Challenges for Botanical Dietary Supplements

Chair: J. Fred Stevens, PhD, Linus Pauling Institute, Oregon State University

Wednesday August 14, 8:30AM - 12:10PM
Botanical Dietary Supplement Research: Priorities and Challenges from the Funders Perspective

Wendy J. Weber, ND, PhD, MPH

National Center for Complementary and Integrative Health, National Institutes of Health, Bethesda, MD, USA

BIOGRAPHY

Wendy J. Weber, ND, PhD, MPH, is the Branch Chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH) at NIH. She joined NCCIH as a program director in 2009. Dr. Weber is the point-of-contact for natural product-related clinical trial Funding Opportunity Announcements (FOAs). She is the program officer for the NIH Common Fund-supported Health Care Systems Research Collaboratory Coordinating Center. Dr. Weber is an integral part of the planning and oversight of the NIH-DoD-VA Nonpharmacologic Approaches to Pain Management Collaboratory. She is also the lead on the Pragmatic and Implementation Studies to Improve the Management of Pain and Reduce Opioid Prescribing program, which is part of the overall NIH Helping End Addiction Long-Term (HEAL) Initiative.

At NCCIH, Dr. Weber oversees a portfolio of pragmatic clinical trials, natural product clinical trials, studies of complementary medicine to promote healthy behavior, and complex complementary/integrative medicine intervention research. Dr. Weber earned a Doctor of Philosophy in epidemiology and a Master of Public Health from the University of Washington. She earned a Doctor of Naturopathic Medicine (N.D.) from Bastyr University. Prior to joining NCCIH, she was a research associate professor at Bastyr University, where her research included the study of herbal treatments for pediatric conditions. Her clinical practice focused on the treatment of children and adolescents with mental health conditions, abdominal pain, headaches, and allergies.

ABSTRACT

Dr. Wendy Weber will provide an overview of the National Center for Complementary and Integrative Health’s (NCCIH) Strategic Priorities for funding Natural Products research. NCCIH is one of the 27 Institutes and Centers of the National Institutes of Health, the world’s largest biomedical research
entity and provider of federal funds. She will provide an overview of NCCIH’s new approach to funding natural product clinical research, including recently published funding opportunity announcements.

She will describe exciting findings from the NIH Botanical Centers and the Drug-Herb Interaction Center program, which are jointly supported by NCCIH and the NIH Office of Dietary Supplements. A summary of the NCCIH product integrity process for natural products research and the NCCIH clinical research oversight process will be described. Finally, Dr. Weber will highlight various resources to guide potential applicants in securing funding for research grants and training opportunities for students, post-doctoral fellows, and junior faculty.
Clinical Pharmacology for Botanicals in Drug Development

Chongwoo Yu, PhD

Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

BIOGRAPHY

Dr. Yu is a Master Clinical Pharmacology Reviewer in the Office of Clinical Pharmacology (OCP) at the U.S. Food and Drug Administration (FDA). Dr. Yu received his PhD in Analytical Chemistry with the focus on Drug Metabolism and Mass Spectrometry from the University of Illinois at Chicago. Subsequently, Dr. Yu has worked in the Department of Pharmacokinetics, Dynamics, and Metabolism (PDM) at Pfizer (Ann Arbor, MI) and the Drug Metabolism and Pharmacokinetics (DMPK) Department at Schering-Plough (currently Merck; Kenilworth, NJ) for several years. At both organizations, Dr. Yu has been heavily involved in carrying out various types of drug metabolism, pharmacokinetics, and drug-drug interaction (DDI) studies using mass spectrometry.

Since 2007 when Dr. Yu first joined the Agency, Dr. Yu’s work has been focused on the evaluation of bone, reproductive, and urologic drug products. Dr. Yu’s research interests include: (1) DDIs involving hormonal contraceptives; (2) effect of body mass index (BMI) / body weight on effectiveness of hormonal contraceptive products; (3) bioanalysis in drug development, and (4) clinical pharmacology in testosterone replacement therapy (TRT) development.

Dr. Yu served as a member of FDA guidance working groups including those for the: (1) Bioanalytical Method Validation Guidance; (2) Clinical Combined Oral Contraceptive Drug Interaction Guidance; (3) Labeling for Combined Oral Contraceptives Guidance; and (4) International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) M10 Bioanalytical Method Validation Guidance. Dr. Yu currently serves as the chair of the FDA OCP Bioanalytical Research (BAR) Scientific Interest Group (SIG).

ABSTRACT

Clinical pharmacology plays an important role in drug development, especially in determining the optimal dosage regimen for drugs including botanicals. This involves the evaluation of the drug's
pharmacokinetics and pharmacodynamics, food effect, drug interaction potential, bioanalysis, exposure-response relationship for safety and efficacy and considerations when being used in specific populations. The scope of clinical pharmacology programs for botanical drug development will be discussed.

Case examples will be presented to highlight the utility and importance of clinical pharmacology in botanical drug development and how clinical pharmacology was used to translate clinical trial results into actionable information for the approval of botanical drug products. In summary, clinical pharmacology plays a significant role in ensuring that drug products are safe and effective and that they are delivered in the right dose, at the right time, to the right patient.
Dietary Supplements: Regulatory Challenges and Research Resources

Paul M Coates, PhD
Former Director, Office of Dietary Supplements, National Institutes of Health, Silver Spring, MD, USA

BIOGRAPHY
Dr. Coates directed the Office of Dietary Supplements (ODS) at the National Institutes of Health from 1999-2018, in its mission to strengthen knowledge and understanding of dietary supplements. Through a range of initiatives made possible by an energetic and knowledgeable staff, he established ODS as a strong and authoritative voice for rigorous science in dietary supplements and related areas of nutrition. ODS continues to address many of the issues in dietary supplements, from evaluation of the literature to supporting and conducting science, and translating the results of that work into reliable and effective information for the public.

Dr. Coates was Acting Director of the NIH Office of Disease Prevention (ODP) from 2010-2012. Dr. Coates also served from 1996–1999 as Deputy Director of the Division of Nutrition Research Coordination (DNRC) at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). In that role, Dr. Coates helped to coordinate human nutrition research efforts, both at the NIH and between the NIH and other government agencies. Dr. Coates was Co-Chair of the joint DHHS/USDA Steering Committee overseeing plans for the National Nutrition Summit that was held in Washington in 2000. He was a member of the Federal Steering Committee that oversees the development of the Dietary Reference Intakes. He was Co-Executive Secretary of the Interagency Committee on Human Nutrition Research and Chair of the Federal Working Group on Dietary Supplements.

In 2011, he received the Conrad A. Elvehjem Award from the American Society for Nutrition (ASN) for public service in nutrition. In 2013, he became a Fellow of the ASN and currently serves on the ASN Board of Directors. He was lead editor of the Encyclopedia of Dietary Supplements and associate editor of The American Journal of Clinical Nutrition.

Before joining the DNRC, Dr. Coates was NIDDK’s Program Director for the Type 2 Diabetes Research Program (1993–1996) and Project Officer for the multi-center clinical study, Epidemiology of Diabetes Interventions and Complications (1994–1996). From 1994 until his
departure from NIDDK, he maintained an active role in career development and fellowship
training in the Division of Diabetes, Endocrinology, and Metabolic Diseases.

Prior to his career at NIH, he was on the faculty of the Children's Hospital of Philadelphia and the
University of Pennsylvania School of Medicine. He did postdoctoral training in the Department of
Human Genetics and Biometry at University College London, after receiving his Ph.D. in human
genetics from Queen's University in Canada.

ABSTRACT

There is no global consensus on how dietary supplements (DS)/natural products/complementary
medicines/food supplements should be defined. Even in countries with similar cultures, legal
systems, and levels of economic development, regulations applying to these products vary
considerably. A further challenge is that DS products can evoke emotive and polarizing
viewpoints. The prevalence of DS use has increased dramatically in the last few decades, as has
the application of state-of-the-art scientific methods to explore their ingredients. Progress on
the evaluation of botanical and other non-nutrient DS ingredients has been considerable, and yet
challenges still exist. Fortunately, a number of research resources have been made available to
advance this work, notably from the NIH Office of Dietary Supplements (ODS) and its
collaborators in government, academia, and the DS industry.

The ODS Analytical Methods and Reference Materials Program accelerates creation and
dissemination of much-needed tools to enhance the reliability and reproducibility of research
using DS products. The Dietary Supplement Label Database now contains full label information
for over 75,000 products, including historical information on those no longer in the marketplace;
this is useful in monitoring trends in DS use in the population, and the contribution that DS make
to the total intake of important nutrients. The Population Studies Program provides tools for
integrating the nutrient intakes from foods and DS, as well as evaluating patterns of DS use in
large surveys such as NHANES. Probably the most important resource offered by ODS is its
Communications Program, which translates research findings into useful information for the
public and other stakeholders. This includes online fact sheets about numerous nutrient and
non-nutrient DS ingredients. ODS also offers an annual 3-day intensive course on issues in DS
research.

Details of these and other ODS initiatives are available at www.ods.od.nih.gov.
Safety of Botanical Dietary Supplements

Paula N. Brown, PhD

Director, Natural Health and Food Products Research Group
Canada Research Chair, Phytoanalytics
British Columbia Institute of Technology

BIOGRAPHY

Paula Brown graduated with a Bachelor of Science Combined Honours in Chemistry & Biochemistry from Dalhousie University, completed her Masters of Science in Chemistry on natural product synthesis at Simon Fraser University under the supervision of Dr. BM Pinto and her PhD in Chemistry at the University of British Columbia on plant metabolomics with Dr. Susan Murch. Dr. Brown has supported the natural health & food product industry for two decades conducting applied research on product quality, safety & efficacy at the British Columbia Institute of Technology. Supported by grant funding and industry contracts Dr. Brown has engaged in projects focused on health policy, regulatory affairs, product formulation, botanical authentication, analytical method development & validation, chemometrics and therapeutic monitoring for preclinical and clinical studies.

Dr. Brown was appointed Fellow of the AOAC in 2009 having been an active volunteer, participating on 15 AOAC Expert Review Panels, directing 4 collaborative studies, publishing numerous validation studies and has taught method development & validation workshops for Health Canada, The American Society for Pharmacognosy, the United States Pharmacopoeia and the NHP Research Society of Canada. In 2009 she was appointed to the American Botanical Council Advisory Committee, the inaugural Natural Health Products Program Advisory Committee for Health Canada and became Chair of NSF’s Joint Committee for Dietary Supplements.

In 2017, she joined the USP Expert Committee for Botanical Dietary Supplements and Traditional Medicines and the American Herbal Pharmacopeia Advisory Board. She is the 2017 Recipient of the Neil Tower’s Award and is currently the President of the NHP Research Society of Canada. Dr. Brown is the Dietary Supplement & Traditional Medicine Section Editor for Journal of the AOAC International and holds the Canada Research Chair in Phytoanalytics.

ABSTRACT

Product quality and authenticity has been a concern at the forefront of the natural products industry after significant media attention has continually presented negative articles in this
regard. Unfortunately, many botanical products in the market today differ substantially in form, potency and even route of administration from the traditional herbal medicines from which they were derived. With a multitude of ingredient combinations seen in products that not only incorporate previously unseen herbal ingredient combinations, but the addition of technical ingredients such as flavourings and emulsifiers it is difficult to justify the relationship between history of safe use and modern safety for these products.

The measurands selected to represent quality determinants, in particular for identity, must too evolve to ensure they are fit for their intended purpose. Univariate measurements of phytochemicals in an analytical method validation framework already exist; however combining such quantitative measurements with an identity parameter is highly desirable but challenging to do. Very limited literature exists in providing guidance in the authentication of botanical-based products in a practical sense. The challenges presented by a continuously changing botanical product landscape will be discussed along recent approaches employed to interpret plant secondary metabolite data sets for authentication and improved safety.
Natural Product-Drug Interaction Research: Cultivating Best Practices

Mary Paine, PhD

College of Pharmacy and Pharmaceutical Sciences, Washington State University, Spokane, WA, USA

BIOGRAPHY

Dr. Mary Paine is a professor in the Department of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, Washington State University. She received her BS in pharmacy at Oregon State University, her PhD in pharmaceutics at the University of Washington, and completed a post-doctoral fellowship in clinical pharmacology at the University of Michigan. Her longstanding research program, funded continuously by the National Institutes of Health, focuses on adverse interactions between conventional medications and natural products.

Dr. Paine leads the Center of Excellence for Natural Product-Drug Interaction Research, a multidisciplinary effort involving clinical pharmacologists, natural products chemists, and health informaticists to provide leadership in the study of these complex interactions. She has coauthored more than 95 publications as original research articles, reviews, editorials, and book chapters. She is currently an associate editor for the journals Clinical Pharmacology and Therapeutics and Drug Metabolism and Disposition.

ABSTRACT

Humans have consumed botanical dietary supplements and other natural products (NPs) for medicinal purpose since antiquity. Nowadays, the marketing and use of NPs for health and wellness benefits thrive worldwide, with global sales projected to exceed $200 billion within the next few years. In parallel with rising NP sales are increasing concerns about patients supplementing their prescribed pharmacotherapeutic regimens with these perceived safe and effective products, increasing the risk for adverse NP-drug interactions. Common pharmacokinetic mechanisms underlying NP-drug interactions include induction and inhibition of drug metabolizing enzymes and transporters by the NP, leading to altered systemic or tissue drug concentrations and potentially, suboptimal therapeutic outcomes. Unlike for drug-drug interactions, harmonized guidances for assessing NP-drug interactions do not exist.

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Because NPs are inherently complex chemical mixtures that vary substantively between brands and sometimes batches of the same brand, a multidisciplinary effort involving clinical pharmacologists, NP chemists, and health informaticists is needed for rigorous assessment and dissemination of the drug interaction liability of NPs. The National Center for Complementary and Integrative Health established the Center of Excellence for Natural Product Drug Interaction Research (NaPDI Center) in September 2015.

A key deliverable of the NaPDI Center is a set of recommended approaches to guide researchers in the proper conduct of NP-drug interaction studies. These approaches will be based on results generated from a series of ongoing interaction projects examining four systematically selected NPs as precipitants of pharmacokinetic NP-drug interactions. The aggregate data are being entered into a data repository that will be disseminated to researchers via a public access portal. The efforts of the NaPDI Center should lead to improved design of future NP-drug interaction research and ultimately, evidenced-based information for health care providers and patients about the optimal management of these complex interactions.
Botanical Ingredient Adulteration: How Some Suppliers Attempt to Fool Commonly Used Analytical Techniques

Stefan Gafner, PhD

Chief Science Officer, American Botanical Council
Austin, TX, USA
Technical Director, ABC-AHP-NCNPR Botanical Adulterants Program, University of Mississippi, Oxford, MS, USA

BIOGRAPHY

Stefan Gafner received his degree in pharmacy at the School of Pharmacy, University of Berne, in Berne, Switzerland. He obtained a PhD in pharmaceutical sciences, with a focus on the chemistry of medicinal plants, from the University of Lausanne in Switzerland, and conducted postdoctoral research on cancer chemopreventive natural products at the University of Illinois—Chicago in the College of Pharmacy’s Department of Medicinal Chemistry and Pharmacognosy. For over a decade, Dr. Gafner has served as a director of analytical chemistry in the R&D department of natural personal care products company Tom’s of Maine.

He is currently Chief Science Officer of the American Botanical Council, an independent, nonprofit research and education organization. He is also technical director of the ABC-AHP-NCNPR Botanical Adulterants Program, a large-scale collaborative program initiated by the American Botanical Council (ABC), the American Herbal Pharmacopoeia (AHP), and the National Center for Natural Product Research (NCNPR) at the University of Mississippi to educate members of the herbal and dietary supplement industry about ingredient and product adulteration.

ABSTRACT

Stefan Gafner¹, Mark Blumenthal¹, Steven Foster², John H. Cardellina II³, Ikhas A. Khan⁴, Roy Upton⁵

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The chemically complex nature of herbs and botanically-derived ingredients calls for unique quality control processes of herbal products. One of the universal regulatory requirements in industrialized nations around the world is the appropriate testing for identity and authenticity of botanical materials. However, unscrupulous suppliers often take advantage of a lack of specificity in test methods used to confirm the identity of a botanical ingredient by providing materials that may comply with these identity tests even if they do not correspond to the material declared on the label.

Examples of such practices are the adulteration of cranberry (*Vaccinium macrocarpon*) extracts with proanthocyanidin-rich materials such as peanut (*Arachis hypogaea*) skin or grape (*Vitis vinifera*) seed extracts, the substitution of bilberry (*Vaccinium myrtillus*) or elderberry (*Sambucus nigra*) fruit extracts with anthocyanin-rich extracts from other plants, e.g., mulberry (*Morus* spp.) or wild cherry (*Prunus avium*) fruits, or the undeclared addition of natural or synthetic isolates, such as curcumin or rutin, to turmeric (*Curcuma longa*) rhizome or ginkgo (*Ginkgo biloba*) leaf extracts, respectively.

In order to educate members of the herbal and dietary supplement industry about ingredient and product adulteration, the American Botanical Council (ABC), the American Herbal Pharmacopoeia (AHP), and the National Center for Natural Product Research (NCNPR) at the University of Mississippi have initiated the ABC-AHP-NCNPR Botanical Adulterants Program. As part of this effort, this presentation will give examples of herbal ingredient adulteration reports published over the past ten years with an emphasis on cases where standard chemical tests may not be adequate to detect the adulterating materials.
Contributed Talk

Regulatory Approvals for Clinical Studies of Botanical Products – *Centella asiatica* as a Case Study

**Amala Soumyanath, PhD**

Associate Professor of Neurology
Oregon Health and Science University, Portland, Oregon USA

**BIOGRAPHY**

Dr. Amala Soumyanath received her Pharmacy degree and PhD from the University of London, UK. As a faculty member at King’s College London (1990-2002), and later Oregon Health and Science University (2003- present) she has been active as a teacher and researcher in the field of pharmacognosy.

Her research applies modern chemical and biological techniques to investigate traditional herbal medicines as a source of (a) evidence-based herbal extracts for use in rational phytotherapy and (b) novel drug leads for development as conventional medicines. Dr Soumyanath’s research has encompassed botanical remedies for diabetes, skin diseases and currently, neurodegenerative disorders. She has received multiple federal grants for collaborative projects examining the neurotropic, neuroprotective, and cognitive enhancing properties of *Centella asiatica*. These studies have spanned the full spectrum from preclinical evaluation and chemical characterization of *Centella asiatica* extracts to clinical studies examining the effects of well- characterized extracts of this botanical.

**ABSTRACT**

Amala Soumyanath\(^1\), Kirsten Wright\(^1\), Armando Alcazar Magana\(^2\), Maya Caruso\(^1\), Nora Gray\(^1\), Donald Matthews\(^1\), Randall Woltjer\(^4\), Ronald M. Laethem\(^5\), Caroline Moseley\(^5\), J. Fred Stevens\(^3\,^6\), Claudia S. Maier\(^2\,^3\), Joseph Quinn\(^1\)

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Botanical products are widely used by the public as dietary supplements with increasing popularity. However, their evaluation in clinical trials commonly requires prior approval by the Food and Drug Administration (FDA), an Institutional Review Board (IRB), and the funding organization. When a therapeutic outcome is pursued, the botanical is no longer considered a dietary supplement, necessitating approval as an "Investigational New Drug" (IND) from the FDA. Botanical products present unique challenges due to their complexity, variability, and multi-target activity. Thus the FDA has issued special guidelines for the content of FDA IND applications for botanicals, which differ somewhat from the guidelines for single chemical drugs. In addition, the widespread previous human use of botanical products may reduce the requirement for detailed toxicity studies.

However, differences in product composition due to varying sources and preparation methods may reduce the relevance of safety data obtained from current human use and published toxicity studies if they relate to other types of extracts of the same botanical. We will describe our process to obtain FDA IND, IRB and funding organization (National Center for Complementary and Integrative Health (NIH/NCCIH)) approvals for our clinical studies on the neurotropic botanical *Centella asiatica*. While we have robust preclinical data to support the evaluation of a *Centella asiatica* water extract (CAW) for cognitive endpoints in humans, we will describe additional preclinical studies we have performed on this extract including safety, effects on cytochrome P450 isoenzymes, detailed chemical characterization and predefined stability studies all as a necessary part of our FDA IND application. This presentation will provide an overview of the type of data, information and relative emphases that are required in the applications for FDA IND, IRB and NIH/NCCIH approval of our clinical trial protocols.
Botanical Supplements: From Safety to Application

Chair: Richard van Breemen, PhD,
Linus Pauling Institute, Oregon State University

Wednesday August 14, 1:30PM - 5:10PM
Qualitative and Quantitative Analysis of Residual Pyrrolizidine Alkaloids in Commercial Borage Oil Products

Dejan Nikolic, PhD
University of Illinois at Chicago
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BIOGRAPHY

Dejan Nikolic is a Research Associate Professor in the Department of Pharmaceutical Sciences (formerly Department of Medicinal Chemistry and Pharmacognosy) in the College of Pharmacy, University of Illinois at Chicago.

Dejan received PharmD degree from University of Belgrade and PhD degree in Medicinal Chemistry from the University of Illinois at Chicago working under supervision of Dr. Richard van Breemen. After graduation, he joined the newly established UIC/NIH Center for Botanical Dietary Supplements Research where he is currently a Co-Leader of the Analytical Core that provides mass spectrometric support to the Center.

His research interests include structure elucidation of natural products using mass spectrometry, determination of ADME properties of active plant ingredients as well as development of modern UHPLC MS-MS methods for quantitative analysis of natural products. He has authored and co-authored more than 100 publications and two book chapters.

ABSTRACT

Dejan Nikolic1, Richard van Breemen2
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Borage (Borago officinalis) is an annual herb cultivated for production of its seed oil. Borage oil is rich in γ-linolenic acid, which is actively being investigated for its beneficial effects on cardiovascular health and other conditions. However, borage seeds are known to contain pyrrolizidine alkaloids (PAs). Some members of this group of alkaloids are known hepatotoxins and some may be genotoxic and carcinogenic. As these compounds do not have known beneficial effects and because the long-term effects of low-level exposure are not well understood,

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The presence of PAs in dietary supplements is generally considered undesirable. Therefore, it is of importance to develop methods to identify and quantify residual levels of these compounds. In this study, commercially available borage oil supplements were extracted using diluted acid and concentrated on cation-exchange solid-phase extraction cartridges. Resulting extracts were analyzed on a high-resolution quadrupole/time-of-flight mass spectrometer for qualitative and on a triple quadrupole mass spectrometer for quantitative analysis. Residual PAs were detected in all tested preparations, although with large variability in content ranging from 0.19-4240 ng/g oil. This suggests that PAs despite being relatively polar compounds do transfer into the oil during the supplement processing. The phytochemistry of borage PAs is much more complex than previously thought. The main characteristic of the alkaloid metabolome is presence of an unusual class of glycosidated PAs. In addition to the known compounds containing a single hexose (thesinine glucoside), we identified several novel analogs containing di- and tri saccharide units as well as compounds containing new structural templates. Even though the amount of measured residual hepatotoxic alkaloids was generally low, we recommend that quality control procedures be implemented to ensure that the final products do not contain these compounds.
Untargeted Metabolomics for Authentication of Botanical Dietary Supplements

Nadja B. Cech, PhD

Department of Chemistry
University of North Carolina,
Greensboro, NC, USA

BIOGRAPHY
Dr. Nadja B. Cech is Patricia A. Sullivan Distinguished Professor of Chemistry at UNC Greensboro. She applies her expertise in mass spectrometry to solve challenging problems in natural products research, largely supported with funding from the National Institutes of Health. Work in the Cech group focuses on the development of strategies to understand synergy and complexity in the biological activity of botanical extracts. Dr. Cech’s interests in this area stem from a long history of involvement in alternative medicine; her family owns and operates one of the largest medicinal herb seed companies in the country, and she spent her childhood working on their farm.

Dr. Cech supervises a research group of sixteen students and postdoctoral research associates. She is the recipient of the 2011 Jack L. Beal Award for Best Paper in the Journal of Natural Products by a Young Investigator, and the 2017 Thomas Norwood Award for Undergraduate Research Mentorship. Dr. Cech a member of the research team for the NCCIH-funded Center of Excellence for Natural Product Drug Interaction, and Co-Director of the Medicinal Chemistry Collaborative (https://mcsquared.uncg.edu/).

ABSTRACT
Dietary supplements, which include botanical (plant-based) natural products, constitute a multi-billion-dollar industry in the US. Regulation and quality control for this industry is an ongoing challenge. While there is general agreement that rigorous scientific studies are needed to evaluate the safety and efficacy of botanical natural products used by consumers, researchers conducting such studies face a unique set of challenges. Botanical natural products are inherently complex mixtures, with composition that differs depending on myriad factors including variability in genetics, cultivation conditions, and processing methods.

Unfortunately, many studies of botanical natural products are carried out with poorly characterized study material, such that the results are irreproducible and difficult to interpret. To address this challenge, our research group has developed untargeted mass spectrometry metabolomics approaches to compare commercial dietary supplements and determine which are most representative of those used by consumers. An important element of these studies is the

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calculation of a “composite score”, which is a quantitative metric that classifies the similarity among samples based on principal component analysis data. Several case studies will be presented illustrating how this approach has been applied to select study materials of green tea (*Camellia sinensis*), goldenseal (*Hydrastis canadensis*) and kratom (*Mitragyna speciosa*) for clinical evaluation.

**GRAPHICAL ABSTRACT**
Black Cohosh: Confusion Regarding the Mechanism of Action of a Botanical Dietary Supplement

Edward J. Kennelly, PhD

Lehman College,
City University of New York
Bronx, NY, USA

BIOGRAPHY

Dr. Edward J. Kennelly is a full professor at Lehman College, City University of New York. Since his doctoral work in plant biology at Washington University St. Louis (1993), Dr. Kennelly’s research has centered on natural products from food and medicinal plants that impact human health. Prior to joining the faculty of CUNY in 1998, Dr. Kennelly worked as a Senior Staff Fellow at the US Food and Drug Administration (1996-1998) and as a Postdoctoral Fellow and Research Professor in Pharmacognosy at University of Illinois at Chicago School of Pharmacy (1993-1996). He served on the FDA Food Advisory Committee for the Center for Food Safety and Applied Nutrition (2009-2012).

Dr. Kennelly has published over 125 peer-reviewed publications in the field of natural product chemistry, and his research has been supported by the US National Institutes of Health, the United States Department of Agriculture, the Chinese Ministry of Education, and the State of New York. Dr. Kennelly is the Editor of the American Society of Pharmacognosy Newsletter, and served as the ASP Vice President (2014-2015) and President (2015-2016). Dr. Kennelly served as a foreign expert to Minzu University of China’s 111 Project (2008-2017). He was a Fulbright Scholar at the Chinese University of Hong Kong’s Institute of Chinese Medicine (2014-2015) where he conducted research on how modern Traditional Chinese Medicine as practiced in Hong Kong, and is a member of ICM’s external advisory board (2016-present).

ABSTRACT

On February 11, 2019, Food and Drug Commissioner issued a statement on the government’s new efforts to strengthen the regulation of dietary supplements. Many medicinal plants are sold in the US as dietary supplements, and are therefore regulated under the 25-year-old Dietary
Supplement Health and Regulation Act. However, numerous problems with the quality assurance of these products have been documented.

Recent developments in the field of separation science and the application of statistical modeling provide an important foundation for analyzing the complex chemistry of botanicals, and can be useful to address issues of both safety and efficacy. Using modern analytical chemistry techniques like LC-qToF-MS, my laboratory has been able to identify key marker compounds, and correlate certain metabolites with biological activities from a number of different medicinal plants and functional foods.

For example, products made with black cohosh (*Actaea racemosa*) constitute one of the most popular botanical dietary supplements in the US market for women’s health, but its bioactive constituents continue to be explored, and concerns about adulteration of this product are well-documented. Using validated analytical methods, we found about a third of black cohosh products in our study were adulterated. We also found that even authentic black cohosh is not estrogenic, as is often claimed. Problems with the quality control of botanical dietary supplements sold in the United States are not unique to black cohosh.
Polyphenols from Hops (*Humulus lupulus*) for Mitigating Metabolic Syndrome and Inflammatory Bowel Disease

Jan F. Stevens, PhD

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**ABSTRACT**

Jan F. Stevens1,2, Adrian F. Gombart2,3, Claudia S. Maier2,4, Thomas O. Metz5, Ryan D. Bradley6

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Dietary polyphenols exert a broad spectrum of beneficial effects in various models of disease. Despite many investigations, no clear mechanism of action has emerged to explain their beneficial health effects. We explore the use of untargeted, mass spectrometry-based metabolomics and lipidomics approaches to elucidate mechanisms of polyphenol bioactivity *in vivo*; in particular, the effects of xanthohumol (XN) from hops (*Humulus lupulus*) on energy metabolism in rodent models of metabolic syndrome (MetS). XN has received increasing attention in recent years due to its reported anti-obesity, anti-inflammatory, anti-hyperglycemic and anti-hyperlipidemic activities in animal models of MetS.

As gut microbiota mediate the physiological impacts of dietary polyphenols, we also study the interaction between gut microbiota and XN. Gut microbial metabolism of XN yields the estrogenic metabolite, 8-prenylnaringenin, which is a potential health concern in the development of XN as a dietary supplement for prevention or treatment of MetS. We approached this concern by reducing the double bond of XN’s α,β-unsaturated keto moiety to yield the hydrogenated derivatives, α,β-dihydro-XN (DXN) and tetrahydroxanthohumol (TXN), which cannot be metabolically converted into 8-prenylnaringenin. Data from cell culture and rodent models of MetS indicate that the hydrogenated XN derivatives, DXN and TXN, have

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potential to prevent or treat the metabolic impairments associated with diet-induced obesity and MetS without risk of estrogenic adverse effects. In view of the role of gut dysbiosis in the development and progression of inflammatory bowel disease and our observation that XN alters the gut microbiome and reduces the formation of pro-inflammatory cytokine levels in our MetS model, we are beginning to investigate the effects of XN on gut inflammation in humans. We are conducting two prospective clinical trials with XN (24 mg q.d.): one with 24 healthy adults and one with 24 adults diagnosed with Crohn’s Disease (Funding by NCCIH grants R01AT009168 and R01AT010271).

GRAPHICAL ABSTRACT
Impact of an Extract from *Artemesia dracunculus* on Metabolic Syndrome

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**BIOGRAPHY**

Elizabeth (Beth) Floyd received her PhD in Biochemistry in 1997 and joined the faculty at Pennington Biomedical Research Center in 2004 after completing postdoctoral fellowships at Washington University in St. Louis and Louisiana State University in Baton Rouge. In 2017, she became Co-Director of the Pennington Biomedical/Rutgers University Botanical and Dietary Supplement Research Center. Dr. Floyd’s research group combines cell culture-based experiments and animal models of obesity to understand the mechanisms in adipose tissue and skeletal muscle that underlie obesity-related insulin resistance and the therapeutic potential of botanical extracts in preventing obesity-related metabolic dysfunction.

Dr. Floyd is the author of 63 articles, book chapters and reviews and her research is currently funded by the Louisiana Biomedical Collaborative Research Program, the National Institute of Diabetes and Digestive and Kidney Disorders and the National Center for Complementary and Integrative Health.

**ABSTRACT**

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First described over ninety years ago, the prevalence of metabolic syndrome in the United States reached 35% by 2012. Fueled by the obesity epidemic, the syndrome is a collection of risk factors related to obesity-induced insulin resistance that places an individual with obesity at high risk for developing type 2 diabetes and cardiovascular disease. There is a long history of therapeutic use of plant extracts to treat symptoms related to metabolic syndrome and type 2 diabetes. This includes Metformin, a mainstay of metabolic syndrome and type 2 diabetes treatment, which is based on a guanidine from Galega officinalis (French lilac).
*Artemisia* species are also widely used in traditional medicine and our preclinical studies show that an ethanolic extract of *Artemisia dracunculus* (Russian tarragon), termed PMI-5011, has therapeutic potential in treating metabolic syndrome. Using animal models of obesity-induced insulin resistance, we found that PMI-5011 mitigates obesity-induced insulin resistance and improves glucose metabolism by enhancing insulin signaling in skeletal muscle. Reduced skeletal muscle protein degradation is an important benefit of PMI-5011-mediated enhanced insulin signaling that may translate into preservation of muscle mass in obesity.

Five phytochemicals were identified in PMI-5011 that affect glucose metabolism and insulin responsiveness. Among them, 2’,4’-dihydroxy-4-methoxydihydrochalcone (DMC-2) and its isomer, 2’,4-dihydroxy-4’-methoxydihydrochalcone (DMC-1) account for the hypoglycemia effects of PMI-5011. These studies also show that DMC-2 is sufficient to stimulate insulin signaling in skeletal muscle and studies *in vivo* indicate skeletal muscle is the primary target of DMC-2 and PMI-5011 activity. In a recent clinical study, we found that PMI-5011 is safe and well-tolerated. Moreover, DMC-2 is bioavailable within six hours of oral administration in humans, providing support for future studies to determine the efficacy of the Russian tarragon extract in preventing obesity-induce metabolic syndrome by enhancing insulin action in skeletal muscle.
Enhanced Detoxication of Air Pollutants with Broccoli-based Interventions

Thomas Kensler, PhD
Fred Hutchinson Cancer Research Center
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BIOGRAPHY

Thomas Kensler received his Ph.D. in toxicology from M.I.T. Following postdoctoral fellowships at the McArdle Laboratory for Cancer Research, University of Wisconsin and at the National Cancer Institute in Bethesda, MD, he joined the faculty of the Johns Hopkins Bloomberg School of Public Health, Baltimore MD in 1980. In 1992 he was promoted to the rank of Professor. In 2010 he moved his primary appointment to the University of Pittsburgh as Professor in the Department of Pharmacology & Chemical Biology and in 2018 to the Fred Hutchinson Cancer Research Center in Seattle. He also holds several Visiting Professorships in China.

Dr. Kensler’s research interests are in environmental carcinogenesis and cancer prevention. His work demonstrates that activation of KEAP1-NRF2-signaling pathway is a key adaptive response to environmental and endogenous stresses and can be effectively targeted by thiol-reactive small molecules. He has led several clinical trials of inducers of the Nrf2 pathway in the Qidong region of China. Recent trials have focused on interventions with broccoli sprout-derived beverages (rich in sulforaphane) as modulators of aflatoxin and air pollutant metabolism and DNA damage.

Dr. Kensler is a past chairman of the NIH Chemo/Dietary Study Section and is currently a Senior Editor for Cancer Prevention Research. He has received several honors including the 2007 AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention, the 2009 Society of Toxicology Translational Impact Award and the 2011 Friendship Award from the, People’s Republic of China, their highest award for foreign civilians. He is a 2018 Clarivate Highly Cited Researcher.

ABSTRACT

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Airborne pollutants have collectively been classified as a known human carcinogen and, more broadly, affect the health of hundreds of millions of people worldwide. Benzene is a frequent component of air pollution and strategies to protect individuals against unavoidable exposure to this and other airborne carcinogens could improve the public’s health. China is one of the world’s largest emitters of anthropogenic air pollution and levels of outdoor air pollution in China are among the highest in the world.

Our prior studies in Qidong, an area of rapidly growing economic development in the Yangtze River Basin, measured high levels of certain internal dose biomarkers of air pollutants including benzene, aldehydes and polycyclic aromatic hydrocarbons. We have evaluated the strategy of inducing detoxication of air pollutants through activation of NRF2 signaling using a broccoli sprout beverage containing sulforaphane and its biogenic precursor glucoraphanin. Several key challenges in the design of clinical chemoprevention trials, especially food-based trials, are the selection of the dose, formulation, and dose schedule of the intervention material. We have recently completed a randomized, placebo-controlled, multi-dose trial of broccoli sprout beverage to determine the lowest effective level that enhances benzene detoxication adjudged by enhanced excretion of the urinary biomarker, S-phenyl mercapturic acid (SPMA). A dose/formulation that evoked a urinary elimination of ~25 µmol sulforaphane metabolites per day significantly increased the rate of urinary excretion of SPMA; lower doses were not effective. Tablet-based formulations provide equivalent internal doses of sulforaphane with decreased inter-individual variability and may portend a practical and frugal population-based strategy to attenuate associated long-term health risks of air pollution. Supported by NIH grants R01 CA190610 and R35 CA197222 and the Washington State Andy Hill CARE Fund.
Contributed Talk

Long-Term Effects of a Botanical Cardiovascular Support Formula on Blood Pressure in Adults with Prehypertension and Stage 1 Hypertension

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BIOGRAPHY
Jennifer Ryan is a full-time Investigator at National University of Natural Medicine in Portland, OR. Prior to her medical training, Dr. Ryan was a basic scientist at Sanford Burnham Prebys Medical Discovery Institute and Ludwig Institute for Cancer Research. Her current projects involve examining the clinical safety, tolerability, and biologic mechanisms of various botanicals, probiotics, and prebiotics.

ABSTRACT
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Background:
The authors recently reported results of a safety study on a botanical formula in adults with prehypertension and stage 1 hypertension. Primary findings suggested the formula is safe for long-term use in the studied population. Exploratory findings included significant decreases in systolic and diastolic blood pressure (BP). A secondary analysis was recently performed to further elucidate effects on BP.

Methods:
Participants (n=30) were asked to take one caplet of a botanical formula per day for six months. Outcome measures, including clinical biomarkers, validated questionnaires, and vital signs were collected at baseline, after three months, and after six months. For the secondary analysis,
participants were categorized as meeting JNC-7 criteria for either prehypertension (PH) or stage 1 hypertension (S1H) according to baseline values. BP data were reevaluated according to subgroup.

**Results:**
At baseline, 30.0% of the study population met criteria for S1H. In contrast, only 4.0% and 5.3% met criteria for S1H after 3 months and after 6 months, respectively. Over the 6 month period, mean BP decreases in the entire study population were 13.6 mmHg systolic and 9.4 mmHg diastolic (p<.0001). However, subgroup analysis indicated that BP decreases were higher in participants with S1H. Systolic BP decreased 20.8 mmHg and diastolic BP decreased 15.2 mm Hg (p<.05).

**Conclusions:**
The most recent findings suggest the investigated formula had a greater effect on BP in adults with S1H than in those with PH, further providing justification for additional research on the formula. Future studies should expand the study population to include adults with stage 2 hypertension, in order to further explore magnitude of effects on BP. Forthcoming work should also examine escalation of the dose of the formula, as well as biologic mechanisms of action, which may include potassium-sparing and diuresis effects, as well as alteration of blood viscosity.