Herbal Medicines

by Stephen J. Currier, Paul D. Johnston, and Kenneth J. Gorelick

Among complementary and alternative therapies, herbal medicines hold a special place. Most drugs originally came from natural sources, and new ones, most recently paclitaxel (Taxol), are regularly discovered. Further, in many minds, "natural" means "safe," despite much evidence to the contrary. Herbal medicines have been readily available since passage of the Dietary Supplement Health and Education Act of 1994. Consequently, more people are choosing to use herbal medicines, and that choice raises specific issues for physicians.

In contrast to pharmaceuticals, herbal drugs are not standardized. The types and quantities of active ingredients can vary substantially based on the region where the herb is grown, the time in season when it is harvested, and the species of the plant. Herbs contain many compounds of uncertain biological activity, and no firm data exist on the safety, drug interactions, or efficacy of many herbal medicines.

These problems can be readily solved by providing a means of appropriately standardizing herbal products to provide a consistent potency per dose, and then conducting clinical and nonclinical tests to ascertain their role in the pharmaceutical armamentarium.

Standardized herbal products are those whose makers use pharmaceutical technology to ensure uniform dosage of specific herbal constituents. Herbs, like all plants, are exquisitely complex, and manufacturers differ on testing methods and selection of compounds used as the standards. Nevertheless, standardization is critical because product variability is considerable. Once an herb has been standardized, the standard can be used to assure consistency in manufacture.

The biological activity of an herbal product depends not only on its active constituents but also on its inactive ones. We have found that pharmacologically inactive substances can interfere with or enhance the potency of active compounds. A method of standardization should therefore assure consistent content in active ingredients as well as consistent biological activity. Makers of most herbal products that are claimed to be standardized have only begun to address these issues. Most "standardized" herbal drugs available today are intended to provide consistent quantities of specific, readily determined classes of chemical components, although even this loose definition is not always met.

For example, echinacea products are commonly standardized for the percentage of total phenolic compounds. These products may be made from either or both of two prevalent Echinacea species. The characteristic phenolic compound in *E. angustifolia* is echinacoside, but in *E. purpurea* it is cichoric acid. Similarly, "standardized" ginseng contains a defined percentage of ginsenosides, but there are more than 30 different ginsenosides that can contribute to the biological activity of a product.

In each case, the components of the class (phenolic compounds and ginsenosides, respectively) have different biological activities, resulting in a "standard" that cannot describe the actual potency and activity of the product. Furthermore, recent studies of herbal products have shown that there are many more classes of biologically active compounds, as well as more individual compounds with activity, than were historically considered.

Development of a medically meaningful form of standardization is a two-step process. First, the relevant biological activity of the total extract (treated as a sin-

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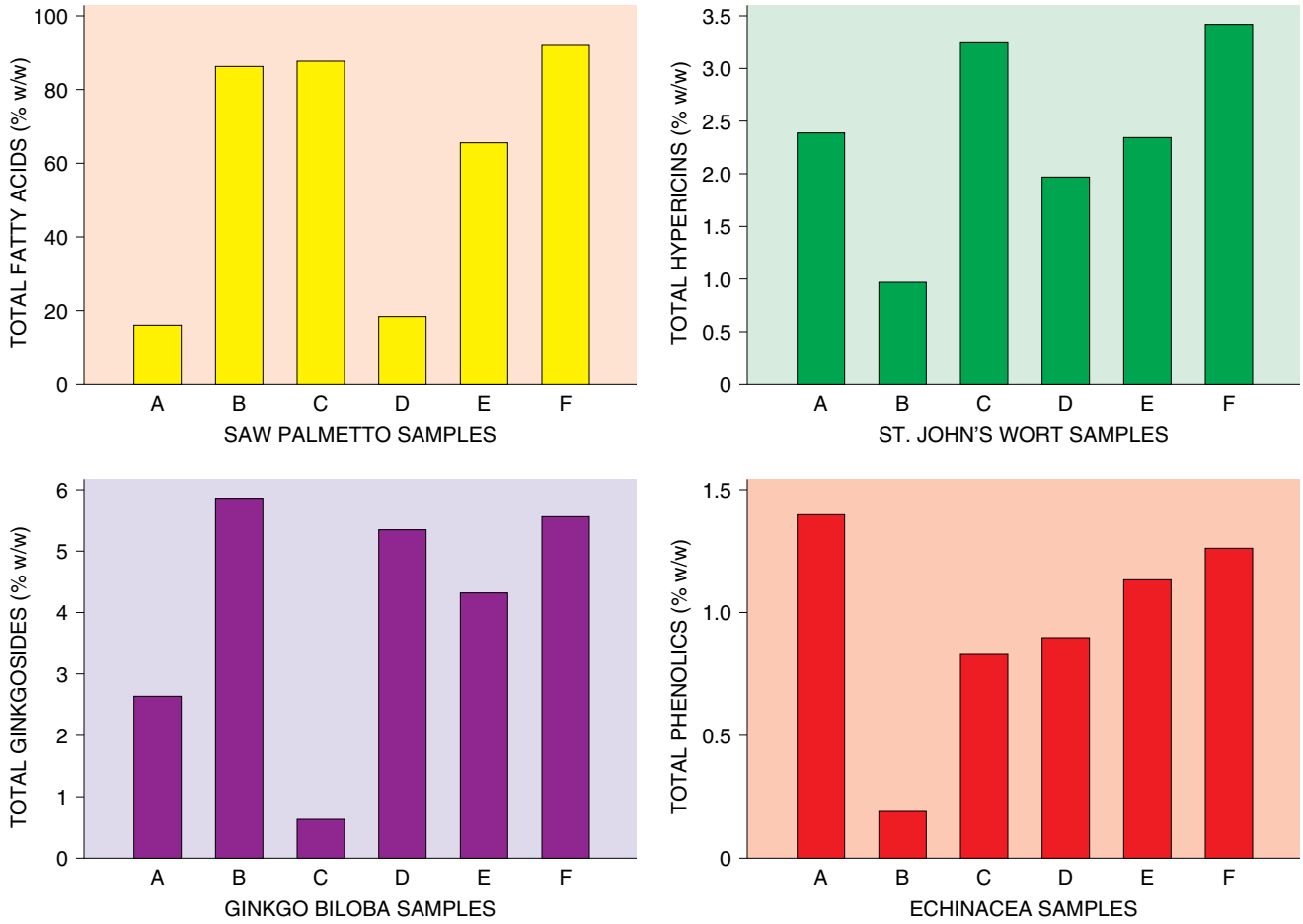
This series of articles is edited by John D. Young.



Examples of variability in measured amounts of the "standardized" component in four herbal dietary supplements purchased from pharmacies or health food stores. Different brands were tested for each product, so that the letters A to F do not signify the same brand's products in each category. None of the products tested was manufactured by PharmaPrint, Inc.

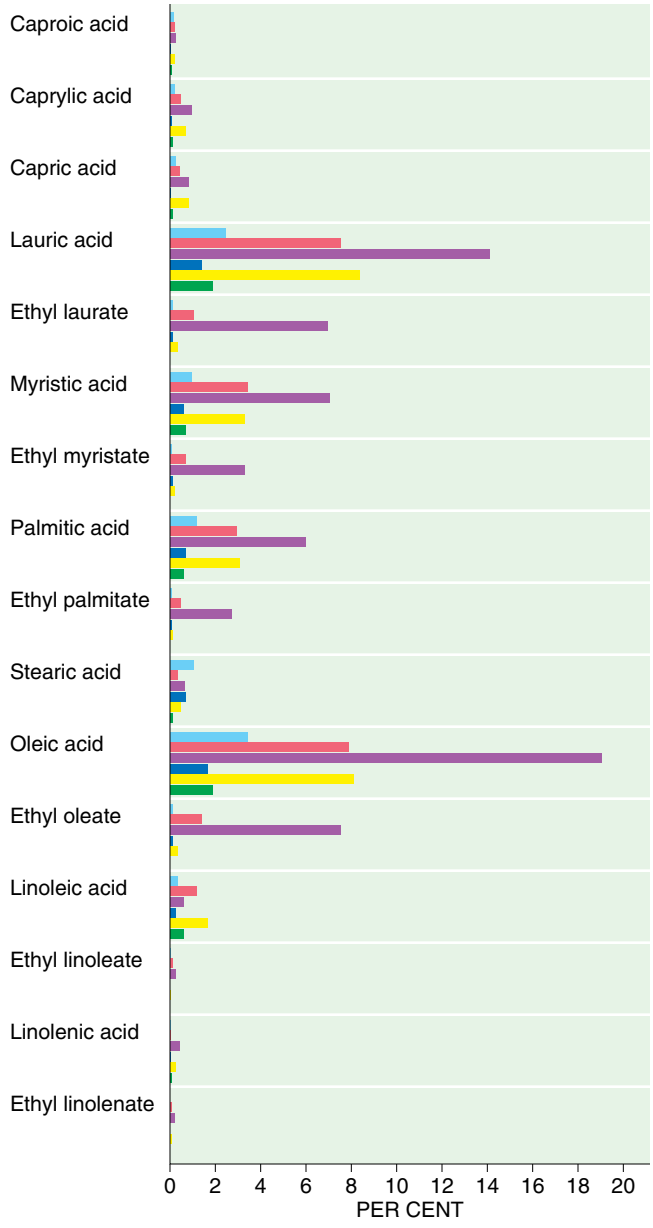
gle drug) must be determined. Then there must be rigorous identification of the individual compounds that contribute to the activity. Because herbal components that lack independent activity can nonetheless alter the activity of other compounds, it is important to assay bioactivity of the final product, not just that of individual constituents. By doing this, the contributions of both active and inactive constituents of the herbal drug are monitored and controlled.

Constituents that are monitored need not be the historically used markers that help provide taxonomic identification of the botanical. It is essential to monitor compounds with proven biological activity in the selected in vitro bioassays. Using both bioassays and analyses of biologically important constituents can assure consistent manufacturing of these complex, multi-component products.

After the careful construction of the biological and chemical fingerprint of an herbal medicine, this information must then be incorporated into a manufacturing process that can deliver final products of purity and potency similar to those of traditional medications. Use of selected, relevant bioassays and determination of the content of specific active ingredients assures that when an herbal product is released, each lot of drug and each individual pill or capsule meets the specifications that have been established.

Application of this methodology is complex and expensive by comparison with the standards now required of herbal products. Raw materials must be tested and must be rejected if potency and content are not in range. Similar tests must be passed when the herb is processed into a "purified" multi-component drug (the "active pharmaceutical ingredient") and once more when the dosage form (the "final drug product") is manufactured.

Protracted stability testing under the types of storage conditions likely to be encountered must also be performed on the active ingredient and the final product, using all of the dosage forms and types of packaging that will be employed. Only herbal medications manufactured in this manner can be viewed as yielding a



Biologically active fatty acids and fatty acid esters in six commercially available saw palmetto berry extract products. Ethyl esters were measured directly, and free fatty acids were measured as methylated esters, using gas chromatography.

consistent, reproducible effect. Otherwise, the outcome of clinical trials and clinical use of the product may be subject to significant variation in drug potency that is an unavoidable concomitant of the use of agricultural products.

Skepticism about herbal drugs arises largely because of the lack of meaningful clinical trials, but two other issues are essential to clinicians and regulatory authorities. The first is product safety, purity, and manufacturing consistency, and the second is drug interactions.

Today's market provides two sorts of herbal products. Those from dietary supplement manufacturers are found in health food stores, pharmacies, and grocery stores. These manufacturers were the principal beneficiaries of the 1994 Act and have never manufactured pharmaceutical products. Meanwhile, American Home Products, Warner Lambert, and Bayer have also introduced herbal products. Injecting the prestige and name recognition of established drug manufacturers into the market place has raised the ante in the multi-billion dollar world of herbal product sales.

Certain herbal products merit closer attention than others because more data exist, because their use is widespread, or because they are used in settings where polypharmacy is common. Saw palmetto, St. John's wort, ginkgo biloba, and echinacea head this list.

All research into the safety and efficacy of herbal drugs is on a weak footing because of the variability of the products. Nonetheless, published data tend to support a medicinal role for saw palmetto and St. John's wort, are weaker for ginkgo biloba, and are contradictory for echinacea. These studies in general suffer from poor design, inadequate patient numbers, and variable manufacturing conditions. Most published studies of saw palmetto used Permixon, an extract of a type not available in the U.S.

Pharmaceutical agents are regulated by either the Center for Drug Evaluation and Research or the Center for Biologic Evaluation and Research of the FDA. These Centers enforce safety and efficacy regulations and oversee the manufacturing and promotion of drugs. Only drugs manufactured to the standards of "current Good Manufacturing Practices" (cGMP) can be sold. Failure to meet cGMP can result in a product's removal from the market.

These regulations assure purity, content in active ingredients and excipients, and consistency from pill to pill and from lot to lot of drug. Safety studies, including drug interaction studies, in animals and people, and adequate, well-controlled clinical trials assure safety and efficacy. A New Drug Application is required and is rigorously reviewed prior to drug approval. All labeling must be approved by the FDA, and any promotional material is subject to its review and approval.

In contrast, under the Dietary Supplement act, herbal products are regulated as foods by the Center for Food Safety and Nutrition. There are no requirements to show either safety or efficacy for food products, nor are there any requirements for content or consistency. The required Good Manufacturing Practices instead focus on the absence of putrefaction, contamination, and poisons, such as insecticides.

SUMMARY OF DOUBLE-BLIND RANDOMIZED CONTROLLED CLINICAL TRIALS

Herbal Drug	No. of Studies	Total Patients	Key Findings
Saw palmetto	18	2939	Improved symptoms, minimal side effects (less sexual dysfunction than with fluoxetine)
St. John's wort	23	1757	Significant improvement in clinical depression; few side effects
Ginkgo biloba	3	597	Improved memory; stable or slowed deterioration in Alzheimer's disease; few side effects
Echinacea	3	545	Contradictory reports of efficacy in prevention of upper respiratory infections; possible shortening of duration and improvement of URI symptoms; few side effects

Saw palmetto: Timothy J. Wilt et al., *JAMA* 280:1604-1609, November 11, 1998.

St. John's wort: Klaus Linde et al., *BMJ* 313:253-258, August 3, 1996.

Gingko biloba: Pierre L. Le Bars et al., *JAMA* 278:1327-1332, October 22/29, 1997;
S. Kanowski et al., *Pharmacopsychiatry* 29:47-56, March 1996;
K. Wesnes et al., *Human Psychopharmacology* 2:159-169, 1987.

Echinacea: Dieter Melchart et al., *Archives of Family Medicine* 7:541-545, November/December 1998;
D. Melchart et al., *Journal of Alternative and Complementary Medicine* 1:145-160, 1995;
Wolfram Grimm and Hans-Helge Müller, *American Journal of Medicine* 106:138-143, February 1999.

Manufacturers of dietary supplements must notify the FDA within 30 days after a new product is put on the market, and the FDA has no authority over promotional material. Marketing of dietary supplements is instead overseen by the Federal Trade Commission, which is empowered only to halt a promotional campaign after a sponsor has failed to prove that its claims are reasonably supported. The FTC's actual requirements for making claims are far less stringent than those used by the FDA to regulate drug promotion.

The FDA can force a dietary supplement off the market only when compelling data show that it is dangerous. So far, the 38 deaths directly linked to ephedra (ma huang), an "energy booster," have not been sufficiently compelling.

In contrast, four deaths during phase II clinical trials of an anti-hepatitis drug caused the FDA to place its development on hold, and reports of about 40 deaths associated with each of three other drugs, ticrynafen, benoxaprofen, and temafloxacin, resulted in their withdrawal from the market and, for the first two, criminal penalties against the manufacturers.

The implications of these differences vary with the herbal product and its use. Most of the commonly used agents are safe enough to be used by healthy people without medical supervision, if the users are not taking other drugs. Medical concerns arise when sicker patients use herbal drugs, when more potent herbs are used, and when other drugs are used concurrently. For example, an elderly man with prostatism who opts to use saw palmetto may be using other agents to treat cardiovascular, respiratory, or rheumatic disease. The safety or efficacy of those drugs may be altered by components of the herbal product.

Either the industry or regulatory authorities must take responsibility to study interactions between drugs and herbal remedies. The dividing line between food and drug is less clear than it once was; grapefruit juice is a potent inhibitor of the 3A4 isoform of cytochrome P450 and therefore may interact with drugs. A thoughtful program must be developed that puts consumer needs first while respecting those of growers and manufacturers.

Finally, a true definition of "standardization" that is pharmacologically meaningful must be implemented broadly across the herbal industry. Only in that manner can the results of clinical trials be applied not only to different brands of a product, but also to different bottles of the same brand. Such a standard must include relevant assays of biological potency in addition to meaningful determination of the content in active ingredients.

Adequate and well-controlled clinical trials can then proceed to establish the role of herbal drugs in disease management, and drug interaction studies can identify potential problems with agents that are likely to be used by people who are taking multiple drugs for multiple diseases.

FOR MORE INFORMATION

James E. Robbers and Varro E. Tyler: Tyler's Herbs of Choice: The therapeutic use of phytomedicinals. Binghamton, Haworth Herbal Press, 1999. [A comprehensive guide for medical practitioners.]

Michael T. Murray: The Healing Power of Herbs, 2nd edition. Rocklin CA, Prima Publishing, 1995. [Dr. Murray teaches at Bastyr University in Seattle, a leading center of naturopathic medicine, and his book is targeted to a nonprofessional audience.]

The American Botanical Council, P.O. Box 144345, Austin TX 78714-4345 (http://www.herbalgram.org) is an excellent source for up-to-date information on herbal research and literature.