INTRODUCTION

Plants have been used for medicinal purposes across history and cultures and even across species. Over the past several decades, scientific literature, popular media articles on adverse drug effects, and an increased interest in natural products by the general public have helped fuel a greater scientific awareness of botanical medicine.

A majority of the world still relies heavily on herbal remedies for their primary health care. With the increasing movement of people across countries, there is an accompanying movement of their respective traditional medicines. While globalization of medicine has typically been thought of as being the movement of Western medicine to developing countries, there is now, in China, for example, significant discussion of the "globalization of traditional Chinese medicine" and discussion of how to improve the quality of Chinese medicinal products and interest in developing a body of research evidence for their effectiveness. This is particularly relevant given the establishment of traditional Chinese medicine programs and practitioners around the world. The interest in traditional herbal medicines has also contributed to a resurgence of interest in Western herbal medicine (natural products), particularly in the United States and Europe, and a desire for information about its safety and efficacy.

Further, as societies have improved methods for treating acute medical problems and have improved public health measures, there is now greater attention on the chronic illnesses that are beginning to consume a significant portion of health care budgets, particularly in the face of an aging world population. Some chronic illnesses may be ameliorated, and the search for natural means of optimizing the health of aging populations may be facilitated through the use of botanical remedies. Yet, some of the top-selling dietary supplements, although popular with the consumer, do not possess sufficient scientific data to support their intended use.

Botanical Medicine: From Bench to Bedside is based loosely on the workshop "Clinical Pharmacognosy: Contribution of Pharmacognosy to Clinical Trials of Botanicals and Dietary Supplements" held at the American Society of Pharmacognosy (ASP) Meeting in Portland, Maine. The book offers chapters by leaders in the field from academe and industry that address critical issues facing the field of botanical medicine. These include the challenges of conducting sound scientific studies of botanicals: from the sourcing of appropriate products to details on the preparation of the products and understanding the types of scientific inquiry that will advance this field. This discussion also includes challenges to the dietary supplement industry to continue to improve the quality of botanical products and to increase the industry's commitment to facilitating the collection of data that will provide the evidence base for the safety and effectiveness of the products being produced. This will reassure current consumers and health care providers and bring into the user group clinicians and a wider public who all seek treatments that are safe and effective and that have the fewest side effects possible.

Pharmacognosy, commonly referred to as the pharmacology of natural products, derives from two Greek words, *pharmakon*, or drug, and *gnosis*, or knowledge. Its scope includes the study of the physical, chemical, biochemical, and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources. Research in pharmacognosy often includes studies in the

areas of phytochemistry, microbial chemistry, biosynthesis, biotransformation, chemotaxonomy, and other biological and chemical sciences.

The role of pharmacognosy in furthering the quality of botanical preparations and the quality of clinical research is evident throughout. Examples are provided of high-quality scientific research required to achieve higher-quality preclinical and clinical studies of herbal preparations and better-quality herbal products. Topics in the book were chosen to illustrate many of the issues and a variety of scientific approaches that address the challenges in botanical research.

As the number of studies increases, there is increased concern over the quality and specific composition of botanical preparations that are tested in clinical trials, because the manufacture of poor-quality product may contribute to ambiguous, incorrect, or nonreproducible results. The quality of the outcome is only as good as the quality of the product used. This is true for preclinical and clinical research alike.

For example, several preparations of St. John's wort used in earlier research studies were based on levels of hypericin; valerian extracts were based on valerenic acids; and the popular echinacea extracts are standardized to echinacosides, alkylamides, or phenolic acids. These compounds may be considered as the plants' respective biomarkers but may not necessarily be the components that are key to any therapeutic effect (1, 2). For many botanical medicines, there is little information, or maybe controversy, about which constituents are the "actives" for particular medical indications. Inconclusive or negative results may be due to the use of extracts with less-than-optimal composition. In the absence of an identified bioactive constituent, at a minimum the extract requires identification of a biomarker for the plant. Dosing also is often insufficiently examined prior to initiating a large-scale clinical trial. Optimally, dose-ranging studies should be conducted on the population to be studied before large clinical trials are undertaken.

The methods used in extraction of the plant material can influence the chemical composition of the resulting extracts and potentially, the biological activity. The more information on the product that is provided in research publications, the greater will be the ability to compare among studies and understand differences in results that may emerge.

This book addresses the characterization of phyto- equivalence/generic herbal issues facing the supplement industry. The preparations must be qualified at all stages of research, and the chapters deal with the following stages: preclinical and clinical studies on botanicals and the safety, efficacy, and dose of botanical preparations. We have chosen as topics either popular botanical preparations—for example, valerian, St. John's wort, and cranberry—or subjects that highlight issues germane to broader questions—for example, Iberogast to highlight analysis of multicomponent mixtures, and chaste tree to highlight challenges facing the health practitioner.

The book is organized into three parts: selection and quality of botanical preparations, preclinical and clinical approaches to botanical preparations, and a practitioner's view of the challenges for those interested in exploring botanical preparations.

Part I addresses how high-quality scientific research, and thus clinically relevant outcomes, depend on a well-characterized product including the accurate identification of the plant and its constituents. Chapter 1 addresses product quality issues, botanical standards, and approaches to characterizing product consistency and stresses the importance of including chemical and biological profiling. Accurate identification of plant content requires a careful

analysis (by the company making a product or by another laboratory) of the chosen botanical preparations (intermediate extracts and the end product). Companies providing botanical products for research (or making any product for sale) should be able to provide the researcher with detailed documentation including the plant's Latin botanical name; an authentic voucher specimen; the plant part used, collection dates, and geographical collection location; a detailed description of extraction, drying methods, and preparation; a Certificate of Analysis, the extract "fingerprint" and method of analysis; and the manufacturing protocol following the guidelines of the Food and Drug Administration's (FDA) Good Manufacturing Procedures (GMPs). Chapter 1 reviews the information with which everyone conducting botanical research should at least be conversant. It is with high-quality, reproducible research in mind that the National Institutes of Health's (NIH) National Center for Complementary and Alternative Medicine (NCCAM) has issued guidelines for botanical products used in clinical research.

Chapter 2 offers a review and a critical commentary on botanicals chosen for research on controlling blood glucose levels. With diabetes a growing cause of morbidity and mortality for an already large and rapidly growing number of adults and obese children, botanical therapies to control blood glucose levels are gaining attention. While there are antidiabetic pharmaceutical medications that are well studied for lowering blood glucose levels (3), there are traditional herbal remedies for diabetes used in the United States and elsewhere, and some intriguing basic and clinical research is evolving. Chapter 2 describes the extent of the research to date while pointing out the challenges for future research.

Topical botanical preparations are also emerging as more natural approaches for treating various skin ailments. Studies of these products also exemplify how information on traditional use and some knowledge of the mechanism of action of plant constituents guide current research and product development. This research includes products for skin conditions as well as products to meet a growing demand of a large aging population seeking to remain youthful looking. Chapter 3 is a comprehensive review of botanical preparations used for various skin ailments and safety issues regarding the use of these products.

In Part II, we selected botanicals that exemplify ways to address the issue of whole extract versus particular constituents and to study the complexity of herb-drug interactions (St. John's wort) and the painstaking preclinical work necessary to develop a multicomponent herbal mixture (Iberogast). We also present valerian and hops as examples of herbs studied both individually and in combination for the additive properties conferred by different mechanisms of action.

The chapters in Part II offer examples of the rigorous attention to detail that is necessary at the preclinical stage to achieve botanically relevant and appropriately targeted clinical studies. This is not meant to be an exhaustive discussion of well-researched botanicals. Such a list might include, for example, ginkgo and black cohosh, which have been substantively reviewed elsewhere. Rather, we chose to present botanicals perhaps not as often reviewed, such as St. John's wort, paw paw, and cranberry; Iberogast; a standardized curcuminoid extract from the rhizomes of turmeric; and green tea as a therapeutic intervention in HIV-1 infection.

Cranberry, with a long traditional use in folk medicine, was until recent times manufactured as extracts based on the organic acid content. Although it is well known that cranberries contain up to 25–30% organic acids, there was no serious consideration to link the

bioactivity related to urinary tract infections to the presence of the proanthocyanidins in cranberries. Chapters 10 and 11 lay out the preclinical and clinical evidence linking these tannin-like compounds with bioactivity, as well as discuss evidence for broader use for cardiovascular and other medical indications.

Even if the active compounds or mode of action is not yet clear for many herbal products, nutraceuticals, and dietary supplements, there is a need to enforce quality standards for these products. Product standards define the consistency of the content, using a chemical constituent or a class of compounds (e.g., a phytochemical marker, using the active principal[s] when known), and offer some quality control over potency and efficacy. It should be noted that standardization to one constituent does not guarantee the levels of other components, does not represent any synergistic effects, does not describe unidentified actives, and is not a description of the plant, its part, or the extraction process.

Information about biological activity, using in vivo studies, ideally will provide information to answer the following questions:

- Is there significant evidence for the intended biological activity or improvement of the condition?
- Does the herbal preparation (active compound if known) reach the biological target within the body in a bioavailable form?
- What are the pharmacokinetics of the product?
- What is the required daily dose for achieving the desired effect or a maximum effect (as this may not be derived only from in vivo studies in animals)?
- How does the efficacy profile of the product change over time (i.e., what are the shelf life attributes of the product)?

Questions related to safety can be addressed in a variety of ways, including animal testing (LD50) and evaluating human safety via clinical trials, establishing postmarketing surveillance, and creating an adverse event reporting (AER) system (see Chapter 6 on Iberogast).

In designing clinical studies on botanicals, it also may be helpful to consider knowledge of prior human experience and traditional use to choose the end point most relevant to the plant's use. This will increase the likelihood of obtaining a reproducible and desired clinical end point. Ancient and traditional ethnomedicines are now often modified from "tea-style" consumption (i.e., a diluted form) to concentrates (powders and tablets) by the modern industry. Accompanying claims of safety based on a long history of use are presumptive, given the new formulations and concentrations not seen in traditional use, and rarely sufficiently studied before marketing.

Finally, in Part III, a perspective from a health practitioner is offered. Currently, many products on store shelves raise significant concerns because of insufficient information and misleading label claims. When independently tested, identification and concentration of the labels' ingredients are often found to not match the claim or reveal inconsistencies from batch to batch. These and other concerns relevant to clinical recommendations are discussed in Chapter 12 on the use of chaste tree extract.

In conclusion, our intent is to present information on the science required to achieve (a) better-quality botanical products; (b) research well designed to match the product to its intended use, to ensure adequate quality control, and to take into consideration the complexi-

ties of activities of biological products on biological systems, with the product described adequately to enable reproducibility; and (c) setting clinical end points based on results from historical use or preclinical studies. If we can make a small contribution to this important discussion that will increase the quality of botanical preparations, and thus the quality of research, we may help consumers and manufacturers create safe, effective, and clinically proven botanical medicines.

Raymond Cooper, Ph.D.
Fredi Kronenberg, Ph.D.

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