Herbal Medicines, Phytoestrogens and Toxicity: Risk:Benefit Considerations[1] (44248)

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Abstract. **There are several suggested health benefits of phytoestrogens, particularly those found in soy products. Herbal medicines are also widely thought to confer health benefits. Additionally, drugs are prescribed to improve human health, but unlike phytoestrogens and herbal medicines, toxicities are defined in experimental animals and monitored in humans before and after marketing. Knowledge of toxicity is crucial to decrease the risk:benefit ratio; this knowledge defines appropriate conditions for use and strategies for development of safer products. However, our awareness of the toxicity of herbal medicines and phytoestrogen-containing foods is dramatically limited compared to drugs. Some aspects of the toxicity of herbal medicines are briefly reviewed; it is concluded that virtually all of our knowledge is derived from human exposures leading to acute toxicities. Importantly, detection of toxicity is sporadic, and little information is available from prior animal experimentation. Additionally, well-organized monitoring of human populations (as occurs for drugs) is virtually nonexistent. Important toxicities with long latencies are particularly difficult to associate with a causative agent during or even after large scale exposures, as exemplified by tobacco smoking and lung cancer; estrogen replacement therapy and endometrial cancer; diethylstilbestrol and reproductive tract cancers; and fetal alcohol exposure and birth defects. These considerations suggest that much closer study in experimental animals and human populations exposed to phytoestrogen-containing products, and particularly soy-based foods, is necessary. Among human exposures, infant soy formula exposure appears to provide the highest of all phytoestrogen doses, and this occurs during development, often the most sensitive life-stage for induction of toxicity. Large, carefully controlled studies in this exposed infant population are a high priority.** [P.S.E.B.M. 1998, Vol 217]

Several lines of evidence suggest significant health benefits of phytoestrogens, plant chemicals possessing estrogenic activity. This evidence is reviewed in a number of papers presented in this volume (1–5), and while not the subject of this paper, clearly needs to be considered as part of an overall evaluation of potential health benefits. However, here I wish to discuss certain characteristics of herbal medicines, long used for health purposes, and to explore some broad cultural and scientific relationships that exist between herbal medicines and phytoestrogens. Specifically, both herbal medicines and phytoestrogens are widely believed to be beneficial but can display toxic effects, and these, like the health claims, also need consideration in order to evaluate overall health effects properly.

Toxicologists can be perceived as having a negative impact on the development of a wide range of marketable products that may benefit society. This naive perspective is challenged by one of the important goals of the toxicologist: to provide information on risks to be included as part of a risk:benefit evaluation. The appropriate decision is directly dependent on the proposed use of a product. For example, drugs useful in diseases with high mortality can display serious toxicity but still be appropriate for use, whereas lower toxicity may not be accepted in a product for common minor ailments, such as colds. An important additional consideration is voluntary versus involuntary exposure; risks associated with involuntary exposures are less acceptable than risks from voluntary exposures (6). Thus toxicologists contribute to decision-making regarding whether a product should be on the market, and if so, under what specific

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conditions of use. These decisions are important to protect human health, which can be improved by having knowledge of toxicity. An example is provided by tamoxifen, a drug that is widely used for its beneficial effects as an antiestrogen in preventing recurrence of breast cancer. However, recent findings demonstrate that tamoxifen acts as an estrogen and increases endometrial cancer incidence in breast cancer patients (7). This knowledge has not resulted in the removal of tamoxifen for intended beneficial effects; rather, clinicians now know to monitor patients closely for clinical signs of endometrial abnormalities and to take appropriate medical action when these are found. This knowledge decreases the risk:benefit ratio by lowering the population risk.

This, then, is the context within which the information presented herein should be considered: How can we improve human health by understanding the toxicity of both herbal medicines and phytoestrogens?

Plants are chemical factories that directly provide about 25% of currently used drugs: another 25% of drugs are chemically altered natural products (8). Likewise, phytochemicals with known or potential health benefits are found in plants or plant products marketed either as herbal medicines (9, 10) or foods (11). The latter group includes soybeans, which have a high phytoestrogen content and are a growing component of the human diet. There is, however, a fundamental difference in the safety evaluation of drugs compared to herbal medicines or foods (excluding, in the latter case, chemicals added to foods). Marketing approval for drugs requires careful preclinical, clinical and postmarket evaluation of both safety and efficacy; this is not a general requirement for herbal medicines or foods.

Preclinical safety testing in animals follows well-defined protocols involving short- and long-term dosing for evaluation of organ toxicity and death, and tests for mutagenic and carcinogenic activity, reproductive toxicity, and adverse effects on development, among others. Additional specific investigations may be necessary depending on the drug class or the nature of toxicity found in standard preclinical tests. A significant proportion of potential drugs never get to the market because toxicity data suggest a poor risk:benefit ratio.

Clinical testing, which follows animal testing, involves drug administration to volunteers with close monitoring of both efficacy and safety. Again, a number of drugs fail these evaluations. Once marketed, drugs continue to be scrutinized through post-market surveillance: for example, physicians report adverse effects possibly associated with drug treatment, and reports must be maintained by the drug sponsor. Drugs are occasionally found to have toxicities in postmarket surveillance that were not detected in the rigorous preclinical and clinical testing. These findings can influence marketability, conditions of use, and patient monitoring as appropriate. Most drugs are available only by prescription. Patients are informed of possible adverse effects both by their physician and the drug label, and are monitored by their physician. By these measures, most people are aware that drugs may have toxic effects. This knowledge can lead a patient to associate their drug ingestion with adverse outcomes.

Another difference between many drugs compared to herbal medicines and foods is the purity of the chemical of interest. Many drugs are pure chemicals (with fillers, excipients, etc., added for pharmacological purposes); others, however, are complex mixtures that may be partially purified, such as alcoholic extracts (tinctures). Foods and herbal medicines generally are complex mixtures.

Unlike drugs, herbal or folk medicines and food products directly derived from plants are not generally required to be tested for safety or efficacy. Food safety laws are complex and not the subject of this discussion, but it should be appreciated that chemicals added to foods during processing (e.g., antioxidants, emulsifiers, etc.) do require safety testing.

Herbal products have a long history of use based on religious and cultural traditions in which plants are viewed as sources of health remedies (12). This is clearly shown by the prevalence of plant products among prescription drugs. However, it is also true that plants have evolved defense mechanisms against animal and pest predation. These include thorns and other types of physical protection, as well as chemicals that either make plants unpalatable or that sicken or kill their predators and are widely distributed among plants. Such toxicity occurs in humans. The coexistence of beneficial and adverse effects is as true for plant products as for drugs. An important distinction is that our knowledge of drug safety is much superior to our knowledge of herbal product or food safety; we depend on the mostly random accumulation of reports of adverse effects in humans for the latter products (12), and this reporting system is poorly organized and greatly dependent both on luck and consumer as well as physician alertness.

What do we know about the use of herbal medicines and the attitudes of consumers? In a survey of HIV-positive patients, 22% reported regular use of an average of 4.5 herbal tablets per day. Over one-quarter of these reported adverse effects that could be caused by the herbal products (13). Approximately one in two Hong Kong residents use herbal medicines (14). Brown and Marcey (15) report that over 90% of 100 surveyed adults used at least one botanical remedy or another, with a median number of seven (range, 0–33). Of those with chronic conditions, more (58%) used home remedies than physician-prescribed treatments (21%). These findings demonstrate a strong belief in, and highly prevalent use of, herbal products, a phenomenon that cuts across cultures and economic classes. Additionally, in part due to the lack of adequate safety data, toxicities may not be expected; in fact, the possibility may be vigorously denied. Adverse outcomes, therefore, may not be recognized as being associated with herbal products.

However, numerous herbal products demonstrate toxicity; this relationship between known toxicity and the per-

ception of consumers stands in direct contrast to the more widespread knowledge of drug toxicity detailed earlier. The toxicity of herbal products may be classified as due to misidentification of plants or to toxicity of properly identified plants (16).

Misidentification has been documented for both self-collected plants and in commercial products. Foxglove is the original source of digitalis compounds and some leaf preparations remain available. Death due to arrhythmias and hyperkalemia are well described (17). An elderly man consumed tea prepared from leaves of a foxglove plant found in his back yard; acute cardiotoxicity resulted (17). A couple died following ingestion of tea prepared from foxglove mistaken for comfrey; other cases of foxglove poisoning are known (18). A red variety of common vetch was misidentified and sold as red lentil; vetch contains neurotoxicants (19). Two infants were poisoned with a tea prepared with the herb *Senecio longilobus* mistakenly substituted for *Gordolobo yerba* (12, 18). One infant died and the other suffered chronic liver toxicity. Both of the latter examples were due to commercial products. Likewise, a large American marketer of herbs misidentified deadly nightshade as comfrey, resulting in atropine poisoning (20, 21). In any case, comfrey itself is hepatotoxic and, although widely marketed, should be completely avoided (12, 22, 23).

Misidentification also results from nomenclature problems. Ginseng (English common name) is also called renshen (transliteration), radux ginseng (latinized pharmaceutical name) and *Panax ginseng* (scientific name) (14). Additionally the same common name may be applied to different plants (14). ''Cohosh'' is used in New England for baneberry, which is toxic, while in areas of Appalachia it refers to black or blue cohosh; all three are different genera that show different patterns of toxicity (24). Huxtable (16) provides more detailed examples of nomenclature problems as described above; he as well describes the common confound that one plant may have many different names (e.g., *Heliotropium angiospermun* has 31 common synonyms). Additionally, it is common to be unable to identify components of herbal medicines or teas when consumers present with clear signs of toxicity associated with their consumption (14). For example, an unidentified herbal tea was consumed by four women; one developed a skin rash, whereas the other three had veno-occlusive disease of the liver, from which one died. The tea contained pyrrolizidine alkaloids at a high concentration (25, 26).

However, proper identification alone cannot provide assurance of safety. Ridker (23, 27) lists 26 herbs with known toxicities; all are used to prepare teas, and most are available commercially. Almost 400 different herbs and spices are used for teas, and while more than 10% contain pschyoactive ingredients, it is unclear if they induce responses (28). One chemical class of toxicants found in a number of herbal preparations is the pyrrolizidine alkaloids; over 8,000 cases of veno-occlusive disease of the liver have been reported to be caused by this class of chemicals (16, 29) including probable human embryotoxicity (12, 30).

In addition to teas, herbs are also consumed by smoking. Some 20 years ago, 192 different herbs were available for such use (28). Of the mixtures used in 18 different products, almost half contained psychoactive ingredients.

Sassafras, long consumed as a tea in the southeastern United States, causes diarrhea and is hepatotoxic and hepatocarcinogenic (23). It contains the experimental animal carcinogen, safrole. Licorice (*Glycyrrheza glabin*) can induce a syndrome of toxicities that appears clinically similar to primary aldosteronism (23). Alexander the Great's army used licorice during desert crossings, probably to conserve water by reducing urine output. Licorice contains glycyrrhizic acid, a metabolic precursor of an 11β-steroid dehydrogenase inhibitor which is almost certainly the cause of the primary aldosteronism of licorice (9). Ginseng is consumed by 5–6 million people in the United States. Frequent consumption can produce a syndrome of toxicities (hypertension, confusion, depression, insomnia) and severe hypotension upon withdrawal which together mimic corticosteroid poisoning (8).

Several plants in the southwestern United States contain adrenergic chemicals. One of these, ephedrine, has been consumed as a ''natural amphetamine.'' About 500 reports of adverse effects, including eight deaths, were received in less than two years by the state of Texas (31, 32). Natives of Curacao consume teas prepared from *Croton flavens* and suffer a high incidence of esophageal cancer (33). This plant contains a family of diterpene esters that increase the risk of malignancies when given with a chemical carcinogen (co-carcinogen) or after a carcinogen (tumor promoter). Their potency is comparable to the phorbol-12,13-diesters, such as TPA, which are widely used in experimental carcinogenesis studies. This is the first example that an herbal tea containing co-carcinogens and tumor promotors likely represents the primary carcinogenic risk in epidemiologically identified human malignancy (33).

The examples provided here, as well as numerous others (see Refs. 16, 23, 24, 26) demonstrate that a long history of accepted use of herbal medicines cannot provide great confidence in their safety. In fact, it has been asserted that plants injure or kill more people than animals (12).

Estrogen toxicity is well-known to be associated with plant exposures; phytoestrogens induce infertility (34, 35) and developmental toxicity (36–38) in animals. However, we have little evidence of the adverse effects of herbal preparations that contain phytoestrogens, although attention to phytoestrogens in herbal medicines is increasing (39). Chaparral (*Larrea tridentata*), a desert plant found in the Southwestern United States and Mexico, has long been used as an infusion (tea) for a number of diseases. The high content of nordihydroguaioretic acid in chaparral appears responsible for hepatitis in users of the tea (40, 41). It has also been used as a contraceptive preparation (42), consistent with experimental data showing estrogenic activity and

actions as a reproductive toxicant. It has been marketed as an herbal medication. Obermeyer *et al.,* (40) have shown that the phenolic content, which is 80%–90% of the dry weight, is more effectively extracted in methanol than water. The major phenolic chemicals extracted are flavonoid aglycones and glycosides (quercetin, kaempferol, and luteolin) and lignans (43). Because chaparral is marketed as capsules or tablets, the bioavailability of these estrogenic chemicals is expected to be higher than in teas (40). One of the chemicals that may be responsible for the reproductive toxicity (anti-implantation activity) is 3′-demethoxy-6-*O*-demethyl-isoguaiacin, which is estrogenic in rats (44). Given that one traditional use is as a contraceptive agent (consumed as a tea), increased phytoestrogen bioavailability from capsules or tablets may induce involuntary infertility in unsuspecting consumers. Other herbal products contain phytoestrogens that have been detected in bioassays using either extracts of the herbal medicines or saliva from individuals consuming them (39). An herbal medicine derived from *Vitex agras casta* may increase follicular phase estradiol concentrations and induce an ovarian hyperstimulation condition (45). The phytoestrogen content is unknown.

Despite the fact that numerous herbal medicines are traditionally recommended for various disorders and conditions of female reproduction and pregnancy, and that numerous plants contain estrogenic chemicals, no information unambiguously links the phytoestrogen content of herbal medicines to estrogenic effects in humans. Given the poor monitoring of exposure and effects in humans, it cannot be considered that such a relationship does not exist.

In addition to the high phytoestrogen content in soy products, which are estrogenic and developmentally toxic in animals (38), there are other well-described examples of phytoestrogen-containing plants inhibiting fertility *via* estrogenic activity. These include ''sheep clover disease'' due primarily to the phytoestrogen coumestrol (34, 46) and ''moldy corn syndrome'' in pig and cattle fed corn contaminated by *Fusarium sp.,* which produce the estrogenic β-resorcylic acid lactone, zearalenone (47). Both of these chemicals display typical estrogen effects during reproduction and development. Another example is inhibition of reproduction of California quail by phytoestrogens produced by plants growing in dry conditions (34).

These examples in animals suggest that the phytoestrogen content of herbal medicines and soy products may induce unintended adverse effects on reproduction and development in humans. Herbal product use is prevalent and perceived as safe. Some herbal medicines induce toxicity, and these outcomes are not usually detected by an organized and systematic monitoring of the exposed population. How can we apply these findings to a consideration of the health effects of soy products? First, soy product use is prevalent and perceived as safe; it demonstrates toxicity in livestock and experimental animals; and exposed populations are not systematically monitored for adverse effects. Based on this comparison with herbal medicines, confidence that soy products are safe is clearly based more on belief than on hard data.

A general argument can be made that the long history of apparent safe use of soy argues that it is not toxic, similar to assertions made for herbal medicines. It is important to point out that almost all known human toxicities of herbal medicines are acute; toxicities with long latencies to appearance are infrequently described and are usually associated with long-standing use of a product. Adverse outcomes with long latencies following discontinuation of herbal medicine use have rarely been demonstrated. Does this mean that such toxicities do not exist or that our abilities to detect them are sharply limited? Without numerous well-designed studies, we simply cannot answer the first question, but there are clear examples that demonstrate the difficulty in associating long latency toxicities with a specific chemical exposure. Four such examples are provided.

Since its introduction to Europe 5 centuries ago, tobacco use has increased. However, heavy smoking was relatively infrequent soon after use in Europe began and was not suggested to be associated with lung cancer until 1761 (48). Not until the middle of this century were convincing studies presented linking tobacco use to malignancies, primarily lung cancer (48). To this day, most tobacco companies and some consumers deny the clear and compelling evidence that smoking causes lung cancer, which shows a latency from initiation of smoking to disease detection of several decades. Thus does belief trump data.

Likewise, the use of unopposed estrogen replacement therapy (i.e., lacking a cyclical progestin component) for menopausal symptoms is now well known to increase the risk of endometrial adenocarcinoma (49). The relative risk increases about one unit for every year of use (e.g., 5 years of exposure results in a 5-fold higher risk of disease occurrence). Prescription drugs were causative. Physicians, drug companies, consumers aware of possible drug toxicities, and the Food and Drug Administration were all involved in defining and advising against unopposed estrogen replacement therapy. Yet even under much more favorable conditions than for detection of adverse effects caused by tobacco, almost 3 decades elapsed before a high level of human exposure to unopposed estrogen therapy was unambiguously associated with this serious toxicity.

In both of these examples, most of the individual exposures were continuing at the time of detection of the malignancies. Thus while there was a long latency to disease appearance, exposure was generally concurrent with disease detection, allowing the association of cause and effect to be made more easily.

Two other examples suggest that when exposure is brief, a long latency to disease appearance may be an even more difficult obstacle to finding the causation. Diethylstilbestrol (DES) exposure of 3–5 million women occurred during pregnancy; a majority of female offspring and a

smaller portion of male offspring showed various developmental abnormalities and malignancies of the reproductive tract that were diagnosed some 12–25 years following the exposure (50). Treatment with this estrogenic drug continued for over 20 years before this association was made by alert physicians who saw, in a short space of time, a handful of young women with clear-cell carcinoma of the vagina or cervix (51). This malignancy is extremely rare, particularly in young females, and it was this unusual feature that led to the demonstration of DES causation. If this had been a more prevalent disease in young women, or if it had not occurred at all or more rarely following DES exposure, it is questionable that the much higher prevalence (50) of benign abnormalities of the female reproductive tract would have been associated with DES exposure. This is due to the fact that similar benign abnormalities occur at a lower prevalence in young women not exposed to DES, and thus an increased incidence might have gone undetected. Thus, simple luck and alertness appears to have played a large role in understanding the role of DES in inducing human malignancies and malformations.

Finally, a very informative example is provided by Fetal Alcohol Syndrome (FAS). FAS occurs in some infants of mothers who consumed alcohol during a critical stage of fetal development. It is characterized by a distinctly recognizable pattern of facial abnormalities and other significant problems, primarily but not exclusively, in the central nervous system (52). This syndrome and its association with maternal alcohol consumption was first described in the 1970s (53, 54). Yet alcohol consumption during pregnancy has certainly occurred over several thousands of years. There is no reason to assume FAS is a recent occurrence; it has been described in every species examined, including nonhuman primates, and in all ethnic groups examined (52). Humankind has looked closely at the faces of its newborn infants over the entire period that maternal alcohol consumption has occurred, yet FAS was only described from a cause and effect perspective three-quarters of the way through this century. The latency between exposure and detection is less than nine months, and the features of FAS are clearly visible at birth. This is an extraordinary demonstration of our inability to associate a clear externally displayed manifestation of toxicity with a well-defined exposure over thousands of years in an untold number of cases.

To my knowledge, there are no long-term studies in humans in which a possible association between soy exposure and toxicity has been systematically and rigorously explored. Given the prevalence of soy exposure and the possible health benefits, it is appropriate to include adverse effects in any future large-scale, long-term epidemiological studies. Because reproductive and developmental toxicity have been demonstrated in animals and humans with a wide variety of estrogens, and phytoestrogen exposure has been shown to induce reproductive and developmental toxicity in experimental animals and livestock, these endpoints should receive particular attention. Given the parallels with herbal medicines with respect to attitudes, monitoring deficiencies, and the general difficulty of detecting toxicities with long latencies, I am unconvinced that the long history of apparent safe use of soy products can provide confidence that they are indeed without risk.

One use of soy, in infant formulas, results in a high phytoestrogen exposure during development (55). Consumption of phytoestrogen-containing soy products by women produces demonstrable estrogenic responses at phytoestrogen doses about 5-fold lower than in soy infant formula exposed infants (55–57). Unfortunately we know very little regarding the toxicity of estrogens generally in human infants. Premature breast development, (gynecomastia in males and premature thelarche in females), can be caused by infant exposure to oral contraceptives *via* mothers milk (58). Rhesus monkeys are used as an animal model for human reproduction and development. A low dose of DES (500 ng/Kg) administered daily to infant rhesus monkeys altered the normal postnatal gonadotrophin pattern (59). Such findings raise concerns for the potential adverse effects from an infant diet exclusively composed, in many cases, of only soy infant formula.

Additionally, goiter has been described in soy formula fed infants (60), although iodine supplementation of the formula was thought to reverse this problem (61). However, a recent study shows an increased risk of autoimmune thyroid disease in infants consuming soy formula (62). Some isoflavones found in soy formula inhibit thyroid peroxidase, the key enzyme in thyroid hormone synthesis. Inhibition can be reversible or irreversible depending on whether iodine is present (63). Inhibition of thyroid peroxidase would lower thyroid hormone (T3 and T4) serum levels and thus increase Thyroid Stimulating Hormone (TSH) levels in a homeostatic attempt to increase thyroid hormone production. The increased TSH also increases thyroid growth, potentially leading to goiter and malignancy (63). These findings, taken together, suggest that careful studies of the soy infant formula-exposed population should be undertaken, as it is a well-identified group, and phytoestrogen doses can be estimated with some accuracy. Such studies should include not only the infants currently consuming soy infant formulas, but older children, adolescents, and adults previously exposed. They should incorporate estrogenic and thyroid hormone related endpoints, as well as a wide variety of other endpoints of toxicity, as history has shown us that the specific type of toxicity encountered is not always obvious *a priori.* Additionally, given the potential health benefits of soy (1–4) and particularly the finding of inhibition of chemically-induced breast cancer by developmental treatment of rats with genestein (5), measures of possible beneficial effects should be included. Only by such studies can risk: benefit data be collected in order for health professionals to provide appropriate advice to the public. At present, we are conducting a ". . . large, uncontrolled, and basically

unmonitored human infant experiment . . .'' with uncertain risks and benefits (64–65).

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