Reviews

Challenges and Opportunities Confronting the Botanical Dietary Supplement Industry†

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The intent of this review is to identify and characterize the scientific challenges confronting the botanical dietary supplements industry, explore opposing sides of some controversial issues, and outline an agenda for addressing the more acute problems. The issues posing the greatest challenge to the industry center on quality, safety, and benefit. A key conclusion is that development of the scientific base of the industry has not kept pace with the rapid expansion of the manufacturing and marketing components. Recommendations for addressing the existing challenges are offered.

Introduction

The market for botanical dietary supplements in the United States grew explosively during the mid 1990s. In fact, most projections made during 1998 called for continued expansion of sales by 10% or more for the next several years. From early 1999 to the present, however, the growth rate for sales diminished and now appears to be stabilizing at a rate of only a few percent annually.

What has drawn Americans in ever increasing numbers to botanical supplements? For some, using botanicals is part of a pattern of returning to nature, combined with eating organically grown foods and following a generally healthy diet and physically active lifestyle. For others, botanicals represent a mild alternative to prescription antianxiety agents or sleep aids for dealing with the stress and pressure of daily life. Those born during the great baby boom after World War II are increasingly open to considering various options for maintaining mental acuity, cardiovascular health, and sexual function, as well as avoiding common problems of middle age (e.g., effects of menopause, benign prostatic hypertrophy, and elevated blood pressure and cholesterol levels). Younger generations seek increased energy, endurance, and physical performance, in addition to relief from stress and fatigue. For many Americans of all ages, the continuous escalation of health-care costs has compelled them to consider the concept of preventive health maintenance. The old adage that "an ounce of prevention is worth a pound of cure" translates today to striving toward a lifestyle comprised of more exercise and healthier eating habits, supplemented by vitamins, minerals, botanicals, and other beneficial substances. Consumers seek to maintain the body in a healthy state and minimize the risk or likelihood of illness or disease; for them, supplements play a substantial role in health maintenance. Regrettably, all too many Americans work and play at a frenetic pace, rarely sitting down to a well-balanced meal or obtaining adequate rest; for them, dietary supplements serve as an important adjunct or counterbalance to that lifestyle.

So, with sales increasing and consumers eagerly embracing botanical supplements, the industry should be free of concerns and problems, but that is not the case. Media attention has shifted recently from regulatory questions to a relentless attack on product quality and safety. Thus, the real issues posing the greatest challenge to the industry center on quality, safety, and benefit. *The crux of the problem is that the scientific base of this industry has not fully kept pace with the dynamic expansion of the market and product lines.* The resulting issues and challenges facing the botanical supplement industry are diverse and significant; they also underlie much of the criticism leveled at the industry and its products.[1]

Factors Affecting Botanical Products

This review will focus primarily on factors affecting raw material supply, ingredient and product quality, and the safety and benefits of botanical products. Communication of meaningful, credible information to consumers and the health professional community is another critically important issue for the industry. The central, interlinking issue in the botanical supplements industry has to be *quality*. The quality of the product on the shelf is dependent on the quality of the raw material and the quality of the extraction, formulation, and manufacturing processes. The safety and benefits of a product are directly related to its quality, just as the quality of raw material is dependent on practices in the agricultural supply line. It would seem logical, then, to examine these challenges sequentially, "from seed to shelf," an approach that should highlight specific problems and their interdependence. Since this analysis and review was undertaken, several other groups have examined various aspects of the dietary supplement industry, most with an emphasis on herbal products.[1−7]

Supply. A principal challenge is to develop and maintain adequate supplies of high-quality raw botanicals. Thus, the issues of quantity and quality are necessarily intertwined. It has been difficult enough for suppliers to keep pace with the sustained rapid growth of the botanical dietary supplement market, but dramatic surges in demand for St. John's

† Dedicated to the memory of Varro "Tip" Tyler, long an advocate, advisor, and conscience for the botanical dietary supplement and phytomedicine industries.

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wort (*Hypericum perforatum* L.; Clusiaceae/Guttiferae) and kava kava (*Piper methysticum* Forst. f.; Piperaceae) following favorable television news magazine stories placed enormous pressure on the supply side of the business. An additional complication is that, unlike most food crops, many botanicals are not annual plants. Some root- or rhizome-based botanicals, such as ginseng (*Panax ginseng* C.A. Meyer, *P. quinquefolius* L.; Araliaceae) and kava kava, require a minimum of three to seven years to reach a harvestable stage. Other botanicals require years of growth to reach sufficient maturity for sustainable harvesting; examples include ginkgo (*Ginkgo biloba* L.; Ginkgoaceae), pygeum [*Prunus africana* (Hook f.) Kalkman; Rosaceae], and saw palmetto [*Serenoa repens* (W. Bartram) Small; Arecaceae]. In other cases, high demand might trigger overharvesting, which, in turn, could devastate limited or hard to establish populations (e.g., pygeum, *P. africana*).

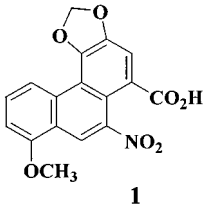
To avoid being caught in dramatic shortages of botanicals, the industry must have a means to project, anticipate, and identify likely or possible shortfalls in the availability of raw materials. Similarly, suppliers will seek to avoid a glut of raw material in the supply pipeline. The physiological activity of many botanicals could diminish during long periods of storage; thus, there are both technical and commercial motivations to avert significant excesses in supply. Therefore, the industry would benefit from a clear understanding of current foreign and domestic networks of supply, market trend analyses and projections, and knowledge of any alternative sources or potential growers.

Twenty-five to thirty years ago, the bulk of consumer demand for herbals or botanicals in the United States could be met by wildcrafting (harvesting from native plant populations). This practice of harvesting from natural habitats continues, but at a pace and style that could threaten the survival of some species and damage certain ecosystems.[8,9] Whereas a herbalist or other traditional practitioner would harvest herbs from select, reliable locations, carefully maintaining the native population, today's wildcrafters are largely contract employees paid by the pound or kilogram. The pressure to deliver specified quantities engenders a tendency to overharvest, putting slow growing or minimally germinating species at risk. In addition, environmental damage from failure to fill holes left after removing wild plants has become a serious issue in the United States. Two states, Montana and North Dakota, have recently enacted legislation to halt indiscriminate harvesting of native populations of *Echinacea*.[10]

Shipments of harvested or wildcrafted botanicals could be intentionally or unwittingly cut or adulterated with other plant species, usually ones growing in the same locale and/or resembling the desired species in physical or morphological characteristics. While this is more likely to result in a dilution of the physiological effect of the final product, it can have dire consequences, as illustrated by two recent examples.[11−17]

In the first case,[11] two women were hospitalized with symptoms suggestive of digoxin poisoning: nausea, shortness of breath, and the sensation of pressure in the chest or an irregular heartbeat. Analyses of serum samples established that both patients had significant blood levels of digoxin. Since neither woman was taking prescribed digoxin, but both had used the same combination herbal product, attention was focused on that product as a possible source of digoxin. In fact, the herbal supplement tested positive for cardiac glycosides. Persistent detective work by Food and Drug Administration (FDA) pharmacognosists and analytical chemists identified the plantain (*Plantago* sp.; Plantaginaceae) ingredient as the source of the cardiac glycosides. The raw material was traced to its source, and it was determined that about three tons of plantain contaminated with *Digitalis lanata* Ehrhart (Scrophulariaceae), the true source of the cardiac glycosides, had been imported into the United States and sold to a number of manufacturers and distributors over two years. All traceable components of the original shipment were removed from commerce at the request of the FDA.[11]

In the second instance, a number of participants in a clinical study of a weight loss product comprised of Chinese herbs developed severe nephrotoxicity, in some cases irreversible and requiring kidney replacement.[12] It was subsequently determined[13] that *Aristolochia fangchi* Y.C. Wu ex L.D. Chow & S.M. Hwang (Aristolochiaceae) had been inappropriately substituted for the expected *Stephania tetrandra* S. Moore (Menispermaceae), probably because of confusion arising from very similar Chinese names for the two rather distinct plants ("Guang Fang ji" vs "Han Fang ji", respectively). Continued monitoring of the study population revealed a dramatically high number of kidney tumors.[14,15] Two similar cases of renal failure were reported in England[16,17] and linked to aristolochic acid (**1**), a constituent of *Aristolochia*. The severity of these cases prompted FDA warnings and a recall of all supplements containing aristolochic acid. The FDA recall/warning was quite broad, including ~600 species of plants, some of which contain little to no detectable aristolochic acid.



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The quantity and quality of botanical raw material will also be affected by agronomic factors: the soil and climate in which a given plant is grown, herbivores, plant pathogens, weeds, time of harvest, and drying and/or storage conditions. Research is needed to identify the best set of growing conditions for each herb of commerce[18] and, conversely, which strain of a given herb will grow best in a given soil and climate.[19,20] Underlying these more obvious factors is an inconsistent or minimal effort in strain selection and development for botanicals. Using chemical analyses for bioactive or marker constituents and/or bioassays for physiological activity, it should be possible to identify strains or seed stock with desirable qualities and conduct additional breeding experiments to identify the best strain(s) for planting and product development.

While some botanicals are grown in cultivation in the United States, a far greater number are available in large quantities only from foreign sources. Foreign supply lines can be complex, with local suppliers assembling harvests from numerous small farms and intermediary suppliers gathering such assemblages from several local sources before forwarding them to brokers. A bulk shipment from one of those brokers may display considerable heterogeneity in content and quality. A further problem is that many foreign countries permit or tolerate the use of pesticides banned in the United States; much foreign soil is contaminated with such pesticides or other persistent organic pollutants. In addition, some botanical raw material and extracts from foreign sources have been found to contain high levels of toxic metals.[21]

A consolidated, standardized approach to resolving raw material supply and quality issues would be development of and adherence to Good Agricultural Practices (GAPs), as either part of or a complement to Good Manufacturing Practices (GMPs). GAPs would outline appropriate general guidelines for the growth, harvest, drying, and storage of botanical raw materials. Individual companies could establish their own GAPs as an expeditious alternative to including them in the GMPs expected to be promulgated soon by the Food and Drug Administration (FDA).

The Dietary Supplement Health and Education Act of 1994 (DSHEA) authorized the FDA to develop GMPs. The Commission on Dietary Supplement Labels strongly recommended establishment of GMPs, and the industry proactively proposed a set of GMPs to the FDA in 1995. The FDA published those GMPs as an Advanced Notice of Proposed Rulemaking (ANPR) in 1997. The FDA Food Advisory Committee has subsequently researched and debated various aspects of the proposed GMPs. The process still has to go through publication of proposed rules, a comment period, and, consequently, issuance of the final GMP rules, followed by a period for implementation. A critical element of GMPs for botanicals must be criteria that provide for verification of the identity of any botanical raw material, whether fresh, dried, or ground powder. Such criteria of identity might incorporate one or more elements of botanical taxonomy, microscopy, organoleptic or chemical analyses, and DNA tests.

Lurking on the horizon are applications of biotechnology to plants used in botanical dietary supplements. There are already several examples of food crops genetically modified to resist herbicides and common or likely plant pathogens, or to kill insect predators. Such technology could soon be applied to botanical crops. Perhaps more relevant to botanical crops would be genetic modifications to increase the production of particular primary (e.g., fatty acids) or secondary (e.g., carotenoids, vitamin E) metabolites. This raises a number of critical concerns, ranging from upsetting natural levels or balances of various physiologically active constituents to elevating concentrations of bioactive substances to levels that produce drug-like effects. There are already patents[22,23] on the genetic modification of nonfood plants or botanicals; more can be expected, as the technology matures and companies seek proprietary positions for specific botanicals. The political,[24] legal,[25,26] ethical,[27,28] and psychological ramifications of genetically modified organisms are quite complex and very likely to impact the botanical supplement industry in several ways. An in-depth evaluation of this topic has been published.[29]

Standards of Quality. The term "standards of quality" refers to procedures and markers for assessing and verifying the strength of the botanical raw material or extract entering the formulation process or present in the final product. Herein resides one of the more difficult challenges with botanicals: how to determine, with assurance and accuracy, that the botanical material formulated into finished product will deliver the expected, promised physiological effect. The problem is that, in many cases, the true bioactive constituent(s) of many botanicals is (are) not known with certainty, and in many, if not most, cases there are multiple chemical components, sometimes from different compound classes, that contribute to the bioactivity. Thus, there is often no simple or direct quantitative chemical analysis that can be used, with absolute certainty, for quality control of botanicals.

Still, the industry needs quality standards, and the struggle to identify an appropriate basis or standard for comparison continues, mostly focusing on a chemical fingerprint for each botanical. Thin-layer chromatography (TLC), infrared spectroscopy (FTIR), and high-performance liquid chromatography (HPLC) are the techniques most frequently used; in cases where the bioactivity is related to more volatile or easily derivatized compounds (e.g., fatty acids), gas−liquid chromatography (GLC) is utilized. Of all these methods, HPLC and GLC are the most definitive, providing high resolution and, depending on the detector used, additional data, such as UV−visible spectra or mass spectral data. FTIR is less specific and, therefore, less conclusive as an indicator of identity in most cases. Chemical fingerprinting would require a basis for comparison, specifically an acceptable reference standard for what comprises an appropriate sample of a given botanical and what level of deviation from that standard would be acceptable. If such reference standards were available, TLC would be an effective and efficient indicator of identity for raw material or extract. The development of software that permits the calculation of the degree of similarity of even the very complex HPLC chromatograms of crude plant extracts may ultimately provide a solution to applying standards of quality to botanical raw materials and extracts.

An alternative approach to a standard of quality would be to focus on physiological activity of the botanical ingredient (raw material or extract) rather than chemical content. If rapid, simple, cost-effective, meaningful bioassays could be established and linked to performance in human clinical trials, the identity of the bioactive chemical constituents in a botanical would be much less an issue, at least for the purpose of defining a standard of quality. The raw material or extract could be checked for an appropriate level of activity in an indicator assay(s) and the formulation adjusted for the desired level of effect.

Developments in high-throughput screening technology and the rapid evolution of receptor screens and molecular targets have fostered considerable interest and effort in this area by a small segment of the botanicals industry. This rapidly moving field may have an enormous impact on this industry in the next several years, even though the elucidation of the specific mechanism(s) of action of certain botanicals may be a significant challenge.

In addition to ensuring the correct chemical and/or physiological profile in botanical raw materials and extracts, it is necessary to be certain that unacceptable adulterants, contaminants, and residues are not present. Food GMPs provide some guidance regarding gross contamination (insect parts, rodent feces, dirt) and microbial load (pathogenic bacteria and mycotoxin-producing fungi), but they tend to be product specific. Beyond the obvious health concerns about microbial contamination, a high microbial count on raw material could also be indicative of improperly dried or stored plant material. In addition to considering these basic issues of wholesomeness, the botanical supplements industry must be concerned with pesticide residues, heavy metal levels, and residues of environmental pollutants, including radionuclides.

The U.S. Environmental Protection Agency has a well-defined program for registering agrochemicals and setting tolerances for specific pesticides (herbicides, fungicides, insecticides, rodenticides) on specific crop plants.[30] Most botanicals were not cultivated in significant quantities until recently and are still relatively minor crops compared to vegetables and fruits. As a consequence, there are relatively few botanicals for which pesticides have been registered and tolerances set. Foreign suppliers present a more vexing

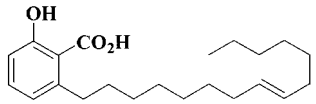
problem. Many countries do not have their own registration/tolerance programs, nor do they recognize and adhere to United States tolerances. Moreover, standards of quality and purity for pesticides are lax or nonexistent in some countries; as a result, poor quality, unregistered pesticide residues may be found in imported botanical raw material, exemplified best by the detection of poor quality quintozene (pentachloronitrobenzene), contaminated by hexachlorobenzene, in ginseng shipments from Asia in 1998.

Elevated heavy metal concentrations can result from the natural uptake of minerals by a botanical crop from soil.[21] Thus, a species with a tendency or ability to concentrate a particular metal, when grown on soil residing over or near a mineral deposit, could develop unacceptably high levels of lead, mercury, cadmium, selenium, or arsenic. However, elevated levels can also result from such plants growing in soil laden with mine tailings, industrial waste, or other environmental pollutants.[31−33] Environmental hazards extend also to radionuclides and persistent organic pollutants, which can also accumulate in some plants.[34] Even nutrient mineral content can vary significantly in botanicals; a recent analysis of tea, for example, revealed 60-fold variation in sodium content, 10-fold variation in manganese, and nearly 30-fold variation in iron.[35] An extreme example of a plant that concentrates high levels of toxic metal in its tissues is the fern *Pteris vittata* L. (Polypodiaceae); this fern has been found to have as much as 7500 ppm arsenic in its fronds.[36] Thus, bulk suppliers of raw botanical materials, manufacturers of extracts, and formulators of finished products need to know where and under what conditions their plant crops are grown. The responsibility to check botanicals for chemical contamination must be assumed by the supplier, extractor, or manufacturer; early identification of problem lots would obviously reduce the costs associated with contaminated botanical raw material.

It is worth noting that Traditional Chinese Medicine formulas often contain toxic heavy metals as intended ingredients,[37] yet western consumers may not know that they are purchasing and consuming such ingredients.

A myriad of questions can be raised about the wide variation in extraction and standardization protocols currently in use by the United States industry. Some extracts are prepared by traditional methods; that is, the methodology closely follows long established procedures. Other extraction methods utilize different solvents or new technologies, such as supercritical fluids.[38] Still other extracts have additional processing steps to render partially purified or concentrated constituents. One way that competing companies attempt to distinguish their products is by varying the preparation and composition of their extracts. Unfortunately, this practice inevitably leads to a number of products derived from the same plant, but imbued with varying chemical content and physiological activity.

Most extraction protocols continue to mimic traditional herbal preparations, primarily aqueous or aqueous alcoholic extractions (e.g., teas, infusions, tinctures), but there are exceptions. Some botanicals are pressed (e.g., garlic, aloe, echinacea), and others might be steam distilled (e.g., garlic). It is certainly feasible to increase the efficiency or yields of extraction for selected classes of plant constituents by altering the method used. Certain approaches can also be used to avoid or remove unwanted, potentially deleterious constituents of a plant or raw material shipment. The rapid development of supercritical fluid extraction in the past decade has provided a powerful and adaptable method for the extraction of natural products without the problems of solvent cost, residue, and waste disposal (or recycling). Countercurrent extraction or chromatography might be explored as a liquid−liquid alternative to liquid−solid chromatography for the removal of potentially toxic or undesirable secondary metabolites, such as ginkgolic acid (**2**) in *Ginkgo biloba* or unacceptable pesticide and other environmental residues. Research and creative thought may lead to innovative approaches, such as response surface methodology,[39] that improve extract yield or quality. An ingenious example is the use of cocoa butter to remove nonpolar pesticide residues from an aqueous alcoholic extract[40]—a clever and efficient substitution of a foodstuff for an organic solvent.



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Any anticipated application of new extraction or cleanup methodology must be made only with due consideration of the fact that altering the content of a traditional preparation may obviate reliance on any history of the botanical's safe use. In essence, the safety and benefit of new preparations, if significantly different from traditional preparations, should be established by appropriate testing. Coupling the development of physiological standardization with more efficient extraction techniques may yield a new generation of botanical products. This latter scenario also illustrates the interdependence of research and development in this industry.

There is a bewildering array of extract formulas in the United States industry and marketplace. The problem is that these products may, and likely do, have differing levels of physiological activity. Moreover, those varied extracts cannot necessarily be compared directly to the traditional preparations with documented safety and efficacy.

Standardization of extracts and, by inference, finished products is closely related to the problem of variation in extraction methodology. Standardization is a term used to describe a variety of approaches for maintaining a consistent batch-to-batch composition.[41] In the European style, standardization refers to a carefully developed and refined extraction protocol applied to raw material of consistent quality, so as to yield extracts whose constituent profiles fall in an accepted, defined, narrow range of concentration; such a total extract will have reliable, consistent biological activity. At the other extreme, standardization may be construed to mean altering extraction protocols, concentrating or diluting extract, or even spiking extract, to bring a marker compound or set of markers to a desired concentration. These latter approaches actually offer a significant likelihood of considerable variation in the chemical composition of an extract from batch to batch, with concomitant variation in physiological activity. Here, too much emphasis is placed on marker compounds, which are not necessarily linked to the biological activity of the plant, and might more appropriately be perceived as indicators of plant identity. Regardless, manipulation of the marker concentration relative to the concentration of other bioactive constituents presents a significant probability of altering the biological activity level or profile of an extract.

To this point, the discussion has focused on issues relating to the quality of the raw botanical materials and the consistency of extracts prepared from them. Another troublesome issue for the industry has been quality control of the final products, regardless of their form—tablet,

capsule, softgel, tincture, or tea. For tinctures and teas, which are extracts and raw material, respectively, the issues covered under standardization apply. For the other dosage forms, admixing with excipients and manufacturing the dosage form add a need for further analysis and control. Manufacturers need to verify that the correct amounts of each ingredient of the formulation are added and blended to a homogeneous mixture and that the finished product is of uniform size, weight, and content.

Recently, the media and public interest groups have conducted several analyses of representative botanical products. While there are reasonable criticisms to be made about the analytical methodology used in most of these cases, there is a consistent pattern of products that clearly do not meet label claims regarding content. This has been borne out by more recent analyses conducted by companies offering to verify product content. The industry simply must adapt or develop, and engage, appropriate quality control procedures to ensure and verify the content and consistency of its products. This would, in turn, be facilitated by the development of standardized, validated analytical methods.

Another measure of the quality of finished goods is whether the product breaks down, dissolves, and is bioavailable after oral ingestion. The correct amount of a botanical in a tablet would be meaningless if it passed through the digestive tract intact. That is why manufacturers must test formulations prior to marketing to ensure that tablets or capsules disintegrate during passage through the gastrointestinal system. There are very straightforward tests for disintegration; test design and conditions may vary, depending on whether the dose form is fabricated to disintegrate in the stomach or the intestine. The industry needs to adapt or design, test, and incorporate appropriate protocols.

Dissolution is a more perplexing problem. Since botanicals are comprised of complex mixtures of hundreds to thousands of compounds, the questions are which compound(s) to measure as indicators of dissolution and what conditions to utilize for dissolution. Addressing these questions is complicated by the lack of certainty as to which compound(s) is (are) responsible for the intended bioactivity. Unless meaningful physiological activity standardization protocols can be developed and applied to the major botanical products, any dissolution testing would have to rely on marker compounds, in the absence of identified bioactive constituents, as indicators of dissolution. This further complicates the problem, because the solubility of the marker compound(s) may be quite different from that of the (other) bioactive constituents. All the same complexities and arguments apply to determinations of the bioavailability of botanicals in dietary supplements, with the additional challenge of analyzing for very small levels of natural products in physiological media.

Still another quality issue is shelf life, or the stability of the manufactured dose form. Some herbs are known to have relatively short shelf lives as raw materials, because of chemical instability or volatility of bioactive constituents. However, the impact of extraction, individual excipients, and the formulation and manufacturing process is less well known, as are the effects of temperature, light, and humidity. An aggressive approach to extending or maximizing shelf life would be to store finished goods under dark, cool, low-humidity conditions. All manufacturers and distributors of finished goods should have a shelf life stability testing program for their products. As was the case for dissolution and bioavailability, the question of bioactivity levels versus content of marker compound(s) comes into play.

Safety and Benefit. Because dietary supplements are regulated as foods, not as drugs, botanical ingredients in the marketplace before October 1994 have been "grandfathered" and do not undergo premarketing FDA review. However, companies marketing supplements based on new ingredients (first marketed after October 1994) must provide evidence of safety to the FDA prior to marketing. Botanicals with a long history of safe human use without significant adverse effects, when marketed in dosages and dosing regimens following the pattern of traditional use, are generally accepted as safe. Therefore, botanicals such as ginseng (*Panax ginseng* L.), garlic (*Allium sativum* L., Liliaceae), ginger (*Zingiber officinale* L., Zingiberaceae), and echinacea [*Echinacea purpurea* (L.) Moench, *E. angustifolia* DC., *E. pallida* (Nutt.) Nutt.; Asteraceae], with hundreds to thousands of years of human consumption, no record of serious deleterious effects, and but few minor side effects, are considered safe when taken as recommended. Well-designed and conducted observational epidemiology studies could be used to buttress the widely, but not universally, accepted safety of such venerable, long-used plants with modern scientific support.[42]

There are, however, scenarios where botanical products could not, de facto, be construed as safe. One such case would be a "new" botanical product, that is, a plant with a dietary supplement application but no longterm use by man for that purpose or one that has only recently been identified in some isolated culture possessing no written history. In such a case, there may be insufficient historical evidence for safe consumption. A hypothetical example would be a plant from South America identified as having beneficial physiological effects by an ethnobotanist interacting with a native society that has no written records. A second scenario would be a new use for a long known botanical preparation; ephedra, or ma huang, may be a prime example of such a botanical. *Ephedra sinica* Stapf (Ephedraceae) has long been touted in the Chinese *materia medica* as a treatment for bronchial congestion and asthma. Ephedrine, the major alkaloid in *E. sinica*, is used in certain antiasthmatic and other bronchial decongestant prescription and over-the-counter drugs in the United States. However, dietary supplements containing ephedra are marketed primarily as adjuvants in weight loss programs and for enhancement of athletic performance. In these circumstances, the intended use of the botanical and its dosing regimen are different from the traditional use, and questions of safety, adverse effects, and efficacy have been raised. In such cases, clinical trials are appropriate to define parameters of safe and effective use.[43−48] A third case involves botanicals that are not prepared or formulated following traditional preparations. Examples would include botanical extracts that have been partially fractionated or from which a single substance has been isolated and purified. Such deviations from traditional preparations would obviously lack direct correlation with historic use. There is also an inherent risk that the process of concentrating and isolating the target chemical constituent also concentrates minor components, perhaps to levels eliciting undesirable side effects.

In some instances, safety issues can arise from confusion due to similarity in the popular or common names used for certain plants. The problems associated with *Aristolochia* spp. and similarities in the names of Traditional Chinese Medicine plants and formulas were discussed

earlier. Another prominent example is the potential for confusion of black cohosh (*Actaea racemosa* L.; syn., *Cimicifuga racemosa* L.; Ranunculaceae) and blue cohosh [*Caulophyllum thalictroides* (L.) Michx., Berberidaceae]. Despite the similarity in their common names and the fact that both are used for women's health issues, they are two very different plants with different effects. In this case, it is important to distinguish the two plants very carefully, particularly because of concerns about possible teratogenicity of blue cohosh.[49] A more general example is the relatively large number of plants commonly referred to as "snakeroot". Safety problems from confused or mistaken identity could be readily avoided by using the proper Latin binomial taxonomy, with authority, and/or consensus common names listed in *Herbs of Commerce*.[50]

While botanical supplements are widely perceived to confer little to no safety risk to the informed consumer, wide variation in human genetics and biochemistry can contribute to adverse reactions. Latent or previously unidentified conditions may predispose certain individuals or groups to a negative reaction to a given botanical.

In addition, the long history of safe use of botanicals does not include our society's current use of prescription and over-the-counter medications. Just like foods[51−57] and drugs, botanicals have the potential to impact the bioavailability, metabolism, and bioactivity of medications, as well as the body's tolerance of and recovery from surgery.[58] Several recent reviews have attempted to compile known and likely or possible herb−drug interactions.[59−62] There is currently more speculation than fact in this area; thus, there is a need for careful vigilance and research to identify, clarify, and elaborate any important herb−drug interactions.

Thus, meaningful, functional, and effective adverse events reporting and post-market surveillance systems are absolutely critical. Although the FDA has a system in place,[63] it primarily records the reports and whatever data are received. This is inadequate; follow-up investigation is necessary to establish or eliminate linkage of the reported adverse effects to the supplement in question. Some companies have established their own hotlines or reporting systems, but these are for internal use and relate only to that company's products. Either a revamping of the FDA system or establishment of an independent, industry-wide system must be an important priority. A recent proposal for an international case report database might be worth considering for botanical dietary supplements.[64]

Clinical trial data for botanical supplements are crucial to any consideration of safety and benefit, but most published studies generate vigorous debate. Detractors of botanical supplements and herbal remedies point to small size and/or short duration of trials and frequent failure to conduct double-blind, placebo-controlled studies. Proponents of botanicals, on the other hand, frequently note that proper formulations or dosing regimens are not followed or that other variables affecting the trial results are not well controlled. There is clearly a need for better design of such trials, proper selection of the formulation and dosages, and careful identification and control of significant variables.[1,65−69]

Underpinning issues of safety and benefit is a requirement for adequate, accessible, and meaningful information about botanicals, their history of use, current use, and record of performance. Perhaps in response to a one-time dearth of readily available, organized data, there is now a proliferation of monographs, databases, reference books, and compilations of data, all spanning a wide range of quality, depth, and detail. This plethora of references, with considerable variation of depth, breadth, and quality, is more daunting than a shortage of source material. Prominent among these efforts are the monographs being developed by the U.S. Pharmacopoeia (USP) and the American Herbal Pharmacopoeia (AHP). The USP began to develop modern monographs on the major botanicals in commerce in 1995, essentially returning to the roots of its genesis in the early 1800s; USP is preparing separate monographs on botanical raw materials, extracts, and dosage forms. AHP is nicely complementing the USP efforts by developing detailed monographs that provide full identity criteria (with macroscopic, microscopic, and TLC imagery), primarily on botanicals not on the USP priority list. These monographs should play a prominent role in providing standards for identity and quality of botanicals.

In addition to the industry's need for information on botanicals—for research, development, marketing, and regulatory matters—there also exists the issue of consumer access to accurate and comprehensible information about botanicals and the dietary supplements derived from them. Consumers are inundated by flyers, pamphlets, and books promoting specific herbs or products, often laden with considerable hyperbole or exaggeration in the claims made for anticipated benefit. The industry has an unquestionable responsibility to provide consumers with truthful, meaningful, and understandable information about botanical dietary supplements. A step in the right direction is the recent publication of a risk−benefit profile of several of the most commonly used botanicals—ginkgo, ginseng, echinacea, saw palmetto, St. John's wort, and kava.[70]

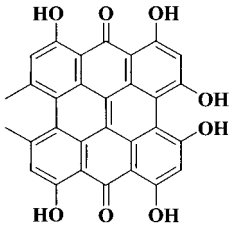
St. John's Wort as an Example. *Hypericum perforatum* L. (St. John's wort, Clusiaceae/Guttiferae) is perhaps the botanical that best illustrates the various problems discussed in this review. Currently the antidepressant most recommended by physicians and most used by consumers in Germany, St. John's wort was the fastest growing botanical product in the United States during 1997−1998. That boom in sales led to shortfalls in the supply of raw material, which, in turn, gave rise to a wide range of quality in the raw material in the marketplace over the next several years. Although good quality St. John's wort was being produced in cultivation under Good Agricultural Practices, the quantities were woefully insufficient to meet burgeoning demand. Anecdotal information suggests that some suppliers turned to a number of alternatives—poorer quality material in cultivation, increased stem-to-flower/leaf ratio to increase harvest weight, wildcrafted *H. perforatum*, other species of *Hypericum*, and early harvesting—in order to fill their orders.

Since there are several widely used and numerous other analytical methods for St. John's wort, it proved relatively easy to find a method that met most acceptance criteria in use at the time, even for poorer quality material. The current trend is decidedly toward HPLC analysis with variable/multiple wavelength or diode array detection, or mass spectrometric analysis.[71−73] Some groups are opting for HPLC with a combination of UV/visible and MS detection. While the older, less specific spectrophotometric analyses are still used by some, they are quickly fading from prominence.

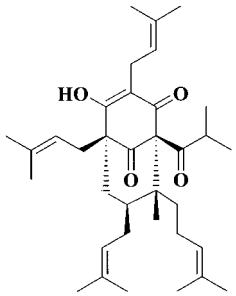
St. John's wort is known to accumulate cadmium.[74] This poses challenges for both cultivation and wildcrafting of this species. St. John's wort escaped from domestic cultivation long ago in the United States and now grows wild, adapting particularly well to disturbed ground, e.g., alongside roads and highways. While such plant populations are

quite convenient for wildcrafting, they are exposed to relatively high concentrations of cadmium from vehicle exhaust.[75] Similary, plant populations growing on mine tailings or industrial waste landfills are also likely to have elevated cadmium levels. Growers of St. John's wort should consider the possibility that a potential growing site may sit over a cadmium-rich ore deposit or lie in a flood plain downstream from such a deposit.

The central nervous system (CNS)-active constituents of St. John's wort remain an issue of controversy and active research.[76−78] For some time, hypericin (**3**) has been regarded as an essential component of the bioactivity of St. John's wort, and recent work has provided additional support for the bioactivity of hypericin.[79] At the same time, hypericin continues to serve as the primary marker compound for *H. perforatum*. However, recent studies point to hyperforin (**4**) as a major, if not the most important, contributor to the antidepressant activity of this plant.[80−85] Verotta et al. have initiated structure−activity relationship studies with hyperforin (**4**), revealing the importance of the enolized cyclohexadione unit in the molecule for pharmacological activity.[86] The extensive research compiled to date indicates that both the hyperforin and hypericin classes of compounds are important for the bioactivity of St. John's wort, with some further contribution from the flavonoids present in the plant.



3



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It would seem, then, that to standardize extracts against hypericin content would be truly meaningful only if the ratios of the other bioactive compounds to hypericin remain relatively constant from batch to batch. Tissue culture of *H. perforatum* var. *angustifolium* was found to produce different, and in some cases novel, flavonoids from the same species growing in the wild.[87] This does not augur well for the concept of a simple solution to supply problems through plant cell or tissue culture. However, tissue culture might be used to provide reference standards of hypericin and pseudohypericin, since experiments with *H. perforatum* shoot cultures revealed that mannan stimulates production of hypericin up to 4-fold.[88] New constituents of *H. perforatum* continue to be isolated and characterized;[89−94] their contributions to the bioactivity of the plant extracts remain to be defined.[95]

The effectiveness of St. John's wort in treating mild to moderate forms of stress, anxiety, and depression has been conclusively demonstrated by the cumulative evidence from more than 30 clinical trials, conducted mostly in Europe.[96] There has been considerable variation in the size and duration of these trials; some were placebo-controlled, while others used prescription antidepressants as positive controls. Despite variations in trial design, St. John's wort proved superior to placebo and comparable or superior to standard antidepressants in the vast majority of the trials. A very consistent observation in all trials was excellent subject tolerance of the herb; complaints of side or adverse effects were equal to or better than placebo or positive controls. Despite these numerous positive trials and subsequent meta-analyses,[97−101] the American medical community, in general, has not eagerly embraced the positive data generated for St. John's wort; consequently, a number of clinical trials have been undertaken in the United States. The first trial to be completed and published was that of Shelton et al., who inexplicably tested St. John's wort versus placebo in patients with long-term major depression.[102] While the herb proved superior to placebo even in this daunting challenge, the patient group as a whole was so nonresponsive that the results were described as not statistically significant. The Shelton trial is a good example of a clinical trial that creates controversy, rather than answers questions. The investigators picked the wrong target, unless they accepted that St. John's wort was effective against mild to moderate depression and wanted to probe the limits of its efficacy; such was not their stated purpose. The ethics of treating long-term, seriously depressed patients, who had not responded to other agents, with either placebo or an herb not recommended for their condition can be questioned.[103−105] However, the most egregious aspect of the report is the authors' conclusion that their trial results negated the accumulated evidence from 31 previous clinical studies!

A major clinical trial of St. John's wort, sponsored by the National Institute of Mental Health and the National Center for Complementary and Alternative Medicine and recently completed, was also targeted against major depression.[106] One cannot help but question whether a trial focusing on an inappropriate study population is a proper use of several million dollars of taxpayer money. Moreover, the results of this study illustrate the enormous challenges clinicians face in conducting trials of antidepressants. In this study, placebo outperformed both sertraline, the positive control, and St. John's wort on the two primary outcome measures. Only when secondary measures were considered did sertraline show superiority to placebo. True to previous studies,[96] St. John's wort provided a superior adverse effect profile to comparative drug treatment, even though sertraline was reportedly used at suboptimal/submaximal doses and St. John's wort was given at recommended (900 mg/day) or higher (1500 mg/day) doses. Fortunately, several other trials, correctly targeting mild to moderate depression, are currently underway in the United States.

Most pharmacological studies of St. John's wort and its constituents have been directed toward elucidating the mechanism(s) of action related to its antidepressant activity.[78,107−118] However, the pharmacological activity of St. John's wort is not limited to antidepressant effects. While the plant has a long history of use as a topical antimicrobial, recent investigations have focused on hypericin's inhibition of topoisomerase IIα[119] and nuclear factor-κB,[120] hypericin's role in inducing apoptosis,[121] and hyperforin's inhibition of the allostimulatory activity of epidermal cells.[122] Hypericin has been implicated as an

anti-HIV constituent of St. John's wort,[123] but failed to show activity in a limited clinical study.[124] Given the reports of HIV-inhibitory activity of prenylated phloroglucinol derivatives from other species of the Guttiferae/Clusiaceae,[125−128] hyperforin should be carefully evaluated for its potential as an anti-HIV agent.

Following reports that prescription serotonin reuptake inhibitors affect blood levels of protease inhibitors in AIDS patients[129] and that St. John's wort might induce the 3A4 isoform of the cytochrome P450 (CYP) enzyme system,[130] Piscitelli et al. looked at the effect of St. John's wort on blood levels of the protease inhibitor indinavir in healthy volunteers. They found a significant reduction in protease inhibitor levels in persons who had taken St. John's wort versus controls.[131] Concurrently, two case reports of transplanted organ rejection linked to St. John's wort were published.[132] Additional case reports appeared over the next year;[133] a recently published review summarized 11 case reports and two case series.[134] In the meantime, pharmacokinetic studies confirmed that St. John's wort reduced blood levels of cyclosporin A in transplant patients, requiring increased doses of the immunosuppressant.[135] Subsequent studies suggested two mechanisms for these herb−drug interactions; St. John's wort apparently stimulates the release and/or activation of the CYP 3A4 enzyme and promotes or potentiates the action of the G-protein pump.[136,137] A recent study comparing the effects of St. John's wort on the pharmacokinetics of two HMGA-CoA reductase inhibitors, simvastatin and pravastatin, revealed that simvastatin levels were significantly lowered, but levels of pravastatin were not.[138] This provided additional support to the suggestion that St. John's wort induces intestinal wall CYP 3A4 more extensively than the hepatic enzymes. The implication from these reports and studies is that St. John's wort is contraindicated for use with drugs metabolized by the CYP 3A4 enzyme; that group of drugs includes immunosuppressants, protease inhibitors, and birth control agents, among others. This is an unfortunate circumstance, since transplant and AIDS patients are two groups of often mildly or moderately depressed individuals who would otherwise derive great benefit from St. John's wort, especially with its very low adverse effect profile. There are apparent exceptions to this seeming contraindication. St. John's wort had no effect on carbamazepine pharmacokinetics, suggesting that autoinducers of CYP 3A4 were less likely to be affected by concomitant use of St. John's wort.[139]

In addition to the relatively recent observations of impact on the pharmacokinetics of certain drugs, St. John's wort has long been recognized as a photosensitizing agent, particularly in fair-skinned individuals taking high doses of the herb. Hypericin (**3**) has been found to induce photopolymerization of lens α-crystalin.[140] Damage to α-crystalin can undermine the integrity of the lens of the eye, leading to cataract formation. Thus, the authors recommended that consumers of St. John's wort should take precaution to protect their eyes from intense sunlight.

This brief look at St. John's wort as an example of the complexity of a medicinal plant is not to be construed as comprehensive. An enormous amount of research on this plant, its constituents, and their bioactivity is published every year. A number of reviews of various aspects of the science of St. John's wort have appeared in the last several years.[141−144]

Recommendations

In reflecting on this iteration of pressure points and challenges, one could construct a scenario for an ideal or utopian industry. In such a scenario, supplies of high-quality raw material would be adequate and readily available. Raw material suppliers would either own the producing farms or have contractual control over production, managing strain development and seedstock selection, growing and harvesting practices, pesticide use, and storage and shipping conditions. Trained, expert botanists would scrupulously identify plant material; chemical composition would be verified by standardized, validated analytical methods and compared to that of certified reference standard plant material. Extracts would be prepared under GMP standards to provide material of consistent, proper chemical composition and physiological potency. Likewise, formulation and manufacturing protocols would be well researched and developed and conducted according to strict GMP standards. At each step, from acquisition of raw material to packaging finished product, rigorous quality control processes and standards would be applied to ensure quality, purity, and consistency.

Of course, an ideal situation is rarely achieved in any endeavor. So, in striving to approach the perfect scenario, what can or should be done to address the problems and challenges that confront the botanical dietary supplement industry?

The botanicals industry must invest a portion of its profits in research in order to resolve problems of supply, improve the quality and consistency of its products, and develop a stronger foundation of credible data to support those products. Support from several governmental agencies should complement industrial research efforts in several areas, as outlined below. Additionally, the considerable expertise and interest in the science of botanicals in academia and other nonprofit institutions can be of great value in helping to address the research challenges before this industry.

The lead federal agency for supplement research is the National Institutes of Health (NIH), particularly the Office of Dietary Supplements (ODS) and the National Center for Complementary and Alternative Medicine (NCCAM). The ODS budget for fiscal year (FY) 2002 is $17 million, and the NCCAM budget for FY 2002 is $104.6 million.

Approximately one-third of the ODS FY 2001 budget ($3.5 million) was spent on the four recently established botanical research centers at the University of Illinois at Chicago, University of California at Los Angeles, Purdue University, and the University of Arizona. Due to its status as an Office, ODS does not have authority to fund investigator-initiated research grants directly. Instead, it supports research by funding the Research Enhancement Awards Program (about $500,000 in FY 2001) and partnering with other NIH centers and institutes. For example, along with NCCAM and the National Institute of Mental Health, it will co-fund a clinical trial examining the effectiveness of St. John's wort for the treatment of minor depression.

In FY 2001, NCCAM funded 24 investigator-initiated research grants that were directly related to botanical dietary supplements. The grants ranged from $75,000 to more than $500,000. Additionally, NCCAM awarded six Small Business Innovation Research grants that support botanicals research. Awards expected in FY 2002 will support research initiatives examining botanical−drug interactions, botanical products development, and herbal therapies for cancer. NCCAM is a major contributor to the botanical research centers program.

The ODS- and NCCAM-sponsored research programs provide an important venue and funding conduit for

academic and academia-industry research programs designed to address the critical problems lying before the botanicals industry. The recently enhanced budgets of ODS and NCCAM are an excellent complement to industry-sponsored efforts, but also afford the opportunity for independent, expert input for defining research priorities.

These developments are in concert with the Council for Responsible Nutrition's (CRN) view that the formation of a public−private partnership of the dietary supplement industry, academic research groups, and government agencies to work both individually and collectively to address and solve the problems and challenges facing this industry is the best approach to addressing the issues discussed herein. To accomplish this goal, the following actions are recommended:

I. Good Manufacturing Practices (GMPs): Industry, FDA

At a minimum, the industry must develop, implement, and strictly adhere to GMPs. While FDA was urged to promulgate GMPs for the dietary supplement industry and, indeed, the industry took the initiative to propose GMPs to FDA in 1995, FDA has been slow to take final action, publishing only an Advance Notice of Proposed Rulemaking in 1997. The industry has taken more aggressive action, through its major trade associations, to design, develop, and engage those practices on its own initiative and to urge FDA to expedite appropriate final rule making. To be meaningful and effective, GMPs must include:

A. Criteria of Identity. Appropriate testing, including taxonomic, chemotaxonomic, microscopic, and organoleptic analyses, must be employed to verify the identity, integrity, and homogeneity of the botanical raw material supply. A desirable attribute would be at least two different analyses, providing a check or confirmation of identity.

B. Standards of Quality. All botanical raw material and/or extracts should be analyzed by chemical and, as they become available and accepted, pharmacological assays to ensure that the correct levels of bioactive and/or marker compounds or bioactivity are present prior to formulation. The analytical methods utilized must be reliable, rugged, reproducible, and validated; preferably, these will be standardized methods accepted and employed widely, if not universally, by the industry. Further, the plant material or extract must be subjected to chemical analyses for the presence of unacceptable or unlawful levels of pesticides and heavy metal/mineral contamination, again using standardized, validated methods. In addition, plant material must be checked for adulterant plant species and other potential contaminants, including environmental pollutants.

C. Quality Control Measures. Protocols for formulation and dosage form manufacturing must ensure homogeneous composition of formulation batches and dosage forms through entire manufacturing runs and between runs. This will require chemical analyses of formulation batches during development of formulation recipes and frequent sampling throughout production runs. While somewhat costly to set up and operate, these analyses are essential to ensure consistency and proper quantity of content in the product reaching the consumer. It is also the industry's best defense against deleterious spot analyses of botanical products by the media and watchdog groups.

II. Reference Materials: Industry, Academia, National Institutes of Health (NIH)

To establish and meet standards of identity and quality and to apply quality control procedures, reference materials must be identified and made available in adequate quantities of consistent composition and purity.

A. Botanical Raw Material Reference Standards. While numerous monographs and taxonomic guides describe various herbs and provide guidance for identifying them, the tremendous variation in chemical content and pharmacological activity among specimens from any one species has thus far precluded any agreement on what would constitute an appropriate, valid raw material reference standard for a given botanical. It is time to move the discussion from why it is difficult to a means to solve the problem.

B. Marker and Bioactive Compound Reference Standards. Some marker/bioactive compounds are commercially available for some of the major botanicals in commerce, but many others are not. Many of the available compounds suffer from high prices, low or inconsistent purity, and intermittent availability. There must be consensus development of markers for the top botanicals and frequent updating of that consensus. Resources need to be marshaled to develop and sustain supplies of high-quality reference standards.

III. Raw Material Supply Issues: Industry, Academia, U.S. Department of Agriculture (USDA), National Science Foundation (NSF), Department of the Interior (DOI), and Analogous State Agencies

A. Strain Selection. It would be invaluable to know the extent of chemical and genetic variation in different strains and populations of individual botanical species of economic importance. Such information, coupled with data on the effects of climate and soil for a given botanical, would enable selection of the most productive strain or variant to grow in a given location.

B. Strain Development. Plant breeding experiments should be conducted in efforts to develop new strains incorporating desirable characteristics from different genetic lines, such as insect or pathogen resistance, secondary metabolite production, germination rate, biomass yield per plant or acre, growing time to harvest, and climate adaptation. Of course, if the relative amounts of the individual bioactive components in a botanical are not maintained in such strains, then the plant would no longer conform to the specimens used historically and specified in various monographs.

C. Seedstock. To cultivate botanicals, adequate quantities of seeds, rootstock, rhizomes, or cuttings of quality plants must be available. Research and development are required to provide such stock, and the seed industry should be encouraged to add botanicals to existing stock offerings.

D. Pathogens and Predators. It would also be of value to have detailed knowledge of any common or opportunistic pathogens that infect a given botanical species and of specific insects that commonly feed on a given species. Such information would be necessary for any efforts to employ biological control measures and would also be useful in selecting or developing appropriate chemical controls. Studies in the ecology of botanical species may help in strain selection; strains naturally resistant to pathogens or insects could be identified and used directly in cultivation or in plant breeding experiments.

E. Elicitors. Some plant natural products are produced as a response to certain forms of stress, such as drought, insect predation, or pathogen intrusion. A series of experiments could be conducted with a variety of potential elicitors and the response followed by chemical analyses for variation in secondary metabolite production. Results

from ecological studies of botanicals may serve to guide identification or selection of potential elicitors. As noted elsewhere in this text, alteration of some but not all secondary metabolites may be problematic for proper formulation and standardization of botanical dietary supplements. However, the use of elicitors, hybrids, or biotechnological manipulations of botanicals may serve to provide adequate supplies of reference standards to the industry.

F. Biotechnology. It is only logical that the rapidly developing tools of plant cell culture and genetic modification will be applied to botanicals. The concerns expressed above for plant breeding experiments also apply to this area of research. Any commercial products developed from botanicals with significantly altered levels of physiologically active metabolites would have to be very carefully defined and characterized, chemically and physiologically. Simpler and more readily available genetic modifications, such as introducing resistance to insects, pathogens, or herbicides, are not likely to affect the secondary chemistry or physiological activity of the derived botanical supplements, but will serve to increase crop yields and, thus, the supply of raw material.

G. Agricultural Research on Botanicals. One way to solve the problems of long, complex supply lines, inadequate quantity or quality of raw material, and contamination with environmental pollutants, pesticide residues, or heavy metals would be to obtain botanical raw material directly from domestic growers who employ GAPs. Many botanicals are ideally suited to serve as alternatives to conventional food or commercial crops, because there is a botanical suited for growth in every temperate and subtropical condition represented in the United States. The industry, USDA, and state agencies should consider promoting the development of botanicals as alternative agricultural crops, particularly in areas where mainstay crops are in declining production or demand.

IV. Phytochemistry: Industry, Academia, NIH, NSF

There should be renewed and sustained efforts to isolate and identify the biorelevant constituents of botanicals. Continuously evolving technology in pharmacological and mechanistic screening, separation and purification of natural products, and elucidation of structures of organic molecules should facilitate progress with some of the botanicals whose bioactive constituents remain unidentified.

V. Extraction and Cleanup Technology: Industry, Academia, NSF

Efforts to improve the efficiency of existing extraction protocols and to develop or adapt new technology could lead to enhanced product quality, reduced costs, and reduced environmental impact of waste stream management. Any such developments will require comparison of the chemical and physiological profiles of the new extracts with those of traditionally prepared extracts.

VI. Analytical Methodology: Industry, Academia, NSF, AOAC International

Research, development, and application of improved separation techniques, detection techniques, and methods for qualitative (identification) and quantitative analysis of botanicals are critically needed. Emerging technology and advances in the field of analytical chemistry should be investigated for their application to botanical supplements, just as efforts must be intensified to develop and validate standardized methods for the analysis and quality control of products.

VII. Product Development and Performance: Industry, NIH, Academia

Additional research on formulation, disintegration, dissolution, and bioavailability is needed.

VIII. Physiological Effects: Industry, Academia, NIH

Research should continue, and intensify, to elucidate mechanisms of action for various botanicals and the development of standardized, validated bioassays of the physiological effect of botanicals and supplements derived therefrom.

IX. Design and Conduct of Clinical Trials: Industry, NIH, Academia

The current standard of randomized, controlled trials is applicable to and should be used for botanicals in most cases, but particular attention must be paid to product specifications, dosage, duration, subject selection, inclusion and exclusion criteria, endpoints, and control of variables.[69]

X. Adverse Effects: Industry, FDA, NIH

Improved and more timely documentation, investigation, and evaluation of any adverse effects of botanicals are sorely needed. It is not sufficient to collect an initial report; prompt, rational follow up is required for any reasonable evaluation and conclusion to be drawn.

Conclusion

The overlap of areas of proposed research focus is obvious from the listings above. Several of the agencies listed above, notably the National Science Foundation, Department of Interior, and federal and state Departments of Agriculture, have not been prominently visible or active in research on botanicals, but there are important roles for each in the research that needs to be done. Collaboration among the industry, academia, and government will be critical to obtaining the most meaningful results in the most cost efficient manner. The American Society of Pharmacognosy has, through interim meetings on the science of botanicals in 1999 and 2001, provided an impetus and forum for these various organizations and entities to meet and engage these challenges together.

Recognizing that in every challenge there is an opportunity, the industry can improve the quality of its products and its appeal to the consuming public by applying scientific rationale and investing in research to tackle these challenges. This would dampen criticism and cultivate interest and enthusiasm for botanical supplements, opening the door to greater credibility and increased market growth.

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