SAFETY ISSUES ASSOCIATED WITH HERBAL INGREDIENTS

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I. INTRODUCTION

To understand safety issues associated with herbal ingredients, it is important to appreciate how they were derived, what regulatory policies (or not) dictate all aspects of their production, and what options are available to making rational choices as to whether they are what they claim to be, do what they contend, and are safe in the context of their use. As globalization of herbal medicine progresses and reports of adverse events continue to escalate, it is recognized that the status quo can no longer ensure consumer confidence and protection of these types of treatments. This is the reason that both international and national policies are being evolved and implemented to address these concerns.

Since the evolution of traditional pharmacopeias has been predicated upon time-honored empirical testing, customary herbal remedies continue to be used by a vast majority of the world's population who depend on traditional medicine for their primary needs. Worldwide, the practice of herbalism continues to expand, and it has been estimated that the industry estimated at $60 billion today will significantly expand during this century (World Health Organization [WHO], 2004). To prove parameters of efficacy, more and more are being clinically evaluated in the context of use. Many have also been found to possess specific bioreactive compounds linked to their medical value, which in turn not only has verified their therapeutic worth, but also has led to new and significant drug discoveries (Lewis and

Elvin-Lewis, 2003). Current surveys are indicating that even in countries where pharmaceutical uses are favored, the popularity of herbal medicine, which began in the early 1970s, has risen markedly in the last decade (Block and Mead, 2003, Eisenberg *et al.*, 1998, Elvin-Lewis, 2001). This generational shift toward herbal use is related to the diminishing trust in conventional medicine that relies primarily on promoting synthetic mechanistic-based drugs for treatments. This is because in spite of their rational design, potency, and rapid action, concerns continue to surface regarding the serious adverse reactions, which are linked to their use. There is a growing belief that herbal medicines are better and safer than modern alternatives. This attitude is further fueled by an increased self-reliance in these populations, the tendency to self-medicate, particularly among the better educated (Klepser *et al.*, 2000), and the lack of knowledge that some of these practices can be harmful. Unfortunately, only a proportion of those using dietary supplements can appropriately interpret use and disclaimer claims (Cupp, 2003), and these claims may not be distributed with the products but as other materials. Also, herbal remedies are not always used alone and may be combined with pharmaceuticals with the notion of enhancing the positive attributes of the treatment or diminishing side effects that are known for the conventional drug (Vuckovic and Nichter, 1997). For this latter reason, the U.S. National Institutes of Health (NIH) has been obliged to introduce new policies involving use of alternative supplements by patients enrolled in clinical trials (Sparber *et al.*, 2004).

Designer "foods" are becoming increasingly popular within the "health food" industry, and they are formulated in ways to supposedly enhance the health benefits of the product by incorporating a wide variety of medicinal herbs, their extracts, and other ingredients in the mixture. These secondary additives are frequently listed on the packaging, but usually in a diminished format, without providing any sense to the consumer as to how each ingredient has been apportioned, what value they might be providing, or if any adverse effects can be expected. A noteworthy example is the wide variety of soy-powder products promoted as a health drink or for weight loss, which can include, among other ingredients, undefined amounts of bulking agents like psyllium from *Plantago ovata.* Psyllium can affect intestinal absorption in both positive and negative ways. While providing a feeling of satiety, improving glycemic control in patients with type 2 diabetes and having the potential to lower cholesterol especially with cholestyramine, it can also decrease the absorption of important nutritional minerals such as zinc, copper, iron, calcium, and magnesium in addition to important therapeutic agents such as lithium, carbamazepine, digoxin, and warfarin (Lewis and Elvin-Lewis, 2003).

Another disconcerting practice is the widely used ploy of substituting the term *cane juice* for that of sugar or sucrose in a broad variety of "health"

foods and breakfast cereal products. While this epithet implies that the sweetening agent is in its "natural" rather than "refined" state, there is no proof that this is the case because the starting point for refined sugar is "cane juice." It remains an allusive device to hide the fact that these products contain sucrose, which in any form should be avoided by many needing to either monitor or restrict their intake of this sweetener.

II. WHAT IS AN HERB?

The WHO defines an *herb* as being fresh or dried, fragmented or powdered plant material, which can be used in this crude state or further processed and formulated to become the final herbal product. Treatment of herbs by squeezing, steaming, roasting, decocting or infusing in water, extracting with alcohol, or sweetening and baking with honey can create "herbal products" such as juices, tinctures, decoctions, infusions, gums, fixed oils, essential oils, and resins. These may be used medically or as the starting material for additional processing and as food ingredients. Depending on the sophistication of the "herbal preparation," these products may be subject to any number of physical, chemical, or biological processes, including pulverization, extraction, distillation, expression, fractionation, purification, concentration, or fermentation. Formulation of the "final product" may require mixing one or more plant preparations with minerals or animal products and constituents isolated from herbal materials or synthetic compounds. These phytotherapeutic formulations may also be referred to as *drugs* or *botanicals,* or when taken orally to provide health benefits, they may be called *dietary supplements,* or even food ingredients in some cases. Additional standardization may include incorporating particular ingredients in amounts consistent with the bioreactivity of certain of their chemotaxonomic markers. These types of herbal products, which are usually clinically validated, are either referred to as *phytopharmaceuticals* or *botanical drugs* (Raskin *et al.*, 2002; WHO, 2000; Wyllie, 2003).

III. SOURCE OF HERBAL INGREDIENTS

The selection of plants to be used in herbal remedies can depend on many factors, and their quality is primarily dependent on the taxonomic expertise of individuals that gather them and the skill of those who prepare them for use. Misidentifying or even selecting the incorrect plant part is often the source of other than expected efficacies and adverse reactions. Those who wild-craft may be able to recognize the plants at only the family or generic

level, whereas other collectors are able to discern specific species and even certain chemotypes. For example, wild crafters collecting "cats' claw" in Amazonia are unable to differentiate between the more common *Uncaria guianensis* and the less common *Uncaria tomentosa* but usually refer to their collections as being the latter species. This places in doubt a number of scientific studies that have been generated on *U. tomentosa*, because the species actually tested is unclear. Without taxonomic verification to suggest otherwise, a more accurate citation for these test materials should have been *U. tomentosa/U guianensis* (Lewis, personal communication, 2005). Individuals who harvest medicinal plants may also be aware of what time of year to collect, store, and prepare the plant or one or several of its parts (leaves, flowers, stems, seeds, roots, rhizomes, fruits, bark, sap, etc.) to ensure optimal potency, flavor, and/or aroma. Also, because types of bioreactive components are often shared between closely related plants (although their concentrations may vary), knowledge of this type may be only of relative importance to the healer who uses them. This is also the reason that many examples exist of related medicinal plants or those possessing similar biosynthetic pathways being selected for comparable uses by populations that do not have any contact with each other or live in disparate parts of world (Elvin-Lewis, 2003, Lewis and Elvin-Lewis, 2003).

Today, to meet the needs of expanding herbal markets, many popular herbs are no longer totally wild-crafted. Depending on national laws, regulatory policies may control the amounts to be harvested from the wild, how they might be propagated for commercial harvest, or if restrictions of export of live material is allowed. Applying resource management to preserve rare or threatened medicinal species is a matter of concern for many countries where such taxa exist, and there is a need to rigidly enforce national regulations and international policies to ensure future availability. Guidelines for the Conservation of Medicinal Plants formulated by the WHO, the International Union for Conservation of Nature and Natural Resources (IUCN), and the World Wide Fund for Nature (WWF) (WHO/IUCN/WWF, 1993) is regularly updated (e.g., July 28, 2004) and forms the basis for providing a framework for the conservation and sustainable use of plants in medicine. Also, to safeguard the world's biological diversity, a recommendation of the Global Diversity Strategy, jointly produced by the World Resources Institute (WRI), IUCN, and the United Nations Environment Program (UNEP), is included in the document.

The following example indicates how appropriate resource management of a rare and endangered medicinal taxa can be accomplished. Chinese ginseng (*Panax ginseng*) has been essentially extirpated in the wild, and export of its seed from China for cultivation elsewhere is prohibited. Also, harvesting of its American counterpart (*Panax quinquefolius*), from its

natural habitat, is carefully regulated to ensure sustainable wild populations (Lewis, 1990), and because it is highly favored over cultivated forms and can vary in composition depending on where it is harvested (Jackson *et al.*, 2003), it is extremely costly (e.g., up to U.S. $500/pound). Though fastidious in its growth requirements, cultivation of several *Panax* species (*P. ginseng, Panax notoginseng, Panax zingerberensis,* in Asia, and *P. quinquefolius* in North America) has become the only viable alterative for accommodating sourcing needs because of its popularity in herbal medicine. In addition, other species may be locally available but are rarely sold commercially (Lewis and Elvin-Lewis, 2003). These species may differ in the presence of certain ginsenosides, and within the commercial arena, there are broad chemical disparities in the quality of products that are available and labeled "ginseng" (Asafu-Adjaye and Wong, 2003; Cui, 1995; Lau, 2003; Liberti and Marderosian, 1978). Similar disparities have been found for Siberian or Russian ginseng (*Eleutherococcus senticosus*) products and their eleutherosides (Harkey *et al.*, 2001).

Resource management of other American species has evolved depending on their ease of cultivation or the need to protect wild populations that have become endangered. Some herbs are more easily grown from seed than harvested from the wild, and today *Echinacea* species are primarily obtained from cultivated rather than natural sources (Anonymous, 2000; APHA, 2004b). Others have become so seriously depauperated by wild crafting that they are now classified as endangered and are listed in Appendix II of the Convention for International Trade on Endangered Species of Wild Fauna and Flora (CITES). Sale of wild-crafted plants Goldenseal (*Hydrastis canadensis*) is disallowed, and not only are permits required for its cultivation and propagation, but when sold, documentation must be provided that roots, rhizomes, or seeds came from legally acquired parental stock, and that the plants were cultivated for 4 years or more without augmentation from the wild (Davis and McCoy, 2000).

Until conservation practices are realistically established, certain medicinal plants will continue to be harvested in a non-sustainable way. Examples can be found wherever guidance or laws are not available to regulate harvesting procedures or where strategies have not evolved to overcome challenges to cultivation. For example, in Africa, there is a tendency to inappropriately harvest the bark of *Prunus africana,* so the tree dies. To prevent depletion of wild stocks in the mountain forests of Africa and Madagascar, conservation practices and breeding programs are being instituted. Similar approaches are being employed for Devil's Claw, *Harpagophytum procumbens,* which grows in southern Africa and Namibia. In Namibia, certified organically grown material is now available (WHO, 2004). In Amazonia, because harvesting *Croton lechleri* sap by tapping the trunk is time consuming and labor

intensive, these trees are usually cut down to obtain maximum amounts of the product. This is a weedy fast-growing tree and plantations are being established in Peru to accommodate commercial needs.

There is a wide variation in the types of cultivars that are grown for commercial purposes, with propagating stock or seeds being derived from customarily available sources or carefully selected to meet commercial standards needed to provide optimal potency of a desired bioreactive ingredient or ingredients. By applying chemical and ethnomedical dereplication methods, it is also possible to identify additional medicinal plants, which share similar or identical metabolic pathways and comparable medicinal uses. Although this knowledge may be used to introduce new marketable products, there are risks in promoting these as replacements unless their parameters of use and safety are well understood and comparable.

The amount of certain bioreactive compounds may be enhanced or transferred to another species by applying current genetic technologies, namely genetic modification (GM) (hence, the protectiveness of certain countries for its genetic resources). Although the utilization of GM may have its detractors (Uzogara, 2000), these techniques when applied correctly have the ability to increase a medicinal plant's potency or provide alternate sources for a rare and desired compound. The potential for the evolution of suitable plant crops as functional/medicinal foods has exciting possibilities such as in the creation of foods with enhanced vitamin content (e.g., yellow rice) or in the evolution of edible vaccines. However, altering medicinal plants in similar ways could also induce unexpected effects, and so their utilization as herbal medicines will have to be cautiously pursued (Littleton *et al.*, 2003; Raskin *et al.*, 2002; Tatlow, 2003; Wiley, 2003).

Regardless of the genetic resource, sourcing of quality raw medicinal plant materials depends on how appropriate agriculture and field practices are applied, the oversight policies in place in the country of origin, and how the manufacturer of the final product might detect overt problems. Nuances in cultivation, collection, harvest, post-harvest processing, transport, and storage can all have an impact on the value of the final product. Whatever the source, the worth and safety of a product may also be affected by overt or inadvertent adulteration with noxious plant species and inappropriate contamination with microbial, chemical (insecticides, herbicides, heavy metals, radio active substances), and insect and animal parts and excreta. Regional guidelines for the production of herbal products following standards of good agricultural practices (GAP), as recommended by the WHO (2003), are in the process of being instituted by the European Union (E.U.), China, and Japan. Also, to prevent insecticide and herbicide contamination, certain producers will claim to grow their herbs organically. The issue of permitting this labeling on products within the United States is now being

addressed under the province of the U.S. Department of Agriculture. The goal is to permit labeling that designates that production of certain herbs or finished "dietary supplements" has conformed to the National Organic Program (NOP). Presently, there is no assurance that similarly labeled products, produced elsewhere, conform to American standards outlined in the Organic Foods Production Act of 1990 (OFPA) (AHPA, 2004b).

Because cultural differences often dictate how diagnosis and efficacy are determined, regional variations in herbal remedies using the same flora are also likely to occur. Much depends on the origins of the medicinal systems that are being applied, the distribution and availability of particular plant species, and the outside influences that are affecting both formulation and application. Clearly, employing a remedy with optimal efficacy is the goal of any competent healer, and certain traditional treatments are often carefully designed for this purpose. Under ideal conditions, care is taken to correctly identify each ingredient, to harvest plants for optimal potency, to prepare the remedies under strict guidelines, and to prescribe them to achieve the best clinical response. For example, conventional Asian pharmacopeias are replete with formulations planned to specifically address this need by not only incorporating several plants that share the same bioreactivity, but also including other groups of plants with complementary activities. These practices are meant to accommodate expected variations in potency, to potentiate the efficacy of the treatment, and to prevent or anticipate any adverse reactions that may occur. However, this does not ensure that every practitioner will adhere to formulatory guidelines set out in these time-honored manuscripts. In both India and China, if certain species are unavailable, usually because of regional disparities, replacements with local taxa are not atypical (Elvin-Lewis, 2001). Also, a practitioner, without changing the name of a remedy, may alter the contents of a traditional formulation to accommodate the patient's specific needs. Such is the case with herbal preparations called "eternal life" (Sanders *et al.*, 1995). These practices can fundamentally alter the parameters of efficacy and make it challenging to understand the basis for any unusual or unfavorable events that may accompany these established treatments.

IV. REGULATORY ASPECTS

Globally, a wide range of conventional policies control the availability of herbal products to the general public. How this is accomplished depends on their derivation and whether they are categorized as medicinals, drugs, botanicals, or dietary supplements. The status of the regulatory situation as viewed worldwide in 1998 is available online (WHO, 1998). However, as

herbalism in all its forms continues to expand, it has become evident that the additional workable regulatory policies and guidelines are needed to ensure that commercial products are reliable, safe, and efficacious. Furthermore, the international community is becoming aware that the accelerated export of herbal medicines and medicinal plants between cultures and continents is creating the need to address these issues in a more proactive manner. In response to these concerns, the WHO (2004) has set forth guidelines to provide national regulatory bodies with appropriate advice. Although this achievement can be applauded, a universal consensus on how these principles might be applied has yet to be realistically achieved. Today, even in developed countries such as the United States, resources are insufficient to provide the surveillance and enforcement aspects that are necessary to prevent many of the scurrilous activities leading to negative health experiences that are inherent to today's practices in the herb trade industry.

A. WHO GUIDELINES

WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants (WHO, 2004) is a comprehensive document that covers appropriate recommendations for good agricultural practices for growing medicinal plants. It addresses issues of plant identification/authentication, the nature of propagation materials, parameters of cultivation and protection, methods of harvest, and types of personnel that are needed. Included are acceptable practices for the appropriate collection of medicinal plants from the wild or cultivated plots. The need to comply with national and international laws regarding obtaining permits for collection and export, in addition to phytosanitation certificates, is stressed. It also outlines technical aspects governing post-harvest processing, bulk packaging and labeling, storage and transportation, the equipment required, quality assurance, documentation, and other relevant ethical and legal considerations associated with intellectual property rights, benefits sharing, protection of threatened and endangered species, and research needs. China, Japan, and United Europe (UE) are actively engaged in adopting these recommendations into their national policies.

In response to the need to better understand the parameters of safety and efficacy of traditional medical treatments, the WHO has prepared general guidelines to aid in the research and evaluation of these methods. This document presents useful methods that can be applied to the study of herbal medicines, procedure-based therapies, and clinical studies. It also includes discussions associated with pragmatic research issues, the ethics involved, the education and training of personnel, and the surveillance systems that might be imposed. It is emphasized that these studies be conducted in a

manner that ensures adequate safety for the subjects, and that prior to initiating the study every effort is made to identify any adverse events that might be encountered. These clinical trials must also be performed within the framework of the prevailing law in a given country or state, and whenever applicable, rescue treatments should be provided to patients given a placebo or unproven treatment (WHO, 2000).

To facilitate needed information exchange, the WHO is also generating monographs on selected medicinal plants. The format is designed to provide information on safety, efficacy, and quality control and to assist in the development of national monographs and formularies. These monographs are not pharmacopeial based but are designed to be "comprehensive scientific references for drug regulatory authorities, physicians, traditional health practitioners, pharmacists, manufacturers, research scientists and the general public" (WHO, 1999). In a regional context, a number of countries are attempting to "harmonize" their regulations to make common marketing of herbal products compatible. This is underway within UE nations and between Australia and New Zealand in what is referred to as the *Trans-Tasman Therapeutics Products Agency*. Challenges still remain because Australia regulates supplements as medicines-therapeutic goods, and New Zealand may consider the same products as traditional foods, enactment is not expected until mid 2006 (Anonymous, 2003).

B. UNITED STATES

In 1994, in response to concerns regarding lack of regulatory mechanisms to protect the public using herbal products, the Dietary Supplement Health and Education Act (DSHEA) was inaugurated. In its regulatory framework and enforcement mechanism, jurisdiction is shared between the U.S. Food Drug Administration (FDA) and the Federal Trade Commission (FTC). The FDA was provided with increased authority to remove unsafe products and regulate advertising claims regarding health benefits but was not required to approve the product before marketing unless it contained substances not grandfathered by use before 1994 (McGuffin and Young, 2004). The FTC was given the mandate to enforce deceptive practices of manufacturing and advertising, to investigate complaints, and to litigate against those violating trade regulations rules (McGuffin, 2002; Soller, 2000). However, by classifying medicinal herbs as dietary supplements, the DSHEA substantially altered the definitions, standards, and mechanisms under which claims of safety and efficacy could be enforced (Talalay and Talalay, 2000). Moreover, this definition tended to confuse the public about the herbs' safety and efficacy and failed to convey that appropriate oversight was lacking (Harris, 2003). As time passed, these policies have evoked

considerable consternation within the professional medical community who are concerned about the vague or oblique claims for health maintenance that are allowed, as well as the increasing number of serious adverse effects, including deaths, being reported. (Bent *et al.*, 2003). Added to this unease is their recognition that regulatory agencies have lacked the resources to respond in a timely manner to safety issues and counter misleading health claims. Many consider that the DSHEA has been ill conceived and that current regulations are limited and ineffectual. They propose that if the current system is to have any value for the consumer, radical changes in policies must take place, even to classifying some dietary supplements as drugs (Angell and Kassirer, 1998; Lipman, 2004; Marcus and Grollman, 2002).

Furthermore, appropriate regulatory oversight of Internet and media marketing practices continues to be a problem in controlling the sale of certain types of potentially problematic dietary supplements or herbal products. Consumers seem to be unaware that many vendors, regardless of their origins, are in violation of DSHEA guidelines or FDA rulings evoked to protect them. To promote these goods, inappropriate health claims are conveyed in such a way that it is obvious, regardless of the verbiage employed, that they are to be used to treat, prevent, diagnose, or cure specific diseases, including cancer (Bonakdar, 2002; Morris and Avorn, 2003). The widespread and inappropriate marketing of *Ephedra* products is but one example (Ashar *et al.*, 2003; Haller *et al.*, 2004) in which the FDA (2004c), should have acted more expeditiously but was bound by interference from lobbying and other interest groups from doing so until 2004 (Marcus and Grollman, 2002; Talalay and Talalay, 2000). Also, certain scurrilous vendors, in spite of notification from the FDA to discontinue these activities, will persist in aggressively promoting forbidden herbal products. Apparently they are willing to take this risk, to clear out inventories, because they believe that litigation is unlikely. There is a growing consensus that to curtail these illegal activities, substantial reform in advertising, regulation, and enforcement is overdue.

The FDA (2004a) is responding to these concerns by recognizing that it must be more proactive regarding issues of safety and enforcement of dietary supplements. Safety alerts for drugs, biologics, medical devices, and dietary supplements are posted through their MedWatch online system (http://www.vmcfscan.fda.gov/~dms/aems.html). The number of cases reported is but the "tip of the iceberg" and in all probability only represents about one-tenth of those actually existing (Marcus and Grollman, 2002). There is also acknowledgment that the overall safety profiles may be unreliable because certain types of unfavorable events tend to be reported more often than others. Nonetheless, it is its intention to improve evidentiary base FDA uses and implement these in a transparent, systematic, and predictable

process. Within this context, any new ''dietary ingredient'' must reach reasonable expectations of safety, which are based upon evidence other than history of use. Although current law requires that any new dietary supplement, not marketed before October 15, 1994, entail a pre-market safety notification to the FDA (AHPA Report, 2004; McGuffin and Young, 2004), improvements in regulatory oversight and enforcement, to cover all herbal products are a welcome addition.

The FDA is also reviewing certain botanicals via the Investigational New Drug/New Drug Application (IND/NDA) process. Priority will be given to those with a long history of safety, particularly for short-term use, because information is unlikely to be adequate to support claims of efficacy for long-term use (Elvin-Lewis, 2001; FDA, 2004b). This process in quite prolonged, and as of the end of 2004, about 228 pre-IND and IND applications have been received. Only half are active, and none of these are in review or have been accepted (Casper, personal communication, 2004).

They are also aware that quality control for manufacturers of dietary supplements must be established so that good manufacturing practices (cGMPs) are applied to ensure the identity, purity, strength, and composition of products that are sold. To expedite this process in 2002, the Dietary Supplements Methods and Reference Materials Program (DSMRMP) was established within the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH). Their mandate is to provide industry, researchers, and regulators with validated analytical methods and appropriate reference materials so that appropriate quality standards are developed to meet labeling claims and regulatory compliance directives, and that quality test materials are used in research (Saldanha *et al.*, 2004). Their strategic plan for achieving this goal by 2009 is now available (ODS, 2004). Unfortunately, it will take time to see whether these titular proposals do in fact serve their intended purpose. To complement these activities within the NIH, the Office of Alternative Medicine was established in 1992 and upgraded into the National Center for Complementary and Alternative Medicine (NCCAM) in 1998. This center is ''dedicated to exploring complementary and alternative healing practices in the context of rigorous science, training complementary and alternative medicine (CAM) researchers, and disseminating authoritative information to the public and professionals.'' It actively supports basic and clinical research to evaluate herbal treatments, as does other institutes at the NIH and other funding agencies. In this way, pharmacognosists, natural products chemists, and toxicologists are able to explore the therapeutic basis and safety parameters of herbal products. Computer Access to Research on Dietary Supplements (CARDS) identifies ongoing federally funded research being conducted on dietary supplements and

TABLE I
PROPOSED CLINICAL EVALUATION PROTOCOL FOR THE DEVELOPMENT OF AN HERBAL DRUG[a]

- Confirm ethnomedical value in country of origin
- Note all parameters of use, particularly among children, the elderly, or others with underlying disease states
- Review traditional formulations to understand rationale of use
- Know variations to standard formulations and reasons for additions or substitutions
- Identify bioreactive components to ensure standardization of content
- Conduct toxicological studies to understand safe parameters of use
- Conduct placebo-based clinical trials with formulation believed to be the best following appropriate guidelines for patient entry, evaluations of efficacy, and so on to comply with regulations where product is sold

[a]Amended from Table I in Elvin-Lewis (2001).

individual nutrients. Clinical evaluation protocols should include those parameters cited in Table I (Elvin-Lewis, 2001). To support these activities, another NIH database, the International Bibliographic Information on Dietary Supplements (IBIDS), can be accessed at the ODS web site (http://odp.od.nih.gov/ods) and contains several hundreds of thousands of citations and abstracts of published international scientific literature on dietary supplements including vitamins, minerals, and botanicals and is updated quarterly. In addition, the American Products Herbal Association (AHPA) has generated a number of useful reference books, namely *The Botanical Safety Handbook,* 2nd edition (McGuffin *et al.*, 1998), and *Herbs of Commerce,* 2nd edition (McGuffin *et al.*, 2000). In the first book, 600 commonly used phytomedicines are described in terms of their medicinal safety, common toxicities, international regulatory status, and standard dosage. The FDA accepts the *Herbs of Commerce* as the authoritative text for label nomenclature related to herbal products. The American Herbal Pharmacopeia and Therapeutic Compendium is preparing monographs of at least 2000 medicinal plants. Also, to aid pharmacists in understanding risks and benefits of herbal products, the U.S. Pharmacopeia (USP) (www.U.S.p.org) is also compiling standard monographs for herbal dietary supplements and dispensatory information (DI). Other references include the National Formulary (NF) (AAHP, 1998), the Homeopathic Pharmacopeia of the United States, the *Physicians' Desk Reference for Herbal Medicines* (PDR, 1998), and the *Encyclopedia of Dietary Supplements* (2005) (Elvin-Lewis, 2001). Following a review of available databases, Walker (2002) considers the Natural Medicines Comprehensive Database, AltMedDex, and the Natural Pharmacist

to be the best in providing suitable information regarding herbal products posed in clinical practice.

C. CANADA

On January 1, 2004, the Natural Health Products Regulations (NHP Regulations), which falls under the Food and Drugs Act, came into effect. These regulations are intended to standardize substances that are safe for over-the-counter (OTC) use by ensuring that these are appropriately manufactured, packaged, labeled, imported, and distributed according to the category of natural medicine to which they belong (e.g., traditional, homeopathic, botanical, or herbal). They will be allowed to make health claims according to structure function, risk reduction, and treatment, or in the case of vitamins and minerals, nutritional support. A health claim requires proof of a causal relationship established by careful scientific evaluations and unambiguous conclusions between a nutrient, drug, or other compound and a disease condition. In cases in which long-term uses of traditional products are known to be safe, Standards of Evidence (SOEs) may be supported solely by traditional references, and most so state on the labeling. There is no distinction between these natural products and a synthetic product manufactured in a facility. Because of either a medical claim, a pharmacological effect, or both, they are classified as drugs and a drug identification number (DIN) will be required. Some may be available only on prescription. Product labeling should be clear and consistent, outlining the contents, source of materials, parameters of storage, its recommended use or purpose, routes of administration, and dosage, in addition to stating any known potential health risks, cautions, warnings, contraindications, or possible adverse effects. Product license holders are required to report all serious adverse effects within 15 days of the event, whether they occurred in Canada or elsewhere.

It is compulsory that new products be licensed with respect to safety, efficacy, and quality. Supporting evidence, based on a risk management approach, may be derived from information in the Canadian Compendium of Monographs or elsewhere. The format of these monographs will follow those already established by the WHO and European Scientific Cooperative on Phytotherapy (ESCOP) and the European community. Understanding the entrepreneurial nature of the industry, Health Canada is willing to provide guidance to small and medium-sized businesses engaged in these endeavors. It will also support original research and capacity building. To enable companies to develop SOEs, supporting safety and efficacy of their products, a transition period ranging from 2 years (for site licensing) to 6 years (for licensing of products already issued a DIN) is being allowed.

The National Health Products Directorate and Health Products and Food Branch of Health Canada believe these new policies, when fully enacted, will serve the consumer well. By meeting quality and safety standards based on good manufacturing practices and only allowing health claims supported by appropriate levels of evidence to accompany natural health products, the basis for rational use has been established (Health Canada, 2004).

D. AUSTRALIA AND NEW ZEALAND

Similar strategies that generally follow European Economic Community guidelines for registration, production, evaluation, and marketing of safe natural health products was established in Australia in 2004 and follow the Australian Regulatory Guidelines for Complementary Medicines. In New Zealand, there are two ways herbal medicines may be manufactured and sold according to the Medicines Act of 1981. Licensing is not required for individualized formulations designed for a specific purpose, which are identified only by their content, but are not accompanied by information regarding use. Alternatively, marketing approval is required for herbal medicines not in that category, and these must meet assessment standards outlined for proprietary medicines by the New Zealand Therapeutics Assessment and Utilization Section of the Department of Health (WHO, 1998a). Harmonization of these two policies through the TTTPA is currently underway (Anonymous, 2003).

E. EUROPEAN ECONOMIC COMMUNITY

Many countries within the UE do not distinguish between medicinal products made from chemical substances and those made from plants or natural material and consider them drugs or medicines, whereas others have a more liberal approach to how uses of herbal remedies may be applied and sold. When defined by presentation or function as a medicinal product and manufactured for commercial purposes, they must now be authorized for marketing. Some form of reconciliation will have to be made so that categories, which are in existence, are appropriately integrated into the system. For example, in Britain three categories of herbal products are available: those that are licensed, others that are exempt from licensing, and dietary supplements, which are unlicensed (Shaw *et al.*, 1997). Germany, Sweden, Denmark, and Switzerland have established regulatory policies regarding the evaluation of herbal products, and the Netherlands, and Portugal regulate them as pharmaceuticals and require GMPs and Good Agriculture Practices to be applied (Bent *et al.*, 2004). The Committee of Human Medicinal Products working with the ESCOP is empowered to harmonize

these inconsistencies and to identify problematic formulations that are likely to cause adverse reactions or promote carcinogenicity. Over the last few years, they have become aware of the meteoric increase in adverse reactions being reported and the need to educate the public more effectively as to the parameters of use of herbal products. The WHO has suggested that information on efficacy, safety, and contraindications be widely disseminated by the mass media and on the Internet (WHO, 1999, 2004).

To aid in these endeavors, the E.U. parliamentary Directive (2004/24/EC) has established a code related to the traditional use of safe herbal medicinal products. This code is being transformed into national law by the 25 E.U. member countries. It introduces a simplified registration system that differentiates between herbal medicinal products that have been marketed in Europe for more than 30 years from others that have 15-year history of use in Europe, and another 15-year use elsewhere. These products are designed to be available to the public without medical supervision, and thus, parameters of preparation, labeling, safety, and use are carefully circumscribed through the generation of community herbal monographs. During the process of establishing these community-generated documents, it is permitted to use other suitable monographs (e.g., German Commission E), publications, or data. For possible extension, the European Parliament will assess this traditional-use registration in 2007 (Cox and Roche, 2004). Long-established use in Europe is a precondition for registration, so it has yet to allow registration of traditional herbal medicines derived from other well-known systems, particularly of Asian origins (e.g., Ayurvedic and chinese traditional formulas [Hasslberger, 2004]).

F. ASIA

Regulatory and surveillance methods are far from consistent within countries using Asian traditional medicines, and significant risks on populations dependent on any of these alternative methods of phytotherapy still exist.

1. India

In India, the Department of Indian Medicine has been renamed the Department of Ayush, covering the traditional practices of Ayurveda, Yoga, Unani, Siddha, and Homoeopathy. This is the first step toward establishing mechanisms by which appropriate mechanisms of evaluation and standardization of herbal products can be achieved so that safety, efficacy, and quality can be ensured and markets elsewhere logically established (Anonymous, 2004; Kurvilla, 2002; Ravinder *et al.*, 2003).

2. *People's Republic of China*

In 1984, the People's Republic of China implemented a Drug Administration Law, which classified traditional Chinese medicine (TCM) herbal remedies as "old drugs," and except for new uses, were exempt from testing for efficacy or side effects. Efficacy is evaluated on "empirical facts or experience" as exemplified by reference data, clinical test reports, and so on, rather than by the pharmacological action of each ingredient (WHO, 1998a). Crude materials and medications recorded in the Chinese Pharmacopeia are approved for safe use if applied according to Chinese medical philosophy and practice (Chan, 2003; the Pharmacopoeia Commission of PRC, 2000), and new herbal products are regulated through the Chinese Ministry of Public Health (Gilhooley, 1989). OTC licenses are required only for Chinese medicinal materials that are in proprietary form, not in their raw or processed state. OTC sale and export of Chinese medicines is common, but supervision is lacking to ensure that they are being ethically conceived. Within this context, it is believed that risks of adverse reactions can be minimized when qualified practitioners use quality products (Hohmann and Koffler, 2002), and ongoing surveillance of adverse reactions identifies problematic practices so that preventive measures can be instituted (Chan, 1997). However, to ensure that consistent parameters of safety and efficacy are known, it has been proposed that quality control of these remedies or new herbal products be achieved by using modern analytical and chemical techniques (Feng and Xie, 2003; Lee, 2000). In addition, quantitative and qualitative data will be needed if evidence-based studies are to have any value (Critchley *et al.*, 2000).

There is a wide variation on how Chinese medicinal formulas are manufactured or formulated outside of China. For example, in Malaysia, the Drug Control Authority requires registration of herbal medicines, which must be prepared according to standards of conformity and safety. In Singapore, regulatory control of Chinese proprietary medicines is governed under several state statutes regarding their appropriate manufacturing, promotion, and sale. These rules carefully outline which ingredients are prohibited and impose limits on the amounts of other substances such as heavy metals that are permitted. Licensing is required for all who are involved in their production and sale. Surveillance is also conducted to ensure that formulas containing toxic heavy metals and undeclared drugs are excluded from the market place (Koh and Woo, 2000). In contrast, there is little control over the manufacturing of Chinese formulas in the Philippines (Hartigan-Go, 2002). In Australia, to provide guidance on the level of anticipated toxicity associated with their use, the development of a TCM toxicology database and monographs is underway (Bensoussan *et al.*, 2000). Health Canada is examining the issues of recognizing TCM as a profession

and identifying practices that would be permitted. It differentiates between TCM products manufactured and requires a DIN and those formulated by an individual practitioner. In the latter case, it recommends that provincial regulations be established to determine which substances with safety concerns can be dispensed by health practitioners in compliance with provincial legislation. To aid in this endeavor, it has developed a list of candidates where safety concerns have been identified and for which an acceptable benefit–risk ratio for non-prescription sale has not been demonstrated (Chisholm *et al.*, 1998). Concerns have also been raised in the United States regarding the inadequacy of laws and regulations to ensure that these products are manufactured under the highest standards, that manufacturers are appropriately licensed, their products appropriately evaluated, and that surveillance systems are in place to ensure that consumers are adequately protected (Ko, 2004). The E.U. has yet to address the issue, because it is involved with harmonizing its policies regarding the use of regional pharmacopeias (Hasslberger, 2004).

3. Japan

Japan is also addressing regulatory issues and is actively engaged in developing a Japanese Pharmacopoeia so that the quality, efficacy, and safety of each product, regardless of its source, are appropriately delineated. Quality control is regulated under Japanese government's policies for "Manufacturing Control and Quality Control of Drugs," and its regulations regarding developing countries' herbal medicines are widely regarded. Claims and rules of combinations are determined on the basis of the pharmacological actions of each ingredient. The Pharmaceutical Affairs Law, designed for prescription and OTC drugs, regulates both herbal medicines designated "quasi-drugs" or "food medicines," as well as Kampo medicines, which are categorized "prescriptions/ethical" and sometimes called "Shosaiko-To" (Anonymous, 1998). Depending on their components, doses, use efficacy, and directions of use, some of these "Shosaiko-To" formulations and Chinese herbal formulations meeting appropriate safety standards may also be sold OTC. The Ministry of Health and Welfare (MHW) registers Kampo drugs, and its acceptance has taken place without clinical validation studies. Nonetheless, about half of conventionally trained Japanese physicians prescribe Kampo medicines, and many more do so for Chinese formulations (Tsumara, 1991; WHO, 1998a). Within Japan's regulatory format, herbal–pharmaceutical combinations for a wide range of products are also allowed (Saito, 2000). Adverse drug reactions are reported voluntarily, through a Pharmacy Monitoring System, and an Adverse Reaction reporting from Manufacturers (WHO, 1998a).

V. WHAT IS AN HERBAL REMEDY?

In definition, herbal remedies used as medicines may be traditionally or serendipitously derived, varying in formulation, preparation, and standardization, sometimes unreliable as to plant identification or to chemical composition, and depending on their cultural source, infrequently validated, in conventional ways, as to efficacy or safety. They may be prescribed by a healer of experience and training or of questionable skill, or they may be used in self-medication. As exemplified in American and African indigenous populations, prayers, mantras, or other forms of healing ceremonies may be used as an adjunct to phytotherapy. The applications of "energy medicine" to potentiate the curative process are still poorly understood (Elvin-Lewis, 2003, 2004).

Depending on its traditional origin, a traditional phytotherapeutic remedy may consist of individual or mixed formulations of plant material and sometimes other products used together or sequentially as infusions, decoctions, tinctures, poultices and salves, eye, ear and nose drops, enemas, purgatives, suppositories, emetics, snuffs, vapor baths, inhalants, oral hygienic or healing aids, and injectables. One plant itself may contain a significant bioreactive compound or a host of bioreactive molecules related or otherwise that will circumscribe its usefulness as a phytotherapeutic agent (Elvin-Lewis, 2001). Only rarely will any medicinal plant yield a compound such as quinine, which is low in toxicity, potent, and unique enough to be worthy of becoming a candidate for pharmaceutical development (Elvin-Lewis, 2003; Lewis and Elvin-Lewis, 2003). Most often, a medicinal plant is likely to contain several useful but less active molecules that can work together to potentiate the totality of its efficacy and safety profile. If used as an anti-infective herbal, for example, several related anti-infective compounds may prevent the development of resistance (Lewis *et al.*, 2004b). Traditionally, uses of plants with known toxic characteristics are carefully circumscribed. It follows that when several plants are employed in combination, usually representing complementary activities, additional optimal therapeutic responses are achieved. This form of combination therapy may elicit additive or synergistic effects that are not apparent when the bioreactive compounds are used independently of one another. The methods described in the ancient pharmacopeias of Asia exemplify this latter approach. Using plants in a sequential manner to affect the same goal is also traditionally applied, and many examples of this nature can be found in certain African and South American medicinal systems (Burkill, 1985, 1994, 1995, 1997, 2000; Elvin-Lewis, 2001, 2004).

It should be emphasized that pharmacopeias are not static entities but are constantly evolving. Those of current Neo-Western origin may incorporate

both traditional and novel uses of phytomedicines, including combining plants from a number of disparate medicinal systems, as well as pharmaceutically active ingredients. A similar trend is occurring in countries that use traditional Asian formulations. Also, as contact increases between isolated indigenous groups and the outside world, modifications to the uses of their medicinal plants are taking place. In addition, some scurrilous entrepreneurs may "invent" a traditional use to promote the sale of a particular plant product. They may go as far as introducing the idea into communities still depending on traditional herbal medicines, so in a few months or years, it appears that it has been conceived in the traditional manner. In a similar fashion, the media may be responsible for promulgating the same sort of fictitious concepts (Lewis *et al.*, 2004). Within this developing global context, one can expect to find deviations in appropriate plant identification, nuances of formula preparation, dosage, and types of treatment regimens, as well as the introduction of herbal remedies lacking authenticated traditional uses. Valuable information regarding safe parameters of use and related adverse reactions might also get lost during this transition. Depending on the regulatory systems imposed, the packaging information accompanying the commercial product may not accurately reflect the quantity and quality of the ingredients or verify its medicinal value. Unless there is a rational reason to believe otherwise, the safety and efficacy of any newly evolved phytotherapy, particularly if it represents a novel polyherbal mixture, must be considered circumspect, until appropriate clinical evaluations can be made.

However, when traditionally applied, most customary formulations derived from recognized pharmacopeias are usually moderate in potency and toxicity, are not fast acting, and when compounded and used appropriately, are unlikely to cause many life-threatening events. Because they are not physiologically inert, adverse reactions can be expected and are probably underreported, especially in parts of the world where mechanisms to acquire such data are not in place or when reporting methods are not user friendly. Generally, these events are unworthy of eliciting major concerns and are an accepted consequence of treatment. Most of these undesirable conditions are considered mild and transitory, causing rashes, headaches, or gastrointestinal (GI) upsets. Linkages to use are more difficult if unfavorable responses are rare, develop gradually, or occur after protracted use. Predictable risks are likely to occur when appropriate regulations do not mandate the proper formulation and labeling of herbal products or when self-medication fosters abuse. Acute toxicity is readily detectable, and accumulating evidence has linked a number of serious or life-threatening events to certain noxious ingredients in traditional (mostly Asian) formulations, to inappropriate or prolonged use, and to the incorporation of adulterants, undocumented pharmaceuticals, or interactions with other medications (Elvin-Lewis, 2001).

In addition, unwanted side reactions are likely to be more prevalent among those that tend to prefer the plethora of new untested and unregulated products available. Unfortunately, these individuals, who frequently self-medicate, are unlikely to report any undesirable incident because it would impugn their judgment and beliefs that herbal products are safe, that the contents and packaging claims regarding use and value are accurate, and that the benefits they hope to obtain are otherwise unavailable.

What is herbalism? Herbal medicine or phytotherapy as practiced today can represent the unique and still private knowledge of a group of indigenous people, the widespread use of traditional knowledge recorded in ancient pharmacopeias, modern monographs, and various ethnobotanical sources, as well as the employment of novel formulations that can incorporate one or more known or unknown medicinal herbs or other ingredients. Knowledge and self-medication may be widespread within a population, known to only a few specialized healers through oral tradition, or applied by trained practitioners using well-documented formulations outlined in the long-established pharmacopeias of Asia or current Western monographs. Today, herbalism is categorized as belonging to four major types: Indigenous, Asian, European, or neo-Western (De Smet, 1993; Elvin-Lewis, 2001).

A. INDIGENOUS MEDICINE

Practices of indigenous medicines occur in circumscribed parts of the world where traditional knowledge is still honored (Amazonia, sub-Saharan Africa, Oceania, etc.). Phytotherapy is very much a part of these customary practices, and it usually follows that when a remedy is widespread in acceptance, its efficacy and safety has a sound therapeutic basis. As evidence of this worth spreads, it is not unusual for it to be incorporated into other established forms of herbalism or phytotherapy. Neo-Western herbalism is particularly prone to adopting these remedies.

B. EUROPEAN TRADITIONAL MEDICINE

European traditional medicine evolved from practices known to ancient Mediterranean civilizations of Egypt, Greece, and Rome, as well as the Muslim world. Their use of medicinal plants is reflected in several noteworthy manuscripts derived from these times, such as the Ebers Papyrus (1500 BC), the De Materia Medica of Disocorides (first century AD), and the text of Jami of Ibn Baiar (eleventh century AD) (Ackernecht, 1973). These phytotherapies and others incorporated from regional indigenous uses throughout Europe, and elsewhere, represent the broad spectrum of practices

represented in the ways modern-day European herbalism is practiced. Although self-medication is widespread, reliance on professionals to provide guidance in diagnosis and treatment is also common. Within the countries that encompass the E.U., practicing herbalists are more likely to undergo formal training, belong to guilds or like organizations, and are required to be registered. Similarly, phytotherapy is also a part of the practice of the professions of Naturopathy, Homeopathy, Chiropractic Medicine, and in some countries, Allopathy (also called *conventional medicine*). For example, in Naturopathy, formulations containing plant extracts or phytochemicals, primary derived from well-known ''gentle herbs,'' are prescribed at pharmacognotically determined levels of efficacy. Uses of herbs by conventional physicians are likewise prescribed, particularly if the treatment requires close surveillance. This is particularly true in Germany, where the Commission E Monographs are used for guidance (Blumenthal *et al.*, 1998, 2000). Homeopathic formulations differ in that they are likely to contain very dilute concentrations of plant extracts, which in higher doses may excite the opposite physiological effect (Steinberg and Beal, 2003). They are far from inert and are known to have the potential to cause a broad spectrum of minor adverse reactions (Franklin, 1999; Glisson *et al.*, 1999; Shaw *et al.*, 1997).

C. NEO-WESTERN HERBALISM

In its totality, European herbal practices have matured, along with American herbal introductions into neo-Western herbalism. The herbal practices that have evolved may represent an amalgamation of many philosophies of treatment and include the use of a variety of novel formulations containing herbal products from disparate cultures and parts of the world. The adoption of herbal uses derived from indigenous medicines is widespread. However, the inventiveness that is inherent to this ever-evolving system continues to challenge regulatory bodies wanting to ensure that these products have value and are not dangerous. Many of these types of products, often disguised as dietary supplements, are available to the self-medicating consumer as unregulated OTC products or on the Internet. Unfortunately, this group of users, often with limited knowledge of herbal medicine, is particularly vulnerable to unsubstantiated promotional claims. Moreover, many in this category have a tendency to rely on unqualified sales personnel or self-appointed ''herbalists'' to guide them, rather than to seek help from appropriately trained and knowledgeable individuals who are professionally recognized and licensed to practice this art.

Unlike their European counterparts, North American herbalists are more likely to be self-taught or to be trained in an array of apprenticeship

programs, many are associated with the American Herbalists Guild or North American Herbalists Guild. These organizations are working toward certification processes so that standards of practice are involved in membership. Several schools of Naturopathy exist in the Unites States and Canada, who train their practitioners to be primary care physicians with knowledge of phytotherapy, homeopathy, and acupuncture. Their holistic approach uses conventional medical diagnostic procedures and therapeutic modalities, as well as natural methods of diagnosis and treatment in an integrative approach to health care delivery. Currently, 12 states and the U.S. territories of Puerto Rico and the U.S. Virgin Islands and 8 Canadian provinces have licensing laws for naturopathic doctors. North American chiropractors also promote uses of certain herbal products. In the nineteenth century, American Eclectic Physicians used phytotherapy in their practices. Many of their therapies were derived from Amerindian herbalism, including the use of *Echinacea.* Today, this herb, which is highly regarded for immune stimulating purposes and to treat colds, is the most popular remedy in North America and Europe (Elvin-Lewis, 2001; Lewis and Elvin-Lewis, 2003).

D. ASIAN TRADITIONAL PHYTOTHERAPEUTIC MEDICINES

Asian traditional medicines are based on ancient pharmacopeias such as the Characka Samhita and Sushruta Samhita of Aryuveda, the Classic of Materia Medica of First Century China, and the Daido Ruiju-ho of Japan, which were written about 2000 years ago and are derived in part from religious healing philosophies of that time, which included the Upanishads (Saito, 2000). Contact between these cultures occurred very early and is reflected in similar concepts of diagnosis, formulation, and treatment that are outlined in these treaties. Noteworthy are the uses of complex formulations, oftentimes only varying in nuance from one system to the other, the presence of plants from disparate parts of Asia, as well as the inclusion of minerals and animal parts as a part of some of the mixtures. Within the Asian context, these medicines are referred to as *drugs.* The components of these mixtures are designed to complement each other so that a satisfactory therapeutic outcome is achieved. What makes these medicinal systems distinctive are the ways regional herbs are incorporated or how methods of diagnosis and treatment are employed.

Throughout Asia, a variety of traditional systems coexist along with conventional medicine, and it is not unusual for patients to rely on several of these methods for maintenance of health or treatment of a particular ailment. In India, for example, several types of practitioners may conjointly share the same hospitals and certain types of training. Like their

conventional counterparts, practitioners of these systems are carefully schooled in the art and science of their profession and are trained to formulate their remedies under strict rules, to prescribe them with care so that therapeutic outcome is predictable, and to anticipate the types of adverse reactions that might arise. Predominant traditional and alternative systems of medicine in India include Ayurveda (Hindu), Siddha (Jain), Unani (Arabic), Yoga, as well as the Tibetan system and those of European origins such as Naturopathy and Homeopathy; together, these systems are referred to under the acronym "AYUSH." Similar choices are available in neighboring countries, and their prevalence is often influenced by the dominant religion of the nation (e.g., Pakistan and the Unani system).

The Chinese Medicinal System continues to dominate traditional medical practices throughout Eastern Asia, Southeast Asia, and the South Pacific regions. Its early spread to Korea and then to Japan occurred between the fifth and seventh centuries AD, respectively. Kampo medicine of Japan is but a simplified derivation of this system, but also includes native plants from indigenous origins. The incorporation and/or substitution of local species into many of these remedies also occur elsewhere. Because modern Chinese traditional medicine is not a static entity, new formulations may include medicinal plants favored throughout the world. These changes are reflected in the 1977 version of the *Chinese Materia Medica* as compiled in the *Encyclopedia of Traditional Chinese Medicine Substances* (Zhong yao da ci dian) (Bensky and Gamble, 1993), and the Pharmacopoeia Commission of PRC (2000). Other sources are also available (Leung, 1990; WHO, 1989). The WHO monographic series is also targeting related Asian pharmacopeias, and several volumes describing these medicinal plants are available for Korea (WHO, 1998b), the South Pacific (WHO, 1998c), and Viet Nam (WHO, 1990, 1999); Japan is developing a pharmacopeia as well (Saito, 2000).

VI. ADULTERATIONS

Within the current global regulatory environment, the detection of adulterated or contaminated herbal products is not always an easy task, particularly because many policies to prevent these events have yet to be fully implemented and ways to identify the problems are not always easy to achieve. The presence of undocumented pharmaceuticals, heavy metals, misidentified plants, noxious plant compounds, and so on is still widespread, particularly in those formulations of Asian origins (Chan, 2003; Elvin-Lewis, 2001; Ernst, 2002b). Also, many Asian medicines traditionally incorporate substances such as heavy metals, which under today's standards of safety should

probably be disallowed or restricted to very low levels. For example, in Singapore legal limits have been set for arsenic at 5 ppm; for copper, 150 ppm; for lead, 20 ppm; and for mercury, 0.5 ppm. They also provide guidelines for permissible numbers of bacteria, yeasts, and molds (Koh and Woo, 2000). Malaysia has also adopted similar guidelines (Ang, 2004). Unfortunately, because of poor quality control during the manufacturing process of air-drying and preservation, certain heavy metals may be present in unusually high concentrations, further compromising the health of those who use them (Chan, 2003; Wong *et al.*, 1993). Other contaminants may be introduced advertently or inadvertently during the manufacturing process, or when storage permits insect infestations or growth of microorganisms. Ideally, herbal remedies should be free of undeclared substances such as pharmaceuticals and plant substitutions, toxic botanicals, metals, and radioactive agents, excessive levels of microorganisms or their toxins, as well as insects, pesticides, herbicides, or fumigation agents.

A. HEAVY METALS

Incorporation of certain heavy metals into Asian traditional medicines is based on the common time-honored belief that metals such as lead, copper, gold, iron, mercury, silver, tin, and zinc are needed for appropriate bodily functioning and that any imbalance can result in disease (Ernst, 2002a). A number of beneficial effects are considered to be associated with their use. Formulators understand that some of these metals are noxious, and therefore, elaborate ways of "detoxification" have been evolved so that they can be "safely" incorporated into their formulas. According to these formulary philosophies, this might be achieved by the combination of other ingredients in the herbal remedy or by subjecting the metal to a series of multifaceted treatments. For example, in Aryuveda, processed lead or "nagabhasma" is produced by subjecting it to a pharmaceutical procedure that involves repeatedly heating the metal until it glows and alternately dipping it in several herbal mixtures before it is combined with arsenic sulfide (Thatte, 1993). Unfortunately, these heavy metals are often present in traditional formulations in excessive amounts due to inherent problems in preparation, deliberate inclusion, or through contamination during the manufacturing process such as the use of metal pots (Yu and Yeung, 1987) or grinding weights (Chia *et al.*, 1973). Another source of adulteration may be via herbs grown in metal-rich soils (Schilcher, 1983).

Clinical poisonings have been reported with herbal or ethnic remedies rich in mercury and lead and other heavy metals from the Far East, India, the Middle East, South Africa, Australia, Western Europe, and North America. Symptoms related to heavy metal intoxication are not always distinctive,

many of which are constitutional, and blood levels may have to be determined to identify the problem. A linkage to the use of a suspect herbal medicine is imperative. For example, lead poisonings may cause abdominal and GI distress, constipation, chest pain, anemia, or seizures; arsenic may lead to hyperkeratosis and muscle wasting; and mercury to weight loss, diarrhea, skin rash, motor and vocal tics, and paraesthesias (Ernst, 2002a).

Mercury poisonings are particularly prevalent among those consuming TCM formulations containing excessive amounts of either red mercuric sulfide (cinnabar, cinnabaris, zhu sha) or mercurous chloride (calomel). Lead can exist as Mi Tuo Seng (Lithargyrum) and has also been found in an Malaysian herbal preparation containing *Smilax mysotiflora* (Ang *et al.*, 2004), in a Loaotian preparation known as Pay-loo-ah, a Korean remedy, Hai ge fen, containing clamshell powder (Borins, 1998), in Taiwan a TCM Cordyceps remedy (Wu *et al.*, 1996), in Indian traditional cosmetics used as eyeliners (surma) (Shaw *et al.*, 1997) and lead containers for toothpaste (Elvin-Lewis, 2001); arsenic compounds are incorporated in various herbal remedies including Xiong Huang (Realgar); and copper as Dan Fan (Chalcanthitum) (Koh and Wood, 2000). Adulteration with cadmium and thallium is also disconcerting, as evidenced by the significant number cases of cadmium and lead intoxication in Texas consumers of "chuifong tokuwan," who had imported the product from Hong Kong (Anonymous, 1989). Alopecia and sensory polyneuropathy was associated with thallium in a Chinese herbal (Schaumburg and Berger, 1992). Manganese poisoning with severe chorea followed the ingestion of Chien Pu Wan in Holland (De Krom *et al.*, 1994; Wauters, 1995). Lists of patented Chinese medicines containing heavy metals, sometimes in excess, have been generated in a number of studies and case reports (Au *et al.*, 2000; Kang-Yum and Oransky, 1992; Koh and Wood, 2000; Liang *et al.*, 1998; Wong *et al.*, 1993) and their toxic effects described (Dukes, 1996; Ennever, 1994; Klaassen *et al.*, 1996; Olson, 1999; Ueng *et al.*, 1997; Wu, 1992). A case of severe dyserythropoiesis and autoimmune thrombocytopenia was associated with ingestion of kelp supplements for slimming, contaminated with arsenic (Pye *et al.*, 1992).

Within Indian traditional pharmacopeias, there is also a preponderance of lead- and mercury-containing formulations, although significant amounts of arsenic and to a lesser degree cadmium may also be found (Kew *et al.*, 1993; McElvaine *et al.*, 1991). Symptoms may represent that of mixed intoxication or reflect one of the heavy metals that are present (Kew *et al.*, 1993; Sheerin *et al.*, 1994). Lead poisonings are particularly prevalent, in part because these toxicities are more readily diagnosed, and because children are especially vulnerable to experiencing serious reactions or life-threatening events (Ernst, 2002a). Unfortunately, parents who have provided Indian remedies to their children are often reticent to reveal the source of

the intoxication in time to provide needed chelation therapy (Eisenberg *et al.*, 1998). Use of local traditional medicines has also been linked to acute lead encephalopathies among infants in Middle East (al Khayat *et al.*, 1997) and to other types of lead poisonings in South America (Levitt *et al.*, 1984). The seriousness of this widespread problem is outlined in a number of interesting case reports (Ernst, 2002a,b).

B. DOCUMENTED AND UNDOCUMENTED PHARMACEUTICALS

In Asian markets, it is not unusual to find traditional herbal remedies containing undocumented pharmaceuticals. However, these illicit practices are now widespread, and serious adverse effects linked to their use have become commonplace (Bury *et al.*, 1987; De Smet, 2002, 2004; Ernst, 2002c; Koh and Woo, 2000). Table II indicates the wide range of undocumented drugs that have been identified, but these are only representative of the possibilities that likely exist. In the current regulatory environment, it has become a monumental task to detect these types of adulterations, and constant surveillance is required to ensure the safety of traditional medicinal products that can be adulterated in this fashion. This concept is compounded by the fact that in certain countries, such as Japan, combinations

TABLE II
EXAMPLES OF UNDOCUMENTED DRUGS FOUND IN HERBAL REMEDIES

Category	Type
Analgesic, antiinflammatory	Aminophenazone, aminopyrine, diclofenac, dexamethasone, dipyrone, phenylbutazone, phenylbutazone, indomethacin, fluocinolone acetonide, diclofenac, mefenamic acid, methyl salicylate, paracetamol, (acetaminophen) ibuprofen
Corticosteroids antiinflammatory	Clobetasol propionate, fluocinonide
Antihistamine decongestant	Chlorpheniramine, cyproheptadine, promethazine
Weight loss	Fenfluramine
Depressants	Barbiturates, bromide
Antipsychotic	Benzodiazepines diazepam
Diuretic and hypertensive	Hydrochlorothiazide
Glucose lowering	Glyburide (INN, glibenclamide) phenformin
Blood thinner	Warfarin
Erectile dysfunction	Sildenafil (Viagra) and tadalafil (Cialis)
Sedative	Estazolam (benzodiazepine)

of herbal drugs with vitamins or pharmaceuticals may be sold legally as OTC preparations. This is only allowed if they are appropriately labeled and their formulations are described in *Drugs in Japan, OTC Drugs (2000–2001),* 12th edition (Japan Pharmaceutical Information Center, 1998). Various adverse reactions can be associated with these drugs, particularly if they are being taken for prolonged periods before they are detected. For example, agranulocytosis with septic shock was a common symptom of a number of cases exposed to aminopyrine, phenylbutazone, and dipyrone; Cushing's syndrome with dexamethasone, indomethacin, hydrochlorothiazide, diclofenac, mefenamic acid, and diazepam; eczema with fluocortolone; coma with phenytoin; excessive increase of International Normalized Ratio (INR) or prothrombin time (PT) with oil containing 50% methyl salicylate; GI tract bleeding, ulcer, and somnolence with mefenamic acid and diazepam; and ecchymotic/purpuric skin lesions with prednisolone and indomethacin; and fatal lactic acidosis with phenformin as described in detail by Koh and Woo (2000) and Ernst (2002c). In addition, hepatic failure leading to liver transplantation or death has been linked to the *N*-nitroso-fenfluramine content in "chaso" and "onshido," marketed in Japan for weight loss (Adachi *et al.*, 2003). The FDA has also issued warnings regarding maternal consumption of "Sleeping Buddha" because this herbal preparation also contains estazolam, a known teratogenic agent. Also a current spate of so-called herbal sexual enhancement products (Vinarol, Viga, Sigra, Stamina Rx, Stamina Rx for Women, Y-Y, Spontane ES, Uroprin, Acta Rx and Yilishen) has been promoted (primarily on the Internet) for erectile dysfunction or as a female equivalent in North America and China (Wooltorton, 2002). Many of these have been found to contain significant levels of prescription phosphodiesterase inhibitors: sildenafil (Viagra) and tadalafil (Cialis), which affect blood flow and thus present serious risks to consumers who have underlying medical conditions such as cardiovascular disease and are on medication with drugs such as nitrates (Mitka, 2003; Thurairaja *et al.*, 2004). The FDA has issued several warnings in 2003 and 2004 regarding their use.

C. PESTICIDES AND FUMIGATION AGENTS

The clinical relevance of the presence of pesticides and fumigation agents in herbal products is unknown. Many may be present in excessive amounts and thus present a potential risk to the consumer. These include the chlorinated and organic pesticides, carbamate insecticides and herbicides, dithiocarbamate fungicide, and triazine herbicides. For example, exposure to Baygon and other carbamate-based insecticides *in utero* has the potential of causing MLL gene fusions (translocation of MLL gene on chromosome

11q23 and its fusion with AF4 on chromosome 4 and ENL on chromosome 19) leading to the development of infant acute leukemia (Alexander *et al.*, 2001). Fumigation agents include ethylene oxide, methyl bromide, phosphine, and sulfide-yielding agents (De Smet, 2002, 2004). The character of many of these substances is described in detail in Lewis and Elvin-Lewis (2003).

D. PATHOGENIC MICROORGANISMS (BACTERIA, FUNGI, VIRUSES) AND TOXINS

It is the nature of raw herbal products or unprocessed food products not to be sterile. Most of the organisms present are saprophytic; however, there is always the possibility that potentially pathogenic organisms can be acquired from a wide variety of sources from the environment, during cultivation, and preparation (Kneifel *et al.*, 2002). Also, if storage is improper or prolonged, certain organisms may multiply or elicit toxins to dangerous levels (Lewis and Elvin-Lewis, 2003). A number of studies on herbal teas and/or medicinal plants in Europe (Holt, 1998), Nigeria (Efunotoye, 1997–98), Japan (Hitokoto *et al.*, 1978), and Argentina (Rizzo *et al.*, 2004) indicate that a wide range of fungal contaminants may be present, and that in some cases mycotoxins (aflatoxin, sterigmatocystin, and ochratoxin A) can also be found. In all these studies, a significant proportion of the samples contained species of *Aspergillus* (with their mycotoxin-eliciting potentials), *Mucor,* and *Penicillium.* A few samples also contained *Rhizopus, Absidia, Alternaria, Aureobasidium*, *Cladosporium, Fusarium,* and *Trichoderma.*

Inhalation of these spores during preparation of these products can be problematic for certain predisposed individuals. For example, *Alternaria, Aspergillus, Cladosporium, Fusarium,* and *Penicillium* are important fungal allergens (Lewis and Elvin-Lewis, 2003), and sensitized atopic individuals are potentially at risk from these sources. However, because of their ubiquity, linkage to an adverse event would be difficult unless appropriate and accurate forms of molecular analyses were applied. In one case, using polymerase chain reaction (PCR) techniques, a naturopathic remedy contaminated with a specific strain of *Mucor indicus* was implicated in the user's development of hepatitic mucormycosis (Oliver *et al.*, 1996). Workers working in the dusty environment of preparing dried herbs are also subject to developing allergies through exposure to bacterial and fungal contaminants. One study among employees working with thyme indicates they were significantly sensitive to the gram-negative bacteria *Pantoea agglomerans,* in addition to the usual fungal allergens (Golec *et al.*, 2004).

Human or animal fecal contamination is always possible when the herbs have been harvested from small rural farms still using as fertilizer either

"night soil" or animal dung or when the workers themselves prepare the products under unsanitary conditions. Although survival of bacterial enteropathogens for any length of time is unlikely in dried material, these and other organisms have the potential of causing GI tract and nosocomial infections (Czech *et al.*, 2001; Wilson *et al.*, 2004). Natural medicinal infusions can also be the source of a number of potentially pathogenic microorganisms (Martins *et al.*, 2001). Because hepatitis E is generally a waterborne disease and can be found in stool, it is possible that it is within this category that a Japanese man acquired hepatitis E from ingesting a virus-contaminated Chinese herbal preparation. Although only one serotype of hepatitis E exists, there are regional variations in nucleotide sequencing of the 3′ terminal region of its complementary DNA (cDNA). Using PCR amplification, Ishikawa *et al.* (1995) found that the hepatitis E virus from the patient's serum showed a high degree of homology (99.8% of 752 nucleotides) with the Chinese strain retrieved from the remedy. Bacterial spores or parasitic ova are more likely to be present, although acquisition of parasites in this manner has yet to be established. Bacterial spore contamination can express itself in a number of interesting clinical ways. For example, an outbreak of cutaneous anthrax (malignant pustule) was reported among Iranian patients applying *Kimbucha* mushrooms to treat their skin lesions (Sadjadi, 1998). Also, multiple cases of infant botulism are known, and though reasonably rare, children younger than 1 year are particularly vulnerable to this disease, which results in blockade of voluntary motor and autonomic functions. It is acquired from ingesting honey contaminated with the spores of *Clostridium botulinum* and the toxin that is produced. Because some herbal products are made with honey, any honey-containing product or supplement should be suspect (Cox and Hinkle, 2002; Tanzi and Gabay, 2002).

E. BOTANICAL SUBSTANCES

Inadvertent or advertent adulteration with plant products is a continuing global concern, and constant vigilance is needed to prevent the serious consequences related to these practices. Table III provides some noteworthy examples. For instance, confusion of Japanese star anise with that of Chinese star anise in herbal teas sold in Europe for infant colic resulted in an epidemic of convulsive disorders among Dutch, Spanish, and French users. Japanese star anise contains a sesquiterpene lactone anisatin, which is neurotoxic and, by being a noncompetitive γ-aminobutyric acid antagonist, can cause symptoms of tremors or spasms, hypertonia, and hyperexcitability with crying, nystagmus, and vomiting (De Smet, 2004; Ize-Ludlow *et al.*, 2004; Johanns *et al.*, 2002; Minodier *et al.*, 2003).

TABLE III
BOTANICAL ADULTERANTS

Adulterant	Instead of	In	Reference
Podophyllum hexandrum	*Clematis Gentiana* sp. (londanco)	Wai-Ling-Sin Lung-Dam-Cho	DeSmet, 2004
Podophyllum emodi	*Gentiana* sp.		But, 1994; Chan, 1997; Drew and Myers, 1997
Digitalis lanata	*Plantago* sp.	U.S. Dietary supplement	De Smet, 2004
Illicium anisatum; I. religiosum (Japanese star anise)	*Illicium verum* (Chinese star anise)	Several European products, herbal tea, etc.	De Smet, 2004; Ize-Ludlow *et al.*, 2004; Johanns *et al.*, 2002; Minodier *et al.*, 2003
Mandragora officinarum	*Panax ginseng*	Chinese herbals	Chan, 1995
Rauwolfia serpentina	*Panax ginseng*	Chinese herbals	Drew and Myers, 1997
Cola spp.	*Panax ginseng*	Chinese herbals	Drew and Myers, 1997
Datura metel Rhododendrum molle	*Innocuous herbs*	Chinese herbals	Tomlinson *et al.*, 2000
Atropa belladona	*Vaccinium myrtillus*	European products	De Smet, 2004
Periploca sepium	*Eleutherococcus senticosus*	Chinese herbals	Miller *et al.*, 2004

Numerous reports of serious herbal poisonings in China, Malaysia, and Taiwan have been linked to adulterations with either *Datura metel* or *Podophyllum emodi* (But, 1994). The great majority of cases involving anticholinergic effects, causing reduced visceral activity, are related to the use of yangjinhua, the dried flower of *Datura metel,* for treating bronchial asthma, chronic bronchitis, pains, and flu symptoms (Chan, 1995). The incorporation of *Podophyllum* into Asian formulations may be related to several Chinese pharmacopeias erroneously referring to xiaoyelian as *P. emodi* (Shang *et al.*, 1994). *Podophyllum* intoxications have elicited severe life-threatening events (Chan, 1997; Drew and Myers, 1997). Adulterations can come from unexpected sources and underscore the wisdom of pregnant women not taking herbal preparations during pregnancy. For example, colchicine has been found in human placental blood of a number of mothers

claiming to have taken Ginkgo or other herbal supplements during pregnancy (Petty *et al.*, 2001).

Ginseng preparations should be particularly suspect because not only is there a wide variation in their ginsenosides content (Asafu-Adjaye and Wong, 2003; Cui, 1995; Lau, 2003; Liberti and Marderosian, 1978), but adulterations with dangerously bioreactive plants have been reported. Noteworthy has been the inclusion of mandrake (*Mandragora officinarum*) containing scopolamine, *Rauwolfia serpentina* containing reserpine, and *Cola* species with its high caffeine content (Drew and Myers, 1997). In the latter case, the stimulatory effects of caffeine could potentiate or mimic those seen with the use of ginseng.

Adulterations are also likely to take place when natural disasters affect the supply of a particular product. Apparently, this has been the case in the aftermath of the 2004 Florida hurricanes when the saw palmetto harvest was adversely affected and prices of available sources trebled. According to a number of established suppliers, the market has been flooded with material contaminated with palm and other types of fatty oil complexes, events that could directly affect the quality of certain available products (Blumenthal, 2005a,b).

VII. PHARMACOKINETIC BEHAVIOR OF PLANT-DERIVED DRUGS

There are many reasons that variable responses to herbal use are seen within human populations. Studies on the pharmacokinetic behavior of quercetin and rutin (Erlund *et al.*, 2000) and quinine and sparteine have been invaluable to understanding this phenomenon. Genetic and racial differences may mediate how certain compounds are metabolized, just as storage and clearance rates may be affected by the age of the individual. When internal organs such as the kidney and liver are affected by disease, their ability to function within normal parameters is affected so that clearance of certain compounds is altered or underlying conditions are exacerbated. For example, plasma levels of quinine are raised during infections such as malaria, and renal clearance is slowed when the urine is alkaline due to low-protein diets. Oral or metabolic clearance rates may also be affected by smoking or by certain drug interactions (De Smet and Brouwers, 1997). In addition, *Vites agnus castus* use has been found to alter normal ovarian function (Cahill *et al.*, 1994).

A number of drug interactions with herbal remedies are noteworthy. A sudden remarkable decrease in cyclosporine trough concentrations can occur when a patient is co-medicated with St. John's wort (SJW) (*Hypericum perforatum*), which is a dangerous event for patients undergoing

transplant therapy (Mai *et al.*, 2000). This herb causes an upregulation of intestinal P-glycoprotein and cytochrome P450 (CYP) 3A4 in the liver and intestine, resulting in impaired absorption and stimulated metabolism of cyclosporine, which leads to subtherapeutic plasma levels. Other CYP 3A4 substrates are also affected so that the protease inhibitors indinavir and nevirapine, oral contraceptives, and tricyclic antidepressants such as amitriptyline are more rapidly metabolized.

The potential for additional drug interactions is also possible with herbs such as milk thistle (*Silymarum marianum*), *Angelica dahurica, Ginseng,* and garlic (*Allium sativum*) preparations, Danshen (*Salvia miltiorrhiza*), and licorice (*Glycyrrhiza glabra*), which have the ability to modulate CYP activity (Ioannides, 2000). A potential clinical benefit may exist for licorice, because oral administration of glycyrrhizin increases plasma prednisolone concentrations and influences its pharmacokinetics by inhibiting its metabolism, but not by affecting its distribution (Chen *et al.*, 1991). With hydrocortisone, its glycyrrhetinic acid potentiates the cutaneous vasoconstrictor response (Teelucksingh *et al.*, 1990).

By demonstrating the presence of compounds or their metabolites in urine, it is possible to study the pharmacokinetics of polyherbal remedies. This was accomplished in renal clearance studies conducted by Homma *et al.* (1992) with the Japanese remedy for bronchial asthma, saiboku-to.

VIII. PROBLEMATIC HERBS AND THEIR ADVERSE EFFECTS

A. TRADITIONAL CHINESE HERBS

1. General

As adverse reactions are reported and studies reveal the source of the problems, the potential danger of using certain botanicals or their compounds is beginning to be recognized. For example, TCM remedies containing *Isatis tinctoria* are commonly associated with adverse reactions (Ko *et al.*, 1999). Also, because of their toxic potential, Taiwan and China control the use of tubers of *Arisaema* species, unprocessed tubers of *Typhonium giganteium* and *Pinellia ternata,* the unprocessed resin of *Garcinia morella,* seeds of *Impatiens balsamina, Pharbitis nil,* and *P. purpurea,* roots of *Knoxia valerianoides,* and flowers of *Rhododendron molle* (De Smet, 2004). Other potent or toxic Chinese medicinal materials meriting some form of regulatory control include those derived from roots of *Aconitum brachypodum, A. carmichaeli, A. coreanum,* and *A. kusnezoffiii,* tubers of *Arisaema erubescens, A. heterophyllum,* and *A. amurense,* fruits of *Croton tiglium,*

flower buds of *Daphne genkwa,* flowers of *Datura metel,* roots of *Euphorbia fischeriana, E. ebracteolata,* and *E. kansui,* seeds of *E. lathyris* and *Hyoscyamus niger,* stem/root bark of *Melia azadarach* and *M. toosendan,* roots of *Phytolacca acinosa* and *P. americana,* resin *of Rhus verniciflua,* and seeds of *Ricinus communis* and *Strychnos nux-vomica* (Tomlinson *et al.*, 2000). In Germany, Madder root (*Rubia tinctorium*) is banned because it contains lucidin, which is mutagenic and carcinogenic (Blumethal *et al.*, 1998). However, *Rubia cordifolia* and other Asian rubiacious plants (*Morinda umbellata, Hymendodictyon excelsum,* and *Damnacanthus indicus*) containing related anthranoids have yet to be similarly categorized and controlled (De Smet, 2004; Kawasaki *et al.*, 1992).

2. *Jin Bu Huan*

Jin Bu Huan, a Chinese patent medicine sold in pill form as an anodyne and painkiller, is perceived as innocuous despite that it contains, levo-tetrahydropalmatine, which is present in *Stephania* and *Cordylis* species and is a potent neuroactive substance. Regrettably, the packaging is often mislabeled, delaying the identification of the offending alkaloid and its association with the distinct serious undesirable conditions, which develop in children or adults. In children, acute life-threatening cardiovascular and neurological manifestations have been reported, whereas prolonged adult use can induce various symptoms from acute toxicity, lethargy (due to low blood pressure, heart rate, and respiratory function), muscle weakness, bradycardia, and coma, to ''extreme fatigue,'' fever, jaundice, and hepatitis. Hepatotoxicity and the development of chronic hepatitis are particularly prevalent (Brent, 1998; Elvin-Lewis, 1991; Horowitz *et al.*, 1996; Ko and Woo, 2000; Piciotto *et al.*, 1998).

3. *Chuen-Lin*

Berberine-containing phytomedicines are valued for a wide variety of medicinal purposes (Lewis and Elvin-Lewis, 2003). The alkaloid can be found in numerous medicinal plants such as goldenseal (*Hydrastis canadensis*) and golden thread *Coptis sinensis* (Huanglian). In Singapore berberine is banned, primarily because of the use in neonates of the Chinese herbal preparation ''Chuen-Lin'' containing *Coptis chinensus/japonicum.* This formulation was found to cause neonatal jaundice and increase the risk of brain damage (Ko and Woo, 2000; Yeung *et al.*, 1990).

4. *Ma Huang (Ephedra)*

The medicinal use of ephedra has been traced back to Neanderthal times and the value of *Ephedra sinica* (Ma Huang) in TCM is well known. In

traditional Asian remedies, it is used to treat fever, chills, and cough, improve the circulation, and promote sweating. All Eurasian species contain ephedrine alkaloids, with ephedrine and pseudoephedrine predominating, in addition to norephedrine, norpseudoephrine, methyl ephedrine, and normethypseudoephedrine. Species in North and South America lack ephedrine, and these may contain only traces of pseudoephedrine. Ephedrine acts as a sympathomimetic (agonistic) on α_1, β_1, and β_2 adrenoreceptors, increasing blood pressure through vasoconstriction, raising heart rate, and stimulating the central nervous system (CNS), whereas pseudoephedrine causes bronchodilation through its β_2-receptor, thus relieving the symptoms of nasal congestion through its α_1-agonist effects (Lewis and Elvin-Lewis, 2003; White *et al.*, 1997). In the dietary supplement industry, *Ephedra* was valued primarily for its stimulatory effects, and until only recently, *Ephedra* and its alkaloids were included in a wide range of products sold to enhance energy, for bodybuilding, or for weight loss. Ingredient panels on these ephedrine-containing products listed ma huang, Chinese *Ephedra*, ma huang extract, *Ephedra* herb powder, *Ephedra* extract, *Ephedra*, *Ephedra sinica,* epidonine, ephedrine, or ephedrine alkaloids (FDA, 2004c). Unfortunately, some of the labeling was targeted to adolescents and young adults, implying their use could provide a "high." To enhance the stimulatory effects and promote this property, a number of these formulations also included caffeine-containing herbs, the alkaloid itself, or other stimulating compounds. Several studies have lauded its merits or demerits for weight loss and bodybuilding (Shekelle *et al.*, 2003a,b) or have considered its adverse effects (Bent *et al.*, 2003).

Its banning by the FDA in 2004 occurred after a long and protracted evaluation of the numerous adverse effects and deaths (including notable sports figures) resulting from the use of these products. Indications under consideration included reports of hypertension, palpitations, tachycardia, myocardial infarctions, and important neurological and psychiatric events (brain hemorrhage, seizure, or psychiatric symptoms). Most disconcerting were the number of sentinel events that occurred in persons aged 30 years or younger, These studies were thorough and extensive, and scrutiny of a large number of cases was made before the final decision was accomplished. The concluding ruling of Section 119.1 dietary supplements containing ephedrine alkaloids reads as follows: "Dietary supplements containing ephedrine alkaloids present an unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested in the labeling, under ordinary conditions of use. Therefore, dietary supplements containing ephedrine alkaloids are adulterated under section 402(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act" (FDA, 2004c). Saudi Arabia has followed

the U.S. banning of ephedra products. Rulings from the E.U. and elsewhere have yet to evolve.

Of course, this restriction has caused some consternation among herbalists or Chinese practitioners who still believe that within the context of traditional use, Ma Huang has its merits. In Canada, the ephedrine alkaloid is limited to levels well below the excesses seen in U.S. products, a policy that allows the continued sale of traditional Chinese *Ephedra* products. Canada also allows *Ephedra* to be included in products used for nasal congestion in the following small doses: 8 mg/dose or 32 mg/day of ephedrine and 400 mg/dose or 1600 mg/day. However, Health Canada has issued several warnings regarding the illegal sale of *Ephedra* and the potential risks that are involved, particularly when it is combined with caffeine or other stimulants.

B. KAVA: A NEO-WESTERN REMEDY WITH POLYNESIAN ROOTS

Use of kava (*Piper methysticum*) extracts as a safe alternative to anxiolytics drugs has been banned in the entire E.U. and Canada, and in Australia the products have been voluntarily removed from the market. In the United States, kava has been the subject of cautions and advisories by the FDA, and its status is still pending depending on the outcome of current investigations (Blumenthal, 2002). The reason for this concern is the seriousness of the adverse events that began to be reported in 1988, when heavy kava use in an Australian aboriginal community triggered unease about its effects on health, its induction of scaly rashes, and its potential for hepatotoxicity in populations already infected with hepatitis B (Mathews *et al.*, 1988). Subsequently, kava dermopathy was also seen in heavy kava drinkers in the Tonga Islands (Ruze, 1900). At that time, effects on impaired vision were also observed (Garner and Klinger, 1985) and were included in the Commission E monographs (Blumenthal, 1998). However, beginning in 1998, a number of serious adverse reactions were reported in Europe in patients taking kava extracts for anxiety. Most of these cases involved liver-related adverse effects, leading to hepatic failure and subsequent liver transplantations (Clouatre, 2004; Moulds and Malani, 2003) and even death (Brauer *et al.*, 2001). In many instances, this linkage to hepatotoxicity remains in dispute because of other potentially hepatotoxic medications being taken concomitantly. However, a number of cases still exist in which kava consumption alone has been implicated (Clouatre, 2004). Other adverse events have been associated with neurological complications, including the exacerbation of Parkinson's disease and interactions with CNS depressants, such as benzodiazepines causing coma (Almeida and Grimsle, 1996; Stevinson *et al.*, 2002). Although its status in the United States remains uncertain, it is agreed that kava drinking is contraindicated if underlying conditions that might

adversely effect liver function exist such as the concomitant intake of prescription drugs associated with liver damage, excessive alcohol use, or preexisting liver disease or infections (Blumenthal, 2002; Waller, 2002).

IX. INADVERTENT OVERDOSING

The use in TCM of "chuanwu" (the main root of *Aconitum carmichaeli*) and "caowu" (the root of *A. kusnezoffii*) in the treatment of various musculoskeletal disorders has led to serious *Aconitum* poisonings, leading to tachyarrhythmias, including tachycardia and fibrillation ventricular arrhythmias and sometimes, death (Chan *et al.*, 1994; Dickens *et al.*, 1994; Tai *et al.*, 1992). A case of tetraplegia has also been reported (Chan *et al.*, 1994). These aconite roots contain aconitine, mesaconitine, and hypaconitine, which are neurotoxins and cardiotoxins. In Hong Kong, awareness of this problem of overdosing has led to stricter adherence to recommended doses, with a subsequent lowering of adverse reactions being reported (Chan, 2002). Shandoguen (root of *Sophora tonkinensis*) is another herb with a low therapeutic ratio. Excessive doses can cause vomiting, diarrhea, headache, dizziness, and in some cases, death. Overdosing with upper respiratory preparations such as lushenwan, containing "chansu," the venom of the toad *Bufo bufo gargarizans* and *B. melanostictus,* can cause cardiac arrhythmias, which can be fatal in children. Local skin inflammations have been linked to its unwarranted use as a topical medicament to treat skin infections (Tomlinson *et al.*, 2000).

Though less toxic, certain herbs used inappropriately for long periods or in excessive amounts can also be problematic. Ginseng (*Panax ginseng; Panax. quinquefolius*) is widely valued as a panacea and adaptogen (Lewis and Elvin-Lewis, 2003), but when taken in high doses, toxic effects similar to caffeine toxicity such as nervousness, mood elevation, insomnia, rash, depression, and morning diarrhea have been described in what is referred to as the "ginseng abuse syndrome" (Siegel, 1979). It has been known to induce manic states in depressive patients (Gonzalez-Seijo *et al.*, 1995) and to cause palpitations, nausea, vomiting, amenorrhea, and blurred vision. Taken in cigarettes, it can exacerbate symptoms in schizophrenics. These effects are possibly due to its dammarenetriol glycoside, which has strong excitatory effects on the nervous system and other components (D'Arcy, 1991; Elvin-Lewis, 2001; Ernst, 1998; Kassler *et al.*, 1991; O'Hara *et al.*, 1998; Saxe, 1987; Wilkie and Cordess, 1994). Because of these stimulatory effects and its link to increasing blood pressure, the British Herbal Compendium does not recommend its use with stimulants, including excessive amounts of caffeine (Bradley, 1992). Estrogenic affects such as mastalgia (Palmer *et al.*, 1978)

and unexplained vaginal bleeding following use of a ginseng face cream (Hopkins *et al.*, 1988) have been reported. It also reduces the effects of warfarin (Yuan *et al.*, 2004). Numerous OTC products claim to contain ginseng, primarily because the word promotes sales, and consumers should be aware of unexpected events that are associated with the use of these products. Its effects on the developing fetus have been discussed elsewhere.

Several Asian remedies contain *Glycyrrhiza glabra* (licorice) or *Glycyrrhiza uralensis* (gancao) (Lewis and Elvin-Lewis, 2003), and these are generally considered safe. Their content of glycyrrhizic and glycyrrhetinic acids, with aldosterone-like properties, can in large doses induce hypokalemia and sodium and water retention (Tomlinson *et al.*, 2000).

X. HERBAL DRUG TRANSMISSION *IN UTERO* OR THROUGH MOTHER'S MILK

Use of herbal remedies by pregnant or nursing mothers can result in the transmission of certain phytochemicals to the fetus or infant. Effects can be transient, grave, or fatal, and much is still unknown about residual effects (Conover, 2003; Pinn and Pallett, 2002). The fetus is particularly vulnerable to herbs, which are toxic, teratogenic, carcinogenic, or possess abortifacient properties. For example, salicylates are potentially teratogenic or embryocidal even when applied externally in Oil of Wintergreen. Ingestion of *Sassafras albidum* as an herbal tea also poses concerns, because transplacental carcinogenesis has been demonstrated in mice. This phenomenon is possibly due to its major carcinogenic component safrole (De Smet, 1992). Care should be taken to avoid other herbal remedies during pregnancy because they may induce menses, infant death, low birth weights or neonatal jaundice. For example, the use of feverfew (*Tanacetum parthenium*) for headaches may induce menses (another traditional use) and terminate the pregnancy (O'Hara *et al.*, 1998); similar abortifacient risks have been linked to rue, parsley, (Blumenthal, 1998; Ciganda and Laborde, 2003), Goldenseal, and sparteine (Benssousan *et al.*, 2000). Herbs and foods rich in unsaturated pyrrolizidine alkaloids may cause fetotoxic or embryotoxic effects (Rasenack *et al.*, 2003), and infant fatalities have resulted from maternal drinking of teas or cough remedies containing these alkaloids (Roulet *et al.*, 1988; Winship, 1991). Ginseng use during pregnancy is also inadvisable (Anonymous, 2003), because neonatal androgenization has been observed (Anonymous, 1991); and during the critical period of organogenesis, its major ginsenosides, Rb_1, has been found to cause teratogenesis in rat embryo cultures (Chan *et al.*, 2003). The chewing of the stimulant Khat (*Catha endulis*) can result in lower birth weights (Eriksson *et al.*, 1991; Ghani *et al.*,

1987), and hydrastine in Goldenseal (*Hydrastis canadensis*) and barberry (*Berberis)* can cause neonatal jaundice. A mother should also avoid taking heparin-containing herbs, because either her fetus or her nursing infant is at risk of developing bleeding disorders (Ernst, 1997). Use of blue cohosh (*Caulophyllum thalictroides*) to promote uterine contractions at parturition is unwise because the plant contains vasoactive glycosides, a toxic alkaloid, and sparteine. In one instance, this practice caused a newborn to develop an acute myocardial infarction, congestive heart failure, and shock, and although the neonate survived, it was ill for several weeks (Jones and Lawson, 1998). A case of fetal alcoholic syndrome may also be related to maternal use for 2 months during the antenatal period of an "Herbal Health Tonic" containing 14% alcohol (Pradeepkumar *et al.*, 1996). Severe congenital lead poisoning in a preterm infant was linked to the mother's long-term ingestion of a lead-containing herbal pill (Tait *et al.*, 2002).

There are a number of reasons nursing mothers should also avoid herbal use (Conover and Buehler, 2004). Should Chasteberry fruit (*Vitex agnus-castus*), be taken at this time, its dopaminergic compounds can reduce pituitary prolactin reserves and thus affect lactation (Wuttke *et al.*, 2003). Other harmful phytochemicals may be found in colostrum and transmitted to the nursing infant, causing serious adverse effects. Examples include evoking catharsis in a nursing infant following the use of Rhein-containing senna laxatives by its mother; the exposure of a nursing infant to hepatotoxic, genotoxic, and carcinogenic echimidine through maternal drinking of Comfrey tea (Winship, 1991); the development of a venoocclusive hepatic illness resembling Budd-Chiari syndrome following the mother's use of a tea containing flowers of *Tussilago farfara* (Tussilaginis Farfare, Flos) and roots of *Petasites officinalis* (Radix petasidis) (Roulet *et al.*, 1988; Spang, 1989); and the development of a fatal illness mimicking Reye's syndrome, through the maternal use of an herbal cough remedy containing the pyrrolizidine alkaloid senecionine (Fox *et al.*, 1978). Hypertension in both an infant and its mother has also been linked to the use of a Chinese herbal medicine (Nambiar *et al.*, 1999).

XI. HERBAL USE IN CHILDREN

The capacity of children to absorb, distribute, metabolize, and excrete certain substances differs from that of adults. With larger livers, children are generally more efficient in their ability to detoxify; however, their developing nervous and immune systems can also make them more sensitive to the adverse effects of certain botanicals. Children are particularly vulnerable to developing significant dehydration and loss of electrolyte balance with the

use of powerful herbal cathartics or diuretics. They are especially at risk in taking herbs containing pyrrolizidine alkaloids, because no safe dose or duration has been determined. Also, even the first introduction of an atopic child to certain herbs has the potential of sensitizing or eliciting a wide range of allergic reactions (Woolf, 2003). Of particular concern is the use of TCM within the pediatric age-group because numerous life-threatening reports have been associated with their use and have been discussed in context throughout the chapter (Chan, 1994; Ize-Ludlow *et al.*, 2004; Minodier *et al.*, 2003; Tomassoni and Simone, 2001).

XII. ALLERGIC REACTIONS

A. TYPE I (IMMEDIATE) HYPERSENSITIVITY

Herbal use can induce allergic reactions in many ways (Lewis and Elvin-Lewis, 2003; Reider, 1994). Those most frequently observed are the symptoms of rhinitis, headache, dermatitis (hives), and/or anaphylactic shock typical of type I reactions, and erosive and weeping lesions of contact dermatitis, typical of delayed hypersensitivity, type IV reactions. The most common incitants are members of the Asteraceous (daisy family), and the cross reactions that occur among them. In the United States, the widespread occurrence of ragweed (*Ambrosia* species) is a major cause of sensitization to large portions of eastern and midwestern populations. Atopic individuals in this category that drink chamomile (*Chamaemelum nobile*) herbal teas (Reider *et al.*, 2000) or use herbal preparations of *Echinachea* (Mullins, 1998; Myer and Wohlmuth, 1998) or *Tanacetum parthenium* (feverfew) (Hausen, 1981) are at risk of developing headaches, exacerbating symptoms of allergy or asthma, or developing other type I reactions including anaphylaxis. Unfortunately, most American chamomile drinkers are unaware of these hazards of potential cross reactivity, because their European counterparts do not share the same prospect of sensitization, unless they are allergic to wormwoods (de la Torre *et al.*, 2001; Subiza *et al.*, 1989) or sensitized during the commercial preparation of the herbal product (Dutkiewicz *et al.*, 2001). Most disconcerting are the increasing number of cases of anaphylaxis (Benner and Lee, 1973; Subiza *et al.*, 1989) and some fatalities related to chamomile use in teas or as enemas (Jensen-Jarolim *et al.*, 1998; Thein, 2001). Allergic conjunctivitis can also be induced by using the tea as an eye wash (Subiza *et al.*, 1990). Several cases of *Echinacea*-associated anaphylaxis have been reported in Australia (Mullins and Heddle, 2001). A case of anaphylaxis has also been reported following the use of milk thistle (*Silybum marianum*) (De Smet, 2004).

B. TYPE IV DELAYED CONTACT HYPERSENSITIVITY

1. Asteraceous plants

Exposure to Asteraceous plants may also result in the development of contact dermatitis. One Serbian study has indicated that it is not unusual to detect sensitization to chamomile (*Chamomilla recutita*), arnica (*Arnica montana*), tansy (*Tanacetum vulgare*), and feverfew (*Tanacetum parthenium*) (Jovanovic *et al.*, 2004). Contact dermatitis, along with asthma and rhinitis, may also accompany occupational exposure to chamomile (Rudzki *et al.*, 2003) and contact dermatitis to feverfew (Hausen, 1981). Similarly, chamomile in cosmetic products can also be a cause of dermatitis (Paulsen, 2002; Rycroft, 2003). Because chamomile-containing products, particularly in shampoos and other OTC products, are so widespread, the linkage to these types of adverse events are likely underreported. Also, use of royal jelly, a thick mixture of honey, pollen, and their allergens, has been associated with several cases of bronchospasm, and topical application of concentrated forms of bee pollen (propalis) to contact dermatitis (Perharic, 1993). Milk thistle has also been known to cause urticaria (De Smet, 2004).

2. Essential oils

Essential oils are found in foods, chewing gums, flavorings, fragrances, and medicinal products and may be ingested, chewed, used in dental products, inhaled as perfumes or in aromatherapy, or applied to the skin for medicinal or other purposes. Whatever the source, they have the capacity to sensitize and to elicit allergic reactions, particularly of the type IV variety. Canker sores (Elvin-Lewis, 2001; Elvin-Lewis *et al.*, 1985; Nolan *et al.*, 1991) and cheilitis (Corazza *et al.*, 2002; Francalanci *et al.*, 2000; Hausen, 1984; Holmes and Freeman, 2001) are examples of their oral manifestations. Eugenol is a primary offender, possibly because its occurrence is so widespread in spices (oil of cloves), herbs, foods (e.g., artichokes), flavorings, cosmetics, fragrances, dental products, and medicines. Similarly, L-carvone in many mint and peppermint oils has been implicated in contact allergies (Anderson, 1978; Corazza *et al.*, 2002; Holmes and Freeman, 2001; Paulsen *et al.*, 1993; Worm *et al.*, 1989), as has cinnamaldehyde found in cinnamon (Drake and Maibach, 1976; Thyne, 1989).

Lavender, jasmine, and rosewood oils used in perfumes and as ingredients of aromatherapy can elicit on inhalation similar allergic reactions in the nasal passages and respiratory tract (Schaller and Korting, 1995; Selvaag *et al.*, 1995a; Sugiura *et al.*, 2000), and with skin contact, dermatitis is possible for these oils, as well as French marigold, cedarwood oil,

peppermint oil, tea tree oil, and Tylang-ylang (Ernst, 2000; Selvaag *et al.*, 1995b). Dermatological conditions can also result from handling allergenic plants and their products (Sasseville, 1999; Simpson *et al.*, 2004). Noteworthy among these examples are the adverse effects associated with the widespread use of tea tree oil (extracted oil of *Melaleuca alternifolia*) in aromatherapy, and its antimicrobial and therapeutic properties are causes for growing concerns. Several of its components, namely D-limonene (and its oxidative derivative D-carvone), α-terpinene, aromadendrene, terpinen-4-ol, p-cymene, and α-phellandrene have been found to be sensitizing agents (Knight and Hausen, 1994). It has been found to have the potential to also elicit allergic contact dermatitis, systemic contact dermatitis, linear immunoglobulin A disease, erythema multiforme-like id reactions, and systemic hypersensitivity reactions (Crawford *et al.*, 2004).

A review by Ernst (2000) considers additional herbal remedies and aromatherapy oils known to elicit allergic skin reactions and other dermatological disorders. Examples of those used as topical medicaments include aloe vera, black cumin oil, camomile, camphor, citrus hystrix, curcumin, bergamot oil, and *Inula helium* massage oil (Ernst, 2000). Tincture of benzoin or balsam of Peru obtained from *Myroxylon pereirae*, used for cosmetic wound healing, is a common allergen (Scardamaglia *et al.*, 2003). An exudative erythema may appear on exposed areas of skin, following airborne exposure to jasmine (Schaller and Korting, 1995). Skin rashes may also be caused by a variety of phytoirritants or compounds that can elicit pruritus and wheals such as histamine-containing nettles (Lewis and Elvin-Lewis, 2003).

Contact dermatitis can also result from the use of a number of Chinese topical formulations, and studies have shown that many of the ingredients have the potential of being sensitizing agents (Chen *et al.*, 2003). Garlic (*Allium sativum*) with its allergen, diallyl disulfide, can cause irritant contact dermatitis, with the rare variant of zosteriform dermatitis, as well as contact urticaria, including the hematogenic variant (Jappe *et al.*, 1999)

3. *Oral medications*

Oral medications may also elicit dermatological reactions. For example, Stevens-Johnson syndrome has been associated with drinking Mai-Meu-Dong-Tang, a Chinese health drink (Mochitomi *et al.*, 1998) or ingesting opiopogonas tubers (Mochitomi *et al.*, 1998b). A lupus-like syndrome can result through the use of yohimbe (*Coryanthe yohimbe*) (Sandler and Aronson, 1993). Garlic is also known to elicit pemphigus, allergic asthma and rhinitis, angioedema (Jappe *et al.*, 1999), and photosensitivity reactions

(Alvarez *et al.*, 2003). Similarly, photosensitivity may be elicited by taking *Psorolea corylifolia* (Maurice and Cream, 1989) or *Hypericum perforatum* (SJW) (Cocks and Wilson, 1998). Widespread skin eruptions have resulted from taking Fang Feng Tong Sheng Wan and Bi Yan Pian (Mather *et al.*, 2000). The use of the Indian remedy guggulipid, derived from the guggul tree, *Commiphora mukul,* and used for the treatment of hypercholesterolemia, is associated with the development of a skin rash in some patients (Szapary *et al.*, 2003) and headache, mild nausea, eructation, and hiccup in others (Singh *et al.*, 1994). Delayed hypersensitivity reactions have been linked to the use of Hexilor (extract of European mistletoe, *Viscum album*), when it is used for adjuvant cancer therapy (Stein and Berg, 1999). Eczema can result from ingestion of *Krameria triandra,* found in a number of Asian traditional remedies (Goday *et al.*, 1999). Stevens-Johnson syndrome and diffuse morbilliform skin reactions have been linked to ginkgo supplement ingestion (*Ginkgo biloba*) (Chiu *et al.*, 2002; De Smet, 2004). Lupus-like syndromes are associated with use of yohimbe (*Coryanthe yohimbe)* (De Smet, 2004).

XIII. DENTAL PRODUCTS

Aside from allergic manifestations elicited by essential oils, adverse reactions related to use of dental products are rare (Ocasio *et al.*, 1999). However, so-called ''natural'' dentifrices always present a risk of damaging the enamel due to the variability in abrasivity of their calcium carbonate sources or contributing to heavy metal toxicity should this compound be derived from seashells that could contain high amounts of mercury (Elvin-Lewis, 2001). Caries rates are always higher in communities that do not fluoridate their water supplies to euflorotic (1 pmm) levels. Many brands of ''bottled'' water lack fluoride, so consumers are at risk of losing the protective effects to enamel that is conferred by this trace element. Some accommodation to this loss is possible, if black or green tea is drunk. Enamel mottling only occurs when fluoride exceeds 2–3 ppm and excessive amounts are drunk (Elvin-Lewis *et al.*, 1980; Lewis and Elvin-Lewis, 2003).

Because oral hygienic products are used on a daily basis and some of their contents may be swallowed or absorbed locally, there is always a concern that long-term effects may occur. One noteworthy example was the association of the use of *Sanguinaria canadensis* root-extract mouthwashes with the development of hyperorthokeratosis, epithelial atrophy, and epithelial atypia/mild dysplasia and an associated squamous cell carcinoma (Allen, 1999; Damm *et al.*, 1999). This phenomenon has been called the *sanguinaria-associated leukoplakia syndrome,* and evaluation of the 143 known cases

indicates that use of this product was a risk factor for the development of these types of lesions (Mascarenhas *et al.*, 2002). The product has been reformulated and the offending extract, with its potentially carcinogenic isoquinoline alkaloids, removed. However, these incidents could have been prevented had the manufacturer heeded the warnings for more than 15 years of leading pharmacologists and toxicologists who counseled them that regular use of sanguinarine, even in small amounts, would be unwise (Elvin-Lewis, 2001). Of current concern is the use of neem products derived from the oil, leaves, and part of *Azadirachta indica* for dental purposes. Though long being valued as chewing-stick, and in crude extract dental formulations for teeth cleaning, as well as for a variety of medicinal purposes, current research is indicating that its bioreactivity profile is not conducive to long-term uses as a dental product. This is because many of its components are used as insect deterrents and anti-feedents, as well as being immunomodulatory, contraceptive, hypoglycemic, and abortifacient (Elvin-Lewis, 2002).

XIV. OCULAR SIDE EFFECTS FROM HERBAL MEDICINES AND VITAMIN SUPPLEMENTS

A recent comprehensive review discusses numerous types of adverse ocular manifestations associated with use herbal and nutritional supplements either topically or systemically (Fraunfelder, 2004). Noteworthy among these are numerous reports linking the use of canthaxanthin used in cosmetics and ingested as a food coloring or for purposes of artificial suntanning. This compound can deposit in all layers of the retina, especially in the superficial layers of the macula causing retinopathy, visual changes such as abnormalities in static threshold perimetry, electroretinography, and dark adaptation. Most individuals are asymptomatic, whereas others may experience diminished visual acuity. These retinal findings are slowly reversible.

Allergic conjunctivitis and/or eye irritation has been associated with the medicinal use of chamomile (*Matricaria chamomilla*) (Subiza *et al.*, 1990) and *Echinacea purpurea* (Fraunfelder, 2004). Hyphema (bloodshot eyes) or retinal hemorrhage has been linked to use of *Ginkgo biloba* (Fraunfelder, 2004) and transient visual loss due to vasospasm with licorice ingestion.

Use of vitamin supplements such as niacin and vitamin A (retinal) in excess of recommended doses has been associated with several cases of cystoid macular edema and intracranial hypertension, respectively (Fraunfelder, 2004).

XV. PROBLEMS ASSOCIATED WITH LONG-TERM USE

The current habit of using herbal remedies to maintain or enhance good health or prevent certain conditions from occurring has resulted in numerous unexpected consequences. Because they are often promoted as safe and efficacious, the consumer is usually unaware that these practices can be harmful, particularly if they are taken for indeterminate periods. In many cases, their endorsed uses may fundamentally differ from how they were valued traditionally, so safety parameters are unknown. This is particularly true in the United States where their sale as a dietary supplement does not require prior FDA approval and appropriate oversight practices, particularly regarding labeling, are not consistently applied. This classification infers that there is little danger to their use, although there is no penalty for withholding reports of adverse effects, and withdrawal by the FDA is only initiated after a prolonged evaluation process (Elvin-Lewis, 2001; Marcus and Grollman, 2002).

What is so disconcerting are the number of problems associated with well-known medicinal herbs such as ginseng, golden seal, ginkgo, milk thistle, cassia, saw-palmetto, valerian, and a variety of stimulants (De Smet, 2004; Elvin-Lewis, 2001; Ernst, 1998; Lewis and Elvin-Lewis, 2003; O'Hara *et al.*, 1998). Symptoms of misuse can vary from trivial to extreme and may include life-threatening events affecting the heart, blood pressure, liver, GI tract, as well as nervous and endocrine systems. Dermatological reactions are considered elsewhere in the chapter.

Goldenseal root (*Hydrastis canadensis*), used as an anti-infective, is generally well tolerated but can when taken in large amounts induce various GI complaints, cause damage to the stomach lining, promote liver swelling and anorexia, and induce hypertension, seizures, respiratory failure, cardiac spasms, psychoses, and death (O'Hara *et al.*, 1998). Leaves of Ginkgo (*Ginkgo biloba*), favored to enhance mental functioning, can induce headache and nausea, and in rare cases cause cerebral and extracerebral hemorrhage, thrombocytopenia, seizures, and ventricular arrhythmia. In addition to causing a number of allergic reactions, single cases of intraoperative hemorrhage, leukopenia, and hypokalemic renal tubular acidosis have been cited following ingestion of *Echinachea* preparations containing its leaf, root, or stalk. As an immune stimulant, it is contraindicated in patients with hyperimmune diseases (e.g., multiple sclerosis). Saw palmetto (*Serenoa repens*) used to control benign prostatic hyperplasia may cause various GI complaints, headache, and erectile dysfunction; a single case of intraoperative hemorrhage has been reported. SJW (*H. perforatum*) used as an antidepressant can cause a multitude of adverse effects from dry mouth, GI upset, dizziness or confusion, restlessness, headache, sexual dysfunction, and frequent urination.

It can elicit dangerous neurological effects by inducing serotonin syndrome–like events, hypomania/mania, and psychotic relapse in schizophrenia, as well as promoting cardiovascular collapse during anesthesia and delaying the emergence from anesthesia. Use of black cohosh (*Cimicifuga racemosa*) for menopausal symptoms and to treat rheumatism can cause nausea, vomiting, and gastroenteritis (Saxe, 1987) and has been associated with cases of hepatitis and hepatic failure. Blue cohosh (*Caulophyllum thalictroides*) may also cause similar symptoms (Sax, 1987). Valerian (*Valeriana officinalis*) used as a sedative can also promote dizziness, nausea, headache, and somnolence and may be hepatotoxic with long-term heavy use. Evening primrose oil (*Oenothera biennis*) used to treat eczema is known to promote weight gain, cause GI upset, and elicit skin complaints; one case of anaphylaxis has been reported. Yohimbe (*Corynanthe yohimbe*), considered an aphrodisiac, can elicit additional excitatory symptoms such as nervousness, anxiety, panic, maniclike symptoms, hypertension, tachycardia, angina pectoris, increased urinary frequency, renal failure, and bronchospasm (De smet, 2004; Elvin-Lewis, 2001; Lewis and Elvin-Lewis, 2003). A reverse of the immunostimulating effects of *Echinacea* has been observed, with leukopenia developing after long-term use (Kemp and Franco, 2002).

Caffeine in guarana (*Paullinia cupana*), mate (*Ilex paraguariensis*), or concentrated green tea (*Camelia sinensis*) elicits a wide range of excitatory symptoms, particularly if it is present in excess. These plant products are frequently present in slimming preparations, and consumers should be aware of their potential to cause palpitations, sweating, insomnia, restlessness, agitations, tremors, headache, polydipsia and polyuria (DeSmet, 2004; Elvin-Lewis, 2001).

Anthranoid laxatives such as aloe (*Aloe vera*), cascara (*Rhamnus purshiana*), and senna (*Senna alexandrina*) can be used in moderation safely, but when used in excess can promote abdominal pain, diarrhea, and severe catharsis. Due to their chronic irritating properties, if used on a long-term basis, they may be a risk factor for colorectal cancer (Siegers *et al.*, 1992). Also, abuse of these laxatives can increase the loss of serum K, thereby potentiating the effects of cardiac glycosides and antiarrhythmic agents (Blumenthal, 2000). Using common names, these data are summarized in Table IV.

XVI. EFFECTS ON INTERNAL ORGANS

A primary function of the liver and kidneys is to detoxify and clear poisonous substances from the body. For these reasons, they are often the first to be affected by the use of toxic herbs. A number of reviews address the global

TABLE IV
HERBS THAT CAN CAUSE PROBLEMS WITH LONG-TERM USE

Herb: common name	GI	Hepatotoxic	CNS	Headache	Cardiovascular	Blood thinning	Allergy	Other	Death
Aloe	X							X	
Black cohosh	X	X							
Blue cohosh	X	X							
Echinacea							X	X	
Evening primrose	X						X	X	
Goldenseal	X		X		X				X
Ginkgo	X		X		X	X	X		
Guarana			X						
Mate			X						
St. John's wort	X		X	X				X	
Tea, green/black			X					X	
Valerian	X								
Yohimbe			X		X			X	

seriousness of this problem and offer explanations as to which mechanisms may be involved. Most of these examine the subject of hepatotoxicity-associated herbal use (Chitturi and Farrel, 2000; Larrey, 1994, 1997; Pak *et al.*, 2004; Pittler and Ernst, 2003; Stedman, 2002; Stickel *et al.*, 2000; Zhou *et al.*, 2004). Herbal effects on the kidney are addressed by Isnard *et al.* (2004), and that of cardiotoxicity by Ernst (2002). The capacity to injure these organs may be associated with one or more plants or other ingredients that are found in offending formulations. Some of these events may be elicited by traditionally formulated phytomedicines, whereas others have been associated with adulterants they might contain. Various herbal teas have also been implicated. Initial linkage to herbal use is not always easy, because many patients, unless solicited, are unlikely to reveal the source. Using common names, these data are summarized in Table V.

A. LIVER

Unfortunately, any diagnostic delay with those herbal remedies that are hepatotoxic can lead to the perpetuation or exacerbation of liver injury (Chitturi and Farrel, 2000). Depending on the level of toxicity, the range of liver damage may be transient and mild so only minor transaminase elevations are detected, whereas in other cases the development of steatosis (fatty liver), cholestasis (suppressed or stoppage of bile flow), acute and chronic hepatitis, zonal or diffuse hepatitic necrosis, hepatic fibrosis and cirrhosis, bile duct injury, venoocclusive disease (VOD) (obstruction of the veins), and acute liver failure causing death or requiring transplantation and carcinogenesis may arise (Stedman, 2002). Other underlying conditions such as alcoholism, liver infections, or concomitant use of other remedies known to adversely affect the liver such as those that induce CYP enzymes may also influence the course of the toxic event and the degree of permanent damage or recovery, that results. Also, females are more predisposed to develop hepatotoxicity, particularly during pregnancy. In addition, during an adverse hepatic episode, the functional integrity of the liver may be altered in ways that the action of conventional drugs is encumbered (Stedman, 2002).

1. Traditional Asian Medicines

Because of their herbal contents, certain Asian traditional medicines have been consistently linked to undesirable hepatic events (Benoussan, 2000; Pittler and Ernst, 2003). It has been estimated that from 1 to 8% of patients using these "drugs" develop elevated liver enzyme levels, which tend to return to normal once therapy is completed (Al-Khaafi, 2000; Dasgupta, 2003; Melchart *et al.*, 1999a,b). In a Taiwanese study, a number of cases of

TABLE V
HERBS WITH ADVERSE EFFECTS ON INTERNAL ORGANS

Common name	Liver	GI	Kidney	Heart and CVS	Death
Aloe			X		
Artichoke				X	
Cascara		X		X	
Chinese foxglove	X				
Celandine (greater)	X	X			
Celandine (lesser)	X	X			
Chaparral	X			X	X
Cloves				X	
Bajialoan	X			X	
Garlic					
Gas Plant	X				X
Germander	X				
Ginseng, Siberian				X	
European mistletoe				X	
Fo ti	X				
Fructus Aristolochiae			X[a]		
Hawthorn				X	
Hyayruro			X		
Impili	X		X		
Licorice				X	
Ma Huang	X				
May Apple	X				
Meadow-sweet				X	
North African thistle	X				
Papaya				X	
Pennyroyal	X				X
Peony	X	X			
Pineapple				X	
Sassafras	X				
Senna	X	X		X	
Skullcap	X				
Sweet birch				X	
Sweet melilot				X	
Sweet woodruff					
Tonka beans				X	
Willow				X	
Wintergreen				X	

GI, gastrointestinal system; CVS, cardiovascular system.
[a]Urothelial carcinoma also.

abdominal pain, elevated liver enzymes, and neurological complications were reported following the use of Bajialoan (*Dysoma pleianthum*), a Chinese remedy used for snake bite, condyloma acuminata, tumors, and lymphadenopathy (Kao *et al.*, 1992). The related taxa, May apple (*Podophyllum*

peltatum), used as a liver tonic is also known to elevate liver enzymes, in addition to evoking symptoms of nausea, vomiting, inflammation, edema of the bowel, and hematological abnormalities (Saxe, 1987).

Serious liver damage may ensue from taking other herbal remedies. Noteworthy are cases linked to Ma Huang with its ephedrine alkaloids. Predominant symptoms include jaundice and liver necrosis (Nadir *et al.*, 1996) including autoimmune hepatitis (Borum, 2001). Hepatotoxicity associated with compound heterozygosity for hereditary hemochromatosis has also been reported (Bajaj *et al.*, 2003). Polyherbal mixtures used to treat psoriasis and eczema are particularly unpleasant tasting, and their use possibly causes nausea and vomiting on their own. However, in some cases, these events may be followed by abdominal pain, jaundice, and liver necrosis (Kane *et al.*, 1995; Perharic *et al.*, 1995). Those cases reviewed by Sticet *et al.* (2000) all contained species of *Paeonia* (Paeoniae Rubrae Radix), and most, the Chinese foxglove *Dictamnus* and the *Rhemannia*. The gas plant or Burning bush, *Dictamnus albus* subspecies *dasycarpus* has been implicated in two fatal cases of severe hepatitis (McRae *et al.*, 2002). Cases of malaise, nausea, vomiting, and jaundice following use of Shou-wu-pian for graying hair and alopecia have been reported. This remedy contains Fo ti, *Polygonum multiflorum*, with its laxative anthraquinones, emodin and pyscin (But *et al.*, 1996; Mazzanti *et al.*, 2004; Park *et al.*, 2001). Chan Su used for heart disease has also been linked to fatal cases of hepatitis (Dasgupta, 2003).

Kampo medicines may also cause liver injuries, although the incidence of these events is considered low (<1%) (Mantani *et al.*, 2002). Those implicated include Saiko-keishi-kankyo-to (Hanawa, 2000), Sai-rei-to (Nishioji *et al.*, 1994), Bukuryo-in-go-hange-koboku-to (Yoshikubo *et al.*, 1997), and Syo-saiko-to (also known in China as Xiao-chai-hu-tang) (Itoh *et al.*, 1995).

Cases of acute hepatitis linked to the use of Jin Bu Huan are less clear, because adulteration with levo-tetrahydropalmatine, an alkaloid present in *Stephania* and *Corydalis,* has been implicated (Brent, 1998; Woolf *et al.*, 1994). Similarly, adulteration may be the cause of a fatal case of VOD attributed to skullcap (*Scutellaria lateriflora*), because this plant does not contain pyrrolizidine alkaloids associated with this syndrome. Nonetheless, in one instance, skullcap was implicated in a case of mild flulike symptoms associated with jaundice and abnormal liver function test results (Enlow, 1996).

Though generally considered harmless and present in a number of remedies for weight loss or to lower cholesterol, adverse effects have also been reported for use of the mints germander (*Teucrium chamaedrys*) and *T. polium.* For example, acute hepatitis, nausea, and asthenia (loss of energy and strength) were common symptoms in nine cases associated with their use

(Dourakis *et al.*, 2002; Pittler and Ernst, 2003). A diterpenoid teucrin A is considered responsible for these symptoms (Larry *et al.*, 1992) possibly due to the oxidation by CYP 3A4 of its furan ring, to reactive epoxide, which reacts with proteins such as CYP 3A and epoxide hydrolase (Zhou *et al.*, 2004).

2. *Neo-western herbalism*

Nausea and jaundice related to the development of necrotizing hepatitis, associated in some patients with marked cholestasis without liver failure, was characteristic of 10 patients using greater celandine (*Chelidonium majus*) (Benninger *et al.*, 1999) or lesser celandine (Strahl *et al.*, 1998) for the treatment of biliary, gastric disorders, and atopic eczema (Pittler and Ernst, 2004). It contains several alkaloids including chelidonine, chelerythrine, sanguinarine, and protopine, some of which are potentially carcinogenic (Lewis and Elvin-Lewis, 2004). Hepatotoxic reactions have also been observed after the ingestion of *Atractylis gummifera, Senna,* and pulegium. The monoterpene pulegium in pennyroyal (*Hedeoma pulegoides* and *Mentha pulegium*) is an abortifacient but can also cause liver damage, shock, and death (Anderson *et al.*, 1996). The generation of p-cresol from extensive pulegone metabolism acts as a glutathione depletory (Zhou *et al.*, 2004). *Cassia angustifolia* (senna) contains a number of bioreactive alkaloids, including anthren. *Cassia* is used as a laxative and is found in slimming formulas and in TCM as *folia sennae.* When taken in excessive amounts, it has been known to cause toxic hepatitis (Beuers *et al.*, 1991; De Smet *et al.*, 1996; Ghali and Lindor, 2004). A number of cases of severe and chronic liver damage, including periportal inflammation and necrosis and fulminant hepatitic failure, requiring liver transplantation, have been associated with the use of Chaparral or creosote bush (*Larrea tridentata*) (Anonymous, 1992; Grant *et al.*, 1997; Sheikh *et al.*, 1997). It is used to treat respiratory tract infections and in short-term and moderate doses is not considered dangerous; however, its use in capsule form is not recommended because there is a danger of overdose (Heron and Yarnell, 2001). *Sassafras albidum* is a popular Appalachian spring tonic; it contains safrole, which is considered weakly hepatocarcinogenic, so its incorporation as a beverage flavoring and root canal antiseptic is no longer allowed in the United States (Lewis and Elvin-Lewis, 2003).

3. *African indigenous medicine*

Hepatitic necrosis has been seen following the use of the North African thistle *Atractylis gummifera* and the Zulu medicinal plant, impila, *Callilepsis laureola.* The glucosides of *A. gummifera* such as atractylate can elicit severe

liver failure (Hamouda *et al.*, 2004; Kairis, 1996). Impila in KwaZulu-Natal has been responsible for several deaths among the Zulu population (Chitturi and Farrell, 2000).

4. *Pyrrolizidine alkaloids and venoocclusive disease*

Hepatotoxic pyrrolizidine alkaloids are widely represented within species of the Asteraceae, Borginaceae, and Fabaceae and can be found in medicinal plants, foods (including honey), or as contaminants. More than 300 plant species have been implicated in the development of VOD, which is particularly harmful to the liver and lungs (Winship, 1991). Abdominal pain, vomiting, hepatomegaly, raised liver enzyme levels, and the development of ascites characterize this condition, and deaths in 20–30% of cases may ensue if intake of the offending substance is not discontinued. Noteworthy cases are those related to use of *Crotalaria, Heliotropium, Senecio,* and *Symphytum.* Mass human poisoning has occurred from ingestion of *Heliotropium lasocarpium* seeds contaminating cereal crops in Afghanistan (Tanden, 1978), Tadjikistan (Chauvin *et al.*, 1994; Drew and Myers, 1997), and *Crotalaria* seeds in India (Tanden *et al.*, 1976). Likewise, outbreaks among sheep have occurred in Australia (Harris and Nowara, 1995) with *H. europaeum* and among horses with *H. indicum* in Costa Rica (Van Weeren *et al.*, 1999). In Africa or Central America, intoxication is sometimes endemic because these plants are often used for making tea. Episodes of "bush tea"–associated VOD have occurred among the Zulus of Natal following ingestion of *Callilepis laureola* (Stickel *et al.*, 2000), in Jamaica, to consumption of *Senecio* or *Crotalaria* species (Bras *et al.*, 1954, Hill *et al.*, 1951), in Argentina following the ingestion of herbal infusions containing *Senecio vulgaris* (Vilar *et al.*, 2000), and in Ecuador from using an herbal tea containing *Crotalaria* (Lyford *et al.*, 1976). Herbal remedies containing *Senecio* have been implicated in numerous cases of VOD reported among children and infants such as a Hispanic infant in Arizona taking "gordo lobo" (Fox *et al.*, 1978; Stillman *et al.*, 1977), and another infant in Brazil, which consumed the herbal tea "maria-mole" (*Senecio brasiliensis*) (Magnobosco *et al.*, 1997). Similarly, an 18-month-old Austrian boy who was mistakenly given Alpendost (*Adenostyles alliariae*) instead of coltsfoot (*Tussilago farfara*) in an herbal tea prepared by his parents developed reversible hepatitic VOD (Sperl *et al.*, 1995). If drunk during pregnancy, herbal teas containing senecionine or other pyrrolizidine alkaloids have also been shown to be the cause of fatal VOD among neonates (Rasenack *et al.*, 2003; Roulet *et al.*, 1987).

Pyrrolizidine alkaloids can be found in numerous plants used in Indian and Chinese medicine (Roeder, 2000; Zhao *et al.*, 1989). For example, a medicinal herbal preparation containing *Heliotropium eichwaldii* and its

pyrrolizidine alkaloid heliotrine (Datta *et al.*, 1978) and an Indian remedy for psoriasis containing pyrrolizine alkaloids have been associated with VOD in a number of Asian patients (Kumana *et al.*, 1985). Comfrey teas, once popular as a European/Western remedy for treatments of inflammatory disorders such as arthritis, thrombophlebitis, gout, and as a treatment for diarrhea, are no longer permitted in Germany, Canada, and the United States (FDA, 2001; Stickel and Seitz, 2000). This is related to their hepatotoxicity in humans and carcinogenicity in animals. These effects are most likely due to various hepatotoxic pyrrolizidine alkaloids such as lasiocarpine and symphytine, as well as their related *N*-oxides (Stickel and Seitz, 2000), which may react with CYP enzymes to form pyrroles that are highly reactive hepatocarcinogens (Huxtable, 1990).

B. THE KIDNEY

Nephrotoxicity is associated with the use of several medicinal herbs (Nortier *et al.*, 1999; Wojcikowski *et al.*, 2004), and various renal syndromes can develop including tubular necrosis, acute interstitial nephritis, Fanconi's syndrome, hypokalemia or hyperkalemia, hypertension, papillary necrosis, chronic interstitial nephritis, nephrolithiasis, urinary retention, and cancer of the urinary tract (Isnard *et al.*, 2004). For example, in South Africa, an herbal remedy containing Cape aloes caused acute oliguric renal failure and liver dysfunction (Luyckx *et al.*, 2002), and another, *Callilepsis laureola,* produced acute renal failure (Seedat and Hitchcock, 1971). In Peru, a remedy containing seeds of *Ormosia coccinea* called "hyayruro" or the "lucky bean," proved to be nephrotoxic and required the patient to be placed on hemodialysis (Guerra, personal communication, 2005). In India, additional nephrotoxins are encountered both in common edible plants (djenkol beans, mushrooms) and in medicinal herbs (impila, cat's claw) (Jha and Chugh, 2003). Flavonoids such as sciadopitysin can cause severe nephropathy (Lin and Ho, 1994). A number of *Aristolochia* species commonly found in TCM have also been associated with undesirable effects on the kidney (Sun *et al.*, 2002) and liver. Herbal metabolites formed during the process of bioactivation can covalently bind to cellular proteins and DNA, leading to toxicity via multiple mechanisms such as direct cytotoxicity, oncogene activation, and hypersensitivity reactions. Aristolochic acids can undergo reduction of the nitro group by hepatic CYP 1A1/2 or peroxidases in extrahepatic tissues to reactive cyclic nitrenium ion, which is capable of reacting with DNA and proteins, resulting in activation of H-*ras* oncogene, gene mutation, and finally leading to mutagenesis (Zhou *et al.*, 2004). A urothelial carcinoma was reported following use of a Chinese herbal medicine containing *Aristolochia fangchi* (Nortier *et al.*, 2000).

C. HEART AND CARDIOVASCULAR SYSTEM

Use of herbal medications for the treatment of cardiovascular problems must be done with care. Although some may be useful, many contain natural glycosides or blood thinners or affect blood pressure. They are not only bioreactive on their own but also serve to potentiate or diminish the action of prescribed medications. Concomitant uses of conventional treatments for cardiovascular problems along with traditional remedies for the same purpose are inadvisable because these combinations can seriously compromise the treatment outcome. Potentially grave adverse effects associated with herbal use are arrhythmias, arteritis, cardiac glycosides overdose, chest pain, congestive heart failure, hypertension, hypotension, myocardial infarction, over-anticoagulation, pericarditis, and death (Ernst, 2003). Effects on the coagulation are particularly noteworthy, and few patients on chronic anticoagulant therapy have completely stable PT/INR values because of interactions with certain drugs and foods, particularly those that contain anticoagulant coumarins or additional like substances (Schulman, 2003). The flavonoid cyanidanol has also elicited hemolytic anemia in several patients (Gandolfo *et al.*, 1992), and in one instance, use of an herbal medicine precipitated massive hemolysis (Baker and Thomas, 1987).

Licorice can also induce hypokalemia and hypertension. These symptoms have been associated with the use of liquorice-flavored chewing gum (DeKlerk *et al.*, 1997), and following its use as a tea sweetener along with the long-term consumption of licorice candy, hypokalemic paralysis developed (Elinav and Chajek-Shaul, 2003). In the kampo medicine "shakuyaku kanzou tou," it induced symptoms of pseudoaldosteronism (Kanda *et al.*, 2004).

European mistletoe (*Viscum album*) berries, present in tonics for the cardiovascular and nervous systems, are also cardiotoxic and neurotoxic and can cause GI tract bleeding (Stein and Berg, 1999). Similarly, Hawthorn (*Crataegus monogyna*) berries or flowers used similarly, can potentiate digitalis activity, increase coronary dilatation effects of theophylline, caffeine, papaverine, sodium nitrate, adenosine, and epinephrine, and increase barbiturate-induced sleeping times (ESCOP, 1997, 1999; Mawrey, 1993; Tyler, l994; Upton, 1999). In addition, excessive use of herbal laxatives such as senna (leaves and pods of *Cassia senna* and other *Cassia* species) and cascara (*Rhamnus purshiana*) can deplete blood electrolytes, particularly potassium, further contributing to the toxicity of digoxin (Miller and Murray, 1998). Digoxin also shares structural similarities to compounds in *Periplocia sepium.* Significantly increased digoxin blood levels in a patient taking Siberian ginseng (*Eleutherococcus senticosus*) were likely due to adulteration with this plant (Awang, 1996). Cases have been described in which increased INR levels have been evoked in patients ingesting herbs such as Wintergreen

leaf (*Gaultheria procumbens*), sweet birch bark (*Betula lenta*), willow bark (*Salix alba*), and meadow sweet (*Filipendula ulmaria*); all contain salicylates whose significant antiplatelet activities can surpass those of aspirin and indomethacin (Samuels, 2005; Teng *et al.*, 1991). In addition, coumarin derivatives found in sweet melilot (*Melilotus officinalis*), tonka beans (*Dipteryx odorata*), and sweet woodruff (*Galium odoratum*) can potentiate the anticoagulating effects of warfarin (Williamson, 2003). Chaparral (*Larrea tridentata*), as a folk tea, can cause hypotension in patients with cancer under treatment (Anonymous, 1992).

Common foods may also potentiate antiplatelet effects. For example, the allicin in garlic (*Allium sativum*) can enhance fibrinolytic activity and inhibit platelet aggregation, as does capsicin in red pepper. Eugenol and acetyl eugenol found in cloves (*Syzygium aromaticum*) (Srivastava 1993), other spices, and artichokes (*Cynara scolymus*) (Lewis and Elvin-Lewis, 2003) can inhibit platelet thromboxane formation and increase formation of 12-HPETE (Wang *et al.*, 1984), in addition to enhancing fibrinolytic activity (Wasantapruek *et al.*, 1974). Because of the bromelian content of either papaya (*Carica papaya)* or pineapple (*Ananus comosus*), there is an increased tendency for bleeding in patients eating excessive amounts of these fruits. Patients should also guard against using garlic as a dietary supplement to lower cholesterol when taking ACE inhibitors to treat hypertension such as lisinopril, because their interactions can cause symptoms of hypotension and fainting (McCoubrie, 1996).

D. GASTROINTESTINAL SYSTEM

Flavonoids in herbal preparations may also affect the GI tract (e.g., cirkan causes chronic diarrhea [Maechel, 1992]); and a phlebotonic French drug, cyclo-3 fort containing *Ruscus aculeatus*, herperidin methyl chalcone, ascorbic acid can elicit colitis (Beaugerie *et al.*, 1994). Reports of nausea and vomiting induced by other herbal remedies are represented throughout the chapter.

XVII. DIABETES

Numerous herbal remedies exist for the treatment of diabetes, and many, which are used ethnopharmacologically to treat symptoms of diabetes mellitus (I and II), have been studied experimentally. Of those traditional remedies examined for hypoglycemic activity, more than 80% were found to possess this potential (Lewis and Elvin-Lewis, 2003; Yeh *et al.*, 2003). Among these is the fruit of karela (*Momordica charantia*), which grows in tropical regions of Asia, the West Indies, and Africa and is used as a food or

bush tea. In one report, a poorly controlled patient taking chlorpropamide experienced much better diabetic control after ingesting karela along with this medication (Aslam and Stockley, 1979). Although this was a positive outcome, this may not always be the case, and care should be taken in using any of these natural therapies or hypoglycemic foods, especially as an adjunct to conventional medicines for diabetic control. There is always the risk that their ability to potentiate hypoglycemic effects could be additive and act adversely. For example, popular hypoglycemic plants with the potential of eliciting additive effects include *Aloe vera* gel and juice (known to India and Central America) (Vogler and Ernst, 1999), gumar leaves (*Gymnema sylvestre*) (used in Asia) (Grover *et al.*, 2002), and the prickly pear, *Opuntia streptocantha* (used by Hispanic populations in the United States and Central America) (Coronodo *et al.*, 2004). A clinical trial among patients with type II diabetes indicates that Pycnogenol, a proprietary mixture of water-soluble bioflavonoids extracted from the French maritime pine (*Pinus maritima*) used as a supplement to standard antidiabetic treatment, can significantly lower plasma glucose levels for about 1 month and improve endothelial function, which retards diabetic retinopathy and improves visual acuity (Liu *et al.*, 2004; Schonlau and Rohdewald, 2001). However, a number of patients also experienced transient unwanted effects such as vertigo, GI upset, headache, nausea, and sleeplessness (Liu *et al.*, 2004). In view of these observations and its commercial promotion for a wide range of conditions, there is a need to appropriately assess its worth and safety. This is essential in relevance to its potential clinical value in the management of asthma (Hosseini *et al.*, 2001), childhood asthma (Lau *et al.*, 2004), mild hypertension (Liu *et al.*, 2004), and its use to prevent traveler's thrombosis (Belcaro *et al.*, 2004) alone or in combination with standardized ginger (*Zingiber officinalis*) root as the polyherbal, Zinopin for this condition, and in the treatment of motion sickness (Scurr and Gulatin, 2004). The potential also exists for interactions between insulin, oral hypoglycemics, and stimulant herbs such as Ma Huang (*Ephedra sinica*) and caffeine-containing beverages, although no cases have been reported (Miller and Murray, 1998). Flaxseed oil (*Liman usitatissimum*) can affect the absorption of glucose or drugs taken simultaneously (Blumenthal, 1998).

XVIII. USE OF PSYCHOACTIVES

Use of psychoactive plants and fungi for recreational, religious, or shamanistic purposes can affect individuals differently and often depends on a number of mitigating circumstances associated with individual responses to their use or abuse. It is not unusual for the consumer to experience various

unpleasant symptoms, especially nausea and vomiting, before experiencing enhanced auditory and visual effects. Users of the peyote cactus (*Lophophora williamsii*) during religious rituals commonly experience symptoms of nausea, chills, and vomiting, accompanied by dislocation of visual perspective and anxiety. Similarly, headache, dizziness, and nausea often accompany the excessive use of nutmeg or mace (*Myristica fragrans*) for recreational hallucinogenic purposes. In the Amazon, the shamanistic or recreational utilization of ayahuasca can cause nausea and vomiting, and these symptoms and limb numbness, facial twitching, and loss of muscular coordination can accompany employment of the South American snuff containing *Virola.* As sequelae to use, the least debatable and most troublesome adverse effect of smoking marijuana is impairment of short-term memory. Among chronic habituates, respiratory conditions such as chronic cough, bronchitis, bronchial irritation, shortness of breath, and chest tightness can also develop (Lewis and Elvin-Lewis, 2003). The consequences of long-term use of psychoactive plants on the CNS are understudied.

XIX. EFFECTS OF SLIMMING AGENTS

A number of studies have shown that use of natural slimming agents can be problematic (Lewis and Elvin-Lewis, 2003) and the overall risk/benefit ratios are not encouraging (Pittler and Ernst, 2004). Except for limited data on glucomannan and hydroxy-methylbutyrate, there is little evidence to support claims that any of these other products (e.g., chitosan, chromium picolinate, *Ephedra sinica, Garcinia cambogia,* Guar gum [*Cyamopsis tetragonoloba*], psyllium seed [*Plantago* species], pyruvate, and yohimbe [*Corynanthe yohimbe*]) are able to promote significant weight loss (Pittler and Ernst, 2004). Within this group, Glucomannan or Konjac flour, derived from tubers of *Amorhophallus konjac*, plantago psyllium, the water-soluble fiber from the husks of ripe seed of *Plantago ovata,* and Guar Gum, a dietary fiber from the Indian cluster bean (*Cyamopsis tetragonologus*), are bulking agents. These substances delay intestinal absorption of carbohydrates, so feelings of satiety are prolonged and glucose hemostasis is maintained for longer periods. These positive effects are often overridden by problems associated with absorption of a wide range of medications and fat-soluble vitamins. The bulking effect can cause bloating and flatulence, so taking them before retiring is not advised. Their use is also contraindicated in patients with intestinal, esophageal, or bowel obstructions (Lewis and Elvin-Lewis, 2003), which in the case of Guar gum resulted in a fatality (Opper *et al.*, 1990; Seidner *et al.*, 1990). In addition, allergic reactions have been associated with the use of glucomannan and psyllium (Lewis and Elvin-Lewis, 2003).

Stimulatory and anorexic effects are properties of caffeine and ephedrine, and these compounds or plants that contain them are often combined to promote optimal results in weight-loss formulations. Consumers respond differently to their excitatory effects, and serious reactions affecting the heart and CNS have resulted in the banning of *Ephedra sinica* and its alkaloids in these products in the United States and Canada. Caffeine is not regulated and can be found in several stimulating beverages such as coffee (*Coffea arabica*), black and green tea (*Camellia sinensis*), Yerba mate (*Ilex paraguariensis*), and guarana (*Paullinia cupana*).

Hydroxy citric acid extracted from *Garcinia cabogia* inhibits citrate cleavage enzyme and suppresses *de novo* fatty acid synthesis and food intake; however, clinical trials have been disappointing, and its use may elicit headaches, stomach pains, and upper respiratory and GI symptoms. Similar ineffective clinical effects have been seen with chitosan, a cationic polysaccharide derived from the exoskeleton of crustaceans. Promoted as a remedy to reduce fat absorption, it can evoke various GI symptoms, from constipation, diarrhea, flatulence, bloating, nausea, and heartburn. Comparable negative effects have been observed by using chromium picolinate, and reported effects in increasing lean body mass and increasing the basal metabolic rate have not translated into clinically meaningful data. On the other hand, hydroxy methylbutyrate use appears to be a promising way to modulate body mass toward a leaner appearance without causing any side effects (Lewis and Elvin-Lewis, 2003; Pittler and Ernst, 2004). *Aristolochia* in Chinese herbal formulations used for weight loss have been found to cause a rapidly progressive interstitial renal fibrotic syndrome and renal failure (Verherweghem *et al.*, 1993). Likewise in Japan, the development of Fanconi syndrome was related to the use of the slimming remedy Kanmokutsu containing *Aristolochia manshuriensis* (Tanaka *et al.*, 2000). The presence of sparteine in a number of herbal remedies used for slimming and diabetes has been reported to cause circulatory collapse and respiratory arrest (Galloway *et al.*, 1992) and classic anticholinergic effects (Tsiodras *et al.*, 1999). Following the use for several weeks of a slimming remedy consisting of the juices of *Sauropus androgynus* with pineapple or guava, an outbreak of rapidly progressive respiratory distress syndrome called *bronchiolitis obliterans* occurred in Taiwan (Lai *et al.*, 1996). Kelp (*Laminaria, Macrocystis, Nereocystis* species) contains high amounts of iodine, which alone or adjunct to supplemental thyroid therapy can enhance thyroid activity. Several cases of transient iodine-induced hyperthyroidism have been reported for healthy individuals taking kelp supplements for slimming; the symptoms disappeared when the supplements were no longer taken (De Smet, 1990; Eliason, 1998; Shilo and Hirsch, 1986). Adverse reactions to the use of kelp-containing skin patches have yet to be reported but would likely have the same potential.

XX. EFFECTS OF IMMUNE STIMULANTS

After the advent of the AIDS pandemic, the prophylactic use of herbal supplements with immunostimulating properties have become widespread with the notion that these confer enhanced protective effects for a normal healthy individual. Although this concept has limited value, many still subscribe to the practice. *Echinacea* (*E. purpurea* or *E. angustifolia*) is possibly the most popular drug in Western herbal practices today and is widely promoted for its value in preventing or obtunding symptoms of the common cold and lower urinary tract infections (Blumenthal, 2000). Its effect for these purposes has yet to be conclusively proven, perhaps because appropriately supervised clinical trials are only now beginning to be conducted (Sperber *et al.*, 2004), the etiology of the common cold is so complex, and optimal doses have yet to be ascertained. Numerous *in vitro* and *in vivo* studies have proven its immunostimulating, bactericidal, virostatic, and wound healing properties and have further demonstrated that its alkamides, glycoproteins, caffeic acid derivatives (cichoric and echnosides), and polysaccharides are related to these phenomena (Lewis and Elvin-Lewis, 2003). Animal studies have shown it can increase the number of circulating leukocytes, promote phagocytosis, and stimulate the production of cytokines. By inhibiting tissue and bacterial hyaluronidases, it improves wound healing (Kemp and Franco, 2002). However, individuals taking immunostimulating herbs who are genetically predisposed to autoimmune disease are at risk of precipitating or exacerbating their symptoms. Several immunostimulating herbs have been implicated in these adverse events. For example, reports of flares of pemphigus vulgaris have been linked to use of *Echinacea* and the alga *Spirulina platensis,* and the development of dermatomyositis following use of a polyherbal containing the algae *S. platensis* and *Aphanizomenon flos-aquae* has occurred. Tumor necrosis factor-α (TNF-α) may play a role in some cases (Lee and Werth, 2004). Recurrent erythema nodosum has also been linked to *Echinacea* use (Soon and Crawford, 2001). Furthermore, atopic individuals using *Echinacea* can develop sensitivity to its allergens or respond by cross-sensitivity to other Asteraceous plants with the consequence of developing allergic episodes of rhinitis, dermatitis, and anaphylaxis (Beilory, 2002; Mullins and Heddle, 2002). *Echinacea* is likely to cause leukopenia if used for long periods, and recommendations to use formulations of Echinacea/goldenseal formulations as a prophylactic measure to ward off colds are, therefore, inappropriate (Kemp and Franco, 2002). Echinacea has also been implicated in a case of hepatotoxicity when used in combination with amiodarone, ketoconazole, and methotrexate (Miller, 1998).

XXI. PERIOPERATIVE USE OF HERBS AND SURGERY

The medical community is becoming increasingly aware and apprehensive of how herbal use may affect the patient's response to surgery or the outcome of healing. Currently, the American Society of Anesthesiologists (ASA) recommends that all herbal medications should be discontinued 2–3 weeks before an elective surgical procedure. Their primary concerns are related to increased risks of bleeding of such popular herbs as *Ginkgo biloba,* ginseng (*Panax ginseng*), and supplement (not culinary) uses of ginger (*Zingiber officinalis*) and garlic (*Allium sativum*), and their additive effects with other anticoagulants. Salicylate-containing plants might also be considered in this category particularly if they are used internally (e.g., black cohosh [*Cimicifuga racemosa*]). Ginseng also has the ability to evoke hyperglycemia. Numerous interactions are associated with SJW, which by its induction of CYP 3A4 increases the requirements for lidocaine, calcium channel blockers, midazolam (versed), and cyclosporin, as well as the interactions with anesthetics and sedative-hypnotic drugs of kava (*Piper methysticum*) and valerian (*V. officinalis*), which can prolong sedation when used with anesthetics or benzodiazepines and barbiturates. Also, with anesthesia, both *Echinacea* and kava may cause liver toxicity in those with concomitant liver disease. *Echinacea,* as an immune stimulant, may result in rejection of an organ transplant or if used on a prolonged basis may result in immunosuppression and otherwise affect the healing process. Though banned in the United States, *Ephedra*-containing products are still available over the Internet and through Chinese herbal practitioners, and any patient taking these is at risk of increasing blood pressure or developing life-threatening cardiac arrhythmias or CNS disturbances. Should either valerian or *Ephedra* be discontinued abruptly, perioperative hemodynamic instability or delirium can develop in a few hours. Ephedra use may evoke life-threatening hyperpyrexia if used with monoamine oxidase inhibitors (MAOIs) and significant arrhythmias with halothane. In addition, hypersensitivity myocarditis, leading to cardiomyopathy, has been observed. Plastic surgeons are particularly concerned about those herbs that can elicit photosensitivity or photoallergic reactions, noteworthy among these are kava and SJW. Although the potential exists for a number of foods such as mustard (*Brassica*), figs (*Ficus carica*), *Citrus* species, and numerous taxa within the Apiaceae including celery (*Apium graveolens*), carrot (*Daucus carota*), dill (*Anethum graveolens*), fennel (*Foeniclum vulgare*), parsnip (*Pastinaca sativa*), and so on, to elicit these reactions, they are likely of little clinical relevance (Ciocon *et al.*, 2004). For a complete list in this category, refer to Lewis and Elvin-Lewis (2003).

XXII. DRUG AND HERBAL INTERACTIONS

There is a wide range of potentially adverse interactions that can occur when conventional drugs are used concomitantly with certain foods and/or herbal medications (Blumenthal, 1998). Once rare, reports of problematical conditions are becoming commonplace (Williamson, 2003). For example, these associations can serve to potentiate or antagonize drug absorption or metabolism, affect the patient's metabolism, or cause unwanted side reactions such as hypersensitivity (Blumenthal, 2000; Brinker, 2001; Cupp, 1999; Izzo and Ernst, 2001). According to Brazier and Levine (2003), most interactions are pharmacokinetic and associated with metabolic affects on CYP enzymes. The most common examples are interactions with grapefruit, warfarin (and other cardiovascular drugs), and SJW (*H. perforatum*). In addition, a wide range of herb–drug interactions are associated with treatment of CNS conditions.

A. GRAPEFRUIT

Although grapefruit (*Citrus paradisi*) would not be generally categorized as an herbal remedy, uses of *Citrus* in folk medicine are widely known (Lewis and Elvin-Lewis, 2003). It is considered a functional food in that it is regularly eaten or its juice drunk because of its potassium, β-carotene, and high vitamin C content. It is also favored in many weight-loss diets. Although it is believed that grapefruit aides in weight loss by impacting on insulin levels and speeding up metabolism, a 2003 study indicates that its naringenin, by impairing glucose uptake in adipose tissue, may exacerbate insulin resistance in susceptible individuals (Harmen and Patel, 2003). The accidental discovery of its ability to interact with a wide range of drugs occurred when grapefruit juice was used to mask the flavor of alcohol in a clinical evaluation of an analogue of the calcium blocker nifedipine, namely felodipine (Bailey *et al.*, 1989). When plasma concentrations proved higher than expected, it was discovered that plasma felodipine concentrations were more than fivefold greater with grapefruit juice than with the alcohol mixture or water (Bailey *et al.*, 1989). This finding serves as an example of how foods that are purposely taken for their healthy benefits may also present serious hazards to health. The elderly are particularly at risk since they frequently consume grapefruit juice, and in spite of packaging inserts that caution of its use with certain drugs, they still may be unaware of the seriousness of the adverse reactions that can be evoked (Bailey and Dresser *et al.*, 2000; Bailey *et al.*, 1998; Dresser, 2004). Moreover, the clinical relevance of these drug interactions with grapefruit juice is not predictable,

TABLE VI
DRUG AND HERBAL INTERACTIONS: GRAPEFRUIT

Drug type	Adverse effects
Cardiovascular: dyslipidemia	Rhabdomyolysis
Cardiovascular: hypotension with dihydropyridines	Excessive vasodilation
Cardiovascular: antiarrhythmic agents	Enhances drug toxicity
Cardiovascular: congestive heart failure	Enhances drug toxicity
Cardiovascular: angina pectoris	Atrioventricular conduction disorders
Cardiovascular: antiplatelet	Attenuates activity
Allergies: fexofenadine	Lowers plasma levels
Ergotamine	Stroke, gangrene
Erectile dysfunction	Serious systemic vasodilation
Appetite suppression: sibutramine	Increases heart rate and blood pressure
Antidiabetic: repaglinide	Hypoglycemia

because oral clearance of drugs can vary, as does the activity of intestinal CYP 3A4 in individual patients. Toxicity is more likely to occur if a patient is given higher than usual doses of a potentially interactive drug and then begins drinking grapefruit juice for the first time (Huang *et al.*, 2004). Table VI summarizes the following data in tabular form.

For example, ingestion of grapefruit juice (e.g., 200–300 ml) or grapefruit segments can cause an irreversible inactivation of CYP 3A4 so that presystemic metabolism is reduced, and after 24 hours, oral drug bioavailability of medications is increased by reduction in intestinal or hepatic efflux transport. At least 20 drugs fit this category (Bailey *et al.*, 1998). Of importance are its effects on a number of cardiovascular drugs (Bailey and Dressler, 2004). Interactions with these drugs may increase the risk of rhabdomyolysis when dyslipidemia is treated with the HMG-CoA reductase inhibitors atorvastatin, lovastatin, or simvastatin or cause excessive vasodilation when hypertension is managed with the dihydropyridines such as felodipine, nicardipine, nifedipine, nisoldipine, or nitrendipin. Studies with elderly patients taking the calcium channel blocker felodipine indicate that a normal dietary amount of grapefruit juice can reduce its presystemic metabolism and elicit a pronounced, unpredictable, and sustained pharmacokinetic interaction. Also, a marked interaction similar to that for grapefruit juice can be found in individuals drinking red wine that have a preexisting high intestinal CYP 3A4 content. Felodipine concentration–blood pressure response relationships affected different blood pressure values seen in these studies (Offman *et al.*, 2001).

Enhancement of drug toxicity for antiarrhythmic agents such as amiodarone, quinidine, disopyramide, or propafenone, and for the congestive heart failure drug, carvediol has been demonstrated. Grapefruit juice may also elicit atrioventricular conduction disorders, if taken with verapamil used to treat angina pectoris as well as attenuate the antiplatelet activity of clopidogrel. Other drugs used in the treatment of peripheral and central vascular disease also have the potential to interact with grapefruit juice. Also, grapefruit juice may markedly lower the plasma concentration of fexofenadine, which is used to treat allergies. In contrast, the therapeutic effect of the angiotensin II type 1 receptor, losartan may be lowered. Interaction between ergotamine for migraine may cause gangrene or stroke. Intervention with nimodipine with stroke may cause systemic hypotension.

By reducing the activity of the P-glycoprotein transporter, GFJ is apparently involved in altering the systemic bioavailability of the immunosuppressive agent cyclosporine and the protease inhibitor, saquinavir. *In vitro* studies indicate that this phenomenon may be due to inhibition of organic anion transporting polypeptides (OATP), which decreases intestinal transport uptake as oral bioavailability is reduced. *In vitro* studies indicate that naringin at 3000 μmol/L and 6′,7′-dihydroxybergamottin at 33 μmol/L can reduce P-glycoprotein activity in half; naragin content in grapefruit segments is sufficiently high to evoke some P-glycoprotein inhibition activity in humans. OATP activity may also be reduced by both orange juice and apple juice, but apple juice differs in the spectrum of uptake transporters, which are affected (Dresser *et al.*, 2002).

The use of grapefruit juice with the appetite suppressant, sibutramine can increase heart rate and blood pressure, and with the antidiabetic agent, repaglinide, hypoglycemia has been observed. Serious systemic vasodilation can occur with the use of sildenafil, tadalafil, or vardenafil for erectile dysfunction, especially if it is combined with nitrate use. Interaction between ergotamine for migraine and grapefruit juice may cause gangrene or stroke. In stroke, interaction with nimodipine may cause systemic hypotension. Although it is recognized that drug responses are variable, and interactive events, leading to serious overdose toxicity, are difficult to prevent, the mandatory avoidance of grapefruit juice during pharmacotherapy is recommended. This is particularly true if the drug to be used is low in inherent oral bioavailability from presystemic metabolism by CYP 3A4 or efflux transport by P-glycoprotein. Clinically relevant interactions seem likely for most dihydropyridines, terfenadine, saquinavir, cyclosporin, midazolam, triazolam, and verapamil and may occur with lovastatin, cisapride, and astemizole (Bailey *et al.*, 1998). The elderly should be carefully advised regarding this risk, because they are likely to consume grapefruit juice unless cautioned to do otherwise (Bailey and Dressler, 2004; Dressler *et al.*, 2000).

B. WARFARIN AND OTHER DRUGS USED TO TREAT CARDIOVASCULAR CONDITIONS

Use of certain herbs with warfarin can affect its therapeutic value and cause life-threatening events (Table VII). For example, the Chinese herb Danshen (*Salvia miltiorrhiza*) may alter the pharmacokinetics of warfarin by increasing its plasma concentrations through enhancing absorption rates and decreasing its clearance (Samuels, 2005), whereas feverfew (*Tanacetum parthenium*) can retard it absorption by significantly suppressing prostaglandin production without inhibiting cyclooxygenase (COX) activity (Heptinstall *et al.*, 1987; Makheja and Bailey, 1981, 1982). Also, the flavones baicalin and oroxylin in skullcap (*Scutellaria baicalensis*) can hinder coagulation (Samuels, 2004), and tannins in Daikon-So (*Geum japonicum*) can inhibit key serine proteinases of thrombin and factor Xa and fibrinogen hydrolysis (Dong *et al.*, 1998). Lessening effects with warfarin have been associated with concomitant use of Passionflower (*Passiflora* species), Juniper (*Juniperus* species), and Vervain (*Verbena officinalis*) and increased with the use of the Reishi mushroom, (*Ganoderma japonicum*), papaw (*Asimina triloba*), ginseng (*Panax* spp), Devil's claw (*Harpagophytum procumbens*), *Ginkgo biloba,* ginger (*Zingiber officinalis*), Red Clover (*Trifolium pratense*),

TABLE VII
HERBAL INTERACTIONS WITH WARFARIN

Common name	Adverse effects
Daikon-So	Inhibits both serine proteinases of thrombin, factor Xa of fibrin hydrolysis
Danshen	Increases plasma concentrations
Devil's claw	Increases effects
Feverfew	Retards absorption
Ginger	Increases effects
Ginkgo	Increases effects, spontaneous bleeding, subarachnoid hemorrhage
Ginseng	Increases effects
Horse-Chestnut	Increases effects
Juniper	Lessens effects
Papaw	Increases effects
Passionflower	Lessens effects
Red Clover	Increases effects
Reishi mushroom	Increases effects
Skullcap	Hinders coagulation
Vervain	Lessens effects

and Horse-Chestnut (*Aesculus hippocastanum*) (Argento *et al.*, 2000; Miller *et al.*, 2004). For example, it has been hypothesized that the pharmacodynamic effects of *Ginkgo biloba,* used to treat generative and vascular conditions associated with memory loss, is related to a combination of platelet-activating factor antagonistic effects, free radical scavenging activity, and modulation of cholinergic function (Nathan, 2000). Its ginkgolides, which are unique terpene lactones, possess specific platelet-activating factor antagonist activities (Williamson, 2003). Unfortunately, in certain patients, use of this herbal remedy can elicit episodes of spontaneous bleeding (Skogh, 1998) such as subarachnoid hemorrhage (Vale, 1998) and, when warfarin, aspirin (acetylsalicylic acid), or ibuprofen are taken concomitantly, may elicit events such as intracerebral hemorrhage (Matthews, 1998; Mehta, 2003), bleeding of the iris into the anterior chamber of the eye (Rosenblatt and Mindel, 1997) due to increases in ocular blood flow velocity (Chung *et al.*, 1999) or fatal intracerebral mass bleeding (Meisel *et al.*, 2003) have been reported. Concomitant use of ginkgo with calcium channel antagonists such as nicardipine, nifedipine, and diltiazem may be unwise (Williamson, 2003) because studies in rats suggest that Ginkgo extract can attenuate the hypotensive response of nicardipine through induction of CYP 3A2 and other liver metabolizing enzymes (Shinozuka *et al.*, 2003). Table VII summarizes these data in tabular form.

The Chinese formula Kangen Karyu contains peony root (*Paeonia veitchii, P. lactiflora, P. ovata*), safflower (*Carthamus tinctorius*), saussurea/costus root (*Saussurea lappa*), cnidium/Schezuan lovage root (*Ligusticum chuanxiong*), cyperus/nut-grass rhizome (*Cyperus rotundus*), and Danshen (*Salvia miltiorrhiza*) (Bensky and Gamble, 1993). This polyherbal is used to reduce blood viscosity and improve microcirculation and can significantly enhance bleeding time (Makino *et al.*, 2002), as well as suppress the metabolism and excretion of warfarin, without affecting its serum binding and absorption (Makino *et al.*, 2003). In isolated cases, elevated INR values have also been associated with a patient taking warfarin, digoxin, atenolol, and fluvastatin and a TCM remedy of Chinese wolfberry (*Lycium barbarum*) (Lam *et al.*, 2001), and another taking warfarin and boldo *(Perumus boldo)* together with fenugreek (*Trigonella goenum-graecum*) (Lambert and Cormier, 2001). Similar INR increases have been noted with two patients taking pumpkin seed (*Curcubita pepo*) and saw palmetto (*Serenoa repens*) for prostate enlargement; in these cases, only one of these individuals was also taking warfarin (Yue and Jansson, 2001). Apparently there is little clinical significance to the observation that a few individuals on either warfarin or procoumon can experience enhanced INR levels when drinking large quantities of tonic water containing quinine (Stockley, 2002). Eating large amounts of mango fruit while on warfarin can also increase INR levels

(Monterrey-Rodrigues *et al.*, 2002). Because bromelian in papaya and pineapple modulates the arachidonate cascade, INR rates are also increased with concomitant use of warfarin (Shaw *et al.*, 1997). In contrast, the vitamin K in a variety of green vegetables, particularly broccoli, in large amounts can act as an antagonist to the effects of anti-coagulant therapy (D'Arcy, 1993); in warfarin overdose, vitamin K is used to normalize the INR.

A ginseng component 2A-1-1 has also been found to inhibit platelet aggregation by blocking the receptor-dependent Ca^{2+} channels (ROC) and inhibiting Ca^{2+} influx of human platelets (Zeng *et al.*, 2004). Prolongation of thrombin, prothrombin, and thromboplastin times is also characteristic of several of the 26 herbs found in Bak Goong Pill, also known as *Bai Geng Wan* (Gou *et al.*, 2003). Gugulipid (*Commiphora mukul*) can diminish the effects of other cardiovascular drugs including diltiazem and propranolol (Dalvi *et al.*, 1994; Singh *et al.*, 1994), and *Plantago psyllium* and *P. ovata* bulking agents can enhance the cholesterol-lowering action of cholestyramine and possibly decrease the absorption of digoxin and warfarin. Glucomannan thickening flour made from *Amorphophallus konjac* may act similarly (Elvin-Lewis, 2001; Lewis and Elvin-Lewis, 2003; Williamson, 2003). Numerous adverse events have been associated with the use of aconite (*Aconitum*), *Ephedra,* and licorice (*Glycyrrhiza glabra*) (Ernst, 2003; Mashour *et al.*, 1998). Together with digitalis, additive effects with thiazide diuretics have been seen with aconite inducing K loss, by increasing absorption and retarding absorption. Fatal hypertension can occur when use of digitalis is combined with *Ephedra* and scotch broom (*Cystisus scoparius*). In addition, a tyramine-induced hypertensive crisis has occurred when rhubarb root (*Rheum officinale*) is combined with digitalis use.

C. ST. JOHN'S WORT

It is believed that SJW, used to treat mild to moderate depression, has the potential to reduce the systemic bioavailability of many conventional drugs and to diminish blood levels of cyclosporine, amitriptyline, digoxin, indinavir, warfarin, human immunodeficiency virus (HIV) protease inhibitors, phenprocoumon, and theophylline. This is based on the concept that enhancement of blood clearance of warfarin, digoxin, theophylline, or ethinylestradiol/desogestrel is mitigated by the presence of SJW. An additive effect has been proposed, because all, including SJW, can cause the induction of the CYP isoenzymes CYP 3A4, CYP 2C9, and CYP 1A2, as well as the transport protein P-glycoprotein, needed to metabolize and remove these drugs from circulation (Henderson *et al.*, 2002; Miller *et al.*, 2004).

In addition, possible pharmacodynamic interactions with selective serotonin reuptake inhibitors and serotonin (5-HT_{1d}) receptor agonists such as triptans used to treat migraine have been identified (Henderson *et al.*, 2002). Taken together with loperamide or selective serotonin reuptake inhibitors (sertraline, paroxetine, nefazodone), delirium or mild serotonin syndromes have occurred (Izzo and Ernst, 2001). One reported incident of a patient taking testosterone after an orchidectomy, in addition to sertraline and SJW, describes a major manic episode accompanied by grandiose delusions resulting in hospitalization (Barbenel *et al.*, 2000). Another case of acute mania and psychosis was related to use by a 23-year-old woman of a polyherbal remedy called "Valdispert balans," which contained high doses of SJW and valerian (*V. officinalis*). As antidepressants, both are used to treat anxiety, but usually not together. She was diagnosed as having substance-induced mood disorder, with manic features (American Psychiatric Association, 2000) and completely recovered after discontinuing the herbal remedy and taking a short course of olanzapine. The authors further caution about the hazards of taking these herbal remedies by patients with bipolar disorders, in the event that its use could trigger a manic attack (Guzelcan *et al.*, 2001). Although numerous case reports accumulate, many clinical trials cited in support of these interactions have been based on evidence collected from inappropriately designed studies, which are lacking in scope and methodological quality, especially regarding the inclusion of controls and randomization (Mills *et al.*, 2005). Moreover, it is now recognized that many non-responders exist, which only tends to confound the issues of treatment efficacy or adversity (Gelenberg *et al.*, 2004).

When SJW is used with the oral contraceptive ethinylestradiol/desogestrel, intermenstrual bleeding has been observed (Izzo and Ernst, 2001). A British survey among female college students taking contraceptive pills indicates that although most (64%) are aware that concurrent use of antibiotics can decrease contraceptive effectiveness, only 14% are aware that SJW can act in a similar manner. This information is disconcerting, because SJW use as a mild antidepressant in these populations can increase the risk of unwanted pregnancies (Hindmarsh and Oakeshott, 2002). Currently, the concomitant use of SJW and warfarin is not recommended by the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRS), and it further advises that those doing so should stop and adjust their dose of warfarin accordingly (Williamson, 2003). A paper by Huang *et al.* (2004) illustrates a number of studies on drug pharmacokinetics and responses to SJW. Table VIII summarizes these data.

TABLE VIII
DRUG AND HERBAL REACTIONS: ST JOHN'S WORT

Drug	Adverse effects
Amitriptyline	Reduces systemic bioavailability
Cyclosporin	Reduces systemic bioavailability
Digoxin	Reduces systemic bioavailability, mitigates clearance
Ethinylestradiol/ desogestrel	Mitigates clearance, intramenstrual bleeding, decrease contraceptive effectiveness
HIV protease inhibitors	Reduces systemic bioavailability
Indinavir	Reduces systemic bioavailability
Loperamide	Delirium, mild serotonin syndromes
Phenprocoumon	Reduces systemic bioavailability
Serotonin reuptake inhibitors: sertraline, paroxetine, nefazodone	Delirium, mild serotonin syndromes
Theophylline	Reduces systemic bioavailability, mitigates clearance
Warfarin	Reduces systemic bioavailability, mitigates clearance

D. HERB–DRUG INTERACTIONS AFFECTING THE CENTRAL NERVOUS SYSTEM

When a patient is undergoing conventional treatment for disorders of the CNS, use of certain herbs, including the smoking of tobacco or cannabis, is not advisable. Heavy tobacco smoking is a common practice among psychotic patients, and this habit can seriously affect the metabolic clearance and pharmacokinetic and pharmacodynamic properties of the psychotropic drugs they are taking. A similar action may also exist for cannabis smoking. This is because the polycyclic aromatic hydrocarbons in tobacco smoke can induce hepatic aryl hydrocarbon hydroxylases that facilitate blood clearance of drugs such as imipramine, clomipramine, fovoxamine, traxodone, tiotixene, fluphenazine, haloperidol, olanzapine, chlorpromazine, and clozapine. Similarly, increased clearance of the benzodiazepines alprazolam, lorazepam, oxazepam, diazepam, and demethyl-diazepam can occur. Plasma concentrations of amitriptyline and nortriptyline may be variably affected by tobacco smoking, whereas carbamazepine is minimally affected, probably because the hepatic enzymes are already stimulated by its own autoinductive properties (Desai *et al.*, 2001). Cannibis smoking may also increase chlorpromazine clearance (Chetty *et al.*, 1994). Cigarette smoking does not appear to affect the use of amfebutamone (bupropion). Smokers receiving

chlorpromazine and benzodiazepines may also experience reduced drowsiness (Desai *et al.*, 2001). Cannibis-induced manias have also been reported for patients concurrently using either fluoxetine (Stoll *et al.*, 1991) or disulfiram (Lacoursiere and Swatek, 1983).

Seizures have occurred in schizophrenic patients taking evening primrose oil alone or with fluphenazine. Its experimental use within schizophrenic patient populations has exacerbated negative symptoms of the disease and can produce electroencephalographic evidence of temporal lobe epilepsy (Vaddadi, 1981). The oil is derived from the seeds of *Oenothera biennis* L. and as ω-6 polyunsaturated fatty acids consists of is linoleic acid (LA) and γ-linolenic acid (GLA). Reduction of plasma levels of phenytoin and loss of seizure control has been associated with concurrent use of the Ayurvedic drug Shankhapushpi (Dandekar *et al.*, 1992). This polyherbal contains *Centella asiatica, Convolvulus pluricaulis, Nardostacys jaatamansi, Nepteta elliptica, N. hindostana,* and *Ansosma bracteatum.* Similar effects have been seen with the traditional Chinese herbal ingredient Paeoniae Radix (*Paeonia veitchii, Paeonia lactiflora, Paeonia ovata*) (Chen *et al.*, 2001). Ginseng may act as an antidepressant antagonist with phenelzine, triazolam, and lorazepam by causing manic episodes associated with headaches, tremulousness, insomnia, irritability, and visual hallucinations (Gonzalez-Seijo *et al.*, 1995). Caffeine in tea, coffee, and other beverages may also increase clozapine serum levels because they are both metabolized mainly by CYP 1A2 and caffeine inhibits clozapine metabolism. In clinical evaluations, possibly because of genetic differences among the participants, ingestion of instant coffee was found to elicit variable responses on the plasma levels of clozapine (Raaska *et al.*, 2004). This may also be due to the ability of other components in the coffee to precipitate out the neuroleptic chlorpromazine and, thus, affect its bioavailability; similar effects are also known for tea (Cheeseman and Neal, 1981). In an earlier clinical trial, tea or coffee drinking had no effect on either blood levels of antipsychotic drugs or their behavior (Bowen *et al.*, 1981). The use of oral contraceptives (e.g., haloperidol) with chasteberry fruit (*Vitex agnus-castus*) is contraindicated; this combination also has a reciprocal weakening effect on dopamine receptor antagonists (Blumenthal *et al.*, 1998).

The combination of herbal sedatives such as valerian (*V. officinalis*), passion flower (*Passiflora* species), and anticholinergic Solanaceae (*Atropa belladonna, Datura stromonium, Hyocyamus niger,* and *Mandragora officinarum)* with alcohol or antihistamines can potentiate the effects of antidepressants, antihistaminics, and antispasmodics, causing drowsiness and obtunding the ability to use machinery (D'Arcy, 1993; De Smet *et al.*, 1996).

Psychoactive activity is potentiated when tetracycline, propanolol, or alcohol is used with either cinnamon (*Cinnamomum zeylanicum*) (in excess

of culinary amounts) or "magic mushrooms" (*Psilocybe semilanceata*) (D'Arcy, 1993; Ernst, 1998).

Blood levels of lithium, used to treat bipolar disorder, must be checked regularly to avoid toxicity. However, in patients taking bulk fiber preparations of ispaghula or psyllium, which could affect its absorption, blood levels may be lower (Toutongi *et al.*, 1990). Alternately, lithium toxicity was elicited in a patient taking a polyherbal diuretic for purposes of slimming (Pyevich and Bogenschutz, 2001), an association that has been well known with other diuretic agents for some time (Jefferson, 1980). Because reserpine (an alkaloid from *Rauwolfia serpentina*) depletes neurotransmitter release, it can reduce the effects of levodopa (Stockley, 2002). Exacerbations of parkinsonian tremor can occur following the chewing of betel nut when patients are taking flupentixol or procyclidine (Deahl, 1989).

E. MISCELLANEOUS HERB–DRUG INTERACTIONS

Herbal effects on absorption can affect the bioavailability of antibiotics and has been demonstrated for Khat (*Catha endulis*) users (Attef *et al.*, 1997). Absorption and decreased metabolism of the asthma drug theophylline are also affected by piperine from black pepper (*Piper nigrum, Piper longum*).

XXIII. SUMMARY AND CONCLUSION

It has been generally considered that when compounded and prescribed appropriately, the safety of traditional herbal medications is high. Most are moderately bioreactive, and thus, within the context of empirical selective methods, their benefits are likely to far outweigh their risks. However, because these have become adapted to current widespread use, are subject to changes and adulterations by entrepreneurs or inexperienced practitioners, and are used without supervision, the possibility of unexpected reactions increases, particularly if they are taken with conventional medications. It is likely that most minor adverse reactions are simply underreported, particularly among those who tend to self-medicate. Although initiatives are underway for global oversight to ensure herbal products are appropriately formulated and administered, the realization of this goal may take many years to achieve. In the interim, there is little option but to rely on the integrity and skill of those that formulate, promote, or prescribe them with the anticipation that one's health is not compromised in the process.

Anyone selecting these methods, particularly in the context of neo-Western herbalism should realize that there is a wide variability in the herbal products that are available and using reliable sources is essential. Prospective

herbal users must be conscious that these formulations are composed of raw materials that can vary in quality or quantity, that they may contain any number of undocumented substances, and their pharmacokinetic and pharmacognostic capabilities can thus be unreliable. Their use can be of benefit, interact with other herbs or drugs, or be potentially harmful. Certain foods, or functional foods, may also potentiate or antagonize pharmaceutical treatments, and under certain conditions, clinical-use restrictions may apply. Also, new data are constantly being generated by research designed to delineate their clinical value and identify any potential dangers that might arise. It may mean that certain well-known products have expanded uses or may no longer be considered safe to use. If one lacks appropriate interpretive skills to understand this information, it is conventional wisdom to seek advice from those with this ability before embarking on a regimen of self-medication. Keeping one's allopathic physician informed of what one is doing is also recommended.

In light of current policies that are unevenly evoked to ensure safety and efficacy, reliance on promotional information, no matter how skillfully executed, this is folly unless authoritative scientific evaluations are well known to back up any claims of worth and parameters of use. There is little meaning in the belief that ''natural'' is safe, any more than one can expect the same for a pharmaceutically derived product. The following guidelines for rational herb use follow many recommendations already outlined by Murphy (1999) and Drew and Myers (1997) (Table IX).

It is also the responsibility of conventional practitioners to apprise themselves of herbal and other alternative practices that are popular within their community of patients. This will allow them to better formulate strategies regarding integrative use and to understand their patients and the implications that it has to their health. This recommendation is made because surveys have indicated that at least one-third of patients are likely to use unconventional therapy; the majority of these do so for chronic conditions but are unlikely to inform their allopathic physician (Barret *et al.*, 1999; Eisenberg *et al.*, 1998). Disconcerting also are the number of children with chronic conditions that are being provided with dietary supplements without their physician's knowledge (Ball *et al.*, 2005). Therefore, care must be taken in interviewing each patient to be open-minded and nonjudgmental during the initial process so that they are willing to reveal the totality of their self-medication or alternative medicinal practices. Formal discussions should help understand their preferences and expectations, and by encouraging patients to keep a symptom diary, potentially harmful situations will become evident on follow-up visits (Eisenberg, 1997). Armed with appropriate knowledge of any potential interactions or adverse effects that might occur, the physician may then be able to guide them as to whether it is

TABLE IX
GUIDELINES FOR RATIONAL HERB USE[a]

- Be informed, seek out unbiased, scientific sources
- For guidance, rely on professionally trained and registered practitioners of herbal medicine
- Be aware that your physician's or pharmacist's knowledge of herbal remedies may be limited
- Inform your physician of self-medication regimens
- Remember that drug interactions can be problematical
- Do not depend on product claims alone
- Read labels carefully, do not exceed recommended dose ranges
- Know benefits and risks of potential side effects
- Know potential drug interactions
- Never use if pregnant or nursing
- Avoid giving to children
- Avoid giving to the elderly
- Do not use for serious illnesses
- Do not use for prolonged periods
- Know your source, formulator, or manufacturer
- Select standardized formulations
- Understand that batch-to-batch variations of the formula may occur
- To avoid misidentification, do not collect plants yourself
- Make sure packaging is appropriately labeled with its contents
- Make sure the labeling includes scientific names
- Store appropriately to prevent loss of potency
- Report any adverse reactions you believe are linked to its use

[a]Amended from Table VIII in Elvin-Lewis, 2001.

TABLE X
EVALUATION OF ADVERSE EffECTS[a]

- Temporal association between exposure and effect
- Disappearance of effect after product discontinued
- Reappearance of effect when product reintroduced
- Association of product use and interactions with medicines
- Occupational chemicals and recreational drugs
- Association of underlying disease states considered
- Association of exposure and effects known in scientific literature

[a]Amended from Table VII in Elvin-Lewis, 2001.

advisable to continue with any particular practice. It is appreciated that practitioners may recognize acute symptoms of toxicity but are unlikely to link effects associated with hepatotoxicity, teratogenicity, or carcinogenicity to use. The guidelines in Table X are related to temporal associations to herbal use and may be valuable when adverse effects are suspected

(Elvin-Lewis, 2001). Many recommendations follow those cited by Murphy (1999) and Drew and Myers (1997).

APPENDIX

COMMON AND SCIENTIFIC NAMES OF MEDICINAL PLANTS

African cherry	*Prunus africana*
Aloe	*Aloe vera*
Angelica	*Angelica dahurica*
Arnica	*Arnica montana*
Balsam of Peru	*Myroxylon pereirae*
Bajialoam	*Dysoma pleianthum*
Belladona	*Atropa belladona*
Birch (sweet)	*Betula lenta*
Black cohosh	*Cimicifuga racemosa*
Blood root	*Sanguinaria Canadensis*
Blue cohosh	*Caulophyllum thalictroides*
Boldo	*Perumus boldo*
Cats claw	*Uncaria tomentosa/guianensis*
Caowu	*Aconitum kusnezoffii*
Cascara	*Rhamnus purshiana*
Celandine (greater)	*Chelidonium majus*
Celandine (lesser)	*Ranunculus ficaria*
Cinnamon	*Cinnamomum zeylanicum*
Chamomile	*Chamaemelum nobile*
Chanwu	*Aconitum carmichaeli*
Chaparral	*Larrea tridentata*
Chasteberry	*Vitex agnus-castus*
Chinese foxglove	*Rehmannia glutinosa*
Chinese wolfberry	*Lycium barbarum*
Cloves	*Syzygium aromaticum*
Coffee	*Coffea arabica*
Creosote bush	*Larrea tridentata*
Cyperus/nut grass	*Cyperus rotundus*
Daikon-So	*Geum japonicum*
Danshen	*Salvia miltiorrhiza*
Devil's claw	*Harpagophytum procumbens*
Echinacea	*Echinacia pallida*
European mistletoe	*Viscum album*
Evening primrose oil	*Oenothera biennis*
Fenugreek	*Trigonella goenum-gracecum*
Fever few	*Tanacetum parthenium*
Fig	*Ficus carica*
Flax	*Liman usitatissimum*
Fructus Aristolochiae	*Aristolochia debilis, A. fangchi*

(*continued*)

APPENDIX (*continued*)

Fo ti	*Polygonum multiflorum*
Gancao	*Glycyrrhiza uralensis*
Gas plant/Burning Bush	*Dictamnus albus subspecies dasycarpus*
Garlic	*Allium sativum*
Germander	*Teucrium chamedrys, T. polium*
Ginger	*Zingiber officinalis*
Ginkgo	*Ginkgo biloba*
Ginseng (Chinese)	*Panax ginseng*
Ginsengs (others cultivated)	*P. notoginseng, P. zingerberensis*
Ginseng (American)	*Panax quinquefolius*
Ginseng (Siberian)	*Eleuthrococcus senticosus*
Glucomannin/Konjac	*Amorhophallus konjac*
Goldenseal	*Hydrastis canadensis*
Golden thread (Huanglian)	*Coptis chinensis*
Grapefruit	*Citrus paradisi*
Guar	*Cyamopsis tetra-gonoloba*
Guarana	*Paullinia cupana*
Guggul tree	*Commiphora mukul*
Hawthorn	*Crategus monobyna*
Himalayan Mayapple	*Podophyllum emodi*
Hindu datura	*Datura metel*
Horse-Chestnut	*Aesculus hippocastanum*
Hyayruro, lucky bean	*Ormosia coccinea*
Impila	*Callilepsis laureola*
Juniper	*Juniperus* spp.
Kava	*Piper methysticum*
Karela	*Momordica charantia*
Khat	*Catha endulis*
Kelp	*Laminaria, Macrocystis, Nereocystis* spp.
Licorice	*Glycyrrhiza glabra*
Magic mushrooms	*Psilocybe semilanceata*
Ma Huang/Ephedra	*Ephedra sinica*
Mandrake	*Mandragora officinarum*
May apple	*Podophyllum peltatum*
Meadow-sweet	*Filipendula ulmaria*
Milk thistle	*Silymarum marianum*
North African thistle	*Atractylis gummifera*
Nutmeg/mace	*Myristica fragrans*
Papaya	*Carica papaya*
Passionflower	*Passiflora* spp.
Papaw	*Asimina triloba*
Peony (Paeoniae Rubrae Radix)	*Paeonia veitchii, obovata*
Pennyroyal	*Hedeoma pulegoides, Mentha pulegium*
Peyote cactus	*Lophophora williamsii*
Pineapple	*Ananus comosus*
Pumpkin	*Curcubita pepo*
Prickly pear	*Opuntia streptocantha*
Psyllium	*Plantago ovata*

APPENDIX (*continued*)

Radix petasidis	*Petasties officinalis*
Rauwolfia	*Rauwolfia serpentina*
Red Clover	*Trifolium pratense*
Reishi Mushroom	*Ganoderma japonicum*
Sangre de grado	*Croton lechleri*
Sassafras	*Sassafras albidum*
Saw palmetto	*Serenoa repens*
Senna (*Folia sennae*)	*Senna alexandrina*
Shandigyeb	*Sophora tonkinensis*
Skullcap	*Scutellaria lateriflora*
Spirulina	*Spirulina platensis*
St. John's wort	*Hypericum perforatum*
Sweet melilot	*Melilotus officinalis*
Sweet woodruff	*Galium odoratum*
Tansy	*Tanacetum vulgare*
Tea (green/black)	*Camellia sinensis*
Tea Tree	*Melaleuca alternifolia*
Tonka beans	*Dipteryx odorata*
Tussilaginis Farfare, Flos	*Tussilago farfara*
Valerian	*Valeriana officinalis*
Vervain	*Verbena officinalis*
Willow	*Salix alba*
Wintergreen	*Gaultheria procumbens*
Yerba mate	*Ilex paraguariensis*
Yohimbe	*Corynanthe yohimbe*

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