Herbal Medicine:
Beyond Testimonials

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The medicinal use and beneficial effects of herbs have been documented for nearly 5000 years. The *Pen Ts'ao*, written in China about 2800 B.C., listed 366 medicinal herbs.[1] Every great civilization has used herbs for this purpose. Similarly, herbal medicine has a rich heritage in European and North American history.

In 1775, William Withering, a young English physician with an interest in plants, was consulted to evaluate a remedy held secret by a woman many considered to be a witch. The remedy consisted of over 20 herbs, with properties that included the induction of violent vomiting, purging and diuresis. It had been used successfully to treat a number of patients with dropsy (congestive heart failure) when traditional treatments had failed. Dr. Withering identified the active ingredient as foxglove (*Digitalis* spp.), and he began experimenting with it. One hundred and sixty-three patients later, he had refined the treatment that included standard amounts of dried, powdered leaves.[2] Digitalis derivatives, which include digoxin and digitoxin, have remained a standard of care in the treatment of congestive heart failure for two centuries.

It is estimated that 25 percent of prescription medicines used today are derived from plants, and another 25 percent are preparations based on plant products.[3] Some notable examples include atropine, codeine, colchicine, L-dopa, ephedrine, etoposide, hyoscyamine, morphine, pseudoephedrine, quinidine, quinine, scopalamine, theophylline, vincrinstine and vinblastine. Furthermore, it is estimated that there are 500,000 plant species on the earth today. Only a small portion of these have been evaluated for medicinal purposes. However, the use of herbs in clinical practice has been largely abandoned in the United States, in favor of thoroughly tested single agents, frequently of synthetic derivation. This is not the case for the rest of the world. In European countries, where medicine is equally advanced, herbal medicines remain some of the most frequently prescribed remedies. On a global scale, the World Health Organization (WHO) estimated in 1985 that 80 percent of the world's population relies solely or very heavily on herbs for primary care needs.[4] In order to meet needs of developing countries where resources are limited, the WHO has developed the Programme on Traditional Medicines, a program which encourages the development of herbal medicines.

Complementary Alternative Medicine

Herbs are classically defined as "seed producing annual, biennial, or perennials that do not develop persistent woody tissue but die down at the end of a growing season."[5] More broadly defined, an herb is any "plant or plant part valued for its medicinal, savory or aromatic qualities."[5] Herbal medicines, properly known as phytomedicinals or phytopharmaceuticals, are "crude drugs of vegetable origin utilized for the treatment of disease states or to attain or maintain a condition of improved

health."[6] Pharmacognosy is the branch of pharmacology concerned with the physical characteristics of phytopharmaceuticals.

The NIH defines herbal medicine as the use of plant and plant products from folk medicine traditions for pharmaceutical use. The practice of herbal medicine is a spectrum of activity that ranges from the consumption of dietary supplements as a means of maintaining good health, to self-diagnosis and treatment of minor illnesses, to physician directed combinations of conventional and herbal medicines for the treatment significant medical problems, to exclusive naturopathy. Herbal medicine encompasses a spectrum of remedies, ranging from self-made teas prepared from self-collected herbs to officially approved medicinal products, which have been subjected to scientific scrutiny. In spite of its growing popularity and acceptance in other countries, it is one of many forms of healing often referred to as "alternative."

A discussion of "alternative" medicine evokes strong opinions and emotions from both those who favor it and those opposed to it. Biases are often conveyed by the words chosen to describe the various types of therapy, such as conventional-unconventional, orthodox-unorthodox, proven-unproven. Yet, the definition of alternative medicine is as vague as the definition of conventional medicine. Eisenberg defined conventional medicine as the system of medicine taught in U.S. medical schools or generally available in U.S. hospitals.[7] Unconventional medicine is everything else. Angell and Kassirer define it as any form of therapy that has been subjected to the scrutiny of the scientific method.[8] Neither definition is adequate. Nevertheless, the system of treatments resulting from the application of the scientific method and its acceptance by the medical community at large has become the standard against which all other forms of healing are measured. But as popular interest in "alternative" therapies has increased, so has the scientific evidence to support it in many instances. As a result, terms that had been previously used pejoratively, such as unconventional, unproven, folk and unorthodox, have given way to the more politically correct complementary, holistic, integrative and natural. Perhaps the most widely used term is Complementary Alternative Medicine or Complementary *and* Alternative Medicine (CAM).

The most frequently quoted study of the use of alternative medicine practices in the United States was published in 1993 by David Eisenberg and colleagues at Harvard. The results are shown in Table 1 and Figure 1. These researchers undertook a telephone survey in which they interviewed 1539 randomly selected persons. Results revealed that one third had used some form of alternative medicine in the previous twelve months. Only one third of those using alternative medicine sought the assistance of a provider. Those who did seek the help of an alternative medicine provider, made on average 19 visits in twelve months. Three percent of patients relied exclusively on alternative therapies. The most common forms of therapy used were relaxation techniques, chiropractic and massage. These data were extrapolated to conclude that in 1990 Americans made an estimated 425 million visits to alternative medicine providers, in comparison to 388 million to primary care physicians. The estimated cost of this was $13.7 billion.[7] This study has been widely criticized for being too inclusive, since many of the types of therapy included consist more of extended self-care rather than alternatives

to conventional medicine. What is not debated is the cost associated with these practices. More recent estimates by industry analysts suggest that expenditures in 1998 could range form $22 - 50 billion.[9] The burden of this expense is largely paid for out of pocket.

Table 1
Prevalence and Frequency of Use of Unconventional Therapy among 1539 Adult Respondents in 1990.

TYPE OF THERAPY	USED IN PAST 12 MO (%)*	SAW A PROVIDER (%)*	MEAN NO. OF VISITS PER USER IN PAST 12 MO
Relaxation techniques	13	9	19
Chiropractic	10	70	13
Massage	7	41	15
Spiritual healing	4	9	14
Commercial weight-loss programs	4	24	23
Lifestyle diets (e.g., macrobiotics)	4	13	8
Herbal medicine	3	10	8
Megavitamin therapy	2	12	13
Self-help groups	2	38	21
Energy healing	1	32	8
Biofeedback	1	21	6
Hypnosis	1	52	3
Homeopathy	1	32	6
Acupuncture	<1	91	38
Folk remedies	<1	0	0
Exercise†	26	--	--
Prayer†	25	--	--
≥1 Unconventional therapy‡	34	36	19
95% CI	31-36	31-41	14-24

*Percentages are of those who used that type of unconventional therapy.
†Respondents who used exercise or prayer were not asked for details about this use.
‡Excluding exercise and prayer.

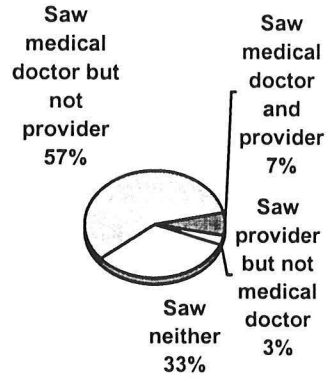


Figure 1. Percentage of respondents reporting at least one principal medical condition who saw a medical doctor or provider of unconventional therapy in 1990.

Using Eisenberg's definition and categories of alternative medicine, Astin attempted to identify why people pursue alternative therapies. In his survey of 1035 randomly selected individuals, he found that predictors of alternative health care use include: more education, poorer health status, or having had a transformational life experience; specific health problems such as anxiety, back problems, chronic pain, or urinary tract problems; classification in a cultural group oriented to environmentalism, feminism, spirituality or personal growth psychology. Dissatisfaction with conventional medicine was not a factor in this study, or that of Eisenberg. The most common types of alternative medicine employed were chiropractic, lifestyle, diet, exercise/movement and relaxation.[10] In short, the most frequent user of alternative medicine is a middle-aged, college-educated female with a holistic philosophy about health. Forty percent of those polled had used some form of alternative medicine in the previous 12 months.

Faced with this explosion of interest, many medical students are seeking training in CAM as part of their "conventional" medical education. Of 117 of the 125 U.S.

medical schools who responded to a recent survey, 64 percent report offering elective courses in alternative medicine, or including it as part of required courses.[11]

Where does herbal medicine fit in all of this? In 1990, Eisenberg found that only 3 percent of persons admitted to using herbal medicines at a cost of $467 million. In 1997, this figure was estimated at $3.6 billion and is projected to be $5.9 billion by the year 2000.[12] It is now estimated that 60 million adult Americans use herbal supplements regularly.[13] Furthermore, in a 1995 telephone survey of 136 customers of two Milwaukee health food stores, the average consumer was taking 5.9 supplements (not exclusively herbs).[14] The reasons for this explosion of interest are multi-factorial, but a major contributor was the Dietary Supplement Health and Education Act of 1994.

Dietary Supplement Health and Education Act of 1994

In order to understand this legislation, it is necessary to review the convoluted legislative process that lead to its enactment. The legislation preceding this act can be summarized in three major movements—those pertaining to purity, safety, and efficacy.

Based on observation and tradition, herbal therapies abounded in the U.S. throughout the nineteenth century. Many of these were effective. Apothecaries all provided extracts which could be used for medicinal purposes. National pharmacopoeias, such as the *U.S. Pharmacopoeia* and the *National Formulary*, included extensive monographs on the production and use of these medicines. Entrepreneurs also abounded and many persons promoted special patent medicines, tonics and elixirs as cure-alls, many containing nothing of which they were purported to have, and some of which were toxic. Prompted by concerns about consumer exploitation with these products and shocking disclosures of contamination in the meat-packing industry, Congress enacted the Food and Drug Act of 1906. Sometimes referred to as the "Pure" Food and Drug Act, the purpose of this legislation was to prevent the interstate commerce of "misbranded and adulterated food, drinks, and drugs."[15] Products were required to be what they purported to be, in the amounts claimed. Although this law was helpful in eliminating contaminated or misbranded medicinal products, it did little to stem the quell of consumer exploitation. For instance, attempts by the Federal Bureau of Chemistry (precursor to the FDA) in 1910 to prosecute the promoter of the worthless patent medicine, "Dr. Johnson's Mild Combination Treatment for Cancer," was unsuccessful. The supreme court ruled that the law did not prohibit false therapeutic claims, only false statements about the identity of the product.[15] Weakened by this decision, the Sherley Amendment was added in 1911 to prevent false claims.

The safety of medicinal products was not addressed until 1938. The previous year, S.E. Massengill Company marketed Elixir of Sulfanilamide, consisting of 8.8 percent sulfanilamide in 72 percent diethylene glycol. Produced for Southerners who preferred to drink their medicines, premarket testing consisted primarily of taste tests. The poisonous nature of the solvent was previously unrecognized and 105 people died.[16]

Stemming from this incident, the Food, Drug and Cosmetic (FD&C) Act of 1938 enacted sweeping changes which required that all *new* drugs prove their safety prior to marketing. Documentation was to be provided through the means of a New Drug Application (NDA), which was then carefully reviewed prior to drug approval. Another important result of the act was the establishment of a clear definition of a drug: an "article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" or an "article (other than food) intended to affect the structure or any function of the body...."[17] Consistent with their intended use, medicinal herbs fell into this category and were classified as drugs.

Although this law addressed the safety of *new* drugs, it did not address the safety of those already on the market. An important provision was that all drugs marketed in compliance with the Pure Food and Drug Act prior to 1938 (some of which we still use today, such as aspirin, codeine), were "grandfathered" in and were not required to provide additional evidence of safety. Most herbal medicines fell under this clause. Nevertheless, they were still subject to post-marketing surveillance and regulation.

With the issues of purity and safety well addressed, the next major piece of legislation occurred in 1962 with the passage of the Kefauver-Harris Drug Amendments. These amendments were prompted by public outcry for better regulation of the drug industry following the thalidomide disaster in Europe and extensive investigation of the drug industry in the U.S. by Senator Estes Kefauver of Tennessee. These amendments required that all drugs be proven safe and *effective* prior to marketing.[15] As an amendment to the FD&C Act, this law applied to all drugs approved for marketing under NDA's subsequent to 1938. In the 24 years following its enactment, 300 chemical entities and 4,000 different drug formulations had been approved and were on the market. An additional 3000 formulations had been approved but not yet marketed.[6] Again, those agents grandfathered into the 1938 law (including most herbs) were not subject to this provision. For two decades following the Kefauver Amendments, the FDA grappled with the implementation of this law. Under the direction of the FDA, the National Academy of Sciences was given the enormous task of extensively reviewing the scientific evidence supporting the use of all over-the-counter medicinals. Although exempted by provisions of the FD&C Act, herbal medicines, which were largely sold over-the-counter, were included in this review. After years of study, the committee concluded that although there was good evidence to support the use of some products, there was insufficient evidence to support the use of many others. In order to establish a single standard for all products, the FDA made a bold administrative maneuver that subjected all medicinal products to the efficacy standards of the Kefauver Amendments, including those previously grandfathered into the 1938 FD&C Act. In a new interpretation of the 1906 Food and Drug Act, the FDA declared that any drug was considered "adulterated" or "misbranded" if the claims on the label could not be substantiated by *data*.[6] Although herbal medicines were supported by a long history of use and anecdotal experience, data was generally lacking. Failing this standard, herbal medicines suddenly became illegal.

The standards of safety and efficacy established by these laws created an approval process for drugs that is unparalleled in the world. New drug approval today may cost as

much as $250-350 million and takes 10-12 years. Since herbal extracts have been available for centuries, they cannot be patented. Consequently, there has been no incentive to invest in the research to prove their medicinal claims.

The illegalization of herb medicinal products did not result in their disappearance. Herbal products remained available on the shelves of health food stores were they were marketed as dietary supplements, food additives, spices and teas. However, any labeling indicating medicinal use was strictly prohibited. Ironically, this regulatory effort intended to protect the public, resulted in many cases of "herbal misadventure." Many people continued to use herbs medicinally, only without adequate information to use them appropriately.

Paradoxically, it was a disaster in the dietary supplement industry that opened the door for the expansion of herbal products. In 1989, eosinophilia myalgia syndrome was diagnosed in hundreds of patients who had taken the supplement, L-tryptophan. Although it was later shown that the cause was a contaminant from a single batch produced by one supplier, this supplement was banned from the market. Furthermore, over the next several years the FDA increased its efforts to regulate the industry. A set of proposed rules in June of 1993 lead to a backlash of popular support and renewed congressional interest in the dietary supplement industry. In response to intense lobbying, Congress passed the Dietary Supplement Health and Education Act (DSHEA) in the fall of 1994.[18] With bipartisan support, the act was sponsored by Senator Orin Hatch of Utah, a state that is heavily involved in the herbal industry. As justification for the act, Congress cited the growing interest in alternative medicine and the need for consumers to be empowered to make choices about preventive health care programs. The purpose of the act was to ensure access to dietary ingredients that millions of Americans deemed essential to their health. Supporters argued that good health practices, including the use of dietary supplements could reduce health-care expenses and prevent disease. National economic interests were also cited, since the nutritional supplement industry consistently projects a positive trade balance.

In short, this amendment did two things—(1)it expanded the definition of dietary supplement and (2) it exempted dietary supplements from the premarketing safety and efficacy evaluations to which traditional drugs are subject. Special provisions of the act include the following:

- The definition of dietary supplement was expanded to include "any product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients."
- Claims may not be made about the use of a dietary supplement to diagnose, prevent, mitigate, treat or cure a specific disease. However, manufacturers may describe the supplement's effects on structure or function of the body or the "well-being" achieved by taking it. All such claims are required to be accompanied by the statement: "This

statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

- The FDA was given the responsibility to establish Good Manufacturing Practices.
- Supplements remain subject to previous laws regarding quality. They must be the product identified on the label and have the strength they are represented to have. Herbal supplements must state the part of the plant from which they are derived.
- Premarketing safety and efficacy studies are not required. Nevertheless, supplements must not pose a significant or unreasonable risk of illness or injury. The responsibility for proving that a product is unsafe is placed on the FDA.
- The Office of Dietary Supplements was established within the Office of Disease Prevention at the NIH.

This redefinition of dietary supplements lead to the explosion in the herbal industry. Without requiring data to support medicinal claims, herbal producers were freed to aggressively market their products with at least broad claims of nutritional support. Unquestionably, the law had its intended effect. The bewildering array of herbal preparations available now is rivaled only by the plethora of conventional over-the-counter medications. It is estimated that there are 1500-1800 herbal products available in the U.S. today.[19] There is also a flood of literature ranging from *The Honest Herbal*[20] and *Herbs of Choice*[6] by Varro Tyler (Emeritus Professor and former Dean of Purdue University School of Pharmacy and Pharmacal Science), to *Earl Mindell's Herb Bible*,[21] *Living Healthy in a Toxic World*,[22] *Planetary Herbology*,[23] and *Natural Health for Dogs and Cats*.[24]

This expanded definition of dietary supplements has lead to some unusual situations. As an example, Cholestin® is an herbal product marketed, as one might guess from the name, to improve cholesterol. Interestingly, it has been discovered that the active ingredient of this naturally occurring compound is lovastatin, which is currently under patent to Merck. Although lovastatin is clearly a drug, attempts by the FDA to regulate Cholestin® have been rejected by the courts.[25] This product remains on the market today, although clearly used for the specific purpose of lowering cholesterol. Ironically, the company that produces it has applied for a patent!

The greatest criticism of this law is that it goes too far in the direction of deregulation. Regardless of this new *legal* definition, the reality is that these supplements have been and continue to be used as drugs to "cure, mitigate, treat or prevent disease." Even avid herbalists acknowledge this. The World Health Organization recognizes herbal medicines as drugs. Similarly, the European Union officially recognizes phytomedicinals as drugs. As such, documentation of quality, safety, and efficacy are required, although the standards for efficacy are somewhat different than those in the U.S.[26] Using these principles of purity, safety and efficacy as a standard, I will review the current status of the American herbal industry.

Purity

One of the major criticisms of herbal medicines is the inconsistency of products. DSHEA gave the FDA charge of developing minimum quality standards, or Good Manufacturing Practices (GMP), for the herbal industry. These guidelines have only recently been formalized and have not been implemented.[27] Several consumer groups, such as the American Herbal Products Association, the Council for Responsible Nutrition and the National Nutritional Foods Association, have attempted to establish pharmaceutical standards. However, implementation is voluntary and inconsistent. Consequently, despite the DSHEA mandate to ensure purity, the industry remains largely unregulated. In order to understand the problems associated with these products, it is imperative that one understand the process used in their preparation.[28,29]

Harvesting/Collecting. The quality of herbal products is directly dependent on the quality of their raw ingredients. Herbs may be harvested from their natural habitat ("wild-crafted") or commercially cultivated to improve consistency. Correct identification and isolation from other species is often difficult. The timing of harvesting is essential since the level of active ingredients will vary depending on the maturity of the plant. In most cases, herbs are harvested just before or shortly after the flowers bloom.

Drying, Garbling, and Grinding. Fresh herbs have a moisture content of 60-80 percent, making them susceptible to decay and contamination. In order to preserve them, most herbs are dried at low temperatures until moisture content is reduced to about 14 percent. Once dried, the portion of the plant to be used is separated from other extraneous matter, such as dirt and debris, a process called garbling. The remaining plant parts are ground into coarse fragments or powder. Many herbs are available for purchase in this form.

Extraction. Active ingredients of herbs are obtained by soaking the plant fragments in a solvent. The resulting solution is given a number of different names, depending on the solvent and the solute. The term tea, is frequently applied to any herbal extract using water as a solvent. Technically speaking, *teas* are produced by steeping herbal parts in boiling water. *Infusions*, on the other hand, use water that has not quite reached the boiling point. Infusions result in a more potent solution since the volatile oils of the herb are not lost in the steam. *Decoctions* are teas made by boiling the hard parts of the plant, such as bark, berries, seeds, or roots. Teas, infusions and decoctions are usually consumed as soon as they are prepared. *Infused oils* may be produced by the same process, but using an oil as the solvent. These are typically applied directly to the skin for therapeutic purposes. A *tincture* is produced by using another type of solvent, such as a water/alcohol mixture. After steeping for a period of time, the solution is filtered and bottled for sale.

The strength of an extract is usually given as a ratio. Tinctures are usually 1:5 or 1:10, meaning that for every 1 gram of raw herb there is 5 ml of solvent. In other words, 5 ml of tincture contains the extracted components of 1 gram of herb.

Concentration. Tinctures are not cost-effective, since the alcohol solution often costs more than the herb itself. Furthermore, tinctures are prone to contamination by bacteria or breakdown of active components if not stored properly. Consequently, extracts are often concentrated by removing solvent by evaporation. The resulting fluid

extract may represent 1 gram of herb per 1 ml (1:1) extract. Solid extracts result when the solvent is completely removed, yielding concentrations ranging from 4:1 to 100:1. This implies that solid extracts are 40-1000 times more potent than tinctures. It also implies that one gram of product represents the extracted ingredients of 40-1000 grams of raw herb.

Addition of Excipients. Most herbal supplements today are sold in tablet or capsule form. Production of tablets and capsules requires the addition of other substances to provide texture and consistency. These are typically the same ones used in the preparation of prescription and over-the-counter drugs.

When the active ingredient of an herb is known, the final preparation is usually standardized and expressed as a percent. For example, 300mg guarana extract standardized to 22% caffeine. In some cases, only the dose of the active ingredient is reported (guarana extract standardized to 66mg caffeine).

Quality Assurance. Various techniques are available to ensure the proper identity and quality of herbal products. Microscopic analysis allows the trained individual to recognize characteristic plant patterns, thus aiding in the initial identification of plants to be used in preparation. Physical evaluation by identifying solubility, specific gravity, melting point and water content further aid in the identification of plant products, as well as establishing purity. More sophisticated analyses such as HPLC, mass spectrometry, and nuclear magnetic resonance spectroscopy are now frequently employed. Finally, biological assays in animals are also sometimes used to ensure that the desired pharmacologic activity is present.

The purity of herbal products is affected by a number of factors. One of the most common problems is **misidentification**. Misidentification is frequently trivial and occasionally fatal. The selection of plant material for herbal medicines requires expertise that often exceeds that of those employed for this purpose. This is particularly common with plant material obtained in developing countries and self-selected material collected by novices. A woman in Missouri suffered atropine poisoning when a tea sold as comfrey was actually composed of nightshade (*Atropa belladonna*).[30] Two cases of misidentification of Digitalis were reported in a recent NEJM article.[31] One of these is the infamous "Chomper" case. Chomper is an herbal laxative which has been used as part of a regimen of bowel cleansing. In this case, Digitalis was inadvertently substituted for the usual ingredient, plantain (*Plantago lanceolata*), which is desired because of its high psyllium content. Difficulty with nomenclature contributes to this. Herbal material is frequently identified by common names, a practice which often leads to misidentification, since the same common name may be applied to several different species, and one species may have many different common names. For example, the common names for *Cimicifuga racemosa* include black snakeroot, black cohosh, cohosh, false cohosh, squaw root, papoose root, blueberry, yellow ginseng, blue ginseng, columbine-leaved leontice, meadow-rue leontice, richweed, battle weed, rattle-root, bugbane, rattlesnake root, heart-leaved rattle top, rattle top, cordate rattle top and heart-leaved snakeroot.[32] Furthermore, in the same geographic region, *Cimicifuga racemosa, Asarum canadense, Sanicula canadensis* and *Sanicula marilandica* are all known as black snakeroot.[30] Intentional **mislabeling** of plant material is also common. For

instance, in a study of ginseng products, 60 percent of samples studied contained little or no ginseng at all.[6]

Another problem affecting the quality of products is **variability of constituents**. The time of year or the developmental stage at which the plant is collected is essential. For instance, the ackee plant (*Blighia sapida*) is harmless when ripe. However, the unripe plant contains high concentrations of hypoglycins, which block glucose synthesis in the liver.[33] Selection of plant parts is also important. The roots of comfrey (*Symphytum officinale)* have higher concentrations of alkaloids than the aerial parts. In capsules prepared from this, the pyrrolizidine content has been found to vary from 270mg/kg to 2900mg/kg.[34] Additionally, growing conditions may affect the concentrations of constituents. For instance, thread-leafed groundsel (*Senecio longilobus*) obtained in Gardner Canyon, Arizona, has been found to have toxic pyrrolizidine concentrations as high as 18 percent, the highest ever recorded.[30] Finally, variation in the extraction process and the length of time an herb is stored may increase or decrease the level of active principles.

Adulteration of herbal products, either intentionally or unintentionally has led to numerous fatalities and adverse events. This problem is most common with preparations obtained from Asia, but cases of preparations originating in the U.S. have also been documented. Contaminants commonly include heavy metals such as lead, mercury, arsenic, silver, copper, cadmium and thallium;[35,36] conventional pharmaceuticals such as corticosteroids, NSAIDS, and benzodiazepines;[37,38] and misidentified toxic herbs.[39] For instance, Sleeping Buddha, a Chinese herbal product was recently removed from the market by the FDA when it was found to contain estazolam, a benzodiazepine.[40] In a study of 260 Asian patent medicines available in California, at least 83 contained undeclared pharmaceuticals or heavy metals, and 23 had more than one adulterant.[41] Contamination of commercially cultivated herbs with insecticides is a theoretical problem, but has not been reported.

Obviously, these lapses in purity are not acceptable. So what is being done about it? Good manufacturing practices that have been formalized by the FDA will soon be in place. Theoretically, these practices would have averted the Chomper incident. In addition, the United States Pharmacopoeia Convention has begun a series of monographs on the quality of herbal products available in the United States. The *USP-NF* has legal status as the National Pharmacopoeia, thus imposing enforceable requirements on the quality of herbal products. Similarly, the World Health Organization and the American Herbal Pharmacopoeia are producing monographs that include quality standards. These standards will likely help, but it will not be an easy problem to solve in light of the huge number of products available. This will be especially true of the mail order trade and ethnic remedies.

Safety

The safety of herbal products depends largely on their purity. Although this is currently not guaranteed, most consumers consider herbs to be safer than conventional medicines. The basis for this belief is history. Herbal medicines have been used for centuries. Although toxic reactions and therapeutic misadventures get a great deal of attention, toxicity is rare. One of the proposed reasons for the safety of herbal medicines is that phytomedicinals are generally very dilute drugs with low concentrations of multiple active ingredients, a principle that corresponds to combination therapy in traditional medicine. No toxicological studies have been done in the U.S. However, in Hong Kong, where 40-60 percent of persons use herbal medicines, one is 20 times more likely to be admitted to the hospital for a toxic reaction to a conventional medicine than to an herbal preparation.[42] Furthermore, stemming from the years they were used primarily as food additives, the US FDA has maintained a list of over 250 herbs which it considers "generally recognized as safe, " the so called GRAS list.[6] Most of the herbs marketed in the U.S. today are on this list.

Nevertheless, hundreds of cases of toxicity have been documented in the literature. Health risks associated with herbal medicines can be either direct or indirect. Direct adverse effects are the same as those to which all drugs are subject, including all types of allergic reactions. These effects may be classified into the following categories.[43]

Type A reactions are dose dependent, pharmacologically predictable events resulting from the direct effects of herbal drugs on human physiology. These include the induction of hypertension and anxiety from the selective α_2-adrenergic receptor agonist, yohimbine (*Pausinystalia yohimbe*);[44] tachycardia from the sympathomimetic amine, ephedrine (*Ephedra* spp.);[44] nicotinic acid poisoning from excessive ingestion of blue cohosh (*Coulophyllum thalictroides*);[45] arrhythmias from aconite (*Acontium mapelus* and other spp.);[46] bradycardia from the cardiac glycosides, oleandrin and neriin, in oleander (*Nerium oleander*);[47] or euphoria, sedation and muscle weakness from kava (*Piper methysticum*).[48]

Type B reactions are idiosyncratic. They cannot be predicted on the basis of pharmacologic principles and are dose independent. Examples of this include allergic dermatitis, progressive renal failure and a lupus-like syndrome in a patient taking yohimbine;[49] anaphylaxis from Chamomile tea (*Chamomilla recutita, C. nobile*), which may occur in persons allergic to ragweed;[50,51] dermatitis from Aloe (*Aloe vera* and other spp); or photosensitization from St. John's Wort (*Hypericum perforatum*).[52]

Type C reactions develop as a result of long-term use and are the result of cummulative effect. Examples include pyrrolizidine alkaloid-induced veno-occlusive disease resulting from the use of comfrey (*symphytum officinale*)[53,54] and thread-leafed groundsel (*Senecio longilobus*);[55] hepatotoxicity from chapparel (*Larrea tridentata*)[56], germander (*Teucrium chamaedrys*),[57] pennyroyal (*Mentha puleguim* or *Hedeoma pulegoides*)[58] and sassafras (*Sassafras albidum*);[59] cyanide toxicity from Laetrile (apricot

pits);[20,60] pseudoaldosteronism from licorice (*Glycyrrhiza glabra*);[61] coagulopathy from coumarins contained in Dong Quai (*Angelica polymorpha*), tonka beans (*Dipteryx odorata*) and woodruff (*Galium odoratum*);[62] and renal fibrosis from aristolochia (*Aristolochia clematis*).[63]

Type D reactions are delayed effects, such as carcinogenicity or teratogenicity. These effects have been well documented for a number of herbs, including sassafras (*Sassafras albidum),* comfrey *(Symphytum officinale), Acorus calamus, Aristolochia* species, *Blighia sapida, Croton tiglium,* and *Genista tinctoria.*[43]

Table 2
Potential Toxicity of Selected Herbs

Common Name (*Scientific Name*)	Popular Use	Toxic Ingredient	Adverse Effects
Cardiac			
Aconite (*Acontium napellus, kusnezoffi, carmichael*)	Topical analgesia	C19 diterpinoid esters (Aconite alkaloids)	Bradycardia, tachydysrhythmias (except SVT), paresthesias, seizures, respiratory muscle weakness, nausea, vomiting, diarrhea
Oleander (*Nerium oleander*)	Cardiac disease, asthma epilepsy, cancer	Oleandrin, neriin, gentiobiosyloeandrin, odoroside A	Bradycardia, tachydysrhythmias, nausea, vomiting
GI			
Pokeweed (*Phytolacca americana, decandra*)	Arthritis, emetic, purgative, cancer	Phytolaccigenin, jaligonic acid, pokeweed mitogen, phytolaccagenic acid	Hemorrhagic gastritis, leukocytosis, volume depletion, respiratory distress, seizures
Liver			
Comfrey (*symphytum officinale*)	Ulcers, hemorrhoids, bronchitis, burns, bruises, swelling	Pyrrolozidine alkaloids (symphytine, echimidine, lasiocarpine)	Hepatic veno-occlusive disease, pulmonary artery hypertension
Chaparral (*Lorrea tridentata*)	Bronchitis, analgesic, cancer	Nondihydroguaiaretic acid (NDGA)	Hepatitis
Germander (*Teucrium chamaedrys*)	Antipyretic, GI disorders, wounds, diuretic, choleretic		Hepatitis, cirrhosis
Pennyroyal oil (*Hedeoma pulegioldes, Mentha pulegium*)	Menstrual irregularities abortifacient, digestive disorders, pediatric URI	Pulegone, menthofuran	Hepatitis (glutathione depletion), renal failure, spongiform encephalopathy, GI bleeding
Sassafras (*Sassafras albidum*)	Stimulant, antispasmodic, "purifier"	Safrole	Hepatotoxicity, hepatoma?

Table 2
Potential Toxicity of Selected Herbs

Common Name (*Scientific Name*)	Popular Use	Toxic Ingredient	Adverse Effects
Renal			
Aristolochia (*Aristolochia clematis*)	Uterine stimulant	Aristolochic acid	Renal fibrosis, renal failure
Licorice (*Glycrrhiza glabra*)	Gastric irritation	Glycyrrhizin	Hypokalemia, sodium and water retention, renal hypertension, lethargy, flaccid weakness
Neurologic			
Ephedra (*Ephedra* spp.)	Asthma, rhinitis, weight loss, stimulant	Ephedrine, pseudoephedrine	Tachycardia, hypertension, seizure, stroke, MI
Jimson weed (*Datura stramonium*)	Asthma	Atropine, scopalamine, hyoscyamine, stramonium	Anticholinergic toxicity
Blue cohosh (*Caulaphyllum thalictroides*)	Abortifacient, mentrual disorders, antispasmodic	Methylcytisine	Nicotinic toxicity
Podophyllum (*Podophyllum peltarum, hexandrum, emodi*)	Cathartic, purgative	Podophyllin	Peripheral neuropathy, encephalopathy, leukocytosis, leukopenia, nausea, vomiting
Immunologic			
Chamomile (*Chamomilla recutita, nobile*)	Digestive disorders, cramps, skin disorders	Allergens	Contact dermatitis, allergic reactions, anaphylaxis (rare)
Metabolic			
Apricot pits (Laetrile) (*Prunus armeniaca*)	Cancer	Amygdalin	Cyanide toxicity, metabolic acidosis, cardiovascular collapse

Adapted from Hung, Lewin & Howland. Herbal Preparations. In *Toxicologic Emergencies*.

An excellent review and thorough listing of the toxic potential of herbs can be found in the chapter by Hung, Lewin and Howland in *Goldfrank's Toxicologic Emergencies*.[45] An overview of some herbal medicines associated with toxicity are listed in Table 2.

Huxtable has identified a number of consumer characteristics which may place users of phytopharmaceuticals at increased risk. These include persons who are long term users, consumers of large amounts, users of a wide variety of herbs, pregnant (fetuses), very young, elderly, seriously ill, malnourished, or on other long-term medications. In

some cases gender and ethnicity are important. Numerous cases of unexpected toxicity have been reported in these groups.[30]

Aside from the direct health risks of phytomedicinals, there are a number of indirect risks. These include the delay in seeking medical attention in a significantly ill person, or the discontinuation of conventional medicines in lieu of unstudied, unproven therapies. In some instances, these may be even more life threatening than the direct toxic effects.

Another important but poorly studied risk is the potential for **drug-drug interactions**.[64] Certain herbal remedies can reduce drug levels of prescribed medicines. Shankhapushpi, an Ayurvedic medicine has been shown to reduce levels of phenytoin and result in increased seizure activity in epileptic patients.[65] Vitamin K from green tea decreases the effectiveness of coumadin.[66] Herbal medicines may increase toxicity of conventional medicines, such as piperine from *Piper* species, which increases levels of both theophylline and phenytoin.[43] The corollary is also true--conventional medicines may also increase potentially toxic levels of herbal constituents. Ciprofloxacin and enoxacin increase xanthine levels in *Cola, Ilex* and *Paullinia* preparations,[67] and quinidine and haloperidol increase levels of sparteine in *Cytisus scoparius* preparations.[43]

As with conventional medicines, some herbal products have potential for abuse, another important factor leading to toxicity. This can be exemplified by recent trends in the use of ephedrine-containing herbs.

Ephedra

Ephedra species are a group of plants found throughout the world. *Ephedra sinica*, commonly known as Chinese ephedra, or Ma Huang, is found in Asia and *Ephedra distacha* (European ephedra) is found in Europe. North American varieties include *Ephedra trifurca*, *Ephedra viridis* (desert tea), *Ephedra americana* (American ephedra), and *Ephedra nevadensis* (Mormon tea). The active ingredient common to these species is primarily ephedrine and to a lesser extent, pseudoephedrine and norpseudoephedrine. The concentration of these compounds ranges from 3.3 percent in *Epedra sinica* to almost none in *Ephedra nevadensis*.[28]

Ephedrine is an amphetamine-like sympathomimetic amine with both α- and β-adrenergic activity. In addition, it enhances the release of norepinephrine from sympathetic neurons. The cardiovascular effects of ephedrine are to increase heart rate, cardiac output, and peripheral vascular resistance, and usually blood pressure. It is also an effective bronchodilator and potent CNS stimulant. Historical uses have included the treatment of Stokes-Adams attacks, depression, narcolepsy, urinary incontinence, and drug induced hypotension. It is available over-the-counter for the treatment of mild asthma and allergic rhinitis. The side effects include hypertension, insomnia, tachycardia and arrhythmias. The usual oral dose is 25-50 mg every 3-4 hours.[44]

Ma Huang is the most commonly used form of ephedra because of its high ephedrine content. It is frequently recommended for the treatment of mild asthma, allergic rhinitis, and the common cold. Of greater interest recently has been the use of Ma Huang to induce weight loss. Because of its stimulatory effects, ephedrine has been promoted to increase thermogenesis, thus increasing caloric expenditure. Methylxanthines and aspirin are frequently added to increase this effect. A more recent combination has been the addition of St. John's Wort, a combination sometimes referred to as "herbal fen-phen." This combination received a great deal of public interest and was widely touted as an alternative to phentermine and fenfluramine. However, the FDA issued a stern warning against the use of this combination in light of many consumer reports of adverse events. Furthermore, it took regulatory action against its promoters, stating that their names reflected an intended use and they were therefore unapproved drugs.[68]

Even more troublesome to the FDA was the promotion of another type of ephedrine product, popularly known as Herbal Ecstacy, Cloud 9, Ultimate Xphoria and Rave Energy. Promoted as stimulants that could increase energy, "inner vision," "sexual sensations," and "cosmic consciousness," these were often taken as an alternative to the designer drug, Ecstasy.[69,70] In some cases these agents were combined with caffeine to increase their effect. These products resulted in at least 800 complaints and 15 deaths.

These misuses of ephedra prompted the FDA to place strict regulations on the marketing of ephedra products. These include a maximum allowable unit dose of 8 mg, a maximum stated daily dose of 24 mg and a duration of use limited to 7 days. Combination products have been banned altogether. In addition, labels are required to carry warnings.[71]

The examples given highlight the point that natural does not equal safe. Nevertheless, the overall incidence of toxic reactions to herbal medicines is much less than with conventional medicines. With regard to safety, WHO has stated: "A guiding principle should be that if the product has been traditionally used without demonstrated harm, no specific regulatory action should be undertaken unless new evidence demands a revised risk-assessment."[72] However, the few scattered reports of toxicity cannot be used as proof of safety, since post-marketing surveillance has never been adequately performed. De Smet concluded that we must not mistake "the absence of reliable evidence of risk for reliable evidence for the absence of risk."[43] Unfortunately, DSHEA did not require post-marketing surveillance or reporting of adverse events by supplement manufacturers. This is an important shortcoming of the act. These studies have been done to some degree in other countries, but it is unclear whether reporting was adequate or whether this information can be generalized to American products. Monitoring in the U.S. is being facilitated in other ways. The FDA has established the Special Nutritionals Adverse Event Monitoring System (SN/AEMS) for recording herbal adverse events. A report of the database is available to the public on the internet. The USP Practitioners Reporting Network also accepts reports of herbal adverse events and forwards them to the FDA. The Institute for Safe Medication Practices forwards reports to both the USP and FDA. In 1999, the American Association of Poison Centers will begin monitoring toxic

exposures to herbal products with the aid of the Toxic Exposure Surveillance System (TESS). Although this may address the issue of acute toxicity, delayed toxicity will be much harder to identify. Clearly, more studies need to be done on potential drug interactions, use in selected patient populations, and side effects.

Efficacy

The efficacy of herbal medicines has been hotly debated. It is in this arena that herbalists have been the most soundly criticized. Skeptics state that herbalists rely too heavily on anecdotal evidence and that well controlled studies are lacking. In fact, some would argue that herbalists and other practitioners of alternative medicine blatantly disregard science. In contrast, herbalists point to a vast literature which supports the effectiveness of phytomedicinals. Thousands of studies have been done with favorable results. Conventionalists contend that these studies are flawed and are uninterpretable, pointing to limitations that include small sample size, short duration of treatment, or lack of follow-up; lack of patient baseline data, demographics and comorbidities; failure to disclose study design, statistical analyses used, adverse patient reactions and/or patient compliance; inadequately described botanical or placebo preparation; or use of monitoring parameters that are not considered standard of care.

With regard to the study of efficacy, the WHO has stated: "In the case of traditional medicines, the requirements for proof of efficacy shall depend on the kind of indication. For treatment of *minor disorders and for non-specific indications*, some relaxation is justified in the requirements for proof of efficacy, taking into account the extent of traditional use; the same considerations apply to prophylactic use."[Emphasis added.][72] In other words, WHO believes that herbal medicines should be measured by a different standard than conventional medicines, because they are used for only minor or non-specific indications, an assumption that cannot be substantiated by patterns of use.

The efficacy of herbal medicines has been most widely studied in Germany, where phytopharmaceuticals have a long tradition of use. In 1978 the Minister of Health in that country established a series of commissions intended to review various classes of drugs, including herbal medicines. The commissions were identified alphabetically, and the one charged with evaluating herbal medicines was designated Commission E. The 24 member commission consisted of physicians, pharmacists, pharmacologists, toxicologists, biostatisticians, representatives of the pharmaceutical industry, and non-medical practitioners. Rather than relying on data submitted by drug applicants, as is the case with the US FDA, the commission actively sought supporting data. However, data used for review was somewhat more lenient than for conventional medicines. They reviewed information regarding traditional use; chemical data; experimental, pharmacological and toxicological studies; clinical and epidemiological studies; case records submitted by physicians; and unpublished proprietary data submitted by manufacturers. Over the next 14 years, the commission published over 380 monographs summarizing their findings with regard to 360 herbal drugs. This series of monographs is

considered the most authoritative in the industry. It includes information about composition, use, side effects, interactions with other drugs, dosages, mode of administration and action. Unfortunately, they did not publish references to the supporting data used to formulate their conclusions. This series of monographs was translated and published in English for the first time this year.[26]

Professor H. Schilcher, Vice President of the German Commission E, has characterized the effectiveness of herbal medicines by the following principles.[26]

1. Phytopharmaceuticals can be applied in a dose-effect manner.
2. Effect can be deduced from the specific ingredients.
3. Because phytopharmaceuticals contain primary active components, secondary components and accompanying compounds, they manifest greater effectiveness and a greater range of therapeutic activity than single isolated compounds.

Effective therapy assumes the availability of high quality pharmaceutical products. The principle of multiple active ingredients at low dosage is the center of the argument for the efficacy of herbal medicines. Whether this is true or not has never been studied.

In order to provide a better feel for the type of efficacy information that is available for herbal medicines, I will review some of the data supporting the use of St. John's Wort.

St. John's Wort

Heralded as the natural treatment for depression and other mild psychiatric disorders, St. John's Wort has received a tremendous amount of attention recently in both the popular press, as well as professional literature.[73] As a result, it is estimated that sales of this drug in 1997 alone were $200 million, a phenomenal amount in light of the fact that total sales for herbal medicines in the U.S. in 1990 were only $467 million.[12] Further evidence of popular interest is the fact that an entire website is dedicated to it--www.hypericum.com. Proof of scientific interest includes an NIH-sponsored, 3 year, multi-center study which began this fall. St. John's Wort has been the subject of at least 23 randomized clinical trials, 4 drug monitoring studies, 2 meta-analyses, and multiple reviews, including one published by the US Pharmacopoeia Convention.[74,75]

St. John's Wort is one of many common names for *Hypericum perforatum* L. Hypericum is an herbaceous perennial which is native to Europe, North Africa, and West Asia, but has been disseminated to many other parts of the world, including the U.S. Commercial preparations are obtained from the aerial parts of the plant, which are harvested shortly before or during the flowering period. Therapeutic preparations include dried chopped or powdered herb, infusions, tinctures, liquid extracts, oil extracts or dried extracts.[75] Standardization of products is currently the subject of a new *USP-NF* monograph.

The major use of hypericum today is in the treatment of mild to moderate depression and anxiety. Traditional uses have included bedwetting, dyspepsia, excitability, exhaustion, fibrositis, gastritis, gout, hemorrhage, hysteria, insomnia, irritability, jaundice, migraine headaches, neuralgia, pulmonary complaints, rheumatism, sciatica, and swelling. Topically it acts as an astringent and may be used for blisters, burns, cuts, hemorrhoids, inflammation, insect bites, itching, redness, sunburns, and wounds. Recent in vitro studies have shown antiviral activity, but this has not been extensively evaluated.[75]

Active ingredients of greatest significance are thought to be hypericin and pseudohypericin, both of which are naphthodianthrones. Additional components of this type include cyclopseudohypericin, isohypericin, and protohypericin. Other active ingredients include phloroglucinols, flavonoids, biflavonoids, xanthones, essential oils and phenolic acids.[76] Commercial preparations are standardized to include at least 0.04% hypericins.[77]

Hypericin is absorbed in 2-2.6 hours, with a time to peak concentration of 4-6 hours and an elimination half-life of 24.8-26.5 hours. Pseudohypericin is absorbed in 0.3-1.1 hours with a time to peak concentration of 2-4 hours and an elimination half-life of 16.3-36 hours.[78]

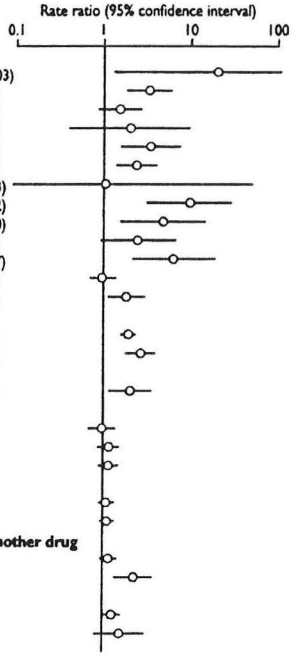
The mechanism of action is not known. Early in vitro studies suggested that hypericum inhibits monoamine oxidase. However, in vivo studies have not been able to confirm this. More recently, studies using rat or mouse brain have shown that hypericum inhibits synaptosomal uptake of serotonin, dopamine, and norepinephrine.[79] One in vitro study revealed reduced levels of serotonin receptors when incubated with hypericum.[80]

Linde and colleagues performed a meta-analysis of all available clinical trials involving St. John's Wort.[74] Their findings are shown in Table 3. Their review included 14 placebo controlled trials of monopreparations, 1 placebo controlled trial of combination therapy, 6 studies comparing monopreparations of hypericum with another drug and 2 studies comparing combination therapies that included hypericum with another drug. Objective data was based on the Hamilton Depression Scale (HDS) in 17 trials and the clinical global impressions index in 12 trials. Both are observer rated scales. Treatment response was defined as a score of less than 10, or 50 percent of the baseline score on the HDS. A rating of "much improved" or "very much improved" defined a response on the clinical global impressions index. Rates of response were determined for hypericum and control groups, which were then reported as ratios for comparison. Thirteen of the fifteen studies comparing hypericum to placebo included data on treatment responders, and five of the eight comparing hypericum to other drugs included this data. In the placebo studies, 94 of 420 patients (22.3%) receiving placebo responded and 225 of 408 (55.1%) receiving hypericum responded, resulting in a pooled rate ratio of 2.67 (95% CI 1.78 to 4.01. In those trials reporting information on the HDS, patients receiving hypericum scored 4.4 points lower (95% CI 3.5 to 5.3). In the three trials comparing single preparations of hypericum to another drug, 101 of 158 (63.9%) patients receiving hypericum were responders and 93 of 159 (58.5%) receiving

conventional drugs were responders, resulting in a rate ratio of 1.10 (95% CI 0.93 to 1.31). Scores on the HDS were only slightly better for hypericum, with a mean weighted difference of 1.01 (95% CI -0.4 to 2.4). In trials that included combinations with hypericum versus standard drugs, 88 of 130 (68%) receiving hypericum responded and 66 of 132 (50%) receiving standard drugs responded, resulting in a rate ratio of 1.52 (95% CI 0.78 to 2.94).

Table 3
Meta-analysis of Controlled Trials of *Hypericum perforatum*

Trial	No of responders: Hypericum	No of responders: Control	Rate ratio (95% confidence interval)
Placebo controlled trials of single preparations			
Halama 1991*[12]	10/25	0/25	21.00 (1.30 to 340.03)
Hänsgen 1994*[11]	27/34	9/38	3.35 (1.85 to 6.08)
Hübner 1994*[15]	14/20	9/20	1.56 (0.89 to 2.73)
Lehrl 1993*[17]	4/25	2/25	2.00 (0.40 to 9.95)
Schmidt 1993*[23]	20/32	6/33	3.44 (1.59 to 7.44)
Sommer 1994*[24]	28/50	13/55	2.37 (1.39 to 4.04)
Osterhaider 1992*[18]	0/23	0/24	1.04 (0.02 to 50.43)
Quandt 1993*[19]	29/44	3/44	9.67 (3.18 to 29.42)
Schlich 1987*[21]	15/25	3/24	4.80 (1.59 to 14.50)
Schmidt 1989*[22]	10/20	4/20	2.50 (0.94 to 6.66)
Hoffmann 1979†[14]	19/30	3/30	6.33 (2.09 to 19.17)
König 1993†[16]	29/55	31/57	0.97 (0.69 to 1.37)
Reh 1992*[20]	20/25	11/25	1.82 (1.12 to 2.95)
Summary rate ratios			
Fixed effects	225/408	94/420	1.94 (1.60 to 2.34)
Random effects			2.67 (1.78 to 4.01)
Placebo controlled trial of combination			
Ditzler 1994‡[25]	20/30	10/30	2.00 (1.14 to 3.52)
Trials comparing single preparations and another drug			
Harrer 1994*[27] (v maprotiline)	27/51	28/51	0.96 (0.67 to 1.38)
Vorbach 1994*[29] (v imipramine)	42/67	37/68	1.15 (0.87 to 1.53)
Bergmann 1993*[26] (v amitryptiline)	32/40	28/40	1.14 (0.89 to 1.48)
Summary rate ratios			
Fixed effects	101/158	93/159	1.10 (0.93 to 1.31)
Random effects			1.10 (0.93 to 1.31)
Trials comparing combination of hypericum and valeriana with another drug			
Kniebel 1988*[32] (v amitryptiline)	57/80	52/82	1.12 (0.91 to 1.39)
Steger 1985‡[33] (v desipramine)	31/50	14/50	2.21 (1.35 to 3.63)
Summary rate ratios			
Fixed effects	88/130	66/132	1.25 (1.03 to 1.53)
Random effects			1.52 (0.78 to 2.94)



* Hamilton rating scale for depression.
† Global assessment.
‡ Clinical global impression index.

In the six trials of hypericum vs. standard therapy, 19.8 percent of hypericum patients reported side effects compared to 35.9 percent of those receiving standard therapy (OR 0.39;95% CI 0.23 to 0.68). Overall dropout rates due to side effects were 4.0% for hypericum and 7.7% for standard antidepressants (OR 0.61; 95% CI 0.27 to 1.38).

The reviewers concluded that the methodology was "reasonable to good," although there were a number of problems that made it difficult to make comparisons. For instance, the patient populations studied were very heterogeneous and classification of depressive disorders was inconsistent. Furthermore, in some cases, scores on the Hamilton Depression Scale did not correlate with the degree of symptoms reported in the

studies. Another problem is the lack of standardization of hypericum extracts. Finally, in studies comparing hypericum to another drug, the dosage of the conventional drug was often subtherapeutic or at the low therapeutic end. One source of concern was the amount of duplication in publication. Several studies were published more than once without reference to prior publications. One trial was published 5 times with two different first authors.[81] The authors concluded that there is adequate evidence that hypericum is better than placebo in treating some depressive disorders. However, due to the small number of patients in studies comparing hypericum to standard therapy, evidence was insufficient to determine whether hypericum is as good as standard therapy. Furthermore, optimal dosing of hypericum or the effect of differing preparations is not known. It does appear to have fewer side effects than standard antidepressants.

Table 4
Spontaneously Mentioned Side Effects of Treatment

Undesired Drug Effects in 3250 Treated Cases (%)		
Gastrointestinal symptoms (nausea 6, abdominal pains 5, loss of appetite 3, diarrhoea 2, gastrointestinal symptoms 2)	18	(0.55%)
Allergic reactions (allergy 6, skin rash 6, pruritus 5)	17	(0.52%)
Fatigue	13	(0.40%)
Anxiety	8	(0.26%)
Dizziness	5	(0.15%)
Other side effects	18	(0.55%)
Total number of undesired drug effects	79	(2.43%)

Other side effects included dry mouth, sleep disturbances, palpitations, weakness, worsening of concomitant conditions were each mentioned by two patients. One patient mentioned each of: tremor, circulatory symptoms, light-sensitivity, visual disturbances, urinary symptoms, burning eyes, euphoria, and tension.

As for safety, in a drug monitoring study of 3250 patients taking hypericum, 79 patients (2.4%) had side effects and 48 (1.5%) terminated therapy. The most common side effects are shown in Table 4.[82] In addition, phototoxicity has been reported at high doses in fair-skinned persons.[52] Studies of carcinogenicity and mutagenicity have been performed on a limited scale in vitro and in vivo and have been found to be negative. Studies in pregnancy, lactation, and children have not been done. No geriatrics related side effects have been reported. No drug interactions have been reported but there are theoretical concerns about interactions with MAO inhibitors and selective serotonin reuptake inhibitors. No laboratory interactions have been identified.[75]

Table 5
Commonly Used Herbs

Common Name (*Scientific Name*)	Popular Use	Active Ingredient	Dose* (cost/month)	Comments
Black cohosh (*Cimicifuga racemosa*)	Menopause	Triterpene glycosides	40 mg QD/BID 2.5% triterpenes ($3-6)	Nausea, vomiting, dizziness, headache
Echinacea (*Echinacea purpurea* & spp.)	Cold and flu symptoms	Caffeic acid derivatives	250 mg QD-TID 4% echinacosides ($6-9)	Avoid in persons with autoimmune disorders
Ephedra (*Ephedra* spp.)	Asthma, rhinitis, stimulant, weight loss	Ephedrine, Pseudoephedrine	25 mg TID/QID	Tachycardia, HTN, palpitations, MI, seizures, CVA
Feverfew (*Tanacetum parthenium*)	Migraine headaches	Parthenolide	50-80 mg QD 0.7% parthenolide ($3.50)	"Post feverfew syndrome," oral ulcers
Garlic (*Allium sativum*)	High cholesterol, hypertension	Allicin	4 gm fresh garlic or 4 mg allicin pot. ($11)	Contact dermatitis, GI upset, antiplatelet activity
Ginger (Zingiber officinale)	Motion sickness, dizziness	Gingerols, Shogaols	1000 mg QD or Q4° prn ($3-7)	No known side effects
Ginkgo (*Ginkgo biloba*)	Memory, arterial insufficiency	Flavonoid glycosides, terpene lactones	60 mg TID 24% flav/6% terp ($15)	GI upset, headache, skin reactions
Ginseng (*Panax ginseng* & spp.)	Improve energy	Ginsenosides	110mg BID 70% ginsenosides ($14)	Ginseng abuse syndrome?
Goldenseal (*Hydrastis candensis*)	Cold and flu symptoms	Hydrastine, Berberine, Berberastine	150 mg QD/TID 10% hydrastine ($10-15)	GI upset, in large doses respiratory failure
Horse chestnut (*Aesculus hippocastanum*)	Varicose veins, venous insufficiency	Triterpene glycosides (escin or aescin)	250 mg BID 20% escin ($6-7)	Pruritis, rarely nausea
Kava (*Piper methysticum*)	Insomnia, anxiety	Kava lactones (kawain)	180 mg 1-2 QD 55% kava lactones ($12-24)	Euphoria, muscle weakness
Milk thistle (*Silybum marinaum*)	Liver disease	Silymarin	175 mg TID 80% silymarin ($18-19)	Mild laxative effect
Saw palmetto (*Sereno repens*)	Prostate enlargement	Complex of free fatty acids	320 mg QD 85-95% fatty acids ($12)	Diarrhea (rare)
St. John's Wort (*Hypericum perforatum*)	Depression, anxiety	Hypericin, pseudohypericin	300 mg BID/TID 0.3% hyericum ($10-13)	Contraindicated with SSRI, MAOI, phototoxicity
Valerian (*Valeriana officinalis*)	Insomnia	Valeric acid (terpenes)	100 mg 1-2 QHS 0.8% terpenes ($3-6)	No known side effects

*Dosing recommendations vary. These are only estimates.

What conclusions can one draw from all of this? The fact is, it does have some efficacy. Furthermore, there are a number of agents that have similar benefit profiles,

including Saw Palmetto,[83] Milk Thistle,[84] Ginkgo biloba,[85] ginger, and valerian. A selection of the most commonly used herbs are shown in Table 5. The question is, how effective are they? Are they as good as the newer agents on the market? What are the longterm outcomes? In an attempt to answer these questions, the US Pharmacopeial Convention is developing a series of botanical reviews. Each of these monographs critically reviews the literature on a specific herb and provides information which is of practical value to both providers and consumers. The WHO is also developing its own set of monographs, as is the European Union, the American Herbal Pharmacopoeia, the British Herbal Compendium, and the American Botanical Council. In spite of these efforts, greater insight is going to require more science. The argument that efficacy studies are not economically feasible is no longer acceptable. This is a multi-billion dollar industry. The resources are available to do adequate trials.

Counseling Patients

One of the most important, if not the most troubling, findings in the study by Eisenberg and colleagues was that seventy percent of users of alternative medicine did not inform their physician.[7] Many patients are unwilling to counsel with their physicians regarding these therapies for fear that they will be made fun of, or dissuaded from a practice which they believe is beneficial. Furthermore, some physicians are afraid to ask about alternative practices for fear that co-managing a patient with an alternative medicine practitioner might place him/her at legal liability. As a result, many physicians are unaware of practices which may affect the efficacy of conventional therapy. Although the explosion of interest in herbal medicine that has occurred in the last 5 years has done much to open a dialogue, this lack of disclosure remains a great concern. Eisenberg has published another article detailing an acceptable approach to counseling patients who seek alternative medical therapies.[86] I have made it a practice to ask my patients about the use of all over-the-counter remedies, including herbs, when I record their medication list.

I believe that appropriate patient education about herbal medicines at least includes the following points.

1. Herbal supplements are crude drugs sold over-the-counter.
2. The quality of herbal preparations is not regulated and cannot be guaranteed. Only purchase products sold by reputable dealers. Avoid those imported from the Far East. Look for evidence of good manufacturing practices. Look for Latin binomial identification on labels. Be an informed consumer.
3. Most herbal products are thought to be safe. However, misuse, overuse, or abuse may contribute to toxicity. Furthermore, the effect of herbal preparations on most conventional medications is not known. Do not take them with any prescribed medicine unless carefully monitored. In patients taking medications with a narrow therapeutic window, use is discouraged altogether.

4. Some herbal products have been shown to be moderately beneficial, but in most cases, efficacy has not been well documented.
5. Remember moderation in all things.
6. Know the limits of self-medication.
7. Seek medical attention for any serious problem.

Simply providing this advice to patients is inadequate. As we have extensively reviewed, there are many herbal preparations with known potential toxicity. Just as consumers need to be informed, so do physicians, if we are to provide the best care possible. Many resources are available to aid physicians in educating their patients. A list of some of the most useful sources are listed "Selected References." It is no longer acceptable for physicians to simply respond to patient inquiries about herbal products with, "I don't know."

Conclusion

In spite of the dramatic change in regulatory status of herbal medicines that occurred in 1994, the legislative history of drugs in the U.S. provides an important paradigm which still must be applied to all medicinal products. Purity (quality), safety and efficacy are standards that all medicinal products need to meet. Government regulation intended to achieve these goals is an inherently slow, cumbersome process. The regulatory process always lags behind the legislative process. As a result, the cart often gets out in front of the horse, as it has in this case. The current state of regulation is inadequate, but steps are being taken to remedy this.

Regardless of the strict efforts to ensure purity and safety, this is not an infallible process. In spite of requirements posed by New Drug Applications, 26 drugs have been removed from the market in the last 10 years. Not all of these were removed by the FDA. Some were voluntarily removed by drug companies because of concerns about legal liability. This concern about liability does provide a *de facto* safety net that provides producers with some incentive to provide quality products. At the moment, this is the main driving force in the U.S. The establishment of good manufacturing practices will greatly improve this situation.

As for efficacy, several of the herbal medicines have been shown to have benefit. What is unclear is how these compare to conventional medicines and what role they will play in general practice. Many herbs have not been shown to be beneficial. Only time and careful study will tell whether they truly are or not. More well conducted efficacy studies need to be done. The resources are available to do this. Consumers are entitled to some degree of certainty that the products they buy have some hope for benefit. It is time that both herbalists and conventional scientists take this more seriously and provide more data from methodologically sound studies.

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