



National Institutes of Health
Turning Discovery Into Health

2013 NIH Botanical Research

Expert Panel Meeting

Sponsored by

**National Center for Complementary and Alternative Medicine
and the Office of Dietary Supplements**

April 29, 2013

Neuroscience Building
Conference Room A1/A2
Rockville, MD 20852

Executive Summary

Background and Purpose

Botanical products are used extensively by the U.S. public and are prominently represented in pharmacopeias throughout the world. Furthermore, significant Federal resources are being devoted to research on botanicals to better understand their chemical composition and biological activities. However, despite this prevalence of use and substantial financial investment, many questions remain about the purported benefits of botanicals and how research in this field should be conducted.

The National Institutes of Health's (NIH) Office of Dietary Supplements (ODS) and National Center for Complementary and Alternative Medicine (NCCAM) convened an Expert Panel on April 29, 2013, in Rockville, MD. The purpose of this meeting was to identify and discuss ways to strengthen NIH's ongoing investment in botanical research in order to advance understanding of the biological effects of botanicals (especially those related to dietary supplements) in human health (including safety).

Within the context of this broad goal, the Expert Panel was asked to address four overarching questions. These began with a big picture focus on the most pivotal challenges facing botanical research over the coming years and then narrowed to more specific issues such as the role of interdisciplinary research in addressing those challenges. The questions follow below in conjunction with the summary of the corresponding Panel discussions. (Appendix A to this report lists the questions in full).

Discussion and Recommendations

Question 1: What are the most critical scientific needs and challenges in research on the role of botanicals in human health?

The Panel concluded that botanical research urgently needs to consistently employ cutting-edge methodologies, especially with respect to interactions. The use of complex products with multiple components, or of combinations of products, is very common, yet the field is just beginning to resolve recurrent questions about the multiple ways in which chemically complex botanical products can potentially interact with equally complex biological systems. Potential synergistic or antagonistic interactions are often postulated, but not clarified. New methods and standards are needed to facilitate chemical characterization and to improve the identification of possible biological actions and relevant interactions. Cutting-edge approaches from fields such as systems biology and modeling provide important tools that need to be applied to these challenges.

The Panel proposed the development of a scientific scaffold to facilitate progress in understanding the chemistry and biology of complex botanical products. The scaffold would provide a framework of best practices, state-of-the-art methods, and data resources to enhance progress and improve reproducibility and consistency. The scientific scaffold would facilitate more efficient determination of major chemical constituents and their range of activities. This scaffold also would aggregate existing "preclinical" predictive data about the biological networks and targets that might be modulated. The data resources developed would facilitate subsequent safety and efficacy studies in animals, if needed, and human subjects, as appropriate.

The second major need identified by the Panel was for more researchers trained in the techniques and issues unique to botanical research and prepared to collaborate in interdisciplinary research. It was noted that there are only a handful of experts in this country in natural product chemistry, pharmacognosy, ethnobotany, and related disciplines and even fewer institutions with active programs in these areas. There was a strong recommendation to use all available mechanisms to ensure the development of the next generation of “botanically capable” interdisciplinary investigators.

The third major need identified by the Panel was for enhanced dissemination of accurate information about botanicals to the general public and to health practitioners. The Panel emphasized the importance of utilizing cutting-edge methodologies to meet this need as well.

Question 2: What are key criteria for prioritizing NIH support of research on the role of botanicals in human health?

Safety issues were the first important priority identified by the Panel. Consideration should be given to clarification of safety concerns, both related to toxic or adulterated products and to products that interact with conventional pharmacological agents. The Panel noted patterns of use in the United States can help establish which products are of high priority for safety assessment, but U.S. Food and Drug Administration (FDA) reports and other resources can also be used to identify areas of concern. The point was made that both prevalence of use and potential safety concerns are constantly shifting in response to new data and new products.

It was noted that in parts of the country that have large immigrant populations, there may be widespread use of botanical products that do not appear on lists of most commonly used products in the United States overall. Therefore, the Panel emphasized the need to explore the full breadth of botanical diversity rather than a narrow subset of medicinal plants. Other demographic subgroups (e.g., elderly, pediatric, those with chronic conditions, etc.) also show a much higher use for particular products than the national average. Use of botanicals among pregnant and nursing women is also common; prevalence of use in such specific populations should also be considered. This includes understanding how use of botanicals by different populations impacts their safety and efficacy. Furthermore, the potential for individual differences in clinical response to inform our understanding of both the botanical and animal biology should be prioritized.

Efficacy studies need to be built upon strong biological hypotheses, developed through the improved methodological approaches described above. Additionally, it was recommended that priority be given to the study of botanical products in ways consistent with their traditional uses. It was the recommendation of the Panel that greater emphasis should be placed on assessment of the capacity of botanical dietary supplements to promote resiliency and general health.

Question 3: Which of the opportunities and challenges facing the field of botanical research require or are most likely to benefit from an interdisciplinary, multi-project collaborative research program, such as a Centers Program?

Addressing the chemical and biological properties of complex botanical dietary supplements is a far more difficult challenge than that for “single chemical entity” drugs. Therefore, the Panel noted the need for interdisciplinary and transdisciplinary approaches to these issues that include expertise from molecular biology, bioinformatics, cell biology, chemistry, ethnobotany, social sciences, pharmacology, and other disciplines. Such an interdisciplinary effort will be critical for

developing rapid, predictive *in vivo*, *in vitro*, or *in silico* models for evaluating botanicals with respect to safety, content, and efficacy that allows for making quick, informed decisions.

Question 4: Are there key or innovative approaches that NIH should consider that have potential to enhance the effectiveness of collaborations in advancing botanical research?

The Panel emphasized the need to bring together experts from different disciplines and sectors (academia, government, industry). One critical need in this area is working to remove administrative and inter-sector barriers to forming multi-institutional, interdisciplinary teams. Another need is increasing coordination and leveraging support of existing programs (including extramural research centers and programs) to facilitate dissemination of basic information, test materials, and other resources.

Panelists noted that it would be extremely beneficial to have centralized resources to maximize access to the materials, tools, and techniques needed to carry out state-of-the-art research on botanicals. Such resources might develop, optimize, and/or provide assays and analytic support designed to answer a defined set of questions that are universal for all products. Consideration should be given to developing biological assays that can support decisionmaking and could be robust for a wide range of botanical preparations, including multicomponent botanical formulas. The Panel also noted the general need to develop and provide resources across the community, such as reference standards, cell lines, bioassay guidelines, etc. Characterized materials should be made available to researchers, especially those who want to be a part of interdisciplinary efforts.

Major points to consider:

- 1. Cultivate and support interdisciplinary, transdisciplinary, and multi-sector collaborations.**
- 2. Develop, adapt, and/or collate cutting-edge methodologies to form a scientific scaffold for the study of complex mixtures, including evaluation of safety, mechanism of action, and synergy.**
- 3. Establish a mechanism(s) to optimize sharing of, and access to, botanical materials, tools, and techniques, including those of the scientific scaffold.**
- 4. Support the training of the next generation of investigators prepared to lead and conduct interdisciplinary research on botanicals.**
- 5. Consider current prevalence of use and traditional use in prioritizing research.**
- 6. Focus on models of resiliency and health maintenance.**

Appendix A
Questions for the 2013 NIH Botanical Research Expert Panel

- 1. What are the most critical scientific needs and challenges in research on the role of botanicals in human health?** *The inherent complexity of botanicals presents both great challenges and great opportunities for innovative research, including research that may provide novel insights into mammalian biology. What are the major gaps, challenges, and opportunities for the next 5 to 10 years in this field? Which of these, if successfully addressed, are likely to have the greatest impact on human health and future research in this field?*
- 2. What are key criteria for prioritizing NIH support of research on the role of botanicals in human health?** *While natural products have been a major source of effective pharmaceuticals, the majority of dietary supplement use in the United States is reportedly for health promotion and/or disease prevention. Considering the diversity of botanicals used, and the even greater diversity of biological activities ascribed to these botanicals and their multitude of constituents, what criteria should be considered in prioritizing research investments—for example, botanicals and their mammalian biological targets, research approaches (e.g., basic, clinical, modeling), research capacity, methodology development, etc? Taking into consideration that there is support for botanical research across NIH, other Federal agencies (e.g., Centers for Disease Control and Prevention, FDA, National Institute of Standards and Technology [NIST], National Science Foundation, U.S. Department of Agriculture [USDA], etc.), nongovernmental organizations, and industry, are there areas where NIH support is particularly critical?*
- 3. Which of the opportunities and challenges facing the field of botanical research (question 1) require or are most likely to benefit from an interdisciplinary, multi-project collaborative research program, such as a Centers Program?** *Some areas of research require or are better poised to benefit from multi-component interdisciplinary research programs than others. Recognizing that research on the biomedical implications of botanicals is an inherently interdisciplinary undertaking requiring the synergistic coordination of many different types of expertise in areas as diverse as pharmacognosy, phytochemistry, and various biomedical research disciplines, what research needs are most likely to benefit from such mechanisms of support by NIH?*
- 4. Are there key or innovative approaches that NIH should consider that have potential to enhance the effectiveness of collaborations in advancing botanical research?** *How can NIH foster/facilitate the most effective interdisciplinary research collaboration? Who are the most critical partners? What are the incentives and disincentives to collaboration? Are there key or innovative approaches, or resources or services that could be leveraged, supported, or shared that should be considered as promising approaches to increase the incentives and/or counter the disincentives?*

Appendix B
2013 NIH Botanical Research Expert Panel Meeting Participants

Expert Panel Members

Shrikant Anant, Ph.D., The University of Kansas Cancer Center
Michael J. Balick, Ph.D., Institute of Economic Botany, The New York Botanical Garden
Alice M. Clark, Ph.D., University of Mississippi
Gordon Cragg, Ph.D., National Institutes of Health
Steven T. DeKosky, M.D., University of Virginia School of Medicine (Panel Chair)
Shiew-Mei Huang, Ph.D., Center for Drug Evaluation and Research, FDA
David G.I. Kingston, Ph.D., Virginia Polytechnic Institute and State University
Tieraona Low Dog, M.D., Arizona Center for Integrative Medicine, The University of Arizona
Charles Serhan, Ph.D., Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital

Other Participants/Observers

Dr. Dale Birkle, NCCAM	Ms. Catherine Law, NCCAM
Dr. Josephine Briggs, NCCAM	Dr. Karin Lohman, NCCAM
Ms. Cindy Caughman, NCCAM	Dr. Padma Maruvada, National Institute of Diabetes and Digestive and Kidney Diseases
Dr. Paul M. Coates, ODS	Dr. John Milner, USDA
Dr. Cindy Davis, ODS	Ms. Ilze Mohseni, NCCAM
Dr. Nancy Emenaker, National Cancer Institute (NCI)	Dr. Nancy Nadon, NIA
Dr. Dan Fabricant, FDA	Ms. Ellen O'Donnell, NCCAM
Dr. Mary Garcia-Cazarin, ODS	Dr. Carol Pontzer, NCCAM
Dr. Barbara Gerratana, National Institute of General Medical Sciences	Dr. Karen Phinney, NIST
Dr. John Glowa, NCCAM	Dr. Josh Rosenthal, FIC
Dr. Martin Goldrosen, NCCAM	Dr. Martina Schmidt, NCCAM
Ms. Anita Greene, NCCAM	Dr. Harold Seifried, NCI
Dr. Judy Hanna, National Institute on Aging (NIA)	Dr. Hungyi Shau, NCCAM
Dr. Jim Harnly, USDA	Dr. Barbara C. Sorkin, ODS
Dr. Craig Hopp, NCCAM	Dr. Derrick Tabor, National Institute on Minority Health and Health Disparities
Dr. Kristen Huntley, NCCAM	Dr. John Williamson, NCCAM
Dr. Flora Katz, Fogarty International Center (FIC)	Dr. Steve Wise, NIST
Dr. Jack Killen, NCCAM	Dr. Dan Xi, NCI
Dr. Peter Kozel, NCCAM	