effective uses (66)	Ineffective uses (66)
Kava	12		17 million (36), 45.25 million (7), 14.68 million (38)	Anxiety, benzodiazepine withdrawal, menopausal anxiety	
Lecithin		7		Hepatic steatosis, dennatitis, dry skin	Gallbladder disease, hypercholesterolemia, Alzheimer's disease and dementia, extrapyramidal disorders
Milk thistle	9		56.70 million (7), 8.91 million (38)		
Pygeum	19		28.21 million (38)	Benign prostatic hyperplasia, prostatic adenoma	
Saw palmetto	4	10	32 million (36), 193.17 million (7), 43.85 million (38)	Benign prostatic hyperplasia	Prostatitis and chronic pelvic pain syndrome
St. John's	3	5	140 million (36), 209.34 million (7),	Depression, anxiety	Hepatitis C virus

(*Continued*)

Wort		55.98 million (38)		HIV/AIDS, polyneuropathy
Valerian	13	44.21 million (7), 16.82 million (38)	Anxiety, insomnia	

Note: In column 2 (7), sales rankings, by dollars, for the top 20 sold in the United States for the year 1999 are given. Column 3 (12) gives the top 10 products in 2002 in an ambulatory adult population (13). Reported sales in dollars are present in column 4. Columns 5 and 6 (66) give the conditions the botanicals have been used for. The Natural Medicines Comprehensive Database at http://www.naturaldatabasc.com (66) distinguishes gradations of evidence for effectiveness, which we have not done here. There is much variability in the data from report to report; even data within the same trade journal data are inconsistent with that from previous reports. This in no way endorses the utilization of dietary supplements for treatment of these conditions. Patients should always seek the advice of their health care provider.

botanical supplements and other CAM are unlikely be informed of alternative therapies their patients are using. Clearly, there is a lack of communication between patients and providers. Some patients may fear disapproval by physicians and wish to give socially desirable answers. However, the majority of patients express a lack of concern about their physician's approval, rather they were more concerned with their physician's inability to understand and incorporate CAM into their medical management (51). Patients are not using alternative therapy because they are dissatisfied with conventional medicine but instead because they value both types of therapy (51).

Many botanical dietary supplements are potentially unsafe because of adulteration and misbranding. Thirty-two percent of botanical medications collected in California contained an undeclared pharmaceutical or heavy metal (8,48). Pharmaceuticals adulterating botanical products are one of the most frequent reasons botanical dietary supplements are placed on the FDA MedWatch site, and this is undoubtedly a small fraction of what actually occurs. Table 2 gives the botanical products placed on MedWatch in the past five years (52). Many of these adulterants are not detected until patient illnesses are first detected. Consumers often do not recognize that many imported products, purported to be traditional medications, are actually recognized pharmaceuticals. For example, a ''Mexican asthma cure'' had a claim on the label that said it contained no corticosteroids and was free of adverse effects, but the product was found to contain triamcinolone, a moderately potent corticosteroid with well-documented systemic adverse effects common to all glucocorticoids. In another example, a patient used an illegally imported Chinese medicine; it was reported to last much longer than the medication the physician had prescribed. The label on the Chinese medicine said it contained astemizole, a long-acting antihistamine withdrawn from the United States as a result of its effect of prolonging the cardiac QTc interval (8). In many cases, patients may not recognize pharmaceuticals that are sold as traditional medicines. In the past, consumers have had difficulty distinguishing between vitamins and botanical products (9,23). It is likely no different for botanicals and pharmaceuticals. This may be problematic because corporations are creating proprietary botanical blends and branding them for use in specific medical conditions. Patients could inadvertently assume they are treating themselves with a medication that has undergone the same rigorous clinical testing as other FDA-approved medications. Patients readily read and trust the directions on labels of dietary supplements (14). In fact 59% of the public incorrectly thought a government body reviewed and approved botanical supplements before they are sold (6,53,54).

There are other risks of contamination to botanical and botanical supplements. Due to stress on the supply of cultivars for botanical supplements, products may vary greatly in their active content. In the era of limited resources, with increasing utilization and decreasing wild production, there is pressure to produce a product. Raw material costs may override the

Table 2 Dietary Supplement Information from MedWatch for Herbal Products from 1999–2003

Product	Company	Date	Reason for action
Ancom antihypertensive compound tablets	Herbbsland, Inc., Tai Chien Inc.	01/17/2003	Contains unapproved reserpine, diazepam, promethazine, and hydrochlorothiazide
Viga tablets	Best of Life International	05/29/2003	Contains unlabeled drug sildenafil
Viga or Viga for women	Health Nutrition (RMA Labs)	06/27/2003	Contains unlabeled drug sildenafil
Vinarol tablets	Ultra Health Laboratories, Inc.	04/09/2003	Contains unlabeled drug sildenafil
Kava (*Piper methysticum*)	All products containing kava	03/26/2002	Kava is associated with liver-related injury including hepatitis, cirrhosis, and liver failure
Nettle capsules	Nature's Way Products, Inc.	07/03/2002	Contains high concentrations of lead
PC SPES and SPES	BotanicaLab	02/08/2002	Contains undeclared amounts of warfarin and alprazolam
Aristolochic acid	All products containing aristolochic acid	04/16/2001	Aristolochic acid is associated with renal interstitial fibrosis with atrophy and loss of tubules, and the development of end-stage renal failure
Kava (*Piper methysticum*)	All products containing kava	12/19/2001	Kava-containing products have been implicated in serious liver toxicity
Lipokinetix	Syntrax innovations, Inc.	11/20/2001	Lipokinetix has been implicated in several cases of serious liver injury
Neo Concept Aller Relief	BMK International	01/22/2001	Contains trace amounts of aristolochic acid, a carcinogen and nephrotoxin

(*Continued*)

Table 2 Dietary Supplement Information from MedWatch for Herbal Products from 1999–2003 (*Continued*)

Product	Company	Date	Reason for action
Aristolochic acid	All products containing aristolochic acid	06/01/2000	Aristolochic acid has been associated with nephropathy
St. John's Wort	All products containing St. John's Wort	02/10/2000	Hypericum perforatum can decrease indinavir plasma concentrations due to the induction of the P-450 metabolic pathway
Tiratricol	All products containing tiratricol	11/22/2000	Tiratricol also known as triiodothyroacetic acid or TRIAC, is a potent thyroid hormone that may result in serious health consequences
Asian remedy for menstrual cramps—KooSar	Tien Sau Tong	01/25/1999	One case report of lead poisoning from a woman who was taking 6 pills per day. There were no other reports of lead poisoning and the product was not recalled
GBL	All products containing GBL	01/22/1999 05/11/1999 08/25/1999	GBL is converted to GHB in vivo. At that time GHB was banned outside of clinical trials approved by the FDA. GHB has been implicated as a potential "date rape" drug

Abbreviations: FDA, Food and Drug Administration; GBL, gamma-butyrolactone; GHB, gamma-hydroxybutyrate.
Source: From Ref. 52.

quality and purity of the product. There are few barriers to bringing new products to the market and many newer entrants may lack expertise to prevent quality issues and contamination in their product (24). This creates the potential for inadvertent poisoning as a result of overdosing or contamination as well as treatment failure through underdosing. Indeed, a study of botanical consistency found that only 43% of the products tested were consistent for ingredients and dose with the benchmark or recommended daily dose. Twenty percent had the correct ingredient but not the stated dose and 37% were not consistent with either ingredients; dose or the labeling was too vague to draw conclusions (37,55). The FDA also found that many botanical products were inconsistent with the ingredients listed on the label and estimated that only 12% to 24% of botanical extracts and 40% to 46% of botanical products contained what was on the label (10).

Adulteration was found to be a problem in another dietary supplement containing androstenedione; although not strictly a botanical, it is regulated in a similar fashion under the auspices of DSHEA. Ingestion of androstenedione contaminated with trace amounts of 19-norandrosterone resulted in a positive test for 19-norandrosterone, a metabolite used to detect nandrolone. Other samples were also found to be contaminated with testosterone (56). The FDA has been cautious in its enforcement of DSHEA after its experience with the passage of The Nutritional Labeling and Education Act of 1990. This act severely restricted unproven claims on foods and dietary supplements. Fearful of the loss of the ability to conduct business as usual, the dietary supplement industry responded with forceful lobbying to the Congress, which responded with DSHEA, exempting dietary supplements from the earlier law.

DSHEA severely limited when the FDA could take action to protect the public and what actions could be taken. The burden of proof to show harm is now placed on the FDA. Moreover, dietary supplement manufacturers are not required to report adverse dietary supplement events. In fact, between 1994 and 1999 fewer than 10 of the 2500 adverse events associated with dietary supplements and reported to the FDA were reported by the manufacturer (53). The Office of Inspector General concluded the spontaneous adverse event reporting "system has difficulty generating signals of possible public health concern" due to "limited medical information, product information, manufacturer information, consumer information, and ability to analyze trends" (57). One weight loss supplement manufacturer is reported to have withheld from the FDA 14,684 complaints of adverse events regarding ephedra, which included heart attacks, strokes, seizures, and deaths (53).

Recently, the FDA has begun to enforce DSHEA more assertively. Ephedra was banned as a dietary supplement in April of 2004 because ephedra presented an "unreasonable risk." However, this ban does not include foods containing ephedra, approved drugs, or Asian medicines, which are allowed to

contain ephedra under the final rule (58). It appears that FDA may address androstenedione in the near future (59,60). In March of 2004, FDA sent warning letters to 23 manufactures or distributors of androstenedione threatening enforcement if they do not immediately cease distribution of androstenedione and within 15 days advise the FDA, in writing, of actions taken (61). The FDA did this on the grounds that androstene dione was not marketed on October 15, 1994 and as such is not presumed safe under DSHEA. Furthermore, the FDA has stated that androstenedione consumption would be considered an unreasonable risk, given what is now known (61–63).

Other botanical products are receiving FDA attention. The acting commissioner of the FDA, Lester Crawford, told members at the American Society for Pharmacology and Experimental Therapeutics in April 2004 that the FDA was compiling data on other botanical products that have been associated with safety issues (64). Kava, used as an anxiolytic, and usnic acid, used for weight loss, have both been associated with liver disease; bitter orange is used as a sympathomimetic in weight loss products to replace ephedra; all the pyrrolizidine alkaloids have the eye of the FDA (64). There are other products that could receive scrutiny of the FDA in the future. Examples profiled in Consumer Reports include a list of what they call ''the dirty dozen herbs listed by risk.'' The botanicals are broken down as follows: ''definitively hazardous'': aristolochic acid; ''very likely hazardous'': comfrey, androstenedione, chaparral, germander, and kava; and ''likely hazardous'': bitter orange, organ/glandular extracts, lobelia, pennyroyal oil, skullcap, and yohimbe (53). These are products with potent pharmacological actions and poorly documented toxicities, and as long as they are available safety will clearly be an issue.

As a result of DSHEA, botanical supplements are presumed safe by virtue of being ''grandfathered'' by the FDA if the product was marketed before October 15, 1994. Products brought to market after that date only require 75-day premarket notification to the FDA with information that substantiates that the ingredients will reasonably be expected to be safe (65). FDA cannot take action until patients are injured but it is increasingly clear relatively rare adverse events may not be detected until a significant number of patients are killed or injured.

Safety Summary

With little knowledge of dietary supplements, many physicians do not ask patients about botanical products and patients are also not disclosing the consumption of these products. Some of these products also have substantial pharmacologic activity that interacts with prescription medications and disease states while other are devoid of any biological activity. Many patients may actually think they are taking something that is rigorously tested and regulated by the FDA when in fact some have been reported have

serious issues with contaminants. Safety has been presumed as a result of DSHEA despite common misbranding, and adulteration. Several dietary supplements have been linked to cancer, renal and liver failure, and even death. The vast majority of products are probably safe but many likely have low level undocumented adverse effects. This leaves the possibility most adverse events likely go unrecognized and untreated. Under current practices, the situation is unlikely to change.

CONCLUSIONS

The profile of the patient who uses a botanical product will likely be someone with higher education, be female, have higher socioeconomic status, have more disposable income, and be older. The market is estimated to be in excess of $5 billion in the United States with an estimated 10% to 20% of the population using botanicals. Utilization of botanical dietary supplements will continue to grow under the deregulation of DSHEA and as they gain acceptance by the public and medical establishment. With increasing stress on the harvesting of wild foliage, corporations must resort to harvesting domestically grown botanical dietary supplements to meet the demand. This should result in a more consistent product base. By increasing direct-to-consumer marketing and branding of specific products, there will likely be an acceleration of market growth. New ads for branded botanicals have already appeared as this chapter was being published. Products will continue to be imported and Internet sales will continue to grow. As more patients use these products and regulatory issues remain, safety will continue to be a concern and the market will likely be difficult to define. Drug–botanical interactions and disease–botanical interactions are only now beginning to be recognized by health care professionals as a potential source of harm, as the prevalence of botanical dietary supplement utilization increases.

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