

Medicinal Herbs in the United States: Research Needs

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Virtually all cultures have, throughout history, used a variety of plants or materials derived from plants for the prevention and treatment of disease. Evidence of the beneficial therapeutic effects of these medicinal herbs is seen in their continued use. Additionally, the development of modern chemistry permitted the isolation of chemicals from medicinal herbs that have served as drugs or starting materials for the synthesis of many important drugs used today. Many more modern drugs have been synthesized as a result of knowledge gained from studies of mechanisms of actions of chemicals first isolated from medicinal herbs. Thus, medicinal herbs have played a major role in the development of modern medicine and continue to be widely used in their original form. Whereas it is generally agreed that most medicinal herbs are safe under the conditions used, some are toxic and should be avoided even though they are readily available, and others have significant adverse side effects when misused. Also, little has been done to investigate potential adverse effects that may be associated with extended or high-dose use of medicinal herbs. Thus, concern has been expressed that the lack of quality control used in the preparation of medicinal herbs, plus their unregulated sale and uninformed use, pose potential adverse health effects for consumers. There is also concern regarding potential herb/herb or herb/drug interactions and possible untoward health effects of medicinal herbs in sensitive subpopulations such as the young and the elderly and certain genetically predisposed individuals. In this paper, we discuss these concerns at some length and make recommendations for additional research and education discussed in the recent International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs. *Key words:* medicinal herbs, dietary supplements. *Environ Health Perspect* 107:773-778 (1999). [Online 25 August 1999] <http://ehpnet1.niehs.nih.gov/docs/1999/107p773-778matthews/abstract.html>

Much of what is today considered "alternative medicine" in the more developed countries was, in the not too distant past, the only medicine. Indeed, a major portion of the world's population still depends almost exclusively on what many in the more developed countries consider alternative forms of treatment for most health-related problems. In most cultures, medicinal herbs have long constituted a major component of these traditional or alternative treatments. Knowledge of the therapeutic properties of plants predates recorded history, and great respect was given to those who possessed and passed on this knowledge to succeeding generations. When consumed, made into teas or infusions, or when applied directly to an injury, certain plants appeared to have almost magical healing properties. Thus, among the treasures sought by early explorers was knowledge of the existence and use of new medicinal plants. These plants and knowledge of their therapeutic uses were returned to the home countries as part of the justification of early explorations. Export of medicinal plants back to the home countries played a major role in disseminating both the plants and knowledge of their medicinal properties and helped to establish both early trade between countries and the basis of modern pharmaceuticals.

Knowledge gained from the use of medicinal herbs and their active ingredients serves

as the foundation for much of modern pharmacology. Drugs such as aspirin, digitalis, morphine, and quinine were all originally isolated or synthesized from materials derived from plants. Perhaps more important to the development of pharmacology has been knowledge gained from studies of the mechanisms of action of naturally occurring chemicals derived from medicinal plants. Studies of chemicals derived from plants have supported the development of new synthetic chemicals that account for a major portion of the drugs used in modern medicine. This fact is well recognized by today's biomedical community that continues to send modern explorers to the corners of the earth to find new plant-related cures for our maladies.

The historic role of medicinal herbs in the treatment and prevention of disease and their role as catalysts in the development of pharmacology do not, however, assure their safety for uncontrolled use by an uninformed public. Concern regarding the current proliferation of widespread, uncontrolled, and largely uninformed or misinformed use of medicinal herbs was the subject of a recent editorial in the *New England Journal of Medicine (NEJM)* (1) and a series of articles in the *Journal of the American Medical Association (JAMA)* (2). The recent International Workshop to Evaluate Research Needs on the Use and

Safety of Medicinal Herbs addressed the need for additional research to support more effective and safe use of medicinal herbs (3).

Use of Medicinal Herbs in the United States

There is little question that many medicinal herbs have preventive and/or therapeutic effects. Thus, like any therapeutic agent, when overdosed or incorrectly used, they also have the potential to induce adverse effects. The likelihood of adverse effects increases when the production and sale of such products is largely uncontrolled and the consumer is not adequately informed as to their proper uses. These concerns have been the major focus of the recent articles (1,2) and the workshop mentioned above. In their editorial in *NEJM*, Angell and Kassirer (1) discussed the significance of the large and rapidly increasing use of medicinal herbs in the United States. They expressed concern for possible risks associated with widespread use of preparations that have not been scientifically tested. They also pointed out that, while most herbal remedies are probably harmless, some may be quite toxic, and the consumer is largely uninformed as to possible adverse effects. In his guest editorial in *JAMA*, Wayne Jonas (4), former Director of the National Institutes of Health Office of Alternative Medicine, endeavored to look at both sides of the issue and stressed the fact that there are positive and negative aspects of both alternative and conventional medicine. He pointed out that conventional medicine excels in the use of scientific methods to authenticate its benefits, whereas alternative medicine depends largely on anecdotal reports. He cautioned, however, that the beneficial effects of medicinal herbs may vary because of the lack of standardization in collection and processing. Thus, while acknowledging the beneficial effects of alternative medicine, Jonas (4) urged increased research to confirm the beneficial and safe uses and further research into the mechanisms that account for the therapeutic effects of alternative treatments. In the same issue of *JAMA*, Fontanarosa and Lundberg (5) pointed out that, although millions of patients use

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alternative practices such as medicinal herbs, these practices have not been subjects of properly designed and conducted randomized control trials. Thus, consumers are spending billions of dollars annually for remedies that may or may not be effective and, in most cases, are not reimbursed by insurance. Fontanarosa and Lundberg (5) also pointed out that, in some incidences, the alternative methods used may, in fact, be contraindicated.

The use of medicinal herbs in the United States, which was quite common in the nineteenth century and early in the twentieth century, declined with increased knowledge of the germ theory of disease and the increased availability of synthetic drugs. The recent resurgence in the use of medicinal herbs is speculated to be due to some disillusionment with conventional medicine and its increased costs plus changes in health care delivery systems that make them more impersonal. There has also been increased interest in the use of "natural" alternatives in the mistaken impression that natural products are always safe. Marketing and use of these "natural" alternatives were greatly facilitated by the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA) (6). The DSHEA included medicinal herbs and other botanical products in the definition of dietary supplements. Thus, unless approved by the Food and Drug Administration (FDA), specific preventative or therapeutic claims cannot be made for medicinal herbs. Evidence of preventive and/or therapeutic effects can, however, be strongly inferred. (Medicinal herbs are more widely used in many other developed countries, such as Germany, than in the United States. They are frequently prescribed by doctors, and their costs are often covered by insurance. However, many of the products that are readily available through a variety of retail outlets in the United States are more closely controlled and are available only by prescription in many European countries.)

As a result of increased interest and promotion and limited control, approximately 40% of the U.S. population is reported to use some sort of dietary supplement. Medicinal herbs now constitute the most rapidly growing segment of the total U.S. pharmaceutical market. According to the Presidential Commission on Dietary Supplement Labels, some 1,500–1,800 botanical products are sold in the United States as dietary supplements or ethnic medicinals (7). These formulations are being consumed by tens of millions of U.S. citizens for both treatment and prevention of a wide variety of health-related problems. Estimates of the market value of herbal medicines in this country vary, but all sources agree it is a multibillion dollar industry.

Concerns Regarding the Use of Medicinal Herbs

A major portion of the world's population depends almost exclusively on herbal products and other alternative methods as the primary defense against or treatment for disease and various organic disorders. Further, many botanical products continue to be used today in a manner identical or very similar to that used for thousands of years. This long history of use lends credibility to support the beneficial effects of herbal medicines in the prevention and treatment of disease. However, although most botanical products are probably safe under most conditions, some are known to be toxic at high doses and others may have potentially adverse effects under some conditions. That is, it must be assumed that if they have beneficial therapeutic effects, the chemicals in medicinal herbs, just as those in synthetic drugs, also have the potential to cause adverse effects. The intensity of adverse effects would be expected to vary with dose, responses of sensitive individuals based on genetic predisposition, diet, drug interactions, and other factors. Because medicinal herbs are not prescribed by physicians or dispensed by pharmacists, reports of their adverse effects are largely anecdotal. Thus, documentation of adverse effects associated with the use of medicinal herbs is largely limited to those reports associated with overdose and allergic reactions.

A number of plants that have been or are currently used as medicinal herbs are also known to be ineffective or toxic and are not recommended for use. The English translation of *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines* (8) lists more than 100 such ineffective or toxic herbs that have been used medicinally but are no longer recommended. Many are still available, however, and are found in retail outlets along with safe and effective medicinal herbs. There have been a number of cases of injury and even death resulting from misuse, contamination, and/or adulteration of medicinal herbs (9). Also, because they are not regulated for content or efficacy, it is not possible to know how often medicinal herbs fail to contain the advertised active ingredient and thus have no effect. It is also impossible to determine when a product might have contained substances that resulted in subtle adverse effects that were not reported. Similarly, it is quite possible that the placebo effect resulting from widespread advertising, popular promotion, and the natural tendency of most common maladies to run their course accounts for much of the beneficial effects achieved with some products.

Other concerns regarding the use of medicinal herbs include the possibility of herb/herb or herb/drug interactions and allergic reactions (7–9). Any pharmacologically active agent has the potential to result in synergistic or antagonistic interaction when consumed with other pharmacologically active compounds. This is no less the case for medicinal herbs. Medicinal herbs that have similar or opposite therapeutic effects as drugs or those that inhibit the metabolism of drugs are the most likely candidates for adverse interactions. Depending on the interaction involved, the action of a synthetic drug may be enhanced or suppressed by co-administration of an herb and vice versa. Because interactions are not systematically documented and such reports are largely anecdotal, concern has been expressed regarding potential interactions involving prescription drugs. Warfarin, for example, is administered to delay blood clot formation and could be potentiated by co-administration of feverfew, garlic, ginkgo, ginger, or ginseng, which have similar actions (10). Taken together, warfarin and one or more of these herbs might cause the patient to hemorrhage. St. John's wort, which is known to enhance photosensitivity (11), should not be used with other known photosensitizers (e.g., tetracycline). Additionally, St. John's wort is known to inhibit monoamine oxidase and may thus enhance the action of other monoamine oxidase inhibitors or serotonin reuptake inhibitors (10). Valerian is not recommended for use with barbiturates because it has been demonstrated to prolong barbiturate-induced sleeping times (12). Concern for the possibility of adverse drug/herb reactions is heightened by the fact that the potential for such interactions is not described on the package inserts for most prescription drugs, and herbal remedies do not require package inserts. Thus, because the consumer is uninformed and many patients do not inform their physicians that they are also using medicinal herbs, the potential for adverse interaction is increased.

Recommendations for the use of prescribed drugs (i.e., dose, manner, and frequency of administration and the period for which they are taken) are reviewed and controlled by the prescribing physician. Because they are usually self-prescribed by the consumer, this is frequently not the case with medicinal herbs. Further, the extended pre-clinical and clinical testing to assure the safety of prescription drugs before they are released to the market is not required for medicinal herbs. Little is known about chronic toxicities that might be associated with their prolonged use. There has been minimal research to address possible adverse reproductive, immunologic, or neurologic

effects or even systemic toxicity and/or carcinogenicity that might be associated with high doses or prolonged use of these products (10). This concern was frequently expressed at the International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs, where it was strongly emphasized that medicinal herbs cannot be assumed safe because they are "natural" (3). Many natural products are quite toxic or carcinogenic. For example, strychnine (one of the most toxic chemicals known), aflatoxin (which is both toxic and carcinogenic), and pulegone (a toxic abortifacient) are all "natural" (8,9). Pulegone is found in the medicinal herb pennyroyal, which can be found in many outlets for medicinal herbs. Medicinal herbs contain a variety of chemicals that are toxic when consumed at high doses and for which little is known about their chronic toxicity. Because the DSHEA exempts dietary supplements such as medicinal herbs from testing (6), the public may be unknowingly exposed to chemicals with the potential to induce a variety of toxicities and/or carcinogenicity on chronic use. Further, because such testing is expensive and is not required, it is unlikely to be performed by the producers or distributors of these products. This does not mean that the industry is not interested in the safety of their products. Rather, as best described by Loren Israelson (3), a spokesperson for the herbal industry, there is a financial disincentive for the industry to support such research. Because these products cannot be patented, funding research into their chronic effects would not confer any proprietary right to the company that supported the work. Thus, research funded by one company could be used equally well by their competitors.

Other concerns regarding the marketing and use of medicinal herbs voiced both in the literature and at the recent workshop are those of standardization and stability (1-3). Unlike pharmaceuticals, botanical products are complex mixtures in which the active ingredients may not be known or may constitute only a small percent of the total product. Some products are, in fact, believed to achieve their beneficial effects through the combined actions of several ingredient chemicals, each of which accounts for a very small portion of the total product. Quality control issues are further complicated by the manner in which these products are produced. That is, unlike synthetic drugs that are produced in highly purified form, medicinal herbs are gathered in the wild or grown in relatively small plots. Thus, the active ingredients may vary significantly with the part of the plant used, the season in which they are harvested, and/or the growing conditions (e.g., weather,

soil, etc.). When these facts are combined with the fact that these dried plant parts are purchased locally by dealers who sell them to the larger distributor, who in turn may further market or formulate and distribute the final product, the potential for misidentification or cross contamination is apparent. Because little is done to monitor the concentration of active ingredients or the possibility of cross contamination through these steps, the content of active ingredients in a given product may vary significantly from one lot to another.

As described by Joe Betz at the recent International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs, sophisticated analytical procedures have and are being developed in this country and elsewhere to analyze the contents of medicinal herbs. Quality control guidelines based on methods described in pharmacopoeias from more than a dozen nations have been described in a recent document prepared by the World Health Organization (WHO) (13). A recent effort by the U.S. Pharmacopeia has provided more detailed methods for the standardization of specific medicinal herbs and dietary supplements (14). Monographs for the specific herbs addressed are being published as they are developed. These methods are only recommended, however, and are not required for any of the products addressed.

As mentioned above, the active ingredients of herbal formulations usually constitute a small fraction of the total product. In some cases, the active ingredient(s) are unknown or only partially characterized. In other cases, beneficial effects are attributed to a combination of active ingredients. Because the stability of chemicals varies according to individual structures of the chemicals and the formulation in which they are found, the stability of active ingredients of medicinal herbs is also a matter of concern. However, the active ingredients of many medicinal herbs are unknown, and for others our knowledge of active ingredients is incomplete. Thus, expiration dates, when present for medicinal herbs, may not be meaningful. Because there has been relatively little research to establish the active ingredient(s) of most medicinal herbs or to document their shelf life, the efficacy of a particular preparation may vary significantly with time or from one brand to another. For those preparations in which the active ingredients are known, methods are available or could be relatively easily developed to determine their shelf life. However, this work is not required and is not being widely employed to assure products of consistent content and quality.

Representatives of the herbal industry who attended the International Workshop on Evaluating Research Needs on the Use

and Safety of Medicinal Herbs agreed that the industry must provide safe products and that current approaches for standardization are inadequate (3). They emphasized that the more responsible members of the industry are working to improve and standardize their products. There is general recognition, however, that some members of this diverse and fragmented industry are marketing over the Internet, through direct sales catalogs, and even in service stations. This lack of industry regulation permitted under the DSHEA allows marketing of products of both questionable quality and content by individuals whose financial interests may, in some cases, override their interest in the safety and efficacy of their product. Descriptions of these products outlandishly infer everything from increased virility and vitality to a state of ecstasy. In some cases, all three conditions and more are promised if one consumes a single pill that is claimed to contain a half-dozen or more herbal products.

The ease of marketing dietary supplements and the lack of regulatory control of such marketing are illustrated by an article published in the *Wall Street Journal* (15). In this case, an individual who was interested in starting a business did so by simply obtaining a source of dietary supplements and marketing over the Internet. His initial product was the testosterone precursor androstenedione that he had formulated into tablets and then marketed as "The Stud Pill for Men." This individual's research for the efficacy and safety of this product was limited to a cursory literature search and no laboratory work. No approval or control by regulatory agencies was necessary. His success (\$30,000 gross in the first month) was such that this individual is now selling a weaker formulation of androstenedione for women as the "Passion Pill for Women" and a formulation of ephedra, found in the herbal product Ma Huang, as "HerbalTrim." Again, research was limited to a brief review of the literature. The literature clearly states that profound toxicity and a number of deaths have been attributed to the use of ephedra or Ma Huang, and a number of adverse effects have been reported for testosterone precursors. These facts apparently did not deter his profit motive. This example of effective marketing, in the absence of regulatory control, is projected to result in \$500,000 gross sales of these products by this individual in his first year in business (15).

As a result of the actions of those who are willing to take advantage of the freedom to market dietary supplements permitted by the DSHEA, the more responsible members of the dietary supplement industry run the risk that consumers might lose confidence in reputable products. Consumers could be

injured by the unscrupulous sale of misformulated or adulterated products. Under the DSHEA there is little that can be done to regulate such uncontrolled and possibly even unscrupulous marketing. However, recent guidelines from the Federal Trade Commission (16) requiring truthfulness and accuracy in advertising of these products may curtail some of the more outlandish claims currently being made.

Workshop speakers suggested that better standardization and quality control may be positive aspects of the recent entry of the major pharmaceutical companies into the medicinal herb market. Mass marketing by the major pharmaceutical companies is also likely to place economic pressure on suppliers who do not have the resources to maintain the good-manufacturing practices necessary to assure quality control and standardized products.

A downside of the entrance of the major pharmaceutical companies into the medicinal herb market is that many people who would not have otherwise used medicinal herbs will be encouraged to use products that have not been proven effective in normal healthy individuals. Increased self-medication also increases the chance of adverse reactions to these products as well as adverse drug/herb or herb/herb interactions. The end result will be millions of dollars spent and not compensated by insurance for little or no beneficial effect.

A final concern regarding the use of medicinal herbs is that of risks posed to sensitive subpopulations. As discussed above, the fact that medicinal herbs are natural does not make them safe. The chemicals in medicinal herbs may be formed naturally in the plant, but they are not natural to the human body. Any compound with a therapeutic effect has the potential to be incorrectly prescribed or overdosed. Increased sensitivity of subpopulations is most frequently attributed to slower metabolism of the compound administered or to an allergic response. Thus, it follows that individuals such as the developing fetus, young children, and the elderly, who are more sensitive to the effects of pharmaceuticals, will also be at greater risk to adverse health effects associated with medicinal herbs. Additional sensitive individuals are seen among those genetic subpopulations that metabolize foreign compounds less rapidly than the general population. Members of each of these various groups may be harmed by what is for most of the population the recommended dose of a drug or herb. Sensitive subpopulations are also at greater risk of adverse herb/drug or herb/herb interactions.

Allergic reactions are not readily predicted and may occur in response to any of a large number of agents including synthetic

and natural drugs. Allergic responses to synthetic drugs are frequently detected in the course of preclinical testing, and this information is provided to the patient and physician. Additional information is obtained on synthetic drugs when patients are monitored by the prescribing physicians and dispensing pharmacists. Adverse responses and allergic reactions are noted and reported to the pharmaceutical companies who have the responsibility to include this information in the package insert for the respective drug. Consumers are thus informed and forewarned of the possibility of adverse reactions and are more likely to recognize these reactions when they occur. Because medicinal herbs are not subject to similar testing and monitoring and they usually do not contain package inserts, the consumer may be unaware that a decline in his or her health is actually an adverse or hypersensitive response to the herbal medication.

Problem Areas, Recommendations, and Actions

Standardization

Numerous speakers and participants at the recent International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs emphasized that herbal medicines are poorly defined mixtures in which the active principal has frequently not been identified. Analysis of available medicinal herb preparations indicate that both the ingredients, active and otherwise, may vary greatly from one preparation to another. The lack of standardization is illustrated by an article in *Consumer Reports* (17) that described the analysis of 10 preparations of ginseng for content of the possible active ingredients, ginsenosides. The analysis indicated that the contents of ginseng per capsule, when measured by weight, varied by more than 6-fold, and the ginsenosides per capsule varied by more than 20-fold. Further, the content of ginsenosides did not necessarily vary in proportion to the weight of ginseng in the capsule. In addition to better standardization of the products, work is needed to confirm the stability of the active ingredient(s) of medicinal herbs. In the absence of adequate standardization and quality control, both consumers and responsible producers of medicinal herbs are at risk. Consumers must have a consistent product of high quality to effectively achieve safe, beneficial effects from one formulation to another. Responsible producers are at risk when inconsistent or ineffective products damage the reputation of the industry.

Recommendations. Where methods for such quality assurance are available, they should be employed industry wide. When

such methods are lacking, research should be undertaken by both the industry and government to identify, certify, and quantify active ingredients and to determine and recommend optimum doses of medicinal herbs.

Formulations of medicinal herbs should be standardized, to the extent possible, to deliver a known amount of the active ingredient(s) in a recommended dose. Where they are known, the stability of the active ingredients should be determined, and all packages should carry meaningful expiration dates.

Package inserts that contain clear instructions regarding doses and possible contraindications should be prepared and required for medicinal herbs.

Action. As discussed earlier, WHO (13) has developed basic methods for the analysis of medicinal herbs, and the U.S. Pharmacopeia (14) is developing and publishing recommended methods for specific herbal formulations. As described by Joe Betz and William R. Obermeyer at the workshop, research at the FDA is currently addressing the need for improved methods to ensure the content and quality of medicinal herbs. Jill Ellis of the National Nutritional Foods Association and Loren Israelsen, of the Utah Natural Products Alliance, two representatives of the medicinal herb industry in attendance at the workshop, emphasized that many components of the industry are working to better standardize their products. The entry of the major pharmaceutical houses into the medicinal herb market is speculated to result in more consistent formulations.

Consumer Education

The American public, overall, comprises a well-educated and sophisticated group of consumers. However, any consumer group must base buying decisions on available information. In the case of medicinal herbs, information about health benefits has been largely limited to that provided by a relatively few advocates of their use and marketers of these products. Thus, most of the available information has been limited to the positive aspects associated with the use of medicinal herbs, with little, if any, discussion of possible adverse effects. The general public is largely unaware that adverse health effects associated with the use of medicinal herbs have been attributed to everything from overdosing to contaminated formulations to the inherent toxicity of the herb of choice. The public is also largely unaware that much of the literature regarding the beneficial effects of these compounds is anecdotal, may be greatly exaggerated or incorrect, and has yet to be confirmed through clinical trials. Most of the clinical trials that have been conducted have been conducted in other countries, and in most

cases, the results have not been translated into English or evaluated by U.S. regulatory officials. Thus, when it comes to medicinal herbs, the American public may not be well-educated consumers.

Recommendations. Because these products are not proprietary but are being consumed by a large segment of the public, federal funds should be used to develop, evaluate, and distribute the most authoritative information available regarding the efficacy and safety of herbal formulations.

Research conducted in other countries should be translated and evaluated by federal regulatory agencies. The most accurate data regarding both beneficial and adverse effects should be used to prepare informative package inserts to be included with all formulations of medicinal herbs. Package inserts should be updated as additional information becomes available.

Action. The National Institutes of Health (NIH) Office of Dietary Supplements (ODS) was established by the DSHEA (6). The purposes of the ODS were defined in the law and include the following:

to more fully explore the potential role of dietary supplements as a significant component of efforts to improve health care, and to promote the scientific study of dietary supplements in maintaining health and preventing chronic diseases and other health-related conditions.

Working with representatives of the scientific community, consumers, and industry, the ODS has developed a Strategic Plan that includes five equally weighed goals and related objectives (18). The Strategic Plan goals include the following:

- Evaluate the role of dietary supplements in the prevention of disease and reduction of risk factors associated with disease
- Evaluate the role of dietary supplements in physical and mental health and in performance
- Explore the biochemical and cellular effects of dietary supplements on biological systems and their physiological impact across the life cycle
- Improve scientific methodology as related to the study of dietary supplements
- Inform and educate scientists, health care providers, and the public about the benefits and risks of dietary supplements.

Additional information on ODS efforts to support research, improve education, and disseminate knowledge is available on the ODS web site (19).

An excellent source of information regarding the use and safety of medicinal herbs has recently been translated from German into English (8). This text, translated by the American Botanical Council, provides a wealth of information on a multitude of herbal formulations. The *Botanical Safety*

Handbook (11), another recently published resource that contains a great deal of valuable information, includes a listing of herbs by Latin binomial, based in part on toxicologic considerations and profiles of commonly used herbal medicines. A third useful reference is the *Physicians Desk Reference (PDR) for Herbal Medicines* (20). This publication presents a comprehensive listing of medicinal herbal products. Each entry provides information and data on source, identity, formulation, dosages, contraindications, and drug interactions where known. The entries also include references to published studies. Information on benefits and risks associated with the use of herbal supplements has recently been made available on the Internet from the FDA through the Center for Food Safety and Applied Nutrition's dietary supplements web site (21) and through the NIH's National Center for Complementary and Alternative Medicine (22).

Not all consumers have access to these relatively expensive books or to the Internet. Further, information for all supplements is not available or may be incomplete. Thus, when it is available, information regarding recommended uses, doses, and possible contraindications would be most assessable if required on a package insert with the respective product.

Herb/Drug and Herb/Herb Interactions

Several speakers and discussants at the International Workshop to Evaluate Research Needs on the Use and Safety of Medicinal Herbs expressed concern regarding the simultaneous use of more than one herbal product and/or the use of herbal products in combination with pharmaceuticals and/or alcohol. Documented incidences of adverse effects, some leading to death, were recounted by discussants at the workshop. Most of these incidences were associated with abuse. However, unrestrained marketing and fraudulent advertising set the stage for such adverse interactions. Patients frequently do not inform their physicians that they are also using herbal remedies. Thus, when a physician prescribes a drug having the same or an opposite pharmacologic action, there is potential for adverse interaction. In other cases these products may be marketed as a combination of herbal compounds to be used as a means of obtaining extra energy, virility, or other desired state and thus set the stage for abuse and adverse interactions when combined with illicit drugs and alcohol.

Recommendation. An initiative is needed in the medical community and among the producers and marketers of medicinal herbs to identify and document herb/drug and

herb/herb interactions. Information obtained from this initiative should be provided to both the herbal and pharmaceutical industries and required on package inserts with the respective products.

Action. A number of health care professionals who have treated patients experiencing adverse interactions have endeavored to bring this information to the attention of the public. However, these efforts are as yet gaining little attention from regulatory agencies or the industry (11).

Potential Toxicity Associated with High Dose or Prolonged Use

Prescription drugs come with carefully written instructions regarding their use and possible contraindications. The time over which these products are used is limited by the expiration of the prescription, and prescriptions are not renewed without the recommendation of a physician. Over-the-counter drugs are not available until extended use has proved them safe at the recommended dose, but medicinal herbs, most of which have not been tested in clinical trials, are readily available to a largely uninformed public. Little is known regarding the potential of these compounds to increase the risk of immunotoxicity, neurotoxicity, birth defects, reproductive problems, or cancer with extended use.

Recommendations. Because medicinal herbs are not without therapeutic effect, they, like other pharmaceuticals, will be toxic at some dose. Medicinal herbs should thus be tested to characterize both their acute and chronic toxicities.

Action. In a continuing effort to address those compounds to which the public is exposed, the National Toxicology Program is currently designing and initiating studies to identify and characterize adverse effects that may be associated with prolonged or high doses of some of the more popular medicinal herbs. Results of these studies will be peer reviewed and made available as soon as they are completed.

Sensitive Subpopulations

It has long been known that the developing fetus, the young, and the elderly may be more sensitive to the effects of certain drugs than the general population. There is also increasing evidence for other sensitive subpopulations as a result of genetic predisposition. In most instances, sensitive subpopulations show an elevated or adverse response as a result of compromised capacity to metabolize the respective drug. Also, individuals of all ages may have allergic reactions to botanical products. Because medicinal herbs are therapeutically active and metabolized in manners similar to synthetic drugs, similar adverse reactions to medicinal herbs can be expected

in sensitive subpopulations. However, such adverse reactions and allergic responses have not been well documented, and information regarding possible adverse responses is not usually provided to the consumer. In some cases, the public has actually been misled when medicinal herbs have been marketed as safe to all ages because they are natural.

Recommendation. Research and data collected from consumers should be compiled and analyzed to identify sensitive subpopulations based on age, sex, nutritional habits, allergic responses, and the presence of specific genes that may predispose consumers to an elevated or toxic response to medicinal herbs.

Action. Little is being done to address the needs of sensitive subpopulations at this time or to publicize the fact that they may be at risk. Once comprehensive studies to characterize the pharmacologic effects of individual agents are completed, it will be possible to design better studies to address this issue.

Summary

Medicinal herbs are some of our oldest medicines. The fact that they continue to be used by millions of people is testament to both their real and perceived beneficial effects. Their increasing use in recent years is clear evidence of public interest in having alternatives to conventional medicine. However, the fact that medicinal herbs are "natural" does not assure their safety. They have not been tested in the manner required for conventional pharmaceuticals. Thus, there is limited data to confirm their efficacy and little or no scientific data regarding possible

adverse effects associated with high doses or chronic use or the hyperresponsiveness of sensitive subpopulations. There is also considerable concern regarding the lack of standardization of herbal preparations and the inadequacy of consumer information. Much needed testing for safety and efficacy cannot be mandated under the present laws regulating the industry. Given the economic disincentive for significant expenditures for such research, the industry is unlikely to conduct this research. Many of the concerns regarding standardization and consumer information could be addressed through reassessment of the DSHEA. However, if testing of medicinal herbs for efficacy and safety is to be conducted, it will probably have to be supported by the government. Results of testing, assessment of data from other countries, and documentation of adverse effects resulting from interactions and hypersensitive responses should provide information to consumers in the form of package inserts with all products.

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