Invited Review

Phytomedicines: Back to the Future†

Varro E. Tyler*

Purdue University, P.O. Box 2566, W. Lafayette, Indiana 47996-2566

Received August 16, 1999

Biochemist and science fiction author Dr. Isaac Asimov once noted, "The matter of prediction is full of pitfalls." That is a gross understatement.

As a youngster, I inherited from an uncle a large stock of popular science-type magazines that were full of colorful predictions of marvels yet to come. Great dirigibles were envisioned as circling the earth on a regular basis, a prediction made before almost all the giant airships were destroyed by storms or explosions. Every person would have a personal autogiro for the commute to the office. Those who have heard the pilot at the La Guardia or O'Hare airport say "We are 12th in line for takeoff, folks" know how impractical that would be in our overcrowded world. When "electronic thinking machines" were envisioned, they were seen not as fitting on one's lap but as occupying whole rooms or even whole buildings with cumbersome arrays of vacuum tubes and mechanical devices.

But even if the prediction of individual events or specific technologies remains a hazardous undertaking, I believe it is possible to foresee general trends based upon an understanding of the past. The old axiom "The past is prologue" is still valid. We do not circle the world with ease in dirigibles, but we do in jets. We do not travel the crowded skies daily to the office on an individual basis, but we can bring the office work home to us via cyberspace accessed through desktop or even laptop computers and modems. The trends are, therefore, valid, and the outcomes are similar.

The well-known German pharmacologist and historian Eduard Rudolf Kobert was a professor at the University of Dorpat in Russia from 1886 to 1897. Remember, that institution was renowned for its scientists in the field of phytochemistry. Georg Dragendorff, famous for his book on plant analysis, was a professor of pharmacy there. Kobert once said (in translation), "Nothing is more characteristic of the immaturity of a science than its belief that nothing more can be learned from its history." Today, we shall test the degree of maturity of our science by looking back at its history, seeing what took place then, and attempting to utilize that information to see how we should best proceed now. In so doing, the history of drug development becomes an important steppingstone to the future of phytomedicine.

History of Drug Development

Examination of the history of medicine and pharmacy reveals a definite pattern. Humankind first utilized materials found in the environment on an empirical basis to cure various ailments. These plants, animal parts, and even microorganisms were initially employed in unmodified form, then as concentrated extracts to improve their intensity and uniformity of action. Subsequently, pure chemical compounds responsible for the activity were isolated, and finally, using these compounds as prototypes, synthetic chemical entities were developed that possessed even greater activity.[1]

The problem with these new synthetic drugs was that as their potency was enhanced, so were their side effects and also their cost. Their use required the close supervision of an expert, a physician, to employ them to best advantage. These three factors caused intelligent people to look around and say, "There must be a better way. Let's back up a bit and see if for some conditions we cannot use the crude drugs without so much processing. They are generally mild, without serious side effects. In addition, they are much cheaper than synthetic drugs, and we can select them ourselves, without obtaining a prescription from a physician. Besides, we do not know everything about herbs. Maybe they can cure things that synthetic medicines cannot."

History Repeats Itself

So, you see, what we are doing is actually starting the entire process of drug development all over again. The evolution has already begun. A decade ago, we saw that crude herbs in the form of teas and encapsulated powders dominated the market. The words "standardized extracts" so prevalent today were practically unheard of, and the pioneering evaluations of herbal safety and efficacy by the German Commission E were as foreign to English-speaking herbal experts as the German language itself.[2]

Thus, although some progress has been made in the development of rational phytomedicine, we are still basically at the beginning of the evolutionary process. It would be my hope that, this time around, we could do things properly. Herbal products were discarded from conventional medical use in the mid 20th century not necessarily because they were ineffective but because they were not as economically profitable as the newer synthetic drugs. Having been used for scores or even hundreds of years, there was little novelty associated with the old plant remedies. Patent protection was not easily obtained, so market exclusivity and patentability were both severely limited.[3] In contrast, many of the synthetic drugs were new

* To whom correspondence should be addressed. Tel: (765)463-5326. Fax: (765)463-7202.

† Presented as a keynote address at the Interim Meeting of the American Society of Pharmacognosy, Tunica, Mississippi, April 29−May 1, 1999.

10.1021/np9904049 CCC: $18.00
Published on Web 10/14/1999

compositions of matter and readily patentable, ensuring high profitability. Instead of throwing out the good with the bad as was done in the 1940s and 1950s, let us evaluate both, keep and even improve the good, as substantial components of conventional medicine. Here is how I envision that this can be and will be achieved.

The Need for Clinical Trials

First of all, I believe that if herbal medicine is to play a significant role in future health care, the therapeutic effects of the individual herbs must be carefully evaluated by well-designed, randomized, double-blind, placebo-controlled studies involving a significant number of human subjects.[4] Those who deny the necessity of such trials are simply denying the existence of reality. Although anecdotal reports of utility are of interest, particularly in giving indications of herbs worthy of further study, they should never be viewed as a substitute for detailed clinical trials.

The cost of such evaluation is a stumbling block, but not an impossible barrier for organizations interested in promoting the public health and not just reaping a profit by the sale of a commodity. A number of herbal marketers have already made, and continue to make, a substantial investment in clinical studies. These include Indena in Italy, which sponsored such trials on a number of herbs including grape seed (*Vitis vinifera* L.) extract; Pharmaton in Switzerland, subsidizer of clinical trials on ginseng (*Panax ginseng* C.A. Meyer); Schwabe in Germany, conductor of many clinical trials on St. John's wort (*Hypericum perforatum* L.); Madaus, also in Germany, sponsor of innumerable studies on ginkgo (*Ginkgo biloba* L.); Lichtwer, again in Germany, well-known for studies on garlic (*Allium sativum* L.); Nutrilite in the United States, promoter of studies on saw palmetto [*Serenoa repens* (Bartr.) Small]; and Pharmanex, also in the United States, with its clinical trials of red yeast (*Monascus purpureus* Went). The above listing comprises the sponsors and a sampling of the herbs studied by them that have come to my attention. My apologies to these and other herbal product producers for omissions in both categories.

Because of the costs involved, sponsorship of clinical trials is sometimes seen as impractical for small companies. However, organizations unable to afford the substantial investment on their own can nevertheless participate by forming research cooperatives with a number of other producers, thus sharing both the cost and the benefits of such studies. Cooperative ventures of this sort are currently being discussed by representatives of several companies.

Problems Associated with Standardization of Herbs and Determination of Phytoequivalence

Once activity is established by clinical trials, it is necessary to standardize that activity to make certain that a uniform amount of it is present in each dosage unit. This can be a very complex matter with herbal products, the activity of which is not due to a single chemical entity but to a mixture of constituents, some of which have not yet been identified. Examples include echinacea (*Echinacea* spp.) with its complex polysaccharides, alkamides, and cichoric acid derivatives, or chamomile (*Matricaria recutita* L.), whose utility is due to terpenoids, flavonoids, and coumarins.[5] Other components may enhance the intensity of the activity by exerting synergistic effects. Still others may detract from the therapeutic utility of the active principles. This is an area in which there is much speculation but relatively little hard knowledge.

At the present time, most herbal products are standardized on the basis of the concentration of a single active or marker compound in a concentrated extract. If the active or the marker compound is present in appropriate quantity, it is assumed that all the other necessary components are also represented and uniform activity is assured. For example, most St. John's wort products are extracts standardized to contain 0.3% hypericin. While this may be a useful criterion, in a crude sort of way, it is actually quite inadequate to ensure therapeutic uniformity.

St. John's wort is now classified as an atypical antidepressant. That means we simply do not know its exact mechanism of action, nor do we know the identity of all of its active constituents.[6] It probably acts by a variety of mechanisms, including selective serotonin and possibly dopamine reuptake inhibition, and its activity is probably due to several constituents, including hypericin, hyperforin, and others. So the only practical way to ensure uniformity of action of the herb is to prepare an extract, determine its activity by pharmacological and clinical methods, and then prepare a qualitative and quantitative chemical profile of all the significant constituents in it by some method such as HPLC, GC−MS, or the like.[7] Other extracts fitting that chemical profile should have identical physiological activities.

The term used in the literature to describe the results of such methodology, that is, clinical studies followed by chemical profiling, is phytoequivalence. It is not a particularly good term because such products are not really phytoequivalent; instead, they are pharmacologically or therapeutically equivalent. But phytoequivalent is well established in the literature, so I suppose it will continue to be used.[8]

Importance of Excipients and Diluents

In determining phytoequivalence, there are other significant factors, in addition to the herbal extract itself, that must be taken into account. Excipients and other diluents used in preparing both solid and liquid dosage forms may have an appreciable influence on the activity of the final product. A recent investigation purported to show that distilled garlic oil lacked hypocholesterolemic effects. However, a study of the dosage form used revealed that the garlic oil was bound to a beta-cyclodextrin diluent from which it was only partially released following ingestion. Further, the tablets utilized were so compactly compressed that they failed to disintegrate completely in the gastrointestinal tract.[9] Obviously, both of these factors would have a significant influence on the activity of the garlic oil preparation.[10] Dosage form composition must definitely be taken into account in determining therapeutic effectiveness and phytoequivalence.

Importance of Bioavailability

Another consideration of importance is the bioavailability of the active constituents of the herb. Before a compound can act systemically it must pass from the gastrointestinal tract into the blood stream. This is an area in which surprisingly little is known for herbal constituents. Compounds, such as berberine and hydrastine in the popular botanical goldenseal (*Hydrastis canadensis* L.), are essentially not absorbed following oral consumption.[11] Studies showing systemic effects in animals have all involved parenteral administration of these alkaloids. Yet goldenseal remains one of the best-selling herbs, is widely promoted, and is accepted by a misinformed public as a nonspecific immunostimulant.

Some companies have long recognized the absorption problem. Indena, for example, complexes some of its herbal

extracts with soy bean phospholipids to enhance availability and markets the product under the trademarked name Phytosome. I have also been told that persons consuming the acetogenins of pawpaw twigs [*Asimina triloba* (L.) Dunal] for purported anticancer effects add a saponin-containing extract of sarsaparilla (*Smilax* spp.) to the herb to facilitate aqueous extraction and absorption.[12]

Phytoequivalent herbal preparations are currently available only in limited numbers. But it is the logical end point in the evolution of rational herbal therapy, and I predict that such products will eventually dominate the market. Possibly, because of the initial expense involved in determining true phytoequivalence, intermediate methods of estimating utility will be utilized on a short-term basis. We already have preparations whose activity is determined by various in-vitro assays, primarily of an enzymatic nature, the results of which are extrapolated to provide an estimate of the product's effect in human beings.[13] This procedure does provide some useful information and is a sound intermediate step prior to full clinical testing and profiling of the specific dosage forms being marketed.

The deficiencies of in-vitro enzymatic assays of plant extracts are obvious. They do not take into account the effects of excipients or other diluents used in preparing the final dosage form. Degree and rapidity of gastrointestinal absorption is unaccounted for in such studies. It seems presumptuous to make efficacy claims only on the basis of such trials conducted prior to clinical testing of the final product.

Isolation of Constituents Not Needed

My personal belief is that rational phytotherapy need not proceed beyond the determination of phytoequivalence of products prepared from standardized herbal extracts. That is, it is not necessary to isolate the active constituents from an herb and market them in highly purified form. It is necessary to determine the identity of the principal actives so that chemical profiling and establishment of phytoequivalence can be made more precise, but beyond this point phytotherapy separates from nonphytotherapy. The multiplicity of constituents in the former type product probably renders infeasible their isolation and marketing as purified compounds. It simply is not obligatory to go beyond the establishment of phytoequivalence for herbal products.

Drug Approval and Quality Standards

When botanical medicine has become fully developed, that is, when standardized products become available as effective therapeutic agents in dosage forms whose phytoequivalence has been determined, I believe that it will naturally merge with medicine making use of synthetic monochemical agents. Herbal products will be approved as drugs by regulatory agencies, and standards of quality will be established and enforced. The need for drug approval and quality standards cannot be overemphasized. The Food and Drug Administration (FDA) simply must find a way to allow drug-approval of effective, but generally nonpatentable, botanicals to take place with a reasonable investment. The $350-$500 million standard now in place for new chemical entities requires modification. A system allowing this has been in place in Germany for many years and has functioned essentially problem free. We should emulate it here. Dr. Robert Temple, director of medical policy at the FDA, is now said to favor this approach.[14] However, apparently he has been unable to convince other policy makers in the Agency because although some 50 botanicals have been submitted as investigational new drugs (INDs), none has yet been approved.

Such approval would bring about the establishment of required standards of quality for phytomedicines. The single biggest problem today in the entire field of herbal medicine is the enormous variation in quality of the products. While variability is expected for the ground-up herbs grown and processed under different conditions, it also exists in the so-called standardized products.[15] Some are of excellent quality; for others the quality ranges from good to poor to very, very bad. The consumer simply has no way of identifying a quality product other than by the perceived reputation of the producer. In some cases, perception is definitely not reality. All of this will change if and when herbal products are allowed to be sold as approved drugs with required standards of quality. Students of medicine and pharmacy will learn about phytotherapeutic agents during their professional academic programs. Doctors and pharmacists will prescribe or recommend both phytomedicines and synthetic medicines for various conditions, depending on which is deemed more appropriate. In other words, phytotherapy, botanical medicine, herbal medicine, whatever you choose to call it, will have become integrated into conventional medicine, and the words "alternative" or even "complementary," at least as applied to herbs, will no longer be appropriate.

Continued Use of Phytomedicines

This brings up the subject of just why phytomedicines will continue to be used once this assimilation takes place. Observation of countries where this has occurred provides several reasons. In the first place, herbs generally have far fewer side effects than do synthetic drugs.[16] Since many exert their effects through a multiplicity of mechanisms activated by several different types of chemical constituents, the total result is a significant one relatively free of the adverse effects produced by large doses of a single agent. One example is saw palmetto for benign prostatic hyperplasia. It exerts many of the same beneficial effects as finasteride without the undesirable effects of the prescription drug.[17]

Another benefit is that because of their milder action without the undesirable properties of synthetic prescription drugs, herbal products can be self-selected in many circumstances. Also, as previously noted, patent protection is unavailable for most of them. These two factors result in a considerable monetary savings to the patients or their insurance carriers. Saw palmetto products typically cost about $0.65 per day at present compared to more than $2.00 per day for finasteride. Herbal products are, and will remain, much more affordable than synthetic drugs. This should prove to be of considerable interest to large insurance companies involved in providing health-care coverage.

Another factor favoring the use of phytomedicines is that they have beneficial properties lacking in synthetic drugs. There is presently no synthetic drug providing the same beneficial immunomodulating effects as echinacea.[18] Currently approved drugs in the United States treat the symptoms of colds and influenza, not the causative viruses. Likewise, there are currently no effective synthetic adaptogenic drugs marketed that compare to the complex mixture of ginsenosides in *Panax* species.[19] Ginseng will almost certainly continue to be sold as an effective tonic, just as it has been for several thousand years.

Problems To Be Solved before Phytomedicines Become Mainstream

To reach this stage where herbal products of assured quality and effectiveness become integrated into mainline medical treatment, several obstacles must be overcome. The prejudice of currently practicing health-care professionals who did not learn about phytomedicines during their academic programs and, consequently, believe all of them to be ineffective forms a barrier that will prevail for some time. Equally obstinate will be the opinions of some traditional herbalists who believe that unprocessed natural products have an innate superiority and that the mystical aura surrounding herbs will somehow be destroyed by extraction and standardization. No less of a stumbling block is represented by certain greedy manufacturers who use hyperbole and faulty processing simply to make money, not to improve the health of the public.

The tenacity of thought and the insularity of belief of all three groups are little short of amazing. Each sponsors conferences or publishes articles in which they speak only to themselves. Skeptics' papers dominate the major medical journals in the United States, and contrary opinions seldom see print. The antiquackery element also sponsors symposia at which herbs are discussed, but no herbal expert is included on the program. The true believers publish only positive articles in their journals, regardless of scientific evidence to the contrary in many cases, and their gatherings discuss such unproven folkloric beliefs as plant energies and the utility of the Doctrine of Signatures. The programs at conventions and displays of manufacturers are dominated by techniques of marketing, not the facts of science. It will take more than a little time to change these attitudes, but they will eventually be forced to yield to indisputable scientific evidence.

Another major challenge that must be overcome before herbs can join mainstream medicine is the quality of much of the literature in the field. Books, pamphlets, journals, and especially these days the Internet are filled with misinformation, much of it written to sell products, some of it written to express a point of view based on hope, not facts, or on misinformation. The Federal Trade Commission (FTC) recently sent e-mail warnings to 1000 Internet sites that made "incredible claims" for drugs, devices, and supplements, including herbal remedies, supposedly of value in preventing AIDS.[14] An example of misinformation in the medical community occurred last year in California when writers in some professional journals there began to express grave concerns about administering anesthesia and its associated drugs to patients consuming St. John's wort because of the latter's monoamine oxidase inhibiting (MAOI) action.[20] People familiar with the herbal literature will recognize that some years ago the botanical was believed to act in this manner on the basis of in-vitro tests which could never be confirmed in vivo. More recent studies have shown that St. John's wort not only lacks MAO-A and MAO-B inhibitory effects, but it functions, at least in part, by its influence on the reuptake of cerebral neurotransmitters and their receptor sites.[21]

Another problem requiring resolution is that clinicians in this country now working with herbal products, but still relatively unfamiliar with them, often do not realize the necessity of adequate dosage form definition in their published papers. Many erroneous and unreproducible results have appeared in the American medical literature because the clinicians accepted at face value the quality of an herb that was adulterated, misidentified, or not appropriately standardized. In addition, they often fail to identify specifically, that is by scientific name, the botanicals in the product tested, as well as the precise dosage administered.[22]

Herbs for a Better Future

However, I cannot help but believe that these challenges will all be solved and that science and quality will ultimately prevail. As consumers become more sophisticated and realize that some herbal products actually work, while others do not, the former will begin to dominate the market, and the latter will gradually disappear.

All this will take some time. It will not happen overnight. It will occur by evolution, not revolution. But I am convinced it will happen. When it does, the people of the world will be healthier, wealthier, and happier. That is the promise of rational phytomedicine. Let us work together to achieve it.

References and Notes

(1) Robbers, J. E.; Speedie, M.; Tyler, V. E. *Pharmacognosy and Pharmacobiotechnology*; Williams & Wilkins: Baltimore, 1996; pp 1−14.
(2) Blumenthal, M., Sr., Ed. *The Complete German Commission E Monographs*; American Botanical Council: Austin, TX, 1998; 685 pp.
(3) Foster, S.; Tyler, V. E. *Tyler's Honest Herbal*, 4th ed.; Haworth Herbal Press: New York, 1999; pp 11−12.
(4) Glaeske, G. In *Phytopharmaka IV*; Loew, D., Rutbrock, N., Eds.; Steinkopff: Darmstadt, Germany, 1998; pp 129−139.
(5) Robbers, J. E.; Tyler, V. E. *Tyler's Herbs of Choice*, 2nd ed.; Haworth Herbal Press: New York, 1999; pp 69−71, 253−257.
(6) Murray, M. T. *Am. J. Nat. Med.* **1997**, *4* (7), 14−19.
(7) Schulz, V.; Hänsel, R.; Tyler, V. E. *Rational Phytotherapy*; Springer: Berlin, 1998; pp 7−8.
(8) Uehleke, B.; Frank, B.; Reinhard, E. *Dtsch. Apoth. Ztg.* **1994**, *134*, 1772−1774.
(9) Lawson, L. D. *JAMA, J. Am. Med. Assoc.* **1998**, *280*, 1565.
(10) Lawson, L. D. *Q. Rev. Nat. Med.* **1998**, Fall, 185−186.
(11) Bergner, P. *Med. Herbalism* **1996**−**1997**, *8* (4), 1, 4−6.
(12) McLaughlin, J. L. Personal communication, February 1, 1999.
(13) Current labels of Centrum herbal products indicate standardization on the basis of enzymatic assays. For example, the activity measure of garlic powder (bulb) is an angiotension converting enzyme assay; that of ginseng root is a phospholipase A_2 enzymatic assay. The exact relationship of some of these enzymatic assays to the various activities of the herbal products is, in some cases, neither clear nor precise.
(14) Brody, J. E. *New York Times* **1999**, Feb 8, D1, D7.
(15) Tyler, V. E. *Healthnotes*, in press.
(16) Tyler, V. E. In *The Inside Story of Medicines*; Higby, G. J., Stroud, E. C., Eds.; American Institute of the History of Pharmacy: Madison, WI, 1997; pp 161−170.
(17) Wilt, T. J.; Ishani, A.; Stark, G.; MacDonald, R.; Lau, J.; Mulrow, C. *JAMA, J. Am. Med. Assoc.* **1998**, *180*, 1604−1609.
(18) Tyler, V. E. In *Botanical Medicine*: *Efficacy, Quality Assurance, and Regulation*; Eskinazi, D., Ed.; Mary Ann Liebert: Larchmont, NY, 1999; pp 13−16.
(19) Li, T. S. C.; Harries, D. *Herb Spice Med. Plant Digest.* **1996**, *14* (3), 1−5.
(20) Jackson, S. H. *Calif. Soc. Anesth. Bull.* **1998**, March−April, 53.
(21) L & P/Lichtwer. *Z. Phytother.* **1998**, *19*, 167.
(22) Bensoussan, A.; Talley, N. J.; Hing, M.; Menzies, R.; Guo, A.; Ngu, M. *JAMA, J. Am. Med. Assoc.* **1998**, *280*, 1585−1589.

NP9904049