

17th Annual OXFORD ICSB

April 3rd - 6th 2017

at the Oxford Conference Center | 102 Ed Perry Blvd, Oxford, Mississippi

The Oxford International Conference on the Science of Botanicals is an annual meeting to discuss approaches for post market surveillance, risk and safety assessment, quality control and adverse event reporting (AER) for botanical dietary supplements (BDS) and natural products as well as regulatory aspects with perspectives from government, manufacturers and trade associations

CONFERENCE AGENDA

- Daily Schedule
- Speaker Abstracts
- Speaker Bios



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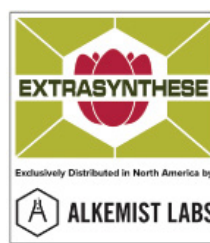
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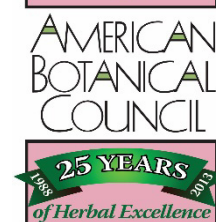
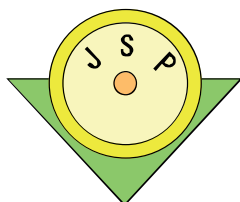


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This conference is supported by a cooperative agreement between the NCNPR and the Center for Food Safety and Applied Nutrition (CFSAN) at the U.S. Food and Drug Administration (FDA). It is co-sponsored by the Shanghai Institute of Materia Medica/CAS, China; the Council of Scientific and Industrial Research (CSIR - India); the Ministry of Indigenous Medicine; Sri Lanka; the American Society of Pharmacognosy (ASP); the Society for Medicinal Plant Research (GA); and the Korean Society of Pharmacognosy.



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THE UNIVERSITY of
MISSISSIPPI

NATIONAL CENTER FOR NATURAL PRODUCTS RESEARCH

April 3, 2017

Dear Friends,

On behalf of the National Center for Natural Products Research, School of Pharmacy, and the University of Mississippi, we would like to welcome you to the “17th International Conference on the Science of Botanicals.” With the help of the Oxford Conference Center, we have put together a program of social and entertainment activities to run alongside our rich and informative scientific agenda. The upcoming year’s meeting will explore the topic of synergy between natural products and human health. To this end, we will review, discuss, and explore the confluence of current research topics related to natural products research and development as well as topics related to safety, quality and regulatory aspects. Further information regarding this conference can also be found at www.oxfordICSB.org. This conference is supported by a cooperative agreement between the NCNPR and the Center for Food Safety and Applied Nutrition (CFSAN) at the U.S. Food and Drug Administration (FDA). It is co-sponsored by the Shanghai Institute of Materia Medica/CAS, China; the Council of Scientific and Industrial Research (CSIR - India); the Ministry of Indigenous Medicine; Sri Lanka; the American Society of Pharmacognosy (ASP); the Society for Medicinal Plant Research (GA); the Korean Society of Pharmacognosy; The Vietnam Academy of Science and Technology (VAST).

We are excited to present a program featuring a roster of internationally recognized experts and researchers in the field of botanicals. We wish to extend our thanks to our speakers for their willingness to participate in and contribute to the success of this meeting.

We invite you to visit the website of the National Center for Natural Products Research at <http://www.pharmacy.olemiss.edu/ncnpr> to learn more about our research program. Oxford and the Ole Miss campus are a beautiful setting, and we hope you will get to explore them, especially if this is your first time to visit here. If there is anything we can do to make your visit more enjoyable, please contact us.

Sincerely,

Ikhlas A. Khan, Ph.D.
Director, National Center for Natural Products Research
Director, FDA Center of Excellence
University of Mississippi

A DIVISION OF THE RESEARCH INSTITUTE OF PHARMACEUTICAL SCIENCES, SCHOOL OF PHARMACY

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Organizing Committee

Cara Welch, Ph.D.

Senior Advisor, Division of Dietary Supplement Programs, CFSAN, FDA

Ikhlas Khan, Ph.D.

Director of FDA Program,
The University of Mississippi.

Larry A. Walker, Ph.D.

Director, NCNPR,
The University of Mississippi.

Mark Blumenthal

Executive Director
American Botanical Council.

Loren Israelsen, J.D.

Executive Director
United Natural Products Alliance.

Rick Kingston, Ph.D.

President,
Safety Call International

Scientific Program Committee

Cindy Angerhofer, Ph.D.

Executive Director, Botanical Research
Aveda, Minneapolis-St. Paul, MN, USA

Joseph M. Betz, Ph.D.

Office of Dietary Supplements of NIH.

Wolfgang Blaschek, Ph.D.

Professor, Pharmaceutical Biology
University of Kiel

De-an Guo, Ph.D.

Director, Shanghai Research Center for
TCM Modernization
SIMM/CAS

Rudolf Bauer, Ph.D.

Institute of Pharmaceutical Sciences
Department of Pharmacognosy
Karl-Franzens-Universitaet Graz.

John Cardellina II, Ph.D.

Distinguished Scientist - Chemistry,
Technical Innovation Center, ReevesGroup
Consultations

K. Hüsnü C. Baser, Ph.D.

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Pharmacognosy, Anadolu University,
Eskisehir, Turkey.

Paula Brown, Ph.D.

Director of Applied Research, Natural
Health & Food Products Research Group.
British Columbia Institute of Technology

Sibyl Swift, Ph.D.

Special Assistant, FDA, Office of Dietary
Supplement Programs.

Stephen O. Duke, Ph.D.

Research Leader, USDA, ARS, NPURU.

Mahmoud A. ElSohly, Ph.D.

Research Professor NCNPR, Professor of
Pharmaceutics.
The University of Mississippi.

Edward J. Fletcher

COO/Botanicals Division,
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Craig Hopp, Ph.D.

Program Officer, NCCAM, NIH

Jinwoong Kim, Ph.D.

Seoul National University, South Korea.

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Jack L. Beal Professor and Chair,
Ohio State University,
College of Pharmacy.

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Professor of Pharmacognosy, Department
of Pharmacognosy, University of Vienna,
Austria.

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CFSAN, FDA.

Amar Chittiboyina, Ph.D.

Senior Research Scientist
NCNPR, University of Mississippi

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Department of Pharmacy,
National Autonomous University
of Mexico.

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Director, Bureau of Clinical Trials and
Health Science
NHPD, Health Products and Food Branch,
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Ironstone, Inc.

Dan Fabricant, Ph.D.

Natural Products Association

Maged Sharaf, Ph.D.

Chief Science Officer
American Herbal Products Association

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Assistant Director, NCNPR
The University of Mississippi.

Guido F. Pauli, Ph.D.

Associate Professor of Pharmacognosy
University of Illinois at Chicago

Eike Reich, Ph.D.

CAMAG Laboratory, Muttenz, Switzerland

Andre Santos, Ph.D.

Americas Market Development Manager
Agilent Technologies, Andover, MA.

Roy Upton

Executive Director, American Herbal
Pharmacopoeia.

Ram Vishwakarma, Ph.D.

Director, IIIM, Jammu.

Jimmy Yuk, Ph.D.

Senior Business Development Manager
Waters Corporation, Milford, MA

Daniel S. Marsman, DVM PhD

Head, Product Safety, Global
Product Stewardship
P&G Health Care, Worldwide



17th Annual OXFORD ICSB

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DAY 1 (Monday, April 3)

8:00 – 9:00 Open onsite registration – Oxford Conference Center (OCC) Lobby

9:00-10:00 Opening Session - OCC Auditorium

Welcome on behalf of the University of Mississippi and the School of Pharmacy

- Joseph Gladden, Interim Vice Chancellor, Research & Sponsored Programs, University of Mississippi
- David Allen, Dean and Executive Director, the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi

Welcome and Introductory Remarks from Organizers

- Ikhlas Khan, Director, National Center for Natural Products Research (NCNPR), University of Mississippi

Introduction of Keynote Speaker

- Larry Walker, National Center for Natural Products Research (NCNPR), University of Mississippi

Keynote Address

- Cara Welch, Senior Advisor, CFSAN, Office of Dietary Supplement Programs, U.S. Food and Drug Administration

10:00 - 10:30

Break

SESSION 1: “Update and Future Perspectives from the FDA” OCC Auditorium”

Moderator and Session Chair: Cara Welch, Office of Dietary Supplement Programs, CFSAN, U.S. Food and Drug Administration

- 10:30-12:00 Sibyl Swift, Office of Dietary Supplement Programs, CFSAN, U.S. Food and Drug Administration
“New Dietary Ingredient Notifications (NDINs): The path from objection to acknowledgement”
Saleh Turujman, Office of Dietary Supplement Programs, CFSAN, U.S. Food and Drug Administration, “Overview of What FDA Expects to See in a Specification Table”
Rahul Pawar, Office of Dietary Supplement Programs, CFSAN, U.S. Food and Drug Administration
“Validation of an LC-MS/MS Method for Analysis of Anti-diabetic, Anti-obesity, and Cholesterol-lowering Drugs in Botanical Dietary Supplements Labelled for Blood Sugar Management”

Conference Photograph

Meet at OCC side patio across from Cedar Room Dining Hall.

12:00 - 1:00

Lunch

SESSION 2a: “Natural Product Discovery and Regulation” OCC Auditorium

Moderator and Session Chair: Michael Smith, Michael J Smith & Associates

- 1:00-1:30 Jinhui Dou, Botanical Review Team, Office of Pharmaceutical Quality, CDER, FDA “US FDA Botanical Drug Guidance and Review Experience (2003-2016)”
1:30-2:00 Rajiv Agarwal, Office of New Drug Product, OPQ/CDER/FDA, “US Regulatory Approaches to Chemistry, Manufacturing, and Controls for Botanical Drug Products”
2:00-2:30 Krista Coventry, Source Nutraceutical, Inc., “Regulatory Considerations for Botanical Ingredients in the Canadian Health Products Marketplace”

2:30 - 3:00

Break

SESSION 2b: “Natural Products Discovery and Development” OCC Magnolia Room

Moderator and Session Chair: Xing-Cong Li, University of Mississippi

- 1:00-1:20 Jeffrey Langland, Southwest College of Naturopathic Medicine, “Mechanistic botanical medicine: defining anti-cancer and anti-viral properties of Sarracenia purpurea”
1:20-1:40 Thomas Brendler, PlantaPhile, “Sceletium tortuosum: a case study for a traditional herbal medicine in modern-day regulatory systems”
1:40-2:00 Michael Tims, Maryland University of Integrative Health, “How Can Chemical Ecology Help Find Effective Herbal Medicine”
2:00-2:20 Muhammad Djati, Brawijaya University, “Combination of Elephantopus scaber and Sauropus androgynus Leaves Extract Effects on Progesterone, Estrogen Hormones Level Modulation and Histopathological Study in BALB/c Mice Typhoid Model”

2:20 - 2:50

Break

DAY 1 (Monday, April 3)

SESSION 2b continued: “Natural Products Discovery and Development” OCC Magnolia Room

- | | |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2:50-3:10 | Giorgis Isaac, Waters Corporation, "Ion Mobility Mass Spectrometry: A New Tool for Complex Natural Product Characterization and Identification" |
| 3:10-3:30 | Maged Sharaf, American Herbal Products Association, "Industry Initiatives to Ensure Continued Quality and Sustainability" |
| 3:30-3:50 | Javad Mussarat, Baba Ghulam Shah Badshah University, "Assessment of Oxidative Stress in Zn ²⁺ Ions, ZnO-Bulk and ZnO-NPs treated <i>Allium cepa</i> roots" |
| 3:50-4:10 | Mohammad Kamil, Health Authority Abu Dhabi, New Natural Products from Plants with Special Reference to Novel Flavonoids, Biflavonoids & their Biological Implications " |
| 4:10-4:30 | Yalda Shokoohinia, Kermanshah University of Medical Sciences, "Cancer preventive investigation of new compounds from <i>Echinophora cinerea</i> , a condiment" |

SESSION 2c: “GMP: Industry Perspective” OCC Auditorium

Moderator and Session Chair: Dan Marsman, P&G Health Care

- | | |
|-----------|--------------------------------------------------------------------------------------------------------------------------|
| 3:00-3:30 | Frank Jaksch, ChromaDex, “Supply Chain Management is the Key to Better Analytical Testing” |
| 3:30-4:00 | Corey Hilmas, Natural Products Association, “Regulatory Risk and Scientific Jenga” |
| 4:00-4:30 | Dan Fabricant, Natural Products Association, “Board Game of Thrones: Legislative Trivial Pursuits to Opportunity Knocks” |

SESSION 3: "Botanical Adulterants Program/ ABC award" OCC Auditorium

- 4:30-5:00 Mark Blumenthal, American Botanical Council

6:00 - 8:00pm

Reception/Mixer at Lyric Oxford

Presentation of the Award for Outstanding Contribution in Natural Product Science

NOTES:

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DAY 2 (Tuesday, April 4)

SESSION 4: "Clinical Toxicology Investigations Impacting Supplement Safety Surveillance" OCC Auditorium

Moderator and Session Chair: Rick Kingston, SafetyCall International

- 8:15-8:45 Victor Navarro, Einstein Healthcare Network, "Dietary Supplement Related Liver Injury"
8:45-9:15 Cristiana Leslie Corrêa, Planitox, "Importance of using a Structured Causality Assessment for cases of herb or dietary supplement-induced liver injury"
9:15-9:45 Rick Kingston, SafetyCall International, "Adverse event reports and the cost of regulatory transparency"

9:45 - 10:15

Break

SESSION 5a: "Prospects for Naturally Derived Cannabinoids as FDA Regulated Therapeutics" OCC Auditorium

Moderator and Session Chair: Larry A Walker, University of Mississippi

- 10:15-10:45 Oliver Kayser, Technical University Dortmund, "Molecular insights into the biosynthesis of cannabinoids"
10:45-11:15 Larry Walker, University of Mississippi, "Clinical evaluation of Cannabis extracts for epilepsy in the US: status and prospects in Mississippi"
11:15-11:45 Jerzy Szaflarski, UAB Epilepsy Center, "Cannabinoids for the treatment of epilepsy"

SESSION 5b: "Analytical Methods and Reference Materials for Botanical Dietary Supplements" OCC Magnolia Room

Moderators and Session Chairs: Stephan Wise, ODS and NIH; and Catherine A. Rimmer, National Institute of Standards and Technology

- 10:15-10:30 Adam Kuszak, ODS and NIH "The NIH Office of Dietary Supplements Analytical Methods and Reference Materials Program"
10:30-11:00 Paula Brown, BC Institute of Technology, "Characterizing and Establishing Authenticity of Botanical Products"
11:00-11:30 James Harnly, US Department of Agriculture, "Authentication of botanical supplements based on correlation with raw ingredients"
11:30-12:00 Darryl Sullivan, Covance Laboratories, "Critical Needs and Use of Reference Materials for Dietary Supplements"

12:00 - 1:00

Lunch

SESSION 5b: Analytical Methods and Reference Materials for Botanical Dietary Supplements" OCC Magnolia Room

- 1:00-1:30 Catherine Rimmer, National Institute of Standards and Technology, "Reference Materials for Dietary Supplements"
1:30-2:00 Holly Johnson, Alkemist Labs, "Challenges in Testing Dietary Supplements"
2:00-2:30 Uma Sreenivasan, Cerilliant Corporation, "Accuracy of Reference Materials for Dietary Supplements"

2:30 - 3:00

Break

SESSION 5b: Analytical Methods and Reference Materials for Botanical Dietary Supplements" OCC Magnolia Room

- 3:00-3:30 Nandakumara Sarma, United States Pharmacopeia, "Pesticide residues in botanicals: What are the rational limits?"
3:30-4:00 Gary Jackoway, MIDI, Inc. "Authentication of Botanicals by Automated Analysis and Chemometrics"
4:00-4:30 Eike Reich, CAMAG Laboratory, "How can HPTLC help the Botanical Industry to improve quality of botanical products in a pragmatic way?"
4:30-5:00 Trish Flaster, Botanical Liaisons, LLC, "Supply chain management making sure you have the your eye on the ingredients"

5:30 - 8:00

Poster Session: chairs - Steven Dentali & Amar Chittiboyina (OCC Oak)

7:00 - 8:00

Dinner (OCC Cedar)



DAY 3 (Wednesday, April 5)

SESSION 7: "International Perspectives on Botanical Research" OCC Auditorium

Moderator and Session Chair: Jinwoong Kim, Seoul National University

- 8:30-9:00 Weidong Zhang, Second Military Medical University, "Discovery and Chemical Biology Study of Novel Active Compounds from TCM"
- 9:00-9:30 Alvaro Viljoen, Tshwane University of Technology, "Quality control and pharmacological activity - Bridging the chasm"
- 9:30-10:00 Allen Bensoussan, NICM, "Vascular dementia and multi-target therapy in Chinese herbal medicine"

10:00 - 10:30

Break

SESSION 8a: "Future Initiatives on Dietary Supplements" OCC Auditorium

Moderator and Session Chair: Loren Isrealsen, UNPA

- 10:30-11:00 Stefan Gafner, American Botanical Council, "TBA"
- 11:00-11:30 Larisa Pavlick, UNPA, "An industry perspective on botanical quality and compliance"
- 11:30-12:00 Stephen Daniells, William Reed Business Media, Inc., "Connecting science, industry and consumers: An editor's view of the natural products industry"

SESSION 8b: "Natural Products Research" OCC Magnolia Room

Moderator and Session Chair: Babu Tekwani, University of Mississippi

- 10:30--11:00 Alexander Crawford, Université du Luxembourg "Fishing for drugs from nature: Zebrafish as a biodiscovery platform"
- 11:00-11:30 Mi-Jeong Ahn, Gyeongsang National University, "Anatomical characterization and chemical profiling of Korean folk medicines"
- 11:30-12:00 Clara Lau, The Chinese University of Hong Kong, "The combined use of Herba Cistanches and statin - a possible solution for statin-induced myotoxicity"

12:00 - 1:00

Lunch

SESSION 9a: Town Hall Meeting OCC Auditorium

1:00-2:00 Moderators: Rick Kingston & Dan Marsman

SESSION 9b: "Natural Product Technology Session" OCC Magnolia Room

Moderator and Session Chair: Guido Pauli, University of Illinois at Chicago

- 1:00-1:20 John MacMillan, Center for High-Throughput Functional Annotation of Natural Products (HiFAN), "TBA"
- 1:20-1:40 Guido Pauli, Center for Natural Products Technologies (CENAPT), "IMPS and Data"
- 1:40-2:00 Jonathan Bisson, John McMillan, Guido Pauli, CENAPT & HiFSA, "Data Transparency and Sharing in NP Research"

2:00 - 3:00

Natural Products Training Laboratory Dedication a partnership with Waters Corporation

3:00 - 9:00

ICSB Picnic - Oxford Conference Center Lawn. Food, Fun, Music and Outdoor Games

DAY 4, (Thursday, April 6)

SESSION 10: “International Efforts on the Development of Traditional Chinese Medicines” OCC Auditorium

Moderator and Session Chair: Cindy K. Angerhofer, Aveda

- 8:30-9:00 Yi Zhun Zhu, Macau University of Science and Technology, “Anti-inflammatory effects of Leonurine (SCM-198): from preclinical studies to bedside”
- 9:00-9:30 Jungui Dai, Institute of Materia Medica, Chinese Academy of Medical Sciences, “Enzyme promiscuity and diversity-oriented structural innovation of natural products and drug discovery”
- 9:30-10:00 Jinwoong Kim, Seoul National University, “Khellactone type coumarins from *Peucedanum japonicum* roots”

10:00 - 10:30

Break

SESSION 11a: “Genetic Authentication of Botanicals” OCC Auditorium

Moderator and Session Chair: Natascha Techen University of Mississippi

- 10:30-10:55 Pietro Piffanelli, PTP Science Park/ Indena, “Next Generation Sequencing Technologies as a powerful tool to botanicals identification and authentication”
- 10:55-11:20 Sara Handy, CFSAN, ORS, & FDA, “Development of a Reference Standard Library of Chloroplast Genome Sequences, GenomeTrakrCP”
- 11:20-11:45 Natalia Ivanova, University of Guelph, “Embracing and Understanding Biocomplexity of Herbal Supplements”
- 11:45-12:10 David Erickson, DNA4 Technologies LLC, “Meta-Genomic analysis of dietary supplement authenticity and complexity”

SESSION 11b: “Safety and Quality Evaluation of Botanicals” OCC Magnolia Room

Moderator and Session Chair: Alvaro Viljoen, Tshwane University of Technology

- 10:30-11:00 Jimmy Yuk, Waters Corporation, “Quantitation of aflatoxins in traditional Chinese medicine”
- 11:00-11:30 Hellen Oketch-Rabah, U.S. Pharmacopeia Convention, “USP Safety Review of Willow Bark”
- 11:30-12:00 Kirsten Tripplett, Traditional Medicinals, Inc., “Botanical Microscopy and Plant Anatomy is Cheap, Fast and Efficient”

12:00 - 1:00

Lunch

SESSION 12: “Analytical Approaches to assess the quality” OCC Auditorium

Moderator and Session Chair: Mahmoud ElSohly, University of Mississippi

- 1:10-1:40 Phil Wylie, Agilent Technologies, “Analysis of Cannabis for Pesticide Residues by GC/Q-TOF”
- 1:40-2:10 Yanhong Wang, University of Mississippi, “Chemical Analysis and Adulterant Characterization of *Eleutherococcus senticosus* and Ci-Wu-Jia Tea by UHPLC-UV-MS Using Novel Informatics Platform”
- 2:10-2:40 Krystina Skalicka-Wozniak, Medical University of Lublin, “What power can liquids provide in separation – the case of counter- current chromatography”

Afternoon tour of NCNPR facilities or Medicinal Plant Garden

6:30pm

Closing Ceremony and Banquet (OCC Cedar)
Registration is required and available on-site.



Key Note Speaker



Cara Welch, Ph.D., came to the Food and Drug Administration in January as a Regulatory Special Assistant in the agency's Division of Dietary Supplement Programs. In this role, Dr. Welch works on new policies and programs involving regulatory compliance matters of significant importance to the dietary supplement industry, with particular interest in cGMP issues. Welch utilizes her chemistry background to provide guidance on assessing dietary supplement manufacturing methods, evaluating test methodologies, and reviewing different cGMP systems regarding their particular public health and regulatory vulnerabilities.

Prior to FDA, Dr. Welch was the Senior Vice President of Scientific and Regulatory Affairs at the Natural Products Association (NPA). While there, she was responsible for implementing policies in response to government initiatives in the regulatory arena; advising association members on regulatory, safety, nutrition and health issues; and overseeing the association's Natural Seal Certification and Dietary Supplement GMP Certification programs. Dr. Welch earned her Ph.D. in Medicinal Chemistry from Rutgers University working with traditional medicinal African plants under the direction of plant biologist Jim Simon. She is a member of the American Chemical Society and the American Society of Pharmacognosy.



Sibyl Swift, Special Assistant at FDA, Office of Dietary Supplement Programs, FDA. Her work experience: the following: Special Assistant, Company Name FDA, Dates Employed Oct 2016 – Present, Employment Duration 5 mos Location College Park, Maryland, Office of Dietary Supplement Programs; Program Coordinator, Company Name FDA, Office of Dietary Supplement Programs, Dates Employed Oct 2014 – Oct 2016, Employment Duration 2 yrs 1 mo, Location College Park, MD; Research Biochemist, Company Name Armed Forces Radiobiology Research Institute, Dates Employed Jan 2013 – Oct 2014, Employment Duration 1 yr 10 mos, Location Bethesda, MD; Postdoctoral Fellow, Company Name Uniformed Services University, Dates Employed Aug 2010 – Dec 2012.

Dr. Swift's education: Texas A&M University, Degree Name Doctor of Philosophy (Ph.D.), Field Of Study Nutrition

Dates attended or expected graduation 2007 – 2010; Texas A&M University, Degree Name Master of Science (M.S.), Field Of Study Kinesiology and Exercise Science; Dates attended or expected graduation 2004 – 2007; Texas A&M University, Degree Name Bachelor of Science (B.S.), Field Of Study Kinesiology and Exercise Science Dates attended or expected graduation 2002 – 2004; Texas A&M University, Degree Name Bachelor of Science (B.S.), Field Of Study Psychology, Dates attended or expected graduation 1998 – 2002

Her awards received: Sydney and J.L. Huffines Institute for Sports Medicine and Human Performance Travel Award 2006-2009; Texas A&M University IFN Travel Award 2007, 2009; American Society for Nutrition Procter & Gamble Student Research Award 2009; Texas A&M University IFN Research Symposium, 1st Place, Graduate Oral Presentation 2009; Texas Chapter of the American College of Sports Medicine Research Manuscript Award 2008; Texas A&M University IFN Scholarship 2007, 2008; Alice L. Jee Young Investigator Award, 38th Annual Sun Valley Musculoskeletal Biology Workshop 2008; Philanthropic Educational Organization (PEO) Scholars College of Education & Human Development Nominee 2007; American Society for Bone and Mineral Research Travel Award 2007



New Dietary Ingredient Notifications (NDINs): The path from objection to acknowledgement

The Dietary Supplement Health and Education Act (DSHEA) describes the requirements for when a new dietary ingredient that is intended to be marketed in a dietary supplement product must be the subject of a New Dietary Ingredient Notification (NDIN), submitted to FDA 75 days before it is introduced to the market. Over the past twenty years, FDA has received fewer than 1,000 NDINs and acknowledged approximately 20% as providing an adequate basis the product is reasonably expected to be safe. FDA believes that providing prospective notifiers with a more clear understanding of the information that they need to include in their notification will increase the probability that they will receive an acknowledgement without objection for those products for which a reasonable assurance of safety can be demonstrated. This objective can be achieved in part with a description of the requirements for NDINs and a discussion of traits commonly observed in successful submissions. It will also be attained through the use of hypothetical examples of notifications that received objections to illustrate how they might be amended in a way that increases the likelihood that they would receive an acknowledgement.



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Saleh A. Turujman, Ph.D., is Lead Senior Chemist in the Office of Dietary Supplement Programs. He is a member of the Dietary Supplement Regulations Implementation Team. He was a member of the USP Council of Experts _ Monograph Development, Pharmaceutical Analysis 1 Expert Committee, 2000-2005; USP Expert Committee, Pulmonary and Steroids, 2000-2008. He is an FDA liaison to six Dietary Supplement Expert Committees since 2008. Along with other faculty members from the Office of Dietary Supplement Programs, he teaches a weeklong course on current Good Manufacturing Practice for Dietary Supplements to FDA inspectors several times a year.



Overview of What FDA Expects to See in a Specification Table

A specification is an explicit set of standards established by the manufacturer, packager, labeler or distributor of a dietary ingredient, dietary supplement, or its components. A specification defines the article and must include, among other requirements, an identity, an assay, and the analytical method used to determine them. Specifications, which should be based on the safety and on the quality requirements of the article, are developed by the manufacturer, packager or labeler of the product of the article, and are evaluated by FDA for adequacy.



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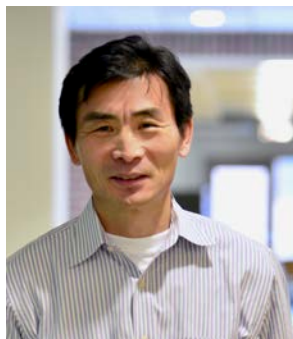
Rahul S. Pawar, Ph.D., was awarded a PhD. in Natural Products from the National Institute of Pharmaceutical Education and Research (NIPER), India in 2003. He pursued postdoctoral research at the National Center for Natural Products Research (NCNPR) at the University of Mississippi from 2003-2007. He is currently working at CFSAN /FDA and serves as the Office of Regulatory Science's Research Coordinator for dietary supplements. His research focuses on development of analytical methods for determination of dietary supplement quality.



Validation of an LC-MS/MS Method for Analysis of Anti-diabetic, Anti-obesity, and Cholesterol-lowering Drugs in Botanical Dietary Supplements Labelled for Blood Sugar Management

Ma J, Pawar RS & Grundel E., Office of Regulatory Science, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740, USA

Many botanical dietary supplements which carry label statements related to blood sugar management are available over the internet. Potential adulteration of such dietary supplements with anti-diabetic and other prescription drugs, some of which have been removed from the market due to adverse events, is of concern. In this study, we developed and validated an LC-MS/MS method to detect and quantitate fourteen anti-diabetic, two anti-obesity, and three cholesterol-lowering drugs in botanical dietary supplements sold for blood sugar management. LODs and LOQs for the 19 drugs ranged from 1 to 250 ng/g and from 4 to 1000 ng/g, respectively. Mean recoveries at six spiking levels from 0.5 to 2000 µg/g ranged from 88 to 112%. The RSDs (%) of intra- and inter-day variations ranged from 0.6 to 9.5 and from 0.6 to 5.4, respectively. Eighty botanical dietary supplements carrying label statements related to blood sugar management were analyzed using this method and none were found to be adulterated with the above 19 compounds. Two additional products known to be adulterated were also analyzed by this method and found to contain the analytes of interest. This method can be used to analyze dietary supplements for possible adulteration with these compounds.



Jinhui Dou, Ph.D., Pharmacologist and Pharmacognosist, Botanical Review Team, Office of Pharmaceutical Science, CDER, FDA. Dr. Dou received his Ph.D. degree in Pharmacognosy from the Pharmacy School of University of Mississippi. After obtaining his doctoral degree, he conducted his post-doctoral research at the University of Kansas on immuno-modulating medicinal plants. He also holds a bachelor's degree in Pharmacy and master's in Pharmacognosy from Beijing University of Chinese Medicine.

Dr. Dou joined the Botanical Review Team (BRT) in CDER in 2002, and is currently the Team Lead and expert reviewer on botanical drugs. He provided pharmacognosy reviews in supporting the approvals of botanical New Drug Applications (NDAs), Veregen and Fulyzaq (now called Mytesi). He has also reviewed hundreds of botanical Investigational New Drug (IND) applications, non-botanical small molecule INDs and NDAs, as a pharmacologist reviewer. His contribution in developing guidance, policies, and regulations had won him numerous CDER, FDA, and HHS awards.

Prior to joining the FDA, Dr. Dou worked as a lead natural products scientist for a biopharmaceutical company on anticancer drug discovery and development from medicinal plants.



US FDA Botanical Drug Guidance and Review Experience (2003-2016)

Jinhui Dou, PhD., Expert Pharmacologist and Team Lead, Botanical Review Team, CDER, FDA, Silver Spring, Maryland, USA

Abstract: FDA CDER established the Botanical Review Team in 2003 and finalized the Guidance for Industry: Botanical Drug Products in 2004.¹ The Guidance outlined that sponsors may reference prior human experience of botanical products (e.g., as dietary supplements and herbal medicines) to support early phase clinical trials under Investigational New Drug (IND) applications. Therefore, to support initial clinical trials for botanicals, the nonclinical pharmacology and toxicology information that must be provided under 21 CFR 312.22(b) may be markedly reduced compared to that expected for new molecule entities without prior human experience. This approach is still acceptable in the revised final [Guidance for Industry: Botanical Drug Development](#).²

Since 2003, CDER gained valuable review experience from over 450 botanical INDs submitted for clinical investigation as treatments for various diseases (e.g., cancer, infectious diseases, and arthritis). The experience also included two market approvals of prescription New Drug Applications (NDAs): Veregen, a topical drug for the treatment of genital and perianal warts, and Fulyzaq (now called Mytesi), an oral drug for the treatment of HIV/AIDS related diarrhea.^{3,4} In the case of Veregen, no bioassay was requested, largely due to the fact that catechins and other small molecules in the drug substance were adequately controlled. For Fulyzaq, clinically relevant bioassays were required as the proanthocyanidin oligomers in the drug substance could not be accurately quantified at molecular level.

Our multiple disciplinary review experience is the foundation of the revised final Guidance, which included recommendations on late phase drug development and NDA submissions. Most importantly, the Guidance described a “totality-of-evidence” approach to apply conventional CMC data and additional information, including raw material control, clinically relevant bioassay(s), and other data generated based on a multiple-batch and multiple-dose clinical trial of the botanical product, to ensure therapeutic consistency.

This presentation will also discuss the combination issue for NDA and augmentation of active compounds under certain conditions to maintain consistency, as outlined in the Guidance, and provide an overview on clinical hold issues for botanical INDs.

1. Lal R. Botanical Drug Review, FDA/CDER SBIA CHRONICLES, Nov. 17, 2015 <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm472934.pdf>
2. Botanical Drug Development: Guidance for Industry (Revision 1, December 2016) <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458484.pdf>
3. Lee, SL; Dou J; Agarwal, R; Temple, R; Beitz, J, Wu, C; Mulberg, A; Yu, LX; Woodcock, J. Evolution of traditional medicines to botanical drugs, *Science (Suppl)*, S32-34, January 2015.
4. Chen, ST; Dou, J, Temple, R, Agarwal, R, Wu, KM and Walker, S. New Therapies from old Medicines, *Nature Biotechnology*, Volume 26, 10, October 2008.



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Dr. Rajv Agarwal received his M.Phil. and Ph.D. degrees in Natural Product Chemistry/Medicinal Chemistry from India and a second Ph.D. degree in Chemistry (Chemistry/Toxicology) from the United Kingdom. He completed his postdoctoral training at the National Institutes of Health, Bethesda, MD.

Dr. Agarwal is working as an Expert Regulatory Review Scientist in the Office of New Drug Products, Office of Pharmaceutical Quality, at the Center for Drug Evaluation and Research. Dr. Agarwal is also the FDA Expert on Chemistry, Manufacturing, and Controls of Botanical drugs and provides consultations on CMC-related issues for botanical drug product submissions within CDER and to the other Centers.

Dr. Agarwal is the recipient of the FDA's Award of Merit, and Scientific Achievement Awards for Excellence in Review Science, as well as the FDA Outstanding Service Award. He is also the recipient of CDER's Regulatory Science and Review Enhancement (RSR) Grant, and two Intramural Grants from the Office of the Chief Scientist: The Chief Scientist Challenge Research Grant and The Office of Women's Health Intramural Scientific Research Grant on botanicals.



US Regulatory Approaches to Chemistry, Manufacturing, and Controls for Botanical Drug Products

Rajiv Agarwal, Ph.D., Expert Regulatory Review Scientist, CDER/FDA

Many botanical products are used widely in the United States. Depending on its labeling and intended use, a botanical product can be a food, a dietary supplement, and/or a drug. If a botanical product is intended for use in diagnosing, mitigating, treating, or curing disease, it is a drug under the Food, Drug, and Cosmetic Act and is subject to applicable drug regulations. The 2004 CDER Guidance on Botanical Drug Products defines the term “Botanical” as a finished, labeled product that contains drug substance from plant origins, which may include plants or plant parts, algae, macroscopic fungi, and combinations thereof. The term does not include highly purified substances or chemically modified substances derived from botanical sources.

In 2016, FDA updated¹ the 2004 Botanical Guidance to better address late phase development and NDA requirements. Due to the complex nature and uncertainty of the “active constituents” of botanicals, FDA may use unique regulatory approaches to assure quality for botanicals, while still ensuring the therapeutic consistency for all marketing batches which is the most critical issues for botanical NDAs^{2, 3, 4}. While conventional chemical characterization remains a critical quality assurance measure, therapeutic consistency may be supported by a “totality-of-the-evidence” approach, including: raw material and raw material process controls, chemistry, manufacturing and controls (CMC), and clinical and nonclinical data to ensure the quality, pharmacological potency, and therapeutic consistency of botanical drugs. The degree of reliance on these other measure for ensuring consistency of quality will depend on the degree of chemical characterization of the botanical.

This presentation provides an overview of the CMC information recommended to support the clinical studies of a botanical drug product under an investigational new drug application (IND) and requirements for marketing under a New Drug Application (NDA) in the United States.

1. Botanical Drug Development: Guidance for Industry, December 2016
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458484.pdf>
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3. Zhu, J, Fan, X; Cheng, Y; Agarwal, R; Moore, CMV; Chen, ST; Tong, W. Chemometric Analysis for Identification of Botanical Raw Materials for Pharmaceutical Use: A Case Study Using Panax notoginseng, PLOS One, Volume 9, 1, January 2014.
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Ms. Krista Coventry is the Director of Regulatory Affairs (Eastern Canada) for Source Nutraceutical, Inc., a Canadian contract research organization. She is a regulatory affairs specialist in the North American health products sector with 15 years of experience providing project management, regulatory strategies and market compliance solutions to industry clients, globally. Krista has expert knowledge of acts, regulations, policies and guidelines relating to natural health products (NHPs) and foods. She has worked extensively within the Canadian regulations to communicate the health benefits of various health products through regulatory efforts, and has vast experience critically evaluating evidence in support of health claims. Krista has also advised numerous clients with products at the interface of the NHP, food, cosmetic and drug regulations navigate the Canadian requirements for pre-market approval.

Krista has extensive experience lecturing on regulatory topics impacting the NHP and food sectors at various industry conferences, workshops and seminars, and also regularly authors articles for several health product industry publications. She has numerous distinguished volunteer affiliations with regulatory-based professional and scientific societies. Krista is the Vice-President of the Natural Health Product Research Society (NHPRS) of Canada; an active member of Health Canada's Food Expert Advisory Committee (FEAC); an active member of the Board of Directors for CAPRA (Canadian Association for Professionals in Regulatory Affairs); Chair of the Canadian Health Food Association's Food Regulatory Advisory Committee (CHFA-FRAC); and an active member of Seneca College's Ad Hoc Program Advisory Committee for the Fundamentals of NHPs program. Krista is also a past member of the International Regulatory Affairs Committees for the Council for Responsible Nutrition (CRN) and GOED (Global Organization for EPA+DHA).

Krista is currently completing a Ph.D. at the University of Guelph, with a research focus on the cardiometabolic effects of NHPs containing omega-3 fatty acids in older adults.



Regulatory Considerations for Botanical Ingredients in the Canadian Health Products Marketplace

Coventry KJ, Source Nutraceutical, Inc. Winnipeg, Manitoba Canada

Today's health-savvy consumer is focused on attaining overall wellness, and will often seek out naturally-sourced medicines, supplements and foods to help support and maintain their health. Herbal remedies and supplements have played a key role in this complimentary medicine paradigm, in both traditional and modern settings. This is reflective in the global herbal supplements market, which has experienced consistently strong growth in the past decade, and was recently valued at \$7 billion in the U.S. alone (2015). This steady progress has been attributed to several factors, including improved consumer confidence in supply chain integrity; new advances in botanical quality assurance; and widespread innovation in global functional food and beverage markets.

In Canada, the government has established a pre-market approval system for the majority of commercially available health products. Despite the considerable stringency of Health Canada's regulatory frameworks, multiple commercialization pathways exist for a variety of health products containing botanical ingredients.

- When formulating dietary supplements (Natural Health Products), pre-approved health claims are attainable for products containing single herbs, or certain combinations of herbs. These claims are outlined in ingredient and/or product monographs, and represent a variety of claims from traditional, herbal and modern medicines alike. Modern health claims can also be pursued by providing relevant clinical data in support of a botanical product's safety and efficacy.
- A new regulatory pathway for fortification of certain foods and beverages was outlined by Health Canada in 2016. Category Specific Guidance for Temporary Marketing Authorization: Supplemented Foods provides parameters for formulating pre-packaged foods and beverages which have been fortified with certain botanical ingredients.
- The Framework for Consumer Health Products (2014) proposed new regulations for non-prescription drugs. Botanical ingredients can continue to be included in over-the-counter formulations if compliant with the updated regulations, once released.



Dr. Jeffrey Langland, Ph.D., received his doctorate degree from Arizona State University in the area of virology in December 1990. His area of interest at that time and still today is investigating and understanding the complex cellular defenses and immune responses against microorganisms. After graduating from Arizona State University, he was a post-doctoral fellow at University of California Davis studying oncolytic viruses, followed by a post-doctoral position at the University of Wyoming comparing similarities between plant and human defenses against viruses. In 1995, he returned to Arizona State University as a Research Assistant Professor. In this capacity he instructed several courses including General Virology and The Biology of AIDS. In August 2007, Dr. Langland became a joint faculty member at Southwest College of Naturopathic Medicine as the instructor for Medical Microbiology, Immunology, and Concepts in Research courses. At SCNM, Dr. Langland mentors students in evidence-based botanical medicine research and training Residents in the preparation of case studies. As a Full Professor and Chair of the Research Department at SCNM, Dr. Langland brings new insight and a cutting-edge approach to research for students and to the field of naturopathic medicine. Dr. Langland is currently involved in various projects characterizing the activity and mechanism of action of various botanicals towards viruses (including pox, herpes, varicella-zoster, HPV, rhinovirus, zika, ebola), bacteria (including MRSA, lyme disease, antibiotic-resistant strains, plague, and others), immune regulation, and cancer.



Mechanistic botanical medicine: defining anti-cancer and anti-viral properties of *Sarracenia purpurea*

Extracts of the botanical *Sarracenia purpurea* have historically been reported to be effective in the treatment of smallpox. We have shown that these extracts have broader antiviral activity inhibiting the replication of several DNA viruses including poxviruses, papovaviruses, and herpes viruses, but not many RNA viruses. The link and target of *S. purpurea* tying these DNA viruses together may be associated with a virally-utilized cellular pathway. Many of these, or related viruses, including human papilloma virus (HPV) and Epstein-Barr virus, are associated with various human carcinomas. Treatment of HPV-cervical carcinoma cells with *S. purpurea* inhibited accumulation of HPV oncoproteins, increased expression of cellular p53, arrested carcinoma cell growth at low doses, and induced carcinoma cell death at higher doses. This extract also inhibited Epstein-Barr virus protein expression and induced cell death in EBV-transformed cells. Thus, *S. purpurea* extracts contain broad anti-viral activity with the potential to induce oncolytic activity in cancerous cells. By deciphering the mechanism of action of botanicals such as *S. purpurea*, additional uses, potential side-effects and more therapeutic synergistic formulations can be discovered.



Thomas Brendler's consultancy business PlantaPhile® is based in the US, Germany, and the UK. It focuses on all aspects of herbal product development, registration and licensing. For the last 22 years, I have developed and managed projects for industry on the use of plants in medicine, food and cosmetics. As a consultant to the Millennium Challenge Corporation, the Centre for Development of Enterprise and the International Trade Centre I have been involved in the preparation, management and execution of various public funded research projects. In 2005 I co-founded the Association of African Medicinal Plants Standards. I currently serve as director of AAMPS and editor-in-chief of the AAMPS African Herbal Pharmacopoeia (2010). I have been author of Herb-CD®, a digital encyclopedia of medicinal plants, and co-authored, edited and contributed to a wide range of publications on phytotherapy and natural product regulation, most notably "Physician's Desk Reference for Herbal Medicines", "Medicinal and Aromatic Plants of Indian Ocean Islands" and "A Practical Guide To Licensing Herbal Medicinal Products". I am a member of the editorial board of Phytotherapy Research and a regular peer reviewer for Journal of Ethnopharmacology, Ethnobotany Research & Applications, Economic Botany and Herbalgram. I also contributed to the translation into English of the German Commission E monographs on medicinal plants. From 2009-2010 I spent one year as a visiting scholar at Rutgers University (NJ, USA), Department of Plant Biology and Pathology, Natural Product Research Group.



***Sceletium tortuosum*: a case study for a traditional herbal medicine in modern-day regulatory systems**

Thomas Brendler^{1,2,3}, ¹Plantaphile, Collingswood, NJ 08108, USA, ² Department of Botany and Plant Biotechnology, University of Johannesburg, South Africa, ³ Traditional Medicinals Inc., Sebastopol, CA 95472, USA

Modern-day regulatory systems governing conditions for how health products enter national markets constitute a barrier of access for traditional herbal medicines on an international level. Regulatory intentions are focused on ensuring that consumers are being provided with high quality products that are safe and efficacious; however, collaterally limit opportunities for traditional herbal medicinal products, especially those that do not already have a long-standing tradition of use established in the respective national marketplaces. Historically, the exploration and exploitation of paradigms of traditional medicine was driven and supported by pure chance, entrepreneurship, colonialism and, last but not least, the absence of regulatory barriers and the Nagoya Protocol. Only thus was it possible for traditional Southern African herbal medicines like Devil's Claw (*Harpagophytum* spp.), Umckaloabo (*Pelargonium sidoides*), African Potato (*Hypoxis hemerocallidea*), Cape Aloe (*Aloe ferox*), Buchu (*Agathosma* spp.) and many more to establish themselves in the European and/or North American marketplace, mostly 50-100 years ago. This case study investigates and compares how a South African herbal medicine with great potential as an anxiolytic and mild antidepressant – Kanna (*Sceletium tortuosum*) – which, while known and used by local healers for centuries, did not benefit from an early introduction into any of the first world's marketplaces, fares internationally in today's regulatory environments. Regulatory categories and their requirements are elucidated and assessed for suitability for Kanna products. It is demonstrated how inadvertent regulatory favoritism combined with the lack of means for adequate protection of intellectual property can obstruct innovation by creating an almost insurmountable economical hurdle for successful product development and introduction into most of the world's health product markets.



Dr. Michael Tims is Director of Herbal Programs at Maryland University of Integrative Health. He has taught at the University of Maryland and Montgomery College, and has had broad experience in the herbal supplement industry as a managing partner of Cash Grocer Natural Foods, as a clinical herbalist, and as an academic researcher focused on the chemical ecology of endangered medicinal plant species. Dr. Tims also collaborated with federal regulators to provide medicinal plant toxicity assessments. He co-developed HerbMed, a web-based herbal database providing access to scientific data on the use and safety of herbal medicine, and he completed an NIH/NIST postdoctoral fellowship developing Botanical Standard Reference Materials.

Some of his research with medicinal plants include exploring the role of lectins as signaling molecules in American Mistletoe (*Phoradendron leucarpum*) to initiate the intercalation of mistletoe and host plant vascular structures; the chemical ecology of *Hydrastis canadensis* rhizosphere and its effect on soil fungi; enzymatic extraction and certification measurements of green tea (*Camellia sinensis*) Standard Reference Materials (SRMs) in leaf powder, extract and finished product forms; development of analytical methods for the simultaneous separation and detection of a full spectrum of secondary metabolites found in kudzu (*Pueria lobata*), soy (*Glycine max*), and red clover (*Trifolium pratense*) and black cohosh (*Actea racemosa*).

His current research interests focus on

1. Understanding the role plant root secondary metabolites play in rhizosphere ecology and how that ecology influences the makeup of medicinal active chemical constituents.
2. Designing botanical pharmacognosy based solutions to the GMP demands faced by small herbal product manufacturers.
3. Rational botanical extraction method design.
4. Pedagogical inquiry into how students acquire innovative and improvisation thinking skills.

Dr. Tims received his BA in English/Writing from George Mason University and his Ph.D. in the Chemical Ecology of Medicinal Plants from the University of Maryland, College Park.



How Can Chemical Ecology Help Find Effective Herbal Medicine

Michael Tims, Maryland University of Integrative Health, Laurel, MD 20723

Secondary metabolites produced by plants are used by them to communicate with the surrounding environment or to defend the plant from attack. Very often those same phytochemicals are the purported active compounds in medicinal plants. This review will cover a broad range of influences on the secondary metabolite profile of medicinal plants, including alleopathy, mycorrhizal and endophytic fungi, light, kin recognition, herbivory, root development, seasonal effects, geography, plants sources from the wild vs. cultivated and plant/plant parasitism. Different plant tissue and several classes of phytochemicals will be investigated – phenolics, sesquiterpene lactones, alkaloids, monoterpenes and alkylamides.



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Muhammad Sasmito Djati, is a native Indonesian, born in Yogyakarta, March 4th, 1961. He attended Brawijaya University for undergraduate education. After earning his master degree in Padjadjaran University with animal sciences major, He then completed his doctoral degree in Bogor Agricultural University, Indonesia and Okayama University, Japan at 1997. Afterwards, He attended Korea University, Seoul, South Korea and doing research about human embryonic stem cell in 2005. Dr. M. Sasmito Djati also has an expertise in molecular reproductive technology and mammalian cell culture. Now, his focus research about herbal medicine such as *Elephantopus scaber* and *Sauropus androgynus* to promote the stability of endocrine and reproductive system in pregnant mice with typhoid model. He also focus on herbal medicine as anticancer treatment using *Elephantopus scaber* and *Polyscias obtusa*.



Combination of *Elephantopus scaber* and *Sauropus androgynus* Leaves Extract Effects on Progesterone, Estrogen Hormones Level Modulation and Histopathological Study in BALB/c Mice Typhoid Model

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Elephantopus scaber and *Sauropus androgynus* are tropical herb plants that are usually used as traditional medicine in Indonesia. Both of them showed anti-inflammatory effect, anti-microbial effect, and reproduction hormone stimulation. The aims of this study were to investigate the efficacy of *E.scaber* and *S.androgynus* leaves extracts combination to promote the progesterone and estrogen hormone and to observe the effects on kidney, histopathologically, of typhoid fever model pregnant mice. Pregnant BALB/c mice were orally infected with *Salmonella typhimurium* (107 CFU/mL). *E. scaber* and *S. androgynus* extracts were administered orally using these formulation (*E. scaber* : *S. androgynus*): 100 : 0 % (P1); 75 : 25 % (P2); 50 : 50 % (P3); 25 : 75 % (P4); and 0 : 100 % (P5); with the initial doses of 200 mg/kg body weight (BW) *E. scaber* and 150 mg/kg BW *S. androgynus*. The blood was collected from an orbital vein at the 9th, 13th, and 17th days of pregnancy. The level of progesterone and estrogen hormones were determined using ELISA assay. Paraffin method and HE staining were used to make kidney slides for histopathological observation. The data were analyzed using one-way ANOVA, with significance level $p < 0.05$, followed by Tukey test. The results showed that P4 could optimize ($p < 0.05$) the level of progesterone at 9th day of pregnancy (8.349 ± 1.178 ng/mL) and 13th day of pregnancy (10.216 ± 2.860 ng/mL), as well as the level of estrogen at 13th day pregnancy (33.422 ± 3.827 pg/mL) ($p < 0,05$). Histopathological observation showed that P2 extract could reduce the percentage of necrosis cell in the kidney (4.6 %) significantly ($p < 0.05$) compared to the control (K+) (10.03 %).

The authors would like to thank to all Laboratory of Animal Physiology Brawijaya University team for their support in conducting this research especially to Dwijayanti RD, Eltavia F, Rahayu S, Rifa'i M and Suwondo A.



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Dr. Giorgis Isaac is a Principal Scientist in the Pharmaceutical Life Sciences at Waters Corporation, Milford, MA. He has over 10 years of experience in the area of metabolomics and lipidomics liquid chromatography-mass spectrometry method development and various data handling informatics tools. He graduated from Asmara University, Eritrea in 1997 with a B.S. in Chemistry. Dr. Isaac continued with his graduate studies at Uppsala University, Uppsala, Sweden (2000-2005), where he worked with Professors Jonas Bergquist and Karen Markides on the development of a wide range of analytical method development for lipid analysis in complex samples. In 2005, Dr. Isaac received his Ph.D. from Uppsala University in Analytical Chemistry. He conducted postdoctoral research in biological mass spectrometry under Professor Ruth Welti at Kansas Lipidomics Research Center, Kansas State University in Manhattan, KS. Prior to joining Waters Corporation in 2010 he was a senior postdoctoral research scientist at the Pacific Northwest National Laboratory (PNNL) Richland, WA (2008-2010) where the focus of his research was mainly to establish a metabolomics and lipidomics platform. He has authored over 25 publications and 4 patents. He has presented poster and oral presentations in various national and international scientific meetings. A major analytical challenge in natural product is the complexity of the samples. Dr. Isaac current research is focusing on novel analytical and informatics method development to solve these analytical challenges in natural product analyses.



Ion Mobility Mass Spectrometry: A New Tool for Complex Natural Product Characterization and Identification

Isaac G, Yuk J, Wrona M, Waters Corporation Milford MA, USA

Natural products chemical profiling and identification is a challenging task because of the sample complexity and the analyses required. NMR, GC/MS and UHPLC/MS are currently used for natural products analysis and lately advancements in ion mobility separation have been used to provide additional analyte selectivity in plant metabolomics and other complex studies. UHPLC ion mobility mass spectrometry (IM-MS) is a combination of accurate mass separations with high resolution mass spectrometry (HRMS) and high efficiency ion mobility based measurements that offer some unique advantages for profiling complex mixtures. IM-MS is a rapid orthogonal gas phase separation technique that allows another dimension of separation to be obtained within an LC timeframe. Ion mobility data were acquired using Vion IMS QToF (Waters Corporation, Milford, MA). Ion mobility allows to differentiate compounds based on size, shape, and charge. The UHPLC-IM-MS spectrometer generates low energy precursor accurate mass and corresponding high energy fragment information, isotope ratios, retention time and averaged collision cross-section (CCS) parameters. The CCS value provides an additional dimension of separation for confident compound identification. Here we present the use of UHPLC separations with IM-MS and novel informatics tools containing natural product CCS database for complex natural product characterization and confident compound identification. The potential of ion mobility for the separation of isomers and chromatographically co-eluting compounds will also be investigated.



Maged Sharaf, Ph.D., M.Sc., B. Pharm. is Chief Science Officer at the American Herbal Products Association (AHPA) where his duties include helping to set quality standards for the botanical products industry and providing guidance and advice to AHPA member companies, related organizations, government agencies, scientific publications, and the popular press.

Before joining the American Herbal Products Association, Dr. Sharaf spent 15 years with the United States Pharmacopeial Convention (USP) assuming several responsibilities including: director, Foods, Dietary Supplements and Herbal Medicines; principal scientific liaison and senior scientific liaison (botanicals), Standards Development; manager analytical services and scientist, Verification Programs; coordinator, Quality Control Laboratory; and project leader, Research and Development Laboratory.

During his tenure at USP, he directed and coordinated the activities of a cross-functional team leading to the launch of the Herbal Medicines Compendium, a resource of public standards for herbal ingredients used in traditional and herbal medicines. He co-developed the Dietary Supplements Compendium, a resource of public standards and guidelines for the dietary supplement industry. He developed botanical standards for inclusion in the United States Pharmacopeia-National Formulary (USP-NF). He participated in building the Dietary Supplement Verification Program, as a public health program, and the Dietary Ingredient Verification Program as a support program for the dietary supplement industry. Dr. Sharaf collaborated with experts from around the world representing governments, academia, pharmacopeias, research institutes, industry, and industry/trade associations.

Before USP, Dr. Sharaf taught courses in pharmacognosy, and pharmaceutical sciences. He has preceding experience conducting bioanalytical assay development and validation, and human bioequivalence studies in support of the pharmaceutical industry; quality control testing of finished dosage forms; dosage forms manufacturing; and retail pharmacy.

Dr. Sharaf earned his Ph.D. in pharmacognosy from the School of Pharmacy, University of Pittsburgh; a master of sciences in pharmacognosy from Al-Azhar University, Egypt; and a bachelor in pharmacy and pharmaceutical sciences from Cairo University, Egypt.

Dr. Sharaf co-authored several scientific publications, is an invited speaker, and a reviewer for a number of scientific journals. He is a member of the Egyptian Association of Pharmacists, American Society of Pharmacognosy (ASP), ASP Constitution and By-Laws Committee, Society for Medicinal Plant and Natural Product Research (GA), American Chemical Society, AOAC International, and Washington Chromatography Discussion Group. He is a council member of the Specialty Committee of Traditional Chinese Medicines–Pharmaceutical Analysis, World Federation of Chinese Medicine Societies; advisory board member, National Institute of Standards and Technology (NIST) Dietary Supplement Quality Assurance Program (DSQAP); scientific advisor, American Herbal Pharmacopeia (AHP); member, USP Nomenclature and Labeling Expert Committee; advisory panel member, and an AOAC International Stakeholder Panel for Dietary Supplements.



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Industry Initiatives to Ensure Continued Quality and Sustainability

Maged H.M. Sharaf, American Herbal Products Association, 8630 Fenton Street, #918, Silver Spring, MD 20910

Companies face new challenges and opportunities due to the rapid growth and globalization of the herbal and dietary supplement industries. To meet new challenges and capitalize on new opportunities, these industries continue to launch new initiatives that ensure sustainable supplies of high quality raw materials, efficient compliance with good manufacturing practice (cGMP) requirements, and broad stakeholder support and participation. This presentation will explore several initiatives by the American Herbal Products Association (AHPA) that support the shared goals of the herbal and dietary supplement industries. The details of a case study will also be presented.



Dr. Javed Musarrat, Professor of Microbiology, Faculty of Agricultural Sciences, Aligarh Muslim University, Aligarh 202002, India

Academic Qualification: MSc., M.Phil., Ph.D (Biochemistry), Aligarh Muslim University, Aligarh, India.

Present Position at AMU: Professor of Microbiology, Aligarh Muslim University, Aligarh, India.

Administrative and Research Experience/Positions held:

Ex-Chair Professor, Al-Jeraisy Chair for DNA Research, KSU, Riyadh, SA

Ex-Dean, Faculty of Agricultural Sciences, AMU, Aligarh, India.

Ex-Chairman, Department of Microbiology, Faculty of Agricultural Sciences, AMU, Aligarh, India.

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Field of Specialization: Molecular Microbiology, Nanotoxicology, DNA damage & mutagenesis,.

Thrust areas of Research: Biosynthesis of Nanoparticles and Nanotoxicology, DNA-Carcinogen Interactions, DNA-based Characterization of Microorganisms, Environmental Genotoxicology.

Publications and other Achievements: Published more than 100 research articles in peer-reviewed and Indexed Journals of International repute. Four (04) Books published at Springer-Verlag GmbH, Berlin/Heidelberg, Germany [ISBN: 978-3-642-01978-4]; [ISBN: 978-3-211-99752-9] and Nova Science Publishers, New York, USA [ISBN: 978-160456929-2]]. Contributed twelve (12) Book chapters. Presented more than sixty 80 papers in International/National conferences and symposia. Received Grants as a Principal Investigator, from various Government funding agencies for ten (10) Extra-mural Research projects. Organized five (05) International and National Conferences/Workshops and Training Courses. Member of more than 20 Academic and Administrative bodies/ Scientific Societies.



Assessment of Oxidative Stress in Zn²⁺ Ions, ZnO-Bulk and ZnO-NPs treated *Allium cepa* roots

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Large-scale synthesis and release of nanomaterials in the environment is a growing concern for human health and the ecosystem. Therefore, we have investigated the cytotoxic and genotoxic potential of zinc oxide nanoparticles (ZnO-NPs), zinc oxide bulk (ZnO-Bulk), and zinc ions (Zn²⁺) in treated roots of *Allium cepa*, under hydroponic conditions. ZnO-NPs were characterized by UV-visible, XRD, FT-IR spectroscopy and TEM analyses. Bulbs of *A. cepa* exposed to ZnO-NPs (25.5 nm) for 12 h exhibited a significant decrease ($23 \pm 8.7\%$) in % mitotic index and increase in chromosomal aberrations ($18 \pm 7.6\%$) in a dose-dependent manner. Transmission electron microscopy and FT-IR data suggested surface attachment, internalization and biomolecular intervention of ZnO-NPs in root cells, respectively. Levels of TBARS and antioxidant enzymes were found to be significantly greater in treated root cells vis-à-vis untreated control. Furthermore, dose-dependent increase in ROS production and alterations in $\Delta\Psi_m$ were observed in treated roots. FT-IR analysis of root tissues demonstrated symmetric and asymmetric P=O stretching of >PO₂⁻ at 1240 cm⁻¹ and stretching of C-O ribose at 1060 cm⁻¹, suggestive of nuclear damage. Overall, the results elucidated *A. cepa*, as a good model for assessment of cytotoxicity and oxidative DNA damage with ZnO-NPs and Zn²⁺ in plants.

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Dr. Mohammad Kamil, Associate Professor, Head TCAM Research Section, Zayed Complex for Herbal Research & Trad. Medicine, PH&P-HAAD

Educational Qualification: B.Sc.; M.Sc.; M.Phil. Ph.D.; D.Sc.; C.Chem.; FRSC (U.K.)

Published ~ 275 papers and abstracts in reputed journals and international conferences; chaired a no. of scientific sessions and presented invited talks as plenary and invited speaker at various International conferences / symposia. Associated with publication of many books; Author of a book and five chapters in different books; Research work cited widely in books e.g. Advance in research, Chapman and Hall, London, New York; Dictionary of Natural Products- Chapman and Hall, London, New York; Encyclopedia of Medicinal Plants of UAE, Vol.1, ; Glimpses in plant research Vol. XI, Today and Tomorrow Publications, India; Flavonoids – Advances in Research since 1986: Chapman and Hall, London, New York, Tokyo, Melbourne. ; Muslim in India (1994); Compendium of Medicinal and Aromatic Plants, Vol.II, ICS, UNIDO, and many others.

Chartered Chemist (London); Fellow and member of various International societies; Member of the Advisory Board for many International journals; Referee of various prestigious Journals e.g. Journal of Complementary and Integrative Medicine, The Berkeley Electronic Press, Journal of Food Composition and Analysis, Elsevier Publication; Reviewer of a couple of International Journals; Honorary Member, International Centre for Integrated Development Research-Nigeria ;Member of Natural Product Registration Committee MoH-UAE;Member of Higher Complementary Medicine Committee –MoH-UAE ;Member Evaluation Committee for TCAM Practitioners & Therapists (MOH, UAE).

Recipient of Common Wealth Award-London; Convention Award of Chemical Society-India; Academic Exchange Fellowship from Association of Common Wealth Universities -London; and various other prestigious honors & awards.



New Natural Products from Plants with Special Reference to Novel Flavonoids, Biflavonoids & their Biological Implications

Mohammad KA, TCAM Research, Zayed Herbal Research Centre, Division of Public Health & Research, Health Authority Abu Dhabi, UAE

The plant kingdom offers a rich source of structural biodiversity in the form of a variety of Natural Products. As we know natural products continue to play an important role especially in pharmaceutical and food industries. For identification purpose the extraction, isolation and characterization of these natural products, using modern techniques is important and needs a good grasp of chromatographic and spectroscopic practical knowledge. Flavonoid covers a large group of naturally occurring, low molecular phenolic compounds found practically in all parts of the plant. Over several decades of research, it has been found that a variety of flavonoids have a remarkable range of activities.

The present paper deals with development of some novel and rare bioactive flavonoids and biflavonoids isolated for the first time from plants and their characterization using recent techniques and possible biological implications along with preclinical studies.

Thanks are due to the Director, Public Health and Research Division and General Director, HAAD for their constant support.



Dr. Yalda Shokoohinia, a visiting scholar at University of Mississippi, NCNPR, Oxford, MS, is an associate professor of Pharmacognosy in Kermanshah University of Medical sciences (KUMS), Kermanshah, Iran, where she has started her career as an assistant professor in 2011. She took her Pharm D degree in 2005 from Isfahan University of Medical sciences, Isfahan, Iran where she obtained her PhD in Pharmacognosy in 2010. She was a visiting scholar of Phytochemistry under supervision of Professor Giovanni Appendino in Eastern University of Piedmont, Novara, Italy in 2008-2009.

Dr. Shokoohinia research areas are phytochemistry, natural product isolation and multidimensional chromatography. She has over 35 papers, numerous abstracts and 280 citations. She has received many honors such as 1st best PhD Student in the Board Exam of Pharmacognosy (2007); 2nd best Student in the national entrance exam of PhD of Pharmacognosy (2005); several best article awards in international and national conferences, several best teacher and researcher of KUMS; the best woman researcher of Kermanshah province (2015) and as silver ranked researcher of Iran (2017).

Through her research in phytochemistry, she has discovered over 90 pure natural products among them 20 were found to have new structures. Besides, she has been the reviewer of more than 15 peer reviewed journals and the section editor of Journal of Reports in Pharmaceutical Sciences. She has supervised more than 40 theses and has the six year experience of teaching in pharmacy in 9 different topics.

In her professional career, she has been the pharmacist of university and hospital drugstores for more than 10 years; the head of department of Pharmacognosy & Biotechnology (2013-2015), the dean of continuous medical education of Kermanshah province (2015-2016) and she is currently the youngest member and the only woman specialist of Iran's national board of Pharmacognosy.

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Cancer preventive investigation of new compounds from *Echinophora cinerea*, a condiment

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Aerial parts of *Echinophora cinerea* (Apiaceae) are used as vegetable and as yogurt and cheese seasoning. It is used for the treatment of digestive disorders in parts of Iran as well. Despite several biological investigations on the plant, our team is the only group working on its chemistry and several research has been performed up to now. Due to importance of chemopreventive effects of edible plants, the phytochemicals of the plant were investigated on several cancerous cell lines.

Powdered aerial parts of the plant were macerated with acetone and EtOH:H₂O (8:2), respectively. The former was fractionated on RP-18 sorbent using mixture of methanol and water and resulted fractions were analyzed by NMR and promising fractions were refractionated and purified using normal or reversed phase column chromatography and preparative HPLC analyses. Hydroalcoholic extract was fractionated by VLC and finally purified using reversed phase HPLC. Structures of pure compounds were determined with 1D and 2D NMR and mass analyses. The effect of compounds on MCF-7, SKNMC, PC3 and PC12 cell lines were investigated.

Three new polyacetylenes (echinophorin A-C, 1-3), an iridoid (Verbenone-5-O-glucoside, 4) and a coumarin (osthol, 5) were isolated from acetone extract. Cell cytotoxicity of pure compounds was evaluated with MTT assay on MCF-7, SKNMC and PC3 cell lines. Echinophorin A and B show cytotoxicity effect on PC3 and SKNMC cell line with IC₅₀ as 23 and 25 µg/ml on PC3, respectively. Six compounds (quercetin-3-O-β-D-glucopyranoside, 6, Kaempferol glycoside, 7, osthol, 5, verbenone glycoside, 4, isoimperatorin, 8 and echinophorin B, 2) were purified from hydroethanol extract. Treatment of PC12 cells with 6 and 5 before exposure to the cisplatin increased cell viability and decreased apoptosis through up-regulation of Bcl2, inhibition of caspase-3 activity and increasing of mitochondrial membrane potential. As well, 5 decreased ROS generation induced by cisplatin. 6 prevented cytotoxicity of H₂O₂ in PC12 cell line and led to a decrease in the generation of reactive oxygen species.

Conclusion: *Echinophora cinerea* is a good source of protective and antioxidant natural products. Since, it is an edible plant, it can be considered as a safe supplementary.



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Frank L. Jaksch, Jr., co-founded ChromaDex®, Inc. in 1999, brought the company public in 2008, listed the company on NASDAQ in April 2016 and serves as Chief Executive Officer (CEO). Under his leadership, ChromaDex has focused on developing a comprehensive natural products chemistry business, expanded into international markets and built an impressive roster of Fortune 500 customers. ChromaDex Corporation (<https://www.chromadex.com/>) (NASDAQ:CDXC), an innovator of proprietary health, wellness and nutritional ingredients that creates science-based solutions for dietary supplement, food and beverage, skin care, sports nutrition, and pharmaceutical products.

Prior to founding ChromaDex, Mr. Jaksch served as the International Subsidiaries Manager of Phenomenex®, an analytical chemistry consumables company, where he managed the company's international subsidiary and international business development divisions. While at Phenomenex, Mr. Jaksch established strategic business offices in Australia, England, Germany and New Zealand.

His broad expertise includes analytical chemistry, biochemistry, processes and product development for natural products, legal and regulatory practices, agriculture and botany. Additionally, he has more than 20 years of management, sales, marketing and business development experience.

Mr. Jaksch holds a Bachelor of Science degree in Chemistry and Biology from Valparaiso University in Valparaiso, Indiana. He is a member of the American Chemistry Society, the American Herbal Products Association, the American Botanical Council and the NSF Joint Committee for Dietary Supplements. He also serves on the board of directors for the Natural Products Association(NPA), where he also serves at the Treasurer. Mr. Jaksch was the co-editor of Current Opinion in Biotechnology: Analytical Biotechnology in February 2014, which highlighted new technologies for quantitative analysis of natural products. He also co-authored "The Handbook of Analytical Methods for Dietary Supplements" with Drs. Mark Roman and Mingfu Wang, which was published by the American Pharmacists Association in June 2005.



Supply Chain Management is the Key to Better Analytical Testing

There has been a lot of focus on the challenges associated with analytical testing of dietary supplement products as well as the ingredients that go into them. The key to solving problems with analytical testing lies outside of the laboratory. Analytical testing is something a company should do to confirm what they should already know through sound supply chain management practices. Qualification, audit, inspection and approval of suppliers or vendors is a key part of an appropriate supply chain management plan. Selection and approval of appropriate analytical testing methods is a critical part of vendor qualification, however it is often overlooked as a part of the process. Business practices, and especially purchasing practices within the industry need to change, and if they do not change, analytical testing will continue to be the whipping post for years to come.



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Corey J. Hilmas, MD/PhD, Executive Director, Dr. Corey Hilmas is NPA's Senior VP for scientific and regulatory affairs. He oversees the development and implementation of all educational, scientific and compliance programs (cGMP, Natural Seal, TruLabel) at the Natural Products Association (NPA); provides guidance on clinical issues, public health, ingredient safety, regulatory compliance, and dietary supplement education; and drafts comments, content, and scientific white papers on behalf of NPA in conjunction with Dr. Daniel Fabricant, CEO and Executive Director. He is also working on producing new educationally driven regulatory compliance efforts similar to those he conducted for industry stakeholders while in the field at the U.S. Food and Drug Administration (FDA). Dr. Hilmas, a medical doctor with a degree from the University of Maryland School of Medicine and a doctorate in pharmacology/neurotox, came to NPA in June 2014 after having served as Chief of the Dietary Supplement Regulation Implementation Branch within the Division of Dietary Supplement Programs for two years. In addition to managing enforcement related to cGMPs, labeling, claims, dietary ingredient safety, and imports/exports, he was the Agency's federal expert witness for dietary supplements and dietary ingredient safety under Dr. Fabricant and received multiple FDA and CFSAN awards for enforcement initiatives. He recently was honored with the FDA Award of Merit, a distinguished achievement as one of the few recipients of this award for the area of dietary supplements, from FDA Commissioner Hamburg for his criminal and civil trial work. Dr. Hilmas also served as Senior Toxicologist for dietary ingredients at the FDA. Dr. Hilmas gained an interest in dietary supplements while investigating the efficacy of two dietary ingredients – galantamine and huperzine-A – for the U.S. Army. Prior to that service, he worked as a nuclear chemist at the Department of Energy in Golden, Colorado. He earned his Bachelor's degree from the University of Colorado at Boulder in biochemistry and molecular biology.



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Corey Hilmas, "Regulatory Risk and Scientific Jenga"



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Daniel Fabricant, Ph.D. is Executive Director and CEO of the Natural Products Association (NPA), the nation's largest and oldest trade organization representing the natural products industry, including dietary supplements, foods, personal care products and more. He is responsible for implementing board policy for the advancement and protection of the natural products industry, while overseeing every aspect of the association's programs and activities. Most recently, Dr. Fabricant served as the Director of the Division of Dietary Supplement Programs at the U.S. Food and Drug Administration (FDA), where he directed agency policy, public affairs and regulatory action regarding regulation of the dietary supplement industry for more than three years. While with the agency, he successfully navigated the large, heavily-matrixed governmental organizational structure to bring life to a regulatory function that was non-existent for almost 20 years. Prior to the FDA, Dr. Fabricant was vice president, global government and scientific affairs, for NPA, responsible for establishing and leading industry coalitions dealing with a range of legislative, regulatory and scientific matters. Dr. Fabricant carried his interest in natural products into the classroom, earning a Ph.D. in Pharmacognosy from the University of Illinois at Chicago, where he has served as an adjunct professor in the Department of Medicinal Chemistry and Pharmacognosy since 2009. Pharmacognosy is the study of drugs derived from natural sources (plants and animals). He has also published extensively and is internationally recognized for his regulatory and governmental public health expertise and natural products research.

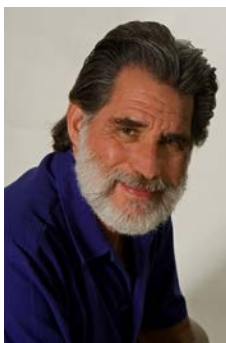


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Dan Fabricant, "Board Game of Thrones: Legislative Trivial Pursuits to Opportunity Knocks"



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Mark Blumenthal is the Founder and Executive Director of the American Botanical Council (ABC), the leading independent, nonprofit organization dedicated to disseminating accurate, reliable, and responsible information on herbs and medicinal plants. He is the Editor/Publisher of HerbalGram, an international, peer-reviewed quarterly journal. For six years he was an Adjunct Associate Professor of Medicinal Chemistry at the University of Texas at Austin, College of Pharmacy, teaching the course "Herbs and Phytomedicines in Today's Pharmacy." Mark is the Senior Editor of the English translation of The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines (1998), Herbal Medicine: Expanded Commission E Monographs (2000), The ABC Clinical Guide to Herbs (2003), and co-author of Rational Phytotherapy, 5th edition (2004). He has appeared on over 400 radio and television shows and has written over 500 articles, reviews and book chapters for many major publications. In 2010 he was awarded the prestigious Tyler Prize in honor of the late Purdue Professor Varro E. Tyler from the American Society of Pharmacognosy. In 2008 he was awarded the "Natural Legacy" award from Natural Foods Merchandiser magazine and he has also been named to Natural Health Magazine's Hall of Fame Award for "...opening America's eye to the healing powers of herbs." He has been a leader in the concerns for more rational regulations of herbal and natural product manufacturing, and education on plant-based medicines for over 36 years.



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Mark Blumenthal, "Botanical Adulterants Program/ ABC award"



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Victor Navarro earned his Doctor of Medicine degree from the Pennsylvania State College of Medicine and completed medical residency followed by chief residency in Internal Medicine at Temple University. Thereafter, he completed his fellowship in Gastroenterology, Hepatology, and Hepatobiliary Endoscopy at Yale University, along with a fellowship training period in Liver Transplantation at the University of Nebraska. In 1994, Dr. Navarro joined the faculty of the Yale University School of Medicine as an Assistant Professor of Medicine and Epidemiology and the Director of its Liver Failure and Transplantation service. He was also the Director of the State of Connecticut Emerging Infections Program Liver Study Unit. His scholarly work while at Yale focused on the population-based epidemiology of chronic liver disease, and also the role of soluble adhesion molecules in liver transplant rejection.

Dr. Navarro joined the clinical pharmacology group at Merck Research Laboratories in 2001 while continuing as an adjunct faculty member at Yale, and in 2002 he assumed a full time faculty position with Thomas Jefferson University, Philadelphia, as Chief of Hepatology and Medical Director for Liver Transplantation. While at Jefferson, he rose to the rank of Professor of Medicine, Pharmacology and Experimental Therapeutics. His scholarly interests focused on drug and dietary supplement induced liver injury. In 2012, he joined the Einstein Healthcare Network, Philadelphia, as Chairman of the Division of Hepatology, and Medical Director for Liver Transplantation, continuing his appointment at the Jefferson Medical College as Professor of Medicine. Recently, Dr. Navarro became the founding Co-Chair for the Department of Transplantation, Albert Einstein Medical Center.

Dr. Navarro is funded by the National Institutes of Health as an investigator for the U.S. Drug Induced Liver Injury Network (DILIN). His main scholarly focus continues to be liver injury attributable to Herbal and Dietary Supplements. Dr. Navarro maintains several lines of investigation in this area and also oversees the DILIN's Repository for HDS, which houses products implicated in liver injury.



Dietary Supplement Related Liver Injury

Victor Navarro, MD, Co-Chair, Department of Transplantation, Albert Einstein College of Medicine, Professor of Medicine, Sidney Kimmel Medical College, Philadelphia, PA

Given the ubiquity of dietary supplement (and herbal medicine) use around the world and the relative rarity of adverse event reports, most supplements can be considered safe. However, many cases exist in the medical literature of a few dietary supplements leading to end organ injury. Liver injury is just one example of end organ injury, that can have devastating effects. Although the true population based epidemiology of injury attributed to supplements is unknown, it is a reasonably safe assumption to posit that the prevalence and incidence of attributable injury to the liver is increasing. The overlay of supplement sales with an increasing recognition of injury through case reports and case series supports this assertion. The actual causes of injury remain an area for much needed research.

Whatever the organ or body system adversely affected, clinical investigators face several challenges in achieving a better understanding of injury due dietary supplements. The most challenging is the chemical complexity of commercially available supplements, many of which comprise multi-ingredient mixtures. Collaboration between chemists and clinicians serve as an important platform to understand the potential effects supplements. This collaboration should be regarded as a necessary step, to benchmark clinical manifestations of organ injury against the chemical composition of supplements. Equally important may be the circumstances in which the products are used. For example, it is known that the pharmacokinetic exposure to some dietary ingredients is affected if consumed in a fasted, versus fed, state. Other circumstances include dehydration, over-exertion, over use, or use with concomitant medications may also predispose to toxicity.



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Cristiana Leslie Corrêa, BS in Pharmacy at the Pontifical Catholic University of Campinas; Master degree in Toxicological Analysis and Ph.D. in Toxicology at the University of São Paulo. Specialist in Analytical Toxicology at the University of Campinas (UNICAMP). Specialist in Toxicological Risk Assessment at a Postgraduate Education in Toxicology Program at the Wageningen University (The Netherlands). Technical Director at Planitox – The Science-based Toxicology Company. Scientific Director at Brazilian Institute of Toxicology. Member of International Life Science Institute (ILSI) Scientific Committee.

Experience in Human Health Risk Assessment. Toxicology consultant in registration and reevaluation process of chemicals, food ingredients, agrochemicals. Experience in organizing and managing courses, workshops and lectures in Toxicology Science.



Importance of using a Structured Causality Assessment for cases of herb or dietary supplement-induced liver injury

Zambrone, F.A.D.; Corrêa, C.L.*

There have been several reports of acute or chronic liver injuries related to the consumption of dietary supplements, mainly linked to botanical preparations. However, the majority of these reports did not apply a structured causality assessment of hepatotoxicity, using temporal associations as the sole criteria for a valid evaluation. Most of them, to some degree, lacked sufficient information related to: patients' history, concomitant use of medication and/or other compounds (including alcohol), observations on discontinuation of use (*dechallenge*), re-exposure to the products, and specifications of product use. Furthermore, data quality is also questionable due to the presence of confounding factors, absence of proper exclusion of alternative explanations, and the use of questionable methods for attributing causality. To guarantee proper causality assessment in cases of herb or dietary supplement-induced liver injury, evaluators must consider: use of a liver-specific causality assessment method, an assessment method validated for hepatotoxicity, a structured quantitative method, assessment performed by qualified hepatologists with clinical experience, regulatory assessment with the assistance of external specialists, and a high degree of transparency in the assessment results. Assigning an association to events is different from assigning causality. To assign causality, scientific and methodological rigor must be employed, which means that information must be complete, understandable and reliable. Moreover, the association of health risks or benefits with habits and behavior is a daily practice, more related with risk perception than scientific proof

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Rick Kingston, PharmD, is the President, Regulatory and Scientific Affairs and Sr. Clinical Toxicologist at SafetyCall International P.L.L.C., a multidisciplinary healthcare firm of nationally recognized experts focused on providing manufacturers an outsourced option for postmarket medical surveillance, product safety assessment and evaluation, and regulatory reporting support for adverse events. His academic career spans more than 30 years at the University of Minnesota where he attained the rank of full Professor in the Department of Experimental and Clinical Pharmacology and currently serves as Clinical Professor, in the College of Pharmacy. Dr. Kingston earned his B.S in Pharmacy at the University of New Mexico, his Doctorate in Clinical Pharmacy at the University of Minnesota and completed a Post-Doctoral Fellowship in clinical toxicology and pharmacokinetics at St. Paul-Ramsey Regional Trauma Center and the University of Minnesota. He was the co-founder and Director of the Minnesota Poison Control System and its Regional Poison Control Center where he served for 18 years. He has authored more than 100 peer reviewed scientific abstracts, publications, confidential technical white papers and textbook chapters. He is co-editor of the recently published Herbal Products Toxicology and Clinical Pharmacology Second Edition published by Humana Press. He serves on numerous scientific panels, advisory boards and non-profit professional organization scientific committees advising on issues of product stewardship, science and safety. He also serves on the advisory board of the American Botanical Council as the resident expert on botanical safety. His professional experience includes a focus in the areas of clinical toxicology and pharmacology, poison control, product post-market safety surveillance, regulatory policy, drug and dietary supplement safety, and academic medicine.



Adverse event reports and the cost of regulatory transparency

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In 2006, the Dietary Supplement and Non-Prescription Drug Consumer Safety Act was passed by Congress requiring manufacturers of OTC drugs and Dietary Supplements to document all allegations of Adverse Events involving their products and report to the Agency those AEs meeting the FDA criteria for Serious Adverse Event “SAE”. The regulations were designed to insure that all AEs suspected or questioned to have a potential relationship with use of an OTC drug or dietary supplement were properly vetted and considered when evaluating the safety of such products. In this regard, the regulations specifically prohibited manufacturers from excluding AEs that were judged highly unlikely to be associated with product use from reporting consideration. Although the database of AEs maintained by the FDA certainly includes AEs that signal a safety issue, it has been estimated that the percentage of AEs with a valid safety signal is less than 2% of all reported events. Recently the FDA began posting a downloadable file of all submitted AEs with very limited detail and although company and product name are included along with reported effects, there is no indication of which events, when evaluated in their entirety, suggested a safety signal as opposed to effects unrelated to supplement use. This has resulted in significant unintended consequences. Whereas manufacturers may have been assured that submitted AEs would not be misconstrued as absolutely being related to product use by FDA staff, the same cannot be assumed when these AEs are released to the public especially in the format that is being used. Furthermore, although FDA qualifies the reports by indicating that any given AE does not “necessarily” suggest a safety issue, the Agency does not indicate which ones they believe do. This approach is likely to frustrate efforts which encourage responsible reporting of AEs while increasing the misrepresentation of those events that are reported. Examples of case reports and how they can and are being misrepresented will be provided as well as methods of addressing and responding to misinterpretation of AEs. Lastly, how this activity may be compromising patient safety will be discussed along with the likely unintended consequences.



Oliver Kayser is Full Professor at the Dortmund Technical University, Germany, at the Department of Biochemical and Chemical Engineering, where he chairs Technical Biochemistry. He received his PhD at the Free University Berlin, Germany, Pharmaceutical Biology, where he worked on the phytochemistry and pharmacology of Umckaloabo (*Pelargonium sidoides*), natural product chemistry of coumarins and aurones, pharmaceutical biotechnology and in vitro and in vivo testing. Afterwards he worked in pharmaceutical industry focusing on drug discovery of secondary metabolites from plants and microorganisms and returned to academics as lecturer and senior scientist in pharmaceutical biotechnology and nanobiotechnology. He was appointed at the University of Groningen in 2003 and studied the biosynthesis of cannabinoids artemisinin. In 2010 he took over the chair of Technical Chemistry and focussed on plant biotechnology, metabolomics and endophytes to understand and assemble the cannabinoid pathway in recombinant host. His work can be characterised by protein engineering of biosynthetic genes, metabolomics for breeding optimisation and endophyte biology.

He has chaired and co-organised several scientific conferences, he is founder of the European Association of Pharmaceutical Biotechnology (EAPB), vice president of the Society of medicinal plants and natural product research (GA) and member on the editorial board of peer reviewed journals in Pharmaceutical Biology and Pharmaceutical Biotechnology. He has published more than 100 peer reviewed papers, 18 book chapters, 7 books, and he holds a visiting professorship at the Medical University of Poznan, Poland.

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Newspaper citations:

1. New York Times:
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<http://www.spiegel.de/wissenschaft/mensch/biosynthese-bakterien-produzieren-cannabis-wirkstoff-a-712513.html>

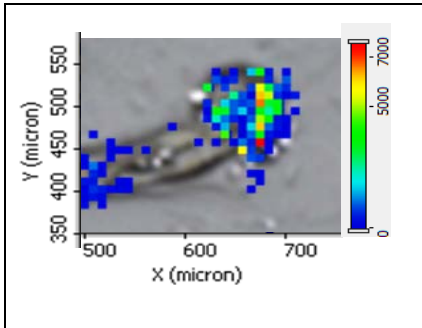
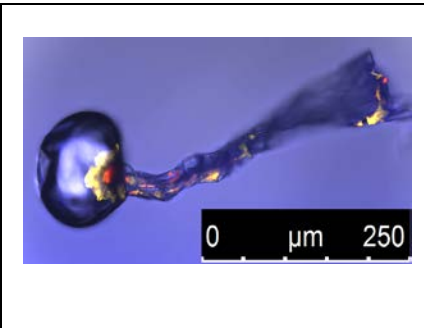

Molecular insights into the biosynthesis of cannabinoids

Oliver Kayser, TU Dortmund University, Technical Biochemistry

Cannabinoids are terpenophenolics characterized by benzochromen ring system and synthesized from olivetolic acid and geranyldiphosphate. Besides of Δ^9 tetrahydro-cannabinolic acid (THCA) more than 100 other cannabinoids are biosynthesized mainly in trichomes located on leaves and with high density on flowers of *C. sativa* (1). Biosynthetically, cannabinoids are prenylated polyketides derived from the polyketide and mevalonate pathway delivering olivetolic acid and geranyl diphosphate, respectively. Biosynthetic precursor of the first committed metabolite towards a high diversity of cannabinoids is cannabigerolic acid (CBGA) being formed by a C-C Friedel-Craft alkylation of olivetolic acid (OA) in the position C10b. It is likely that olivetolic acid is biosynthesized by a candidate type III polyketide synthase (PKS) called olivetol synthase (OLS) and olivetolic acid cyclases, but detailed steps in this biosynthetic ring formation step are still unclear (2). Towards tetrahydrocannabinolic acid (THCA) the oxidocyclase tetrahydrocannabinolic acid synthase (TCAS) is the responsible converting enzyme.

Based on laser dissection microscopy, LC-MS and cryo-NMR the cannabinoid profile and metabolome of dissected head and stem cells was analyzed and semi-quantified (3,4). Here, in all cells cannabinoids and related biosynthetic precursors were identified. Additional Imaging-MS revealed that THCA is located in basal trichome cells in equal concentrations as abundant in studied head cells (Fig. 1a). Applying recent CARS microscopy (Fig. 1b), these results document and confirm distribution of cannabinoids over stalked trichomes and give new insights about trafficking and localization. On the molecular biology level, transcriptome and proteome were studied. We were able to describe a network pattern, that gives first insight into biosynthetic organization of relevant enzymes like OA cyclase, CGA and THCA Synthase.

In our ongoing research, we studied metabolic pattern of genuine essential oil by direct extraction (Fig.1c). Essential oil was analyzed for abundance of proteins compared to metabolic pattern of water steam distilled extracts.

		
<p>Fig. 1a: Imaging-MS profile of THCA in basal trichome cells (left)</p>	<p>Fig. 1b: CARS microscopic study of cannabinoid profile</p>	<p>Fig. 1c: Extraction of <i>C. sativa</i> essential oil for direct GC-MS analysis</p>

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Dr. Larry Walker is the former Director of the National Center for Natural Products Research (NCNPR), and Professor in the Department of Pharmacology at the University of Mississippi. A native of Martin, Tennessee, his undergraduate pharmacy degree is from Mercer University (1975), and his doctorate in Pharmacology from Vanderbilt University School of Medicine in 1979, with emphasis in the areas of renal and cardiovascular pharmacology. He spent periods in postdoctoral research at the Bosch Institute for Clinical Pharmacology in Stuttgart, Germany and in the Department of Physiology at Dartmouth Medical School. He joined the faculty at the University of Mississippi as a Research Assistant Professor in 1981, and has worked for much of his career on research related to the pharmacology of natural products. In 1992, Dr. Walker assumed the role of Program Coordinator of the Drug Discovery and Development Program of the Research Institute of Pharmaceutical Sciences at the University of Mississippi. In 1995 was named Associate Director of the NCNPR. In 2001, he was named Interim Director, and selected as Director in 2002. The NCNPR has currently 85 full-time researchers in the natural products field, with programs in drug discovery, and in the chemistry and pharmacology of medicinal plants. In 2010, he also was appointed as Associate Director for Basic Science Research, Oxford campus, for the University of Mississippi Medical Center Cancer Institute.

Dr. Walker is a co-author of more than 175 papers in peer-reviewed journals in pharmacology, toxicology, and natural products discovery. He is a member of the American Society of Pharmacognosy, American Society of Pharmacology and Experimental Therapeutics, American Society of Microbiology, American Society of Tropical Medicine and Hygiene, American Association of Pharmaceutical Scientists, and the Society for Biomolecular Screening. He served as Editor-in-Chief of the Journal of Biomolecular Screening, and on the editorial boards of Phytotherapy Research and the J. of Pharmacology and Experimental Therapeutics, and has served on numerous grant review panels for the NIH and Dept. of Defense. In 2003 he received the UM School of Pharmacy's Researcher of the Year award, and in 2009 the University's Distinguished Research and Creative Achievement Award.



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Larry Walker, "Clinical evaluation of Cannabis extracts for epilepsy in the US: status and prospects in Mississippi."



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Jerzy P. Szaflarski, M.D., Ph.D. joined the University of Alabama at Birmingham Department of Neurology in the fall of 2013 as a Professor and as the Director of the Division of Epilepsy. He also directs the Level IV UAB Epilepsy Center. Dr. Szaflarski received his M.D. and Ph.D. from Collegium Medicum of the Nicolaus Copernicus University in Torun, Poland. He then completed a neurology residency and later a fellowship in Clinical Neurophysiology and Epilepsy at University of Cincinnati. Dr. Szaflarski initiated his research career with a fellowship at the Medical College of Wisconsin in the laboratory of Dr. Jeffrey R. Binder, where he studied functional magnetic resonance imaging (fMRI) acquisition and analysis.



Cannabinoids for the treatment of epilepsy

Jerzy P. Szaflarski, MD, PhD, University of Alabama at Birmingham and the UAB Epilepsy Center

Approximately 30-40% of patients with epilepsy continue to experience seizures despite adequate trials of numerous anti-epileptic drugs (AEDs). Many of them are not candidates for epilepsy surgery or other non-pharmacological interventions. These patients frequently resort to unconventional therapies with recent focus on cannabinoids as popularized by anecdotal reports and the media. In the last few years several States have approved various forms of “medical cannabis” for the treatment of epilepsy and other medical conditions resulting in more than 50% of the U.S. population having access to cannabinoids despite minimal or lack of scientific support for such access. The goals of this presentation are to review the existing evidence in support of efficacy of cannabinoids for the control of neuronal excitability based on animal studies of various epilepsy models, discuss the potential side effects of cannabinoids in humans, and to discuss the results of human trials with various cannabinoids for the treatment of epilepsy with focus on the results of studies of CBD oil (Epidiolex; GW Pharmaceuticals). The discussion will include data from the randomized controlled trials as well as results of state-sponsored compassionate use programs. In particular, we will discuss the efficacy for the treatment of epilepsy, side effects, drug-drug interactions, effects on quality of life, neuroimaging parameters, and EEG.



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Adam J. Kuszak earned his B.S. in the Pharmacology-Toxicology Program at the University of Wisconsin – Madison, and his Ph.D. from the Department of Pharmacology at the University of Michigan Medical School. Dr. Kuszak first joined the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) as an American Association for the Advancement of Science (AAAS) Science & Technology Policy Fellow in 2014, and currently serves as a Health Science Administrator and Policy Analyst. Prior to joining ODS, Dr. Kuszak completed his postdoctoral training at the National Institute of Diabetes and Digestive and Kidney Diseases.

Dr. Adam Kuszak primarily works with stakeholders involved in the research, analysis, and regulation of dietary supplements to support the administration and implementation of the ODS Analytical Materials and Reference Materials Program. In addition, he works with most of the ODS staff on several initiatives, including the Nutritional and Dietary Supplement Interventions for Inborn Errors of Metabolism Program, the Dietary Supplement Label Database, and the development of ODS dietary supplement Fact Sheets. Dr. Kuszak's primary research interests are in the chemical and biological characterization of complex natural products and understanding their effects on cellular signaling networks.

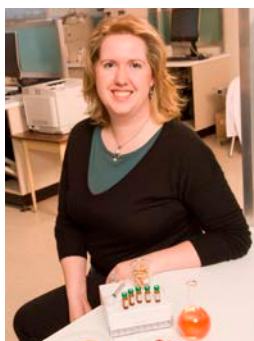


The NIH Office of Dietary Supplements Analytical Methods and Reference Materials Program

Adam J. Kuszak

The manufacture, scientific investigation, and regulatory oversight of dietary supplements all have a need for analytical methods and reference materials that permit the verification of dietary ingredient identity, measurement of constituent amounts in raw materials and finished products, and the identification and measurement of contaminants. The NIH Office of Dietary Supplements' Analytical Methods and Reference Materials (AMRM) Program was created in 2002 in response to a congressional mandate to support and accelerate the validation of analytical methods and development of reference materials for dietary supplements. The AMRM Program has four main goals: 1) Expand the availability of scientifically valid analytical methods for dietary supplements; 2) Produce and make available certified reference materials appropriate for use in method development, validation, and demonstration of laboratory performance; 3) Support public and private partnerships that emphasize the need for chemical and biological characterization of dietary supplements and their bioactive ingredients; and 4) Disseminate information in the peer-reviewed scientific literature to expand the use of validated methods and certified reference materials by the dietary supplement stakeholder community.

This presentation will describe how the AMRM Program works to address challenges and gaps in the quantitative and qualitative characterization of dietary supplements and their ingredients. The AMRM Program's infrastructure, activities, and products will be outlined, with particular emphasis on the collaborative efforts of industry, government, not-for-profit groups, and academic institutions which participate in the Program's priority setting and resource development.



Dr. Paula Brown is the Director of the BC Institute of Technology's Natural Health and Food Products Research Group (NRG), which has been actively supporting the NHP industry for over a decade through applied research activities, including product development, establishment of quality standards and regulatory compliance. By providing fundamental investigations on product quality, safety and efficacy, BCIT supports industry through the entire continuum, from grower to manufacturer, ensuring product integrity is maintained. Dr. Brown has spoken at numerous conferences over the last decade on product quality standards, analytical method validation and is currently the "Quality Focus" columnist for Nutraceuticals World.

An active volunteer, Dr. Brown sits on various Boards, Committees and Working Groups including the Dietary Supplement Joint Committee (NSF) and the Analytical Laboratories and Botanical Raw Material Committees (American Herbal Products Association). She is currently a Director for the Investment Agriculture Foundation of BC which strategically invests federal and provincial funds in support of innovative projects to benefit the agri-food industry. In 2003 she was a founding Director of the NHP Research Society of Canada, dedicated to supporting and promoting scientifically rigorous NHP research and education and most recently she joined the Advisory Board of the American Botanical Council.

Dr. Brown serves on two grant review committees for National Center for Complementary & Alternative Medicine, NIH and is a reviewer for numerous peer-reviewed Journals in the field of analytical chemistry and natural products. A Fellow of the AOAC International (2009), she served as Referee for the Dietary Supplement Methods Committee from 2004-2009, is a current member of the Dietary Supplement Task Force (2003-present), and has participated on seven Expert Review Panels for AOAC. In addition she has directed three full collaborative studies; Goldenseal (Official Methods SM 2008.04), Ginseng (SM 2008.05) and Echinacea (in review).

Dr. Brown is currently a member of the Natural Health Products Program Advisory Committee (PAC), and Chair of it's Product Testing Working Group, convened to make recommendations on policy related to standards of evidence for quality. The mandate of the PAC is to provide the NHP Program Directorates (Natural Health Products Directorate, Marketed Health Products Directorate and Health Products and Food Branch Inspectorate) with advice and recommendations on current and emerging issues relevant to the Canadian regulatory framework for natural health products.



Characterizing and Establishing Authenticity of Botanical Products

Paula N. Brown, Natural Health and Food Products Research Group, British Columbia Institute of Technology

There is continuing demand for high quality, authentic products in the marketplace, and the volume of this demand has significantly outpaced research efforts to produce reliable analytical methods that verify botanical identity. Botanical authenticity is classically achieved by examination of diagnostic macroscopic and microscopic features, however, modern ingredient supply chains are often far removed from identifiable material and traded as highly pulverized dried plant powders. Technologies for acquisition of plant phytochemical profiles have developed rapidly, and in combination with chemometric analyses, shows promise as a tool for qualitative determination of identity and purity with respect to defined adulteration in botanical materials. A standard metabolomics data set contains vast amounts of information and key factors in using the data effectively are experimental design, availability of reference materials, sample preparation and selection of statistical analyses performed. This talk will demonstrate practical experiences in the development of methods using phytochemical profiling for characterization and authentication of botanical materials as a GMP requirement. *Hydrastis*, *Ligusticum* and *Cannabis* data sets by NIR, HPLC and NMR will be used to illustrate the utility of multivariate models for characterization and authentication.



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Dr. James Harnly serves as the Research Leader for Food Composition and Methods Laboratory (FCMDL), part of the Beltsville Human Nutrition Research Center of the US Department of Agriculture. His lab is tasked with the development of new analytical methods for nutrients and bioactive compounds in foods, dietary supplements, and botanical materials in support of nutrition research at USDA. Current projects in the lab include development of new methods for vitamins, metabolomics, and chemical fingerprinting of foods and botanical supplements. His personal research interest is the development of chemometric methods for the identification and authentication of botanical materials. Dr. Harnly received his BA from the University of Colorado and his PhD from the University of Maryland. He joined USDA as a research scientist in 1979 and became the Research Leader in 1997. He has served on the Board of Directors for AOAC International, the Advisory Board of the American Botanical Council, and numerous Expert Committees for US Pharmacopeia and AOAC. He served for 22 years as the US Editor for the Journal of Atomic Spectrometry for the Royal Society of Chemistry and is currently the Editor in Chief for the Journal of Food Composition and Analysis.



Authentication of botanical supplements based on correlation with raw ingredients

James Harnly, Food Composition and Methods Development Lab, Beltsville Human Nutrition Research Center,
Agriculture Research Service, US Department of Agriculture, Beltsville, MD.

Authentication of botanical ingredients (e.g., leaves, stem, rhizomes, and roots) is usually approached by collecting authentic materials, selecting a comprehensive chemical fingerprinting method, developing a multivariate model, setting statistical limits, and then determining if an unknown material fits the model (is authentic) or doesn't (not authentic). Authentication of botanical supplements based on an ingredients model is difficult because processing will result in a loss and/or gain of compounds. The extraction/purification process, mixing with a wide variety of excipients, and addition of extra compounds or ingredients result in different chemical fingerprints for the supplements and ingredients. Marker compounds are usually unique to a botanical, although their bioactivity may not be proven, and should make the transition from raw ingredient to finished supplement to assure identification: e.g., one expects to find flavonol glycosides and triterpene lactones in *Ginkgo biloba* supplements and ginsenosides in American or Asian *Ginseng* supplements. The lack of markers makes identification of a supplement dependent on the presence of less distinctive compounds (their chemical fingerprint) and makes authentication even more difficult. The simplest means of identifying compounds found in both the ingredient and supplement is a point-by-point multiplication of their fingerprints, i.e., Pearson's correlation coefficient. Normalization is not necessary if the correlated spectra are analyzed by principal component analysis (PCA). Thus, if the auto-correlated ingredient spectra matches the cross correlated ingredient-supplement spectra, it can be assumed that the same chemical components are to be found in both. Extra components added to the supplement will not affect this comparison, whereas loss of compounds during extraction can lead to differences. This comparison can be more generalized using binary spectra based on just the presence or absence of the fingerprint feature.



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Darryl Sullivan is the Director of Scientific and Regulatory Affairs for the Nutritional Chemistry and Food Safety Division at Covance Laboratories. Mr. Sullivan acts as the primary liaison with food, nutritional and dietary supplement companies as well as providing expertise on designing comprehensive testing programs to meet scientific and regulatory requirements. In this role he is often called upon as an expert witness for litigation and dispute resolution. He has managed numerous different departments at Covance including lab operations, research and development, client services, sample management, sample preparation and study direction, as well as a satellite laboratory in Michigan. Mr. Sullivan received his BS from the University of Wisconsin-Madison and has more than 30 years of experience in laboratory testing of food and dietary supplements. He is considered to be an expert in the field of validation of analytical methods, having served for three years as Chair of the AOAC INTERNATIONAL Official Methods Board. Mr. Sullivan was a member of the Task Force that redesigned the AOAC Standards Development Process. He is currently the Past President and Secretary of the AOAC INTERNATIONAL Board of Directors, and the Chair of the AOAC Stakeholder Panel on Infant Formula and Adult Nutritionals. He is also the Chair of the AOAC Stakeholder Panel on Dietary Supplements. He is a former member of the Board of Directors of the AOAC Research Institute. He is the Chair of the Analytical Laboratories Committee of the American Herbal Product Association, a member of the USP Council of Experts for Dietary Supplements, and is a member of the Joint Committee on Dietary Supplements of NSF. Mr. Sullivan has developed and validated hundreds of analytical methods in the areas of nutrient and residue testing, and is the author of more than 75 publications and 100's of scientific presentations. In addition, he is the Past Chair of the AOAC Presidential Task Force on Dietary Supplements and co-editor of the book *Methods of Analysis for Nutrition Labeling*. He is also the co-editor of the book *Improving Import Food Safety*.



Critical Needs and Use of Reference Materials for Dietary Supplements

Reference materials are a critical component of any analytical testing laboratory. They become even more valuable when the laboratory is working with Dietary Supplements and natural products. The analysis of dietary supplements often requires the use of new and novel test methods. We do not have nearly as many official Compendial test methods for dietary supplements and we do with foods and food products. This situation often results in the needs for method modification and method development. Whenever a laboratory is modifying existing methods, or validating new methods – reference materials are a critical tool that is required to evaluate the success of the projects.

Dietary supplements are often very complex products with numerous active ingredients. A multi-vitamin multi-mineral tablet can contain as many as 35 active compounds. In addition to vitamins and minerals, dietary supplement often contain active materials from plants and plant extracts. In order to effectively monitor test methods in a large analytical laboratory, reference materials are utilized on an almost daily basis.

Reference materials play a critical role with the analysis of dietary supplements when used for routine analysis – as well as for method development and method modification studies. These tools are essential for effective quality control and evaluation of method accuracy.



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Kate Rimmer received her Ph.D. in analytical chemistry from Florida State University and completed a National Research Council postdoctoral fellowship at the National Institute of Standards and Technology (NIST). In addition to coordinating a dietary supplement quality assurance program she is the program coordinator for dietary supplement reference materials at NIST.



Reference Materials for Dietary Supplements

The National Institute of Standards and Technology (NIST), in collaboration with the National Institutes of Health-Office of Dietary Supplements (NIH-ODS) has been working to develop tools to help the dietary supplement industry establish confidence in their analytical procedures. The majority of the effort has been the development of matrix based reference materials with certified and reference values for toxic and marker compounds. The matrices are selected to represent the “average” materials in the marketplace and often consist of a raw botanical material and an extract of the botanical material. In some cases, a challenge material e.g. chocolate flavored protein powder, or a mixed supplement tablet is included in the suite of materials. Laboratories may use these materials to establish the accuracy and precision of their methods during method development, as quality assurance tools, or to establish in-house reference material traceability to NIST.

In addition to the materials, NIST often develops analytical methods for the determination of specific analytes in the candidate materials and these methods are published in the literature including information about sample preparation/extraction studies, chromatographic separations, detection, and approaches to quantitation. Additional information, such as qualitative thin layer chromatography data or DNA sequences are provided for authentication information. A dietary supplement laboratory quality assurance program has also been developed as an offshoot of the reference material program, allowing the community to demonstrate measurement capabilities and to compare method dependent results.



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Holly E. Johnson Ph.D., is the Laboratory Director for Alkemist Labs, an independent natural products testing lab specializing in Botanicals. Dr. Johnson took her Ph.D. in Pharmacognosy at the College of Pharmacy, University of Illinois – Chicago (UIC), under renowned Pharmacognosist and researcher Dr. Norman Farnsworth. Holly was awarded a National Institutes for Health (NIH) Fellowship and trained at the UIC/NIH Center for Botanical Dietary Supplements. She was a Postdoctoral Research Fellow at the Institute for EthnoMedicine studying the etiology of neurodegenerative disease, and worked for Waters Corporation conducting technical training and regulatory consulting for pharmaceutical and supplements companies. She is currently a Research Associate with the National Tropical Botanical Garden and serves on AOAC Stakeholders Panels and Expert Review Panels for Foods and Dietary Supplements. She is a member of the United States Pharmacopeia's (USP) Medical Cannabis Expert Panel, the AOAC Cannabis Working Group, the American Herbal Products Association's Cannabis Committee, the American Chemical Society's Cannabis Chemistry Subdivision, the Editorial Board of the AOAC International Journal, and serves on the Advisory Boards of the American Botanical Council and the American Herbal Pharmacopeia. Holly has over 20 years experience in natural products chemistry with botanicals and spent many happy years conducting research on medicinal plants and giving courses at the University of Hawaii. Holly serves as a subject matter expert on Cannabis Quality and is active in efforts to establish broadly applicable standards for quality and safety testing that are relevant in the complex regulatory environment.



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Holly Johnson, "Challenges in Testing Dietary Supplements"



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Uma Sreenivasan is Head of R&D for Cerilliant[™] Reference Materials in MilliporeSigma. She leads a team responsible for product development and certification of small and large molecule reference standards for clinical, forensic, dietary, and pharmaceutical applications. Ms. Sreenivasan has extensive experience in bio-organic, synthetic and analytical chemistry, operations, and management. Since 2000, she has served in various roles as Manager of Synthesis Operations, Analytical Laboratory Manager, and Chief Science Advisor overseeing technical issues relating to Cerilliant products. In 2013, as VP Production & R&D she had oversight of manufacturing and development operations. The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.



Accuracy of Reference Materials for Dietary Supplements

Uma Sreenivasan, Mitzi Rettinger, Derrell Johnson, Sherri Pogue, MilliporeSigma, 811 Paloma Drive SuiteA,
Round Rock, TX 78665, USA MilliporeSigma is a business of Merck KGaA, Darmstadt, Germany

FDA requires Good Manufacturing Practices in the manufacture of Dietary Supplements to ensure the identity, purity and potency of active ingredients and to safeguard against contamination and adulteration. Dietary Supplements cover a vast array of active ingredients ranging from vitamins and minerals to phytochemicals, plant extracts, and concentrates. Ensuring accuracy and potency can be an analytical challenge due to the complexity of the analytes and starts with reliable methods and require accurate Certified Reference Materials. Many dietary supplements are complex mixtures of natural products. Active ingredients such as fat soluble vitamins and many phytochemicals are often sensitive to oxygen. Development of accurate standards for these analytes requires control of process from certification through formulation and packaging to ensure stability and accuracy of the reference standard. Reference materials should be characterized for identity, purity, and potency by techniques that are specific and accurate for the analyte. Potency or content includes assessment of related substances and other residual content such as water, solvent and inorganic impurities. Certification should assess content and homogeneity of content from vial to vial. Packaging and handling of reference materials must ensure stability through shipping and shelf life. Critical design criteria in development of dietary supplement reference materials include handling, certification methods, accelerated and real time stability, packaging, and transport. Design examples of Dietary Supplement Certified Reference Materials developed in accordance with ISO Guide 34 and ISO 17025 will be presented.



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Dr. Nandakumara (Nandu) Sarma is the Director for the Dietary Supplements program at US Pharmacopeia (USP) responsible for the development of quality standards (monographs and general chapters) for dietary supplements, admission evaluations, performance standards, and the publication of the USP Dietary Supplements Compendium (<http://www.usp.org/dietary-supplements/overview>). Before joining USP 2006, he was a post-doctoral fellow at National Cancer Institute, Bethesda, and Thomas Jefferson University, Philadelphia and was a Senior Scientific Officer at The Himalaya Drug Company, India. His research experience in the field of dietary supplements includes isolation and analysis of active components of plant materials and their biologic activity. Dr. Sarma holds a Pharmacist degree and a Ph.D. in pharmaceutical sciences (pharmacognosy) from Banaras Hindu University, India.



Pesticide residues in botanicals: What are the rational limits?

Nandakumara Sarma¹, Josef Brinckmann², Robin Marles², Maria Monagas¹,
Gabriel Giancaspro¹, ¹United States Pharmacopeia, Rockville, Maryland; ² Botanical Dietary Supplements and
Herbal Medicines Expert Committee, United States Pharmacopeia, Rockville, Maryland

Botanicals and their products are liable to have common contaminants such as pesticide residues, elemental impurities, residual solvents, mycotoxins and microbial load. Pesticide residues in botanicals are regulated variously around the globe. In the United States, the United States Pharmacopeia (USP) limits for pesticides specified in General Chapter <561> Articles of Botanical Origin are applicable to botanical drugs. Since dietary supplements (DS) in the United States are regulated as a subset of foods, the limits for pesticides in botanical DS are set to the same levels as those for food by the Environmental Protection Agency (EPA). This creates a divide between two different standards for the same article of botanical origin, which is largely affecting the international supply chain of herbs of commerce. In the absence of EPA-established limits for an article, zero tolerance is applied when the ingredient is labeled as a food or as a DS. For example, the EPA crop-specific limit for tricyclazole is 3 ppm for rice (40CFR180.678), while the limit for the same pesticide is held at zero tolerance for botanicals for which crop-specific limits are not established (although the botanical DS may be consumed at much lower levels).

The USP limits for other types of contaminants (<467> Residual Solvents; <2232> Elemental Impurities; <561> Aflatoxins, <2023> Microbiological Attributes) are based on toxicological considerations. Such a science-based approach could be adopted for limiting pesticide residues in botanical DS to address the challenges from the current paradigm of crop-specific limits which are not set by the EPA for most of the commonly used herbs of commerce. Establishing limits for pesticide residues involves consideration of analytical method challenges related to complex botanical matrices, and harmonization across pharmacopeias to facilitate international commerce. Also, general MRLs (maximum residue limits) are desirable for limiting pesticide residues in crops for which EPA or USP limits are not set, in a way similar to how limits are set out in the Canadian and European regulations. Non-point source pesticide contamination observed in organic crops as well as in wild-collected botanicals illustrates that a zero-tolerance approach is not rational, and that science-based Compendial standards could provide a framework to establish toxicologically sound limits.

USP Stimuli article” Need for Clear Regulation of Pesticide Residue Limits for Articles of Botanical Origin.
http://www.usp.org/sites/default/files/events/stakeholder_forums/2016/face-face-meeting-registration-now-open/background-articles-notes-and-stimuli-articles-2016-06-01.pdf (pages 43 - 59).



Gary Jackoway, Vice President, MIDI, Inc., Gary Jackoway has more than 35 years of experience in software development for scientific computing. In his 20 years at Hewlett-Packard, he developed systems for printed circuit board design as well as being a lead software engineer in chemical analysis instrumentation software. During that time, he worked directly with experts in a variety of scientific fields.

At MIDI, Inc., Gary is the primary developer of automated solutions analyzing complex chromatographic data from a wide array of matrices including: microbes, soil, marine oils, edible oils, dietary supplements, and fire debris. He has also developed databases of chemical signatures and proprietary pattern recognition software for fatty acid identification of microbes and other isolates. He has overseen two of these products achieving clearances (AOAC INTERNATIONAL clearance for Anthrax bacterium identification, FDA clearance for Tuberculosis bacterium identification).

Gary earned a B.S. in Mathematics from Stanford University and an M.A. in Computer Science from Duke University.



Authentication of Botanicals by Automated Analysis and Chemometrics

Jackoway G, Sasser M, MIDI, Inc., Newark, DE, USA

Identifying and chemically characterizing botanicals currently requires significant time and effort, lacks a consistent framework, and necessitates a broad range of costly instrumentation for analysis.

This talk describes the development of an automated platform that identifies botanicals based on their chemical composition via automatic peak naming and pattern recognition of chemical signatures, yielding rigorous characterization of botanical materials.

The ongoing platform development is based upon proven chemical analysis technology that has been used for fatty acid analysis and microbial identification for over 25 years and in 45 countries, with two FDA 510(k) cleared products and two AOAC International approved methods.

The challenge is enhancing this extant platform to perform chemical analysis on hundreds of botanical compounds and to provide a database of chemical signatures for the botanical materials. The instrument-independent database will be continually updated to include new ingredients, while platform automation provides rapid and objective results.

The platform includes an extraction method followed by automated chemical analysis using standard analytical instruments (GC or HPLC), and coupled with a calibration standard for pattern recognition and database matching. Extraction methods are standardized where possible while analysis methods are optimized per material. The statistical model for each ingredient is created by utilizing multiple analyses of botanical reference materials and their variants to create breadth of coverage.

This automated platform allows for clinical trials to be run with documented characterization of herbal components. The platform also provides the dietary supplement industry with the tools necessary for establishing the validity and authenticity of the botanical ingredients throughout the supply chain.



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Eike Reich received his doctorate degree in Natural Products Chemistry in 1989 from Humboldt University Berlin, East Germany. From 1990 to 1998 he was Associate Professor of Chemistry at Longwood College, Farmville, Virginia, USA. In 1998 he moved to Switzerland to join CAMAG as Head of Laboratory. His research is focused on applications of High Performance Thin-Layer Chromatography, particularly in the field of botanicals. Dr. Reich has published numerous papers on the subject and contributed chapters to text books and encyclopedias. He is author of the book "HPTLC for the analysis of medicinal plants". As a member of expert committees on herbal drugs of the Swiss, the British, the European Pharmacopoeia (Groups 13A/B, TCM), and the USP expert committee on dietary supplements he is actively contributing to the development of new monographs for plants. He is founding and board member of the International Association for the Advancement of HPTLC.

Dr. Reich is married and has five children.



How can HPTLC help the Botanical Industry to improve quality of botanical products in a pragmatic way?

Reich E, Frommenwiler D, CAMAG-Laboratory, Muttens, BL, Switzerland

The last few years have seen an increase of negative press targeting the botanical industry regarding safety, efficacy and quality of botanical products. In the fiscal year of 2015 about 19% of the US dietary supplement companies that were subject to a FDA's inspection failed to set specification for identity, purity strength and composition of their product. The other 16% failed to verify the identity of a dietary ingredient through an adequate test.

To ensure the quality of botanical product pharmacopoeias, regulators and industry have adopted the quality model for the pharmaceutical industry relying on a suit of tests to check identity, purity, potency of the plant material. This puts the main focus of quality control of botanicals on the assay of (a) marker compound(s). However, this model suits only single compound materials such as most synthetic pharmaceuticals. Herbal drugs on the other hand feature a very complex chemical composition, which can vary due to natural factors, and in most cases a marker represents only 0.02 to 5% of the total composition. From this perspective a chemical fingerprint can provide more information about the quality of a botanical ingredient/product.

HPTLC, the most advanced and fully instrumental form of TLC, is capable of delivering reliable and reproducible results, based on standardized methodology. It is a simple, visual and pragmatic technique. Results generated on different plates in different labs can be compared based on electronical images of the HPTLC fingerprint. Images (fingerprints) can be stored in an electronic atlas or even in a cloud, which can be accessed by different labs, enabling global exchange and collaboration. Since January 1st 2017, general chapters on HPTLC were included in Ph. Eur. (2.8.25) and USP (<203>), as well as in other pharmacopoeias allowing global harmonization.

This paper illustrates how HPTLC can be employed in quality control of botanicals in a simple and pragmatic way and how besides identity additional information from the fingerprint can be obtained concerning purity and strength of the investigated material. We present two case studies: Setting specifications for ID, purity and strength of *Angelica gigas* botanical reference material; A single method for identification, detection of adulterants, and strength of *Ginkgo biloba* products



Trish Flaster is Executive Director of Botanical Liaisons, LLC, an ethnobotanical consulting firm providing botanical standards, international botanical sourcing, sustainable development of botanical ingredients, intellectual property rights, and development and implementation of Botanical Quality Assurance programs.

Trish developed the first virtual herbarium for economic plants. She is also co-founder of IDDI, ingredientID.com, a compliance based company helping companies to confirm ID and specifications required by FDA GMPs. She is focused on reviewing all documents to confirm identification, transparency and chain of custody in the dietary supplement industry.

Skilled in botanical and chemical experience, she also consults in the Cannabis Industry on testing, supply chain, quality and research.

Trish worked for Shaman Pharmaceuticals as their Botanical Sourcing Manager where she was an Ethnobotanist on their international ethnobotanical expeditions, expanded their sustainable international agricultural programs, and developed their in-house botanical program. Prior to this she was the Botanist for Celestial Seasonings where she developed new ingredient sourcing, developed several quality control analytical test procedures, founded their corporate environmental program, and designed and implemented the herb garden. As a past Adjunct Faculty member at Bastyr University, Trish developed the only class on methods of sensory evaluation for botanical identification, she is a Research Associate of the Missouri Botanical Garden, Past External Advisory Board of the NIH Botanical Research Center at the University of Iowa and UCLA, Editorial board member of *Explore: The Journal of Science and Healing*, scientific board member for American Botanical Council, United Plant Savers, and American Herbal Pharmacopeia, founder and Editor of the Society for Economic Botany's Newsletter "Plants and People" where she is a past board member.



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Supply chain management making sure you have the your eye on the ingredients

Flaster TA, Botanical Liaisons, LLC, Boulder CO 80303

The dietary supplement industry has been plagued with attacks about purity and accuracy of the identity of ingredients. The NY Attorney General says DNA is the answer but is it? The supply chain has many gaps in it, and it is now necessary to monitor that chain of custody with more scrutiny so the end products are pure and active. During the past year Botanical Liaisons, LLC has been performing gap analysis for companies creating documents and implementing them to improve oversight of the raw materials from field to facility. This presentation will review strengths and weaknesses and share some of the current new documents.



Dr. Shabana Khan is a Principal Scientist at NCNPR, an Associate Research Professor of Pharmacognosy, Department of Biomolecular Sciences, School of Pharmacy, University of Mississippi and a Visiting Professor at King Saud University, KSA. She obtained her Ph.D. (Biochemistry), M.Sc. (Biochemistry) and B.Sc. (Chemistry) from Aligarh Muslim University, India. She obtained postdoctoral training from University of Zurich, Switzerland and from Department of Medicinal Chemistry, Department of Pharmacology and National Center of Natural Products Research, School of Pharmacy, University of Mississippi. She began her career as a Research Scientist in 2000 at NCNPR, University of Mississippi and was promoted to a Senior Research Scientist in 2006 and a Principal Scientist in 2013.

Dr Khan's research interest has been studying pharmacological properties of natural products in relation to cancer, inflammation and metabolic disorder. She has a special interest in characterizing ADME properties, pharmacokinetics and drug interaction potential of botanicals / dietary supplements and their safety especially when used in combination with conventional drugs which are the substrates of drug metabolizing enzymes and transporters.

She has authored or coauthored more than 160 publications in peer reviewed journals.

She is a member of American Society of Pharmacognosy.



Herb-Drug Interactions: A safety concern for herbal supplements

Shabana I. Khan, National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, University, MS 38677.

The use of herbal supplements is on the rise worldwide for treating many ailments as well as for general health benefits. Since the herbal supplements are often used in combination with conventional drugs the risk for herb drug interactions is also rising and herb drug interactions are becoming important safety concerns for many herbal supplements. Most of the clinically relevant pharmacokinetic drug interactions occur due to the modulation of the activity of drug metabolizing Cytochrome P450 enzymes (CYPs), drug transporter P-glycoprotein (P-gp) and Pregnane X receptor (PXR).

PXR mediated induction of CYPs and P-gp has drawn considerable attention in recent years as one of the major mechanisms involved in drug interactions. St John's Wort (*Hypericum perforatum*) is a well documented example of the herb causing clinically relevant herb drug interactions and its constituent hypericin was found to be responsible for PXR activation and increased expression of its target genes.

Using an in vitro cell based reporter assay, we have screened some commonly used herbs and their constituents for activation of PXR to predict their herb drug interaction potential. Their effects on the expression of major drug metabolizing enzymes (3A4, 1A2, 2C9, 2B6) and efflux transporter (P-gp) were also determined by q-PCR analysis and the enzymatic activities were measured using specific substrates for each enzyme. Some herbs were identified to be potent activators of PXR such as *M. speciosa*, *E. californica*, *B. natalensis*, and *G. glabra*.

ACKNOWLEDGEMENTS This study is partially supported by The United States Department of Agriculture, Agricultural Research Service, Specific Cooperative Agreement No. 58-6060-6-015 and the Food and Drug Administration "Science Based Authentication of Dietary Supplements" award number 2U01FD004246-06.



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Dr. Cynthia Rider is a toxicologist with the National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), where she serves as project leader for a diverse portfolio of testing programs including polycyclic aromatic compounds, botanical dietary supplements (e.g., Ginkgo biloba extract, Garcinia cambogia), and industrial chemicals. In this capacity, she leads multi-disciplinary study design teams in developing research programs to address critical data gaps and inform risk assessment. Dr. Rider's research interests are in evaluating and refining methods to predict mixture toxicity based on data from components or whole reference mixtures. She co-chairs the NIEHS Combined Exposure/Mixtures working group tasked with advancing mixtures research throughout the Institute. She currently serves as Vice President of the Mixtures Specialty Section of the Society of Toxicology. Dr. Rider received her B.S. from Tulane University and her Ph.D. from North Carolina State University in Environmental Toxicology (2005). She completed postdoctoral training in the Reproductive Toxicology Branch of the EPA and Duke University, Nicholas School of the Environment, and became a Diplomate of the American Board of Toxicology in 2011.



Science to Inform Safety Assessment: Botanical Dietary Supplement Research at the National Toxicology Program

Cynthia V. Rider and Suramya Waidyanatha, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA,

The National Toxicology Program (NTP) has evaluated the toxicity and carcinogenicity of a number of widely-used botanical dietary supplements. Key challenges encountered in this research include: determining how diverse products in the marketplace relate to a single reference sample that has been chemically and toxicologically characterized (i.e., determining “sufficient similarity”), identifying the active constituent within the complex mixture, and understanding absorption, distribution, metabolism, and elimination (ADME) properties of botanicals. Current NTP research has been aimed at addressing these challenges. Case studies with Ginkgo biloba extract, black cohosh extract, and Echinacea purpurea extract were developed to evaluate approaches for assessing sufficient similarity. In each case, multiple extracts of each botanical were evaluated for chemical similarity using comparison of chromatographic profiles (untargeted approach) and quantification of known marker compounds (targeted approach). Biological similarity of the extracts was evaluated using both in vitro liver models and short term rodent genomic studies. Statistical and data visualization methods guided by expert judgement were then used to make decisions about similarity of extracts to the reference sample. These data were also used to identify potential active constituents within the mixtures. Along with statistical evaluation of high content chemical and biological data, bioassay-guided fractionation is being used to identify possible actives in black cohosh extract. Finally, ADME data generated for Ginkgo biloba extract in rodents will be compared to available human data to understand how animal doses relate to human exposure. This work will inform future research on botanical dietary supplements and application of data in safety assessments of these products.



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Amy L. Roe, PhD, DABT, has 20 years of experience as a practicing toxicologist in government, pharmaceutical and consumer product industries, through positions at both the U.S. FDA (NCTR) and The Procter & Gamble Company. Her professional experience is in general, descriptive and regulatory toxicology as well as specialized expertise in drug/xenobiotic metabolism and pharmacokinetics. Her industry experience is quite broad and includes toxicology support of drugs, medical devices, herbal/dietary supplements, foods, and water filtration devices. As a project leader, she has led multi-disciplinary drug development teams. Most recently, she has been focused on developing strategies to study herb-drug and herb-herb interactions. She is well-recognized externally in her field as evidenced by her service on a number of professional boards and committees including Executive Member (Secretary) of the American Board of Toxicology, USP Dietary Supplement Expert Committees, SOT Regulatory & Safety Evaluation Specialty Section Council, and NIH/NCCIH Expert Advisory Panel to U54 Center Grant for studying natural product-drug interactions, and Cosmetics Europe ADME Task Group. She also serves on the Editorial Board of Applied In Vitro Toxicology, and she is an Adjunct Assistant Professor at the University of Cincinnati, Department of Environmental Health and Molecular Toxicology.



In Vitro Evaluation of Hepatotoxicity Potential and Intracellular Accumulation of Schisandra Spp. Constituents in Human Sandwich-Cultured Hepatocytes.

VanderMolen K¹, Roe AL¹, Jackson J², Freeman K², Friley W², Black C², Brouwer K¹, The Procter & Gamble Company, Williamstown KY USA 41097¹, Qualyst Transporter Solutions²

Members of the Schisandraceae family of plants have been attributed a wide range of pharmacological activities. Schisandra spp. exist as complex mixtures with multiple constituents capable of interacting with cellular receptors, metabolic enzymes and transporters. Indeed, more than 50 lignans (e.g., schizandrins, schizandrols, gomisins, deoxyschizandrins), have been isolated from Schisandra spp., and authenticated by modern analytical techniques. Despite the long history of use of Schisandra spp. in certain cultures, there is a paucity of non-clinical toxicology studies available in the literature. We were able to locate a single 90-day oral rat toxicology study for Schisandra chinensis in the scientific literature. Based on results from this study which included changes in liver enzymes (ALT, AST), increased liver weight, and changes in endogenous compounds regulated by the liver (cholesterol, albumin), we wanted to further investigate potential hepatotoxicity in a human liver model. We assessed the hepatotoxicity potential of *S. chinensis* and related species; *S. sphenanthera*, utilizing sandwich-cultured Transporter Certified™ rat (SCRH) and human hepatocytes (SCHH). This model is a fully integrated hepatic cell system which maintains drug clearance pathways and key regulatory pathways; and thus generates physiologically-relevant intracellular concentrations of xenobiotics. In vitro hepatocyte toxicity endpoints assessed included viability, cytotoxicity, and apoptosis potential (ATP depletion). *S. chinensis* exposure to hepatocytes resulted in slightly more toxicity in SCRH versus SCHH at the highest dose tested (300 µg/mL). In contrast, *S. sphenanthera* was significantly more toxic to rat hepatocytes (>65% depletion of ATP) than human hepatocytes (11.7% depletion of ATP). Intracellular accumulation and concentration of four key Schisandra spp. constituents; Schisandrin A, Schisantherin A, Schizandrin, and Gomisin A were also monitored. In general, the intracellular constituent profiles were qualitatively similar between the two species; but differed quantitatively, with significantly higher intracellular concentrations observed in rat hepatocytes. The differences in concentration profiles in constituents may relate to differences in observed toxicity.



Cindy Angerhofer joined Aveda as Director of Botanical Research in 2003 with a promotion to Executive Director in 2009. She has established and developed a team of scientists to perform basic and applied research on botanical ingredients, with emphasis on phytochemical analysis, bioassay, and sustainable sourcing. She is responsible for anticipating and responding to product development needs for biologically active ingredients and for representing the Aveda brand. Cindy has helped establish a research program that explores the science of medicinal herbs, essential oils, and the quality of botanical extracts.

Cindy earned a B.A. in Chemistry from Gustavus Adolphus College and completed a professional internship and certification as a Medical Technologist. After four years contributing to Vitamin E research at the Minneapolis VA Hospital, she pursued a Ph.D. in Pharmacognosy from the University of Minnesota. As a post-doc and Assistant Professor, she taught courses in the medicinal and biological chemistry of natural substances for graduate and professional students at the University of Illinois at Chicago College of Pharmacy. While at UIC, she established a bioassay screening program for antimalarial natural products and received funding from NIH (NIAID) and WHO in support of this work which led to the identification of many antimalarial lead compounds. She directed Research and Product Development for Tom's of Maine, Inc. for five years leading to the development of topical cosmetic and OTC products in addition to a novel line of herbal dietary supplements. She has consulted for non-profit and for-profit organizations in the natural products industry. Cindy has designed and delivered introductory, science-based curricula on medicinal herbs for pharmacists and other health care professionals as well as seminars for consumer and trade audiences. She currently serves as President of the American Society of Pharmacognosy, and on the Advisory Board for the American Botanical Council. She frequently reviews manuscripts for several scientific journals in natural products and has authored more than 45 peer-reviewed publications.



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Cindy Angerhofer, TBA



Prof Namrita Lall has been placed in the Essential Science Indicators list of the top 1% of publication outputs (citations) in the discipline PHARMACOLOGY and TOXICOLOGY. She has international recognition for her research into the potential of medicinal plants for pharmaceutical and cosmeceutical purposes. She has made a significant contribution to the field of Medicinal Plant science. Several medicinal plants with valuable biological activities have been discovered which led to several patents. She has obtained several international patents including 3 US patents, 4 PCT-patents, 5 South African patents, co-authored about 105 research articles in peer reviewed journals and eight book chapters. The H-index for her research articles is 26 (i10index is 49) and 22 according to google scholar and ISI web of Science respectively (<http://www.researcherid.com/rid/A-2635-2012>). She has recently been awarded National Research Chair in Plant Health Products from IKS, by the NRF/DST in 2016.

Among several awards received in recognition for her work, a few are “The Order of Mapungubwe”, South Africa’s highest honour from the Honorable South African President Jacob Zuma (April 2014), Distinguished Young Women in Science Award by Naledi Pandor, Honorable minister of the Science and Technology of South Africa (August 2011), prestigious United Kingdom Royal Society/National Research Foundation award, South Africa (2005), “National Research Foundation/ Center National de La Recherche Scientifique (CNRS) award” (2004-05), University’s “Young Exceptional Performers award (2002), S2A3-Gencor bronze medal by South African Association for the Advancement of Science (April 1997), Council award of a Gold medal for BSc Honours (April 1994), Outstanding achievement award for PhD (March 2002) and UNESCO-L’Oreal Award for Women in Science (one of the 10 selected candidates internationally, March 2002).

She has established networks with leading researchers all around the globe including in the USA, England, France, Egypt, India, Cameroon, Italy, Ireland, Tanzania, Mauritius and Japan. She is the member of numerous international scientific committees including “The American Chemical Society”, The Society of Cosmetic Chemists of South Africa and the Advisory Board for the Phytomedicine research at the JSS College of Pharmacy OOTY, India.

She has been actively involved with two undergraduate modules (Module leader of one third year module and for 3 Honours modules) and is one of the founders for the development of a new specialized field, called “Medicinal Plant Sciences” at postgraduate level in January 2007 at the University of Pretoria, South Africa which is one of its kind in South Africa. Prof Lall’s research area involves antituberculosis natural product leads from medicinal plants, cytotoxicity of plant extracts/compounds, anticancer activity of medicinal plants, isolation and purification of bioactive principles from plants. About 14 pharmaceutical and cosmeceutical products which have resulted from her research programme is close to commercialization. Eighteen Masters and Fifteen PhDs have graduated under Prof Lall’s supervision. Majority of them were South Africans and a few with other nationalities (One German, Cameroonian, Mozambican, Indian, Iranian and an Egyptian). At present, she is the main supervisor of seven Masters, four PhD-students and co-supervisor of one PhD-student.

She has presented 3 keynotes, 2 plenary talks (USA, Malaysia, China, India) and seven invited talks at international conferences. She is also invited as a visiting scientist in first-rate laboratories and had presented lectures to postgraduate students in France, Mauritius and in India on the efficacy of medicinal plants. She has demonstrated commitment to community by interacting positively with traditional health practitioners and engaging them in advancing traditional medicines towards conventional pharmaceutical products.



The commercialization of Academic knowledge; applied research on South African medicinal plants

Lall N1, Twilley D1, Blom A1

Medicinal Plant Science, University of Pretoria, Gauteng, South Africa

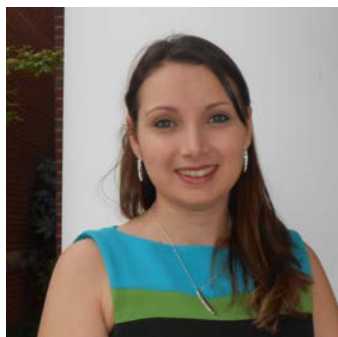
South Africa has a healthy supply of plants (about 23,500 species of higher plants). Plants for the treatment of infectious diseases, tuberculosis, acne, cancer, melasma, periodontal diseases etc. have been scientifically investigated.

Progressive macular hypomelanosis (PMH) is a hypopigmentary disease characterised by the presence of hypopigmented spots found on the chest and back. PMH disease is mainly caused by the bacteria *Propionibacterium acnes*. During present study, plants *Hypericum* sp. and *Withania* sp. proved to be the most active, resulting in 50 % inhibition of the bacteria's growth at concentrations lower than 70 µg/mL. The co-culture of normal human melanocytes (NHM) and normal human keratinocytes (NHK), were exposed to different concentrations of the semi pure fraction of sample 1 based on its stimulating effect on melanin production, the study showed that the melanin transfer was induced by S1. This is a novel report; on plant-samples inducing melanin transfer.

South Africa has the second highest incidence rate of skin cancer in the world, through ongoing research a southern African plant was found to inhibit the DPPH free radical with a 50% inhibitory concentration (IC50) of 5.13 µg/ml. Thereafter, the active during clinical trials was able to boost the SPF of a P3 standard from 17.1 to 32.4. The reduction in erythema was significant enough for the active to increase the SPF value of the standard, which is due to the potent antioxidant effect reducing the formation of free radicals after UV exposure. Furthermore, another plant, showed potential against the cancer; melanoma cell line with an IC50 value of 31.32µg/ml. During the cyclooxygenase inhibitory activity the semi pure fraction of the plant was found to have an IC50 value of 62.03µg/ml. A novel terpenoid with a selectivity index value of 5.1 µg/mL has been identified, the SI value was found to be better than the existing cancer-drug for melanoma cancer.

A number of other medicinal samples were subjected to clinical studies and have been recommended for their use for TB, oral care, melasma, acne etc. The research results have attracted a number of national and international Pharma and cosmetic companies who are willing to commercialise the samples and purified compounds emanated from our research which might eventually lead to entrepreneurship.

The University of Pretoria, the department of Science and Technology SA, National Research foundation.



Cristina Avonto, Ph. D., Research Scientist, National Center for Natural Products Research. Dr. Avonto joined Dr. Ikhlas Khan's research team as a natural products chemist in 2011.

Her current work is focused on the safety of natural products and botanicals in cosmetics and dietary supplements, with a special emphasis on development and application of non-animal methods for skin sensitization risk assessment. As part of her research at the National Center for Natural Products Research, she was involved in the *ex-novo* development of two *in chemico* methods to identify and characterize electrophilic compounds as potential skin sensitizers. Her professional experience also includes the isolation and characterization of secondary metabolites from plant sources, as well as authentication and analytical profiling of plant extracts, cosmetic preparations and dietary supplements.

Dr. Avonto received her Ph. D. in Science of Bioactive Substances in 2010 from the University of Eastern Piedmont "Amedeo Avogadro" (Italy), where she worked on the isolation and chemical derivatization of natural products targeting chemo-sensorial receptors of biomedical relevance. She focused on the importance of electrophilicity in targeting nociceptors of biomedical importance (such as TRPA1) and on the development of an NMR method to identify reversible Michael acceptors as potential anticancer agents. She also worked on the synthesis of triterpene derivatives as antidiabetogenic compounds.

She received her Master of Science in Industrial Biotechnology in 2007 from the University of Milano-Bicocca (Italy) and her Bachelor of Science in 2004 from the University of Eastern Piedmont "Amedeo Avogadro", where she worked in the isolation of potential anti-malarial compounds from *Mirtus communis*.

Dr. Avonto has one patent pending and published over 20 research papers and over 30 poster presentations. She is a member of the Society of Toxicology and American Chemical Society, and served as reviewer for several international scientific journals.



Can we apply *in chemico* methods to skin sensitization risk assessment of botanicals? A case study of tea tree oil.

Cristina Avonto¹ Amar G. Chittiboyina,¹ and Ikhlas A. Khan^{1,2}, ¹National Center for Natural Products Research;

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Tea Tree Oil (TTO) commercial preparations are commonly used for the treatment of eczema, acne, skin infections, wounds, burns, insect bites and mycosis. TTOs are rich in monoterpenes and the quality and stability of TTOs are responsible for their biological properties. In some incidences, TTOs of poor quality or stability have been regarded as a concern due to the possible occurrence of skin sensitization upon topical exposure to the oil. Skin sensitizers are usually electrophilic in nature and capable of covalently binding to skin proteins. Non-animal methods, such as *in chemico* methods, can provide a useful tool to predict the ability of skin allergens to bind to biological nucleophiles. However, no method has so far been validated for the characterization of potential mixtures and little information is available in the literature.

Chemical methods could provide a rapid and inexpensive approach to add mechanistic information to complex dynamics, such as the presence and/or generation of electrophilic species in complex botanical mixtures like essential oils. As a case study, the high throughput fluorescence-based assay (HTS-DCYA) was applied to the investigation of authentic and non-authentic TTOs to understand how chemical composition relates to the stability and possible adverse effects of the oils. Aged authentic TTOs contained an increased amount of reacting components. Moreover, a small highly reactive substituted cyclohexenone was found as a degradation by-product after radical activation of the endoperoxide ascaridole.



Weidong Zhang, Adjunct Professor/Principal Investigator

Education:

1984. 09-1988. 07 School of Pharmacy, Second Military Medical University BA
1988. 08-1991. 07 School of Pharmacy, Second Military Medical University MS
1991. 08-1994. 09 Second Military Medical University Teaching Assistant
1994. 10-1995. 08 Second Military Medical University Lecturer
1995. 09-1998. 09 Shanghai Institute of Pharmaceutical Industry PhD
1998. 10-2000. 02 Paul Sabatier of France Visiting Prof.
1999. 09-2003. 08 School of Pharmacy, Second Military Medical University Associate Prof.
2003. 09- School of Pharmacy, Second Military Medical University Prof.

Main Achievement/Awards

National Outstanding Young Scientist Foundation of China (2007)
Recently published 400 papers.

Research Interests:

Bioactive components from traditional Chinese medicine (TCM) and compound traditional Chinese medicine; Quality Control of TCM; Metabolism in vivo; Systems biology; New drug R&D of TCM.

Selected Publications :

Jiang Jiang Qin, Li Yan Wang, Jia Xian Zhu, Hui Zi Jin, Jian Jun Fu, Xiao Feng Liu, Hong Lin Li, Wei Dong Zhang. Neojaponicone A, a bioactive sesquiterpene lactone dimer with an unprecedented carbon skeleton from *Inula japonica*. Chemical Communications, 2011, 47, 1222-1224.
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Discovery and Chemical Biology Study of Novel Active Compounds from TCM

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The discovery of novel bioactive constituents from TCM is very important for the R&D of new drug and innovation of basic research. Because of the high chemical diversity, novel natural products provide dozens of probes for the biologists, which play an important role in the study of chemical biology.

During the recent years, our group systematically investigated the chemical constituents and biology functions of more than 150 herbal medicines. Totally, 6,600 natural products, including 706 novel compounds and 20 new skeleton compounds were isolated and identified. We carried out chemical biology study based on these novel bioactive constituents from TCM. By now, more than 40 leads with novel structures and demonstrated drug targets were discovered.

Based on the experiences in my lab, I introduce the idea and routine of studies on effective constituents of Chinese herbal drugs and chemical biology study based on the novel bioactive constituents from TCM. I hope these ideas will offer a good perspective for future TCM study.



Alvaro Viljoen, Born in 1969, Pretoria South Africa. Completed a BSc, BSc Hons. (cum laude) and MSc (cum laude) in Botany at Stellenbosch University. In 1994 Alvaro commenced with a PhD at the University of Johannesburg on the chemotaxonomy of the genus *Aloe*. In July 2005 he was appointed as a research fellow in the Department of Pharmaceutical Sciences, Tshwane University of Technology (Pretoria). More than fifty post-graduate students have graduated under his supervision since 2002. His research interest is the phytochemistry and biological activity of medicinal and aromatic plants indigenous to South Africa. He has authored / co-authored >200 peer reviewed papers mostly on the phytochemical exploration and biological activity of indigenous medicinal and aromatic plants. He has been elected on to the editorial board of the Journal of Essential Oil Research (Francis & Taylor), Phytochemistry Letters (Elsevier), he is the Editor-in-Chief of Journal of Ethnopharmacology (Elsevier) and reviewing-editor for South African Journal of Botany (Elsevier). In October 2013 Alvaro was awarded the National Research Chair in Phytomedicine a position which he holds concurrently as Director of the MRC Herbal Drugs Research Unit in South Africa.

www.alvaroviljoen.com



Quality control and pharmacological activity - Bridging the chasm

A.M. Viljoen, M. Sandasi, S. Chaudhary, I. Vermaak, Department of Pharmaceutical Sciences, Faculty of Science, Tshwane University of Technology, Private bag X680, Pretoria 0001, South Africa

The herbal medicine industry has often been criticised for lacking in suitable and relevant quality control procedures, which has tarnished the image of the industry. The inherent complexity of herbal extracts and the intricate cycle from the cultivation of a medicinal plant through to the finished product poses a plethora of challenges to ensure and maintain quality. Several elegant analytical procedures are constantly published and proposed for the routine quality control of herbal raw material and formulated products. Often, these methods are unrealistic and are not practical neither economically viable to be implemented in the plant-to-product pipeline. Furthermore, there is an obvious dichotomy in the approach to quality control as the research is most often acutely focused on the botanical matrix and not integrated with pharmacological activity. In the past 15 years, analytical techniques and data processing methods (chemometrics) have revolutionised natural products research. Seemingly, the discipline of herbal quality control has not embraced this development and generally remains stagnated focussing on botanical chemical profiling and fingerprinting. Natural products (and Pharma) have embraced the reality and value of systems biology, metabolomics and the importance of synergy. While we embrace holism, quality control is still mainly reductionist.

The paper proposes a multi-layered approach to develop relevant quality control protocols for medicinal plants. Methodology has now been well developed to generate complex analytical data matrices for any herbal extract. Pharmacological data (including toxicology) should ideally be superimposed over the chemical data to determine which compounds (alone or in combination) elicit the most favourable pharmacological response or are associated with toxicity. Once the bioactive molecules have been identified, simple and realistic methods should be proposed for routine quality control of biologically relevant molecules.

This approach could act as the “Carrick-a-Rede” to bridge the gap between theoretical quality control and pharmacology.



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Professor Alan Bensoussan [PhD, MSc(Res), PGDipEd, DipAc, BSc, AdvCac (China)] is Director of NICM at Western Sydney University. He is one of Australia's prominent integrative medicine researchers with a focus on Chinese medicine spanning 30 years. He was Chair of the Advisory Committee for Complementary Medicines of the Australian Therapeutic Goods Administration (2011-14) following eight years of prior committee service, and served on the National Medicines Policy Committee (2008-11). He regularly serves as a consultant to the World Health Organisation and other national and international government agencies. Bensoussan has published over 160 scientific papers and two books, including a review of acupuncture research (1990) and a major government report on the practice of traditional Chinese medicine in Australia (1996), which led to national regulation of Chinese medicine practitioners in Australia in 2012 – the first western nation to do so. He has forged a broad network of links with national and international organisations within government and industry, including major collaborative research projects with key institutions in China. In 2013 Professor Bensoussan received the prestigious International Award for Contribution to Chinese Medicine in Beijing and in 2014 Bensoussan was awarded the Lady Cilento Award by the peak Australian industry association recognising an individual's lifetime achievements and contributions to the community.



Vascular dementia and multi-target therapy in Chinese herbal medicine

Alan Bensoussan¹, Dennis Chang¹, Jianxun Liu^{1,2}, ¹NICM, Western Sydney University, Australia. ²Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Chinese herbal formulations comprise complex combinations of compounds reputed to work through differing but supportive pharmacological mechanisms. Identifying key active compounds and evaluating the multi-target impact of these compounds is critical to justifying clinical claims. Bioassay-guided fractionation techniques have been used to optimise and standardise a formula for vascular dementia (VaD), consisting of extracts of Ginkgo biloba, Panax ginseng and Crocus sativus. Studies have demonstrated the role of the formula and key active compounds in reversing cerebral ischemia, cognitive impairment and other related mechanisms in dementia. The dosage regimen and mechanisms of action were determined in a series of preclinical studies. Acute and chronic toxicity studies, Phase I and II clinical trials were conducted to determine safety and efficacy.

In rodent models the formula significantly improves acquired dysmnnesia caused by scopolamine, reserpine and sodium nitrate, and reverses relevant biochemistry changes in memory and learning impairments induced by obstruction of the common carotid or right middle cerebral arteries. The formula has anti-cholinesterase effects and increases blood flow in the brain. A Phase II trial of 340 Chinese patients with 'probable' VaD demonstrated significant improvement in the VaDAS-cog, the primary efficacy parameter for cognitive function, with no severe adverse events. The multi-target effects result in improved cognitive function in VaD patients. A Phase III trial has commenced in Australia. VaD has no current approved pharmaceutical therapy.



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Stefan Gafner, PhD, Chief Science Officer, American Botanical Council. For more than a decade, Dr. Gafner has served as a research scientist and director of analytical chemistry in the research and product development department of Tom's of Maine, a leading manufacturer of natural oral and personal care products. Among other products he researched and developed at Tom's, Dr. Gafner co-developed a breath-freshening licorice (*Glycyrrhiza glabra*, Fabaceae) extract that is a component of Tom's bestselling Wicked Fresh® toothpaste.

Dr. Gafner received his degree in pharmacy at the University of Bern School of Pharmacy in Bern, Switzerland. He earned his doctorate in pharmaceutical sciences — with a focus on phytochemistry (the chemistry of plants) — at the University of Lausanne in Switzerland, from the internationally respected phytochemist Professor Kurt Hostettmann. His doctoral thesis focused on the search for new antibacterial and antifungal compounds from African medicinal plants in three plant families (Asteraceae, Bignoniaceae, and Myricaceae). Dr. Gafner conducted his postdoctoral research at the University of Illinois – Chicago, in the College of Pharmacy's highly regarded Department of Medicinal Chemistry and Pharmacognosy (the study of medicines from plants and other natural sources).



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Stefan Gafner, *American Botanical Council*, "TBA"



Larisa E. Pavlick, V.P. Global Regulatory and Compliance, United Natural Products Alliance.

Service:

- The U.S. Food and Drug Administration, as a Consumer Safety Officer (Investigator), Jan 2009 – Oct 2016
- Dietary Supplement Consulting Independent Consultant Frederick, Jan 2003 – Oct 2006 / Nov 2008 – Jan 2009
- Life Force International, Director of Product Quality Systems, Poway, California Mar 2008 – Dec 2008
- Univera Life Sciences and Unigen Director of Product Development Product Manager, Regulatory Affairs Associate, Feb 1997 – Oct 1999 / Nov 2006 – Mar 2008
- NSF International Sales Manager, Ann Arbor, Michigan, Feb 2005 – Aug 2005
- Industrial Laboratories, Business Development Manager Wheatridge, Colorado, Jan 2001 – Sept 2003
- Amrion Product Coordinator Senior and New Buyer, Thornton, Colorado Nov 1999 – Dec 2000

Experience and Background:

Quality and Regulatory
Operations
Product Development and Brand Management
Purchasing
Sales and Marketing

Education

Bachelor of Science, Major in Biology University of Colorado, Denver, CO
Master of Business Administration (course work only, degree incomplete) University of Phoenix, Denver, CO



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Industry perspective on botanical quality and compliance

The top 2017 regulatory concerns, based on a poll of UNPA members, falls into two categories including new regulatory requirements to be implemented and dietary supplement product quality attributes. Some of the top product concerns include dietary supplement claims, intentional adulteration, botanical identification, Prop 65, and pesticide residue, to name a few. These top product concerns also correspond to current regulatory trends and the top FDA citations seen on the Form FDA 483-Inspectional Observations and in recent regulatory action. The frequency of the top FDA citations has been consistent over the past ten years. Based on Ms. Pavlick's industry background and experience as an FDA investigator, many firms have had a difficult time understanding the expectations. There are many interpretations of 21 CFR Part 111-Dietary Supplement GMPs, especially related to finished product release. These misunderstandings often lead to official observations by the FDA and potential regulatory action. How can we as an industry improve? In this session, Ms. Pavlick will help with the solutions and share her insights.



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Stephen Daniells is the Senior Editor of William Reed Business Media's market-leading publications NutraIngredients-USA and FoodNavigator-USA. He obtained his PhD in chemistry from the Queen's University of Belfast, Northern Ireland, and held post-doctoral research positions in The Netherlands and France before taking the leap into journalism in 2005. In 2015, he received the American Herbal Products Association's Special Award for Journalistic Excellence. He has presented at numerous industry and association events, including conferences organized by the International Scientific Association for Prebiotics & Probiotics (ISAPP) and the United Natural Products Alliance (UNPA), and he chairs William Reed's Probiota Americas and Food Vision USA events. He lives in Chicago.



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Connecting science, industry and consumers: An editor's view of the natural products industry

The last couple of years have been a time of uncertainty and challenges in the dietary supplements industry. Stephen Daniells, Senior Editor of the leading trade publication *NaturalIngredients-USA* and *FoodNavigator-USA*, will give his perspective on the current state of affairs for the industry and its consumers, and look at areas of innovation and opportunity for industry and researchers alike.



Dr. Alexander Crawford is Principal Investigator of the Chemical Biology Group at the Luxembourg Centre for Systems Biomedicine (Belval, Luxembourg), and is an Honorary Research Fellow at the Marine Biodiscovery Centre and Department of Chemistry of the University of Aberdeen (Scotland). He is also Project Manager of PharmaSea (www.pharmasea.eu), a European Union-funded research consortium focusing on drug discovery from

marine microorganisms, and is the founding CEO of Theracule, a spin-off company focusing on personalized drug discovery and orphan drug development for genetic CNS disorders. Dr. Crawford was previously the founding CEO of two drug discovery companies in Germany, and held research positions at the Flanders Institute for Biotechnology (Leuven, Belgium) and the Whitehead Institute for Biomedical Research (Cambridge, Massachusetts). He

earned a PhD in pharmaceutical sciences at the University of Leuven, an MPhil in neuroscience at the Max Planck Institute for Developmental Biology (Tübingen, Germany), and an SB in biology at the Massachusetts Institute of Technology.

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Fishing for drugs from nature: Zebrafish as a biodiscovery platform

Dr. Alexander Crawford, Chemical Biology Group, Luxembourg Centre for Systems Biomedicine, Belval,
Luxembourg

Emerging challenges within the current drug discovery paradigm are prompting renewed interest in secondary metabolites as an attractive source of novel, structurally diverse small molecules that have been evolutionarily 'pre-selected' for bioactivity. With the recent validation of zebrafish as a biomedically relevant model for functional genomics and in vivo drug discovery, the zebrafish bioassay-guided identification of natural products is an attractive strategy to generate new lead compounds in a number of indication areas. We have recently developed a number of in vivo, microgram-scale, high-throughput bioassays based on zebrafish embryos and larvae for the systematic identification and pharmacological characterization of bioactive natural products. Zebrafish offer the ability to rapidly evaluate – at a very early stage in the drug discovery process – not only the therapeutic potential of natural products, but also their potential hepato-, cardio-, and neurotoxicities. Due to the requirement for only microgram quantities of compounds to be tested, in vivo assays based on zebrafish are useful not only for bioassay-guided isolation, but also for the subsequent derivatization of bioactive natural products prioritized for further development as drug discovery leads.

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Dr. Mi-Jeong Ahn obtained her B.S. (1991) in Pharmacy, M.S. (1993) in Biochemistry and Ph.D. (2003) in Pharmacognosy from Seoul National University. She worked as a researcher at LG Chemical Research Park from 1995 to 1996. In 2006, she worked as Assistant Professor in College of Life Science & Natural Resources, Gyeongnam National University of Science and Technology, and moved to College of Pharmacy, Gyeongsang National University as Associate Professor in 2011. She has served as Vice Dean and Dean of College of Pharmacy. Her research has been focused on 1) Standardization of herbal medicines: Identification of botanical origin by inner morphological characteristics and chemical profiles, 2) New drug development from ethnomedicinal natural resources, 3) Chemical analysis of natural products by spectroscopy.



Anatomical characterization and chemical profiling of Korean folk medicines

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Rumex and Boehmeria species are perennial herbs in the family of Polygonaceae and Urticaceae, respectively, and widely distributed over eastern Asia. These plants have been used as folk medicines, but botanical origins of these drugs have not been pharmacognostically confirmed yet. In this study, anatomical characterization and chemical profiling were carried out to differentiate among five Rumex species and ten Boehmeria samples. The inner morphological characteristics of these specimens were observed using transverse or vertical sections, which were prepared using a microslicer or a handslicer. HPLC-DAD analysis was performed to verify the differences in chemical profiles among the species. Druse was found in the upper surface of *R. acetosa* leaves only. *R. acetosa* and *R. acetosella* showed V-like petioles, while the other species displayed elliptical ones. Fewer vascular bundles were observed in the transverse sections of the petioles of *R. acetosa* and *R. acetosella*. *R. longifolius* showed the highest number of vascular bundles in the flower stalk. In addition, the five species could be differentiated by other internal morphological criteria such as the shape of the main vein of leaves, number of collenchyma cell layers, and the frequency of stomata. While the root of *R. crispus* showed the highest content (11.8 mg/g DW) of the three major anthraquinones, emodin, chrysophanol and physcion, it also exhibited the lowest content (1.92 mg/g DW) of three anthraquinone glycosides. In contrast, while the content (1.12 mg/g DW) of the above three anthraquinones was lowest in the root of *R. acetosa*, this species exhibited a high content (13.6 mg/g DW) of the glycosides. *R. acetosella* particularly exhibited a high content of the anthraquinones (6.94 mg/g DW) and their anthraquinone glycosides (21.8 mg/g DW). Meanwhile, microscopic data of Boehmeria species also showed discriminative inner morphological characteristics such as collenchyma cell layer, thickness of cortex and frequency of druse. The HPLC profiles exhibited more than four characteristic peaks. OPLS-DA multivariate statistical analyses were successfully applied to the inner morphological characteristics and HPLC profile data to differentiate each species.

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Keywords: Rumex species, anatomical characteristics, HPLC profiles, anthraquinones, anthraquinone glycosides

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Professor Clara Lau is the Associate Director of the Institute of Chinese Medicine at The Chinese University of Hong Kong. She also serves as the Associate Director of the Partner State Key Laboratory of Phytochemistry and Plant Resources in West China (CUHK). She has a courtesy appointment as Associate Professor at the School of Chinese Medicine, CUHK and has served as Deputy Program Director/Program Director (2005-2015) of a part-time MSc in Chinese Medicines and Herbal Drugs. With BPharm and PhD in Pharmacy (Pharmacognosy) from King's College London, University of London, United Kingdom, she has a continuous interest in medicinal plants (western herbals and traditional Chinese herbal medicines) and has over 20 years' experience in natural products research. Her major research areas include investigations into potential anti-cancer and anti-diabetic activities of natural products. She has published over 190 refereed journal articles. Besides, she has taught Pharmacognosy for over 10 years and successfully supervised/co-supervised 9 postdoctoral fellows, 8 M.Phil. and 19 Ph.D. students in TCM/natural products research. She currently serves as member of ChP-USP Advisory Group on Monographs for Traditional Chinese Medicine Ingredients and Products; Executive Council Member and Deputy Secretary General of The Consortium for Globalization of Chinese Medicine; Secretary General and Member of the Board of Directors for Good Practice in Traditional Chinese Medicine Research Association; Executive Committee member of Modernized Chinese Medicine International Association; Advisor for Chinese Medicine Council of Hong Kong on Registration of Proprietary Chinese Medicines; and Editorial Board member of journals "Phytomedicine" and "Chinese Medicine".



The combined use of Herba Cistanches and statin – a possible solution for statin-induced myotoxicity

Statins are commonly prescribed western medicines for hypercholesterolemic patients to reduce cholesterol production. Although statins are usually well tolerated, muscle toxicity is still a common clinical adverse effect in which patients experience muscle pain, fatigue and weakness. Patients with severe symptoms such as elevated creatine kinase (CK) levels are even advised to terminate statin therapy until CK is being normalized. Up till now, there is no effective treatment for statin-induced muscle toxicity.

In the past few years, our research team has been investigating the use of Chinese herbs to prevent statin-induced muscle toxicity. Herba Cistanches (HC), also known as Rou Cong Rong, is the dried fleshy stem of *Cistanche deserticola* (family Orobanchaceae). The plant is generally prescribed for pain in loins and knees, and is commonly used in Chinese medicines for muscle problems. Recent pharmacological studies suggested that HC could reduce muscle damage and improve ATP storage in post-exercising rats, and enhanced mitochondrial ATP generation. We therefore hypothesized that HC aqueous extract (HCE) could prevent simvastatin-induced muscle toxicity.

The assessment was based on the ability of this herb-drug combination to reduce the side effects of simvastatin (including elevated CK activity and reduced ATP production) using L6 rat skeletal muscle cells and Sprague Dawley rats. From the results, the present study reported for the first time that HCE could exert in vitro and in vivo protective effects on simvastatin-induced muscle toxicity. Furthermore, the effect of HCE alone or in combined use with statin in high-fat diet-induced hypercholesterolemia was also investigated in C57Bl/6 mice. Surprisingly, HCE could also reduce high-fat-induced hyperlipidemia and liver cholesterol when being used alone or in combination with simvastatin at a reduced dose, with such beneficial effects also being firstly demonstrated.

In conclusion, our study not only suggesting that HCE could be a possible solution for statin-induced myotoxicity, but also implying that HCE might be of therapeutic value as a health supplement when used as adjuvant with simvastatin in hypercholesterolemic patients.

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Dr. John MacMillan is an Associate Professor at the University of Texas Southwestern Medical Center, where his research laboratory focuses on the discovery and characterization of biologically active molecules from microorganisms. This research has focused predominately on the therapeutic areas of infectious disease and oncology, combining phenotypic screening, isolation and mechanism of action studies towards the discovery of more than 100 new natural products. His work in the area of oncology has yielded a first in-class inhibitor of Hypoxia Inducible Factor 2 (HIF-2) that is currently undergoing clinical trials for the treatment of renal cell carcinoma. The MacMillan labs work in the area of natural products mechanism of action has yield multiple approaches, such as FUSION, to look at the mechanism of natural products on a library scale. This work has led to establishment of the Center for High Functional Annotation of Natural Products (HIFAN), which a multi-institutional center funded by the NIH to study the mechanism of botanicals and natural products.

Dr. MacMillan holds a Ph.D. in Chemistry from the University of California, Davis and a B.S. in Chemistry from the University of Iowa. He is the Chilton/Bell Scholar in Biochemistry and the holder of the Martha Steiner Chair in Biomedical Sciences.



High-Throughput Functional Annotation of Natural Products

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Determination of the mechanism of action to botanicals, dietary supplements and natural products (mixtures and pure compounds) is a complex challenge that has limitations to their utility as supplements and therapeutics. Botanicals and dietary supplements are particularly difficult, as these are often complex mixtures that can change in the constituents and concentration of individual compounds. The rapidly growing botanical dietary supplement industry faces a number of challenges regarding the quality, safety and benefit of these products. In order to address these issues, rigorous and sustained efforts are needed to chemically and biologically characterize these products. The Center for High Throughput Functional Annotation of Natural Products (HIFAN) is developing complementary biological platforms to study the mechanism of action of botanicals and natural product libraries and integrate the use of metabolomics and other analytical methods to fully understand the contributions of individual compounds of complex mixtures to a given biological activity.

The two biological platforms that we have developed include: 1) Cytological profiling (CP) is a powerful method for quantifying and comparing the phenotypic effects of small molecules on cells. Combining automated fluorescence microscopy with computer-aided image processing, CP provides an information-rich phenotypic profile for each tested sample. Rather than focusing on a single narrowly defined phenotype, CP uses multiple cytological probes to generate hundreds of quantifiable cytological features, giving rise to a phenotypic fingerprint of each compound. 2) Functional Signature of Ontology (FUSION) takes advantage of gene expression signatures in mammalian cell lines to generate mechanism of action hypotheses. By probing the expression signatures of small molecules and genetic perturbations (siRNA, miRNA) we utilize pattern-matching tools that produce verifiable mode-of-action. We carry out this analysis using a minimal mRNA reporter cohort and technologies for high-throughput quantitative multi-analyte detection. The endogenous reporter gene signatures resulting from each perturbation were assembled into a similarity matrix using Euclidean and Mahalanobis distance distributions. In this way we produce FUSION maps that link bioactive agents to the molecular entities and/or biological processes they engage in cells.

In this presentation, we will describe the biological platforms and describe the analytical chemistry and chromatography challenges associated with our efforts to carry out comprehensive biological characterization and the need to generate well defined samples to study synergistic interactions.



Black Holes and Golden Spices in NP Research

Guido F. Pauli, Jonathan Bisson, Charlotte Simmler, James Graham

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The study of Natural Products (NPs) for drug discovery, new target identification and traditional medicine support is impacted by a distribution of effort similar to phenomena observed in linguistics, ecology, and physics, among others. By mining the manually curated NAPRALERT database (<https://www.napralert.org>) for the last 80 years of research in pharmacognosy, it has been shown that general interpretation of in vitro biological outcomes is likely limited by the strong bias toward the identification of already commonly described as bioactive and often widely occurring compounds. The study of the occurrence-bioactivity-effort space of NP research from the last century led to the identification of 39 most occurring, often highly abundant, and exceedingly investigated phytochemicals, which could be considered as panaceas according to their bioactivity profiles. Some of these compounds have been termed Invalid Metabolic Panaceas (IMPS), due to their non-specific biological properties leading to improbable lead characteristics[1]. Some IMPS such as quercetin were also described as PAINS (Pan-Assay Interference compounds), and an overlapping subset of these also show aggregating properties in bioassay conditions. Collectively, IMPs, PAINS, and aggregators are groups of molecules that have a marked potential to misguide the discovery of “real” leads and active principles, disrupt bioassays, and potentially mask or hide other bioactive components of the studied material. Hence, NP research can be erroneously absorbed by the Black Hole of these prototypic compounds, preventing meaningful drug discovery.

An exemplary case of the “attractive forces” of problematic NP molecules is curcumin, the widely known constituent of the golden spice turmeric and its plethora of reported biological effects [2]. Curcumin is known to be chemically/physiologically unstable, has poor ADME properties, and remains unsuccessful as a drug lead candidate when considering the wide range of randomized double blind clinical trials. In fact, curcumin has been described as an IMP exhibiting disrupting behavior by interfering with the bioassays, notably through fluorescence interference, aggregation in culture media, or cellular membrane disruption - to name a few effects. As such, curcumin should be considered an improbable lead compound. Improbable and invalid leads receive an unwarranted amount of attention and distract resources that could better be used to study the alternative bioactive principles and mechanisms of, e.g., turmeric.

Learning from both the shiny side of the NP Black Hole and the darker side of Golden Spices can generate insights that foster new discoveries in the NP domain, and subsequently inspires the development of alternative approaches to a more efficient discovery of bioactive NPs that are ecologically and biologically meaningful and have increased potential as drug leads. Moving the field of NPs from belief and/or hype requires new rationales such as the following: focusing on minor low abundant constituents for structural novelty; evaluating potential interference of tested phytochemicals in bioassay readouts; and improving the knowledge of the chemical processes that occur during biological investigations.

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Data Transparency and Sharing in NP Research

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Natural Product (NP) research is a domain located at the intersection of a plethora of domains such as biology, biochemistry, botany, ethnobotany, pharmacy, and chemistry. To be efficient, NP research requires a wide variety of data sources within these disciplines. Unfortunately, most of the information produced in the past is lost on the researchers' hard drives and on printouts. Frequently enough, the only broadly accessible information are peer-reviewed reports in academic journals, which are located behind paywalls that are not surmountable by all. The achievement of data transparency requires sharing modalities that are formal, accessible, open, and freely available, allowing the entire NP community to use its own products. Such data sharing models require both well-established and widely accepted procedures as well as adapted repositories that can handle the diverse nature of the data produced by NP research.

Sharing and annotating of NP data also require approaches that make the data searchable and accessible. Fundamental limitations and idiosyncrasies limit in the mapping of most of the existing databases currently used by NP researchers. One timely goal is to connect existing repositories of bibliographical data, chemical structures, and biological activities, including data outside the NP literature, by establishing a controlled vocabulary in the form of an ontology. The success of the Gene Ontology in the world of biomedical research shows what a formal and logic-based approach to knowledge management can bring to science. And such an approach would greatly enhance our capabilities at exchanging information.

We will demonstrate how relatively simple data sharing strategies can generate new and meaningful scientific outcome and foster collaboration. The presentation is aimed at encouraging the NP research community to collaborate and work (inter-)actively on the development of NP data transparency and sharing mechanisms.



Dr. Yi Zhun Zhu is a Chair Professor of Pharmacology and dean of School of Pharmacy, Macau University of Science and Technology. Dr. Zhu got his Bachelor of Medicine at Shanghai 2nd Medical University (now Shanghai Jiaotong University) in 1989 and M.D./Ph.D. from Faculty of Medicine, University of Heidelberg, Germany in 1995. He joined as a faculty member of the Department of Pharmacology, National University of Singapore (NUS) in 1998 after postdoc training at Kiel University and industrial experience at Hoechst Marion Roussel (now Sanofi). Dr. Zhu was recruited as dean and distinguished professor of pharmacology of School of Pharmacy, Fudan University and served until Feb. 2016. Dr. Zhu published more than 160 peer-reviewed papers with more than 4800 citations and edited 2 books for his work. He is an editor-in-chief for Cardiovasc. Regenerative Med. and associate editor for J Alzheimer Diseases, Biosci. Reports academic editor for PLoS One and editorial board member of CNS Neuroscience & Therapeutics, Journal of Pharmacology and Drug Metabolism, Frontiers in Neurotrauma etc. Dr. Zhu is also editor-in-chief for the national text book of Pharmacology (7th and 8th edition [Chinese version] and 1st edition [English version], People's Medical Publishing House), Dr. Zhu was awarded 'National Distinguished Young Scientist from Natural Science Foundation of China (NSFC) in 2008 and Chief Scientist of National Key Research Program (973) and Chief-PI for the National Platform of Drug Discovery in 2009. Dr. Zhu further received National Award for Innovative Research Work of the Returnees in 2009 from the State Council and Magnolia Award from Shanghai Government in 2010. Dr. Zhu was awarded 2011 Cheung Kong Chair Professorship by the Ministry of Education, China. In 2014, Dr. Zhu was awarded 'Health China' top 10 figures of the year. His research focuses on drug developments especially for heart and brain. Two novel compounds as drug candidates have been completed pre-clinical trials and are moving to clinical trials now.



Anti-inflammatory effects of Leonurine (SCM-198): from preclinical studies to bedside

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Leonurine (SCM-198), an active alkaloid of Traditional Chinese Medicine Herba leonuri, has various pharmacological properties such as anti-apoptosis and anti-oxidant. In the present study, we investigated the anti-inflammatory effects of leonurine in both in vitro and in vivo. We also studied the effect on the progression of atherosclerosis in hypercholesterolemic rabbits and underlying mechanisms. Treatment with leonurine dose-dependently inhibited U937 cells adhesion to TNF- α -activated HUVEC as that achieved by treatment with dexamethasone. This was associated a reduction in cell adhesion molecules expression and monocyte chemoattractant protein (MCP-1). These effects were also accompanied by inhibitions of endothelial expression of cyclooxygenase-2 (COX-2), phosphorylation of p38, degradation of I κ B α , and nuclear translocation of NF- κ B. In addition, the elasticity of the arteries and hemodynamic status improved, accompanied with a decrease in smooth muscle cell migration and, macrophage infiltration, as well as the expression of platelet-endothelial cell adhesion molecule-1 (PECAM-1) in the aortas. Our results demonstrated for the first time that the anti-inflammation properties of leonurine in endothelial cells, at least in part, through suppression of NF- κ B activation, which may have a potential therapeutic use for atherosclerosis. In our rabbit atherosclerotic model, SCM-198 dose-dependently ameliorated the progression of atherosclerotic lesions and vascular dysfunction accompanied by the suppression of inflammatory factors and oxidative stress. These findings suggested that SCM-198 might be a potential agent for the treatment of pathological inflammation and it has been completed for the preclinical trials for filing NDA (New Drug Application) by FDA.



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Dr. Jungui Dai, Professor of the Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College. He obtained his BS and MS degrees in Botany in 1996 from Central China Normal University, and Ph. D degree in Pharmacognosy in 1999 from Peking Union Medical College. He did postdoctoral research at Peking University and Niigata University (JSPS foreign fellowship). He joined the faculty of Institute of Materia Medica, CAMS & PUMC as an associate professor in 2003, and was promoted to a full professor in 2007. His research interest is focused on the biosynthesis and biocatalysis of natural products. He has authored and co-authored over 100 peer-reviewed papers in international journals, including Nature Chemical Biology, Angewandte Chemie International Edition, Organic Letters, Advanced Synthesis & Catalysis, The Journal of Biological Chemistry, Chemistry-A European Journal, Journal of Natural Products.



Enzyme promiscuity and diversity-oriented structural innovation of natural products and drug discovery

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ABSTRACT: It is increasingly accepted that enzyme promiscuity is not a rare phenomenon; rather, it appears to be widespread and may even be an inherent feature in the biology. The promiscuous enzymes are highly valuable in many synthetic applications, ranging from the laboratory to industry, especially in reactions that are difficult to access by chemical methods such as carbon–carbon bond formation and ring system construction. Therefore, there is a large drive to discover or develop ‘universal’ enzymes that can be used for general chemical syntheses and drug discovery. In the present speech, the enzyme promiscuity of novel glycosyltransferases and prenyltransferases and their application in diversity-oriented structural innovation and drug discovery are introduced. In particular, the molecular mechanisms of enzyme promiscuity of a novel aromatic prenyltransferase, AtaPT, and structure-guided mutagenesis for altering the specificity and promiscuity, will be discussed.



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Jinwoong Kim graduated College of Pharmacy, Seoul National University in 1979, and received master degree in science in the same College. Then he went to USA for doctoral studies at the University of Illinois at Chicago, graduating with a Ph.D. in Pharmacognosy in 1988. and moved to University of Oklahoma in Norman as postdoctoral fellow. He joined the College of Pharmacy, Seoul National University, his alma mater, in 1989, where he rose to the rank of Professor in 1999. He published about 140 papers in international journals, 10 books or book chapters, and 12 patents including 2 US Patent. He served Korean Society of Pharmacognosy as a President in 2009, and currently works as editorial advisory board members in the international scientific journals such as *Planta Medica*, *Journal of Ethnopharmacology*, and *Drugs of the Future*.



Khellactone type coumarins from *Peucedanum japonicum* roots

Kim Jinwoong, College of Pharmacy, Seoul National University, Republic of Korea

Peucedanum japonicum Thunberg (Umbelliferae) is distributed in Asian countries including Korea. Its roots have been used traditionally for cold. Previous studies on chemical constituents of this plant revealed that the roots contained coumarins, chromones, polyacetylenes, sugar alcohols, and steroid glycosides. In this study, sixteen new angular dihydropyrancoumarins, and twenty-four known coumarins were isolated from *P. japonicum* roots. The structures and absolute configuration of diacylkhellactones were determined by partial hydrolysis, the Mosher method, and X-ray crystallography. Some enantiomers were also found to be present in this species.



Dr. Jimmy Yuk is the Senior Business Development Manager for Natural Products at Waters Corporation.

In this role, Dr. Yuk develops novel analytical methodologies using liquid chromatography-mass spectrometry (LC/MS) to understand the complexities of natural products. Dr. Yuk collaborates with many academic and industry leaders to investigate challenging natural product research questions to further the analytical knowledge in this field. Dr. Yuk's research expertise for the past 10 years has been in the area of chemometrics especially in the area of targeted and non-targeted approaches.

Prior to Waters, Dr. Yuk worked as a research scientist in R&D for Bruker Biospin. He has written analytical methods and publications focusing on metabolomic approaches in natural products using NMR spectroscopy. He has published various research articles and co-authored two book chapters in the utilization of NMR spectroscopy for the quality control of natural products in the industry.

Jimmy has presented his work in many international conferences and is actively involved in various natural products professional affiliations such as the American Society of Pharmacognosy (ASP), Metabolomics Society, and is a statistics committee member for the Association of Analytical Communities (AOAC). Dr. Yuk obtained his B.Sc in Biological Chemistry and his Ph.D. in Analytical Environmental Chemistry from the University of Toronto. During his Ph.D., he developed metabolomic approaches in complex environmental mixtures using NMR, GC-MS and hyphenated LC-NMR-SPE-MS technologies.



Quantitation of aflatoxins in traditional Chinese medicine

Smith K, Issac G, Yuk J, Wrona MD, Waters Corporation, Milford, MA USA 01757

Aflatoxins are toxic secondary metabolites of certain fungi that can grow on crops. Traditional Chinese Medicines (TCM) often contain cultivated products and therefore testing for toxic contaminants in the raw materials or products becomes necessary. The Chinese Pharmacopeia (ChP) sets the regulatory limit as well as the analytical method of measurement. This work shows the application of the method for quantitation of aflatoxins in the TCM coix seed as well as their measurement in a selection of commercially available raw materials. The method has sensitivity of 2.5 pg/mL for aflatoxin B1, B2, and G1 and 5 pg/mL for aflatoxin G2 with a 5 μ L injection volume. Linearity was 4 orders for each analyte which accommodates the ChP methodology without modification or sample dilution. The analytes were baseline separated and had an RSD less than 0.9% for 200 injections in matrix. All six of the coix seed samples acquired tested positive for aflatoxin B1 from 0.037 to 1.51 μ g/kg; however, these values are below the regulation of 5 μ g/kg. This study shows the importance of monitoring potentially dangerous aflatoxins in TCM where sensitivity for low concentration substances are required



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Dr. Hellen Oketch-Rabah is a Pharmacognosist and currently a Senior Scientific Liaison at the United States Pharmacopoeia in the Department of Dietary supplement and Herbal Medicine where she leads the effort in critically evaluating literature information pertaining to the Safety and Benefits of Dietary Supplements for purposes of determining articles to be admitted for USP monograph development. She is also an invited Expert Committee member of the 2017-2021 Joint (FAO/WHO) Expert Committee on Food Additives.

Previously Dr. Oketch-R was the Principal Scientist at Herb Pharm Inc. a dietary supplement manufacturing facility in Oregon, where she managed the Analytical and R & D laboratory and new product development.

As a private citizen, Dr. Oketch-Rabah leads a non-profit organization (ElimuSfoundation.org) that supports girls and boys in STEM education. Dr. Oketch received her Ph.D. in Pharmacognosy from the Royal Danish School of Pharmacy in Denmark. B.Ed(Sc.) and M.Sc., from Kenyatta University in Nairobi, Kenya. She has presented at more than 40 scientific conferences, published 30 peer-reviewed articles, written 2 book chapters, and was an interviewee in the scientific documentary on herbal medicines titled "*Numen the Nature of Plants*". Hellen is an active member of the Society of Toxicology (SOT), American Society of Pharmacognosy (ASP) and Sigma Xi.



USP Safety Review of Willow Bark

Oketch-Rabah HA¹, Dog TL², Sarma ND¹, Giancaspro GI¹, United States Pharmacopeia (USP), Rockville, MD, USA¹,
Chair USP Admission Evaluations Joint Standard Setting Sub-committee (USP Admission Evaluations JS3) USP
Rockville MD, USA²

Willow Bark is obtained from several species of *Salix*, and is a dietary ingredient in many dietary supplements (DS) in the USA market. The USP Admission Evaluations Joint Standard Setting Sub-committee (USP Admission Evaluations JS3) that is responsible for the admission of dietary ingredients for monograph development performed an evidence-based review of willow bark to assess potential health concerns.

Most published clinical trials administered 70% hydro-alcohol extracts and delivered 120- 240 mg salicin daily for up to 6 weeks. All studies involved adult patients; no studies involved special populations e.g. pregnancy or breast feeding mothers. Some publications advise caution in the use of willow bark because of potential risk of increased bleeding, salicylates cross the placenta and new-borns eliminate them very slowly; others cautioned concurrent use with aspirin and other salicylate drugs or by persons sensitive to aspirin. The most common non-serious adverse effects of willow bark included gastrointestinal side effects e.g. upper abdominal pain, nausea, and dyspepsia. A few allergic reactions were also reported. Post-market surveillance data obtained from government reporting portals showed that most adverse events cases were associated with multi-ingredient products, and in most cases taken concurrently with other medications; thus causality assignment was uncertain.

Importantly DS products containing willow bark deliver up to 240 mg of salicin (that can be metabolized into 113 mg salicylic acid among other metabolites) and yet these products are not required to include a label warning. In contrast the OTC low dose aspirin (80 mg strength) that delivers 62 mg salicylic acid is, required by law, to include guidelines on the use in pregnant women and children, as well as contraindications pertaining to blood coagulation. In the interest of protecting public health, the USP Admission Evaluations JS3 determined that USP monographs for willow bark (*Salix* Species Bark, *Salix* Species Bark Powder, and *Salix* Species Bark Dry Extract) shall contain a cautionary labeling statement as follows: "Not for use in children, women who are pregnant or nursing, or by persons with known sensitivity to aspirin". DS products that claim compliance with USP standards for willow bark are required to carry this label caution.

The authors would like to acknowledge with great appreciation the advice and suggestions provided by members of the 2010 – 2015 cycle of the USP Dietary Supplements Admission Evaluations Standard Setting Subcommittee (USP Admission Evaluations JS3). Funding for this review was provided by the United States Pharmacopeial Convention (USP).



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Kirsten Tripplett, Ph.D. is an expert in plant anatomy and classic botany techniques and serves as the Botanical Scientist and Identity Specialist at Traditional Medicinals, Inc.(TM), Quality Control Lab. She is responsible for macro- and microscopic identification of incoming herbal ingredients, and is “anatomically intimate” with over 125 herbs. In addition to her identity work at the microscope, Kirsten launched an ever-growing Botanical Reference Materials (BRMs) collection, a medicinal plants herbarium (composed primarily of herbal ingredients in TM finished products), as well as a collection of potential adulterants commonly found in the dietary supplement industry. These resources equip and support TM’s specialists with necessary tools for accurate and rigorous identification of a diverse portfolio of herbal ingredients. Additionally, they allow greater insight into chemo-morphological variations across (and within) plant species and between sources and crop-growing regions. With these resources TM’s identity specialists are well-equipped and versed with plant diversity and identification.

Kirsten’s great passion is plants, from landscape-scale down to powders, from the field to the microscope.

Dr. Tripplett has studied botany and ecology since she was a child. After “discovering” the joys of combining classic botany with the study of plants are used by indigenous peoples in tropical rainforest environments, she became an ethnobotanist. She focused on contemporary and ancient uses of plants, especially plant resins as well as chocolate, by the Maya people of southern Mexico and Central America. With extensive experience in rainforest ecology in the Americas and Malaysia, floras of four U.S. states, archaeological botany and ethnobotany, Dr. Tripplett brings diverse skill sets and insights to all of her botanical analysis and identification work. She also wants to make a plug: all dietary supplement manufacturers should consider bringing a botanist on board; your products will be all the better for doing so!

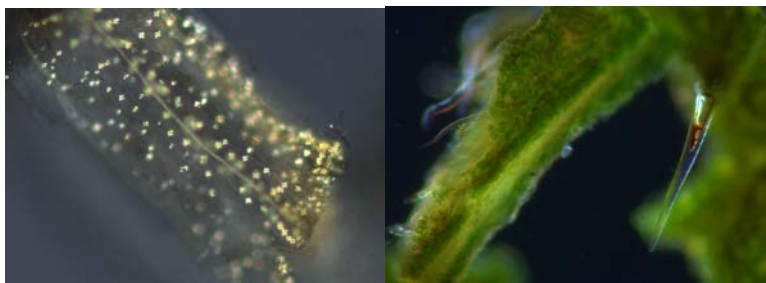


Botanical Microscopy and Plant Anatomy is Cheap, Fast and Efficient

K Tripplett, Quality Control, Traditional Medicinals, Inc., 4515 Ross Road Sebastopol, CA 95472 USA

Establishing internal specifications for composition, purity, strength and botanical identity of incoming plant materials in the U.S. dietary supplement (DS) industry can be challenging for many manufacturers. The Code of Federal Regulations (21 CFR 111.70) currently requires at least one scientifically valid identification test for incoming herb components, to prevent intentional (economic) or accidental (safety) adulteration or contamination of dietary supplements (DS). Pharmacopeial monographs provide a suite of officially recognized standards and methodologies, and an integrated approach to identifying those criteria. Monographs are usually composed of three to four identification (ID) methods: Organoleptic, macro-/microbotanical, chemical and analytic. Botanical microscopy relies on classic morphology and anatomy to identify plant species and/or the plant part utilized; and in many cases, serves as a stand-alone means of ID. Using microscopy, identification of simple and complex herbs in both powder form and larger-particle formats is fast, relatively inexpensive and accurate, making it a powerful ID tool. In addition to verifying identity, microscopy can help prevent adulteration or contamination. Additionally, a botanist can establish and curate reference materials in the form of herbaria and Botanical Reference Materials (BRMs) collections. Bringing a botanical identity specialist on staff in a QC lab can result in a sound and rigorous comparative reference collection for most ID processes, thereby increasing the rigor of ID techniques and adulterant contamination for manufactures and processors and CFR compliance.

A program is presented for establishing a QC botanical identity program, vision, scope and application. Several types of practical and useful plant reference collections, and effective and strategic ways to use these resources, are presented.





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Pietro Piffanelli has a 15 year experience in genomics applied to the nutraceutical and biomedical sectors. Presently, he is leading the R&D and Business operations of the PTP Science Park with a specific focus on supporting the identification and authentication of botanicals and their derived products. His team developed customized DNA-based analytical tools to certify the purity and identity at the species and variety levels. The use of Next Generation Sequencing (NGS) technologies enables the implementation of innovative analytical approaches to define molecular markers even in species where no genomics data are available. The NGS-based strategies enrich the analytical toolbox to authenticate botanicals.



Next Generation Sequencing Technologies as a powerful tool to botanical's identification and authentication

Next Generation DNA sequencing-based technologies (NGS) are emerging as highly reliable and powerful tools to authenticate botanicals, identify medicinal plants species and varieties in herbal products and dietary supplements.

The use of Next Generation Sequencing analytical strategies paved the way to precisely assign a dry extract to a defined plant species and detect adulterants

The use of DNA mini-barcodes enables the routine analysis of highly processed botanical's matrices ensuring the ingredient's verification and purity, product's certification and the respect of consumer's choices.

The most appropriate use of genomics-based technologies enables to authenticate botanicals derived from native plant species, complementing and integrating the generated genetic data with those from chemical and metabolomics approaches.

The use of NGS-based strategies to precisely define the composition of multi-ingredient extracts opened new perspectives to the use of this technology to test the purity and pinpoint the presence and identity of adulterants in botanical's dry extracts.

DNA-based analytical strategies hold the potential to develop of a suitable platform for precise authentication and purity of herbal products.



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Sara Handy obtained her Ph.D. in Oceanography at the University of Delaware in 2007, working under the direction of Dr. David Hutchins. In 2007, Sara started a postdoctoral position the University of Maryland with Dr. Charles Delwiche in the department of Cell Biology and Molecular Genetics. In 2009, Sara began her work at the U.S. Food and Drug Administration in the Center for Food Safety and Applied Nutrition. As a biologist in the Office of Regulatory Science, Sara works to develop methods to identify plant and animal species in foods using a variety of molecular methods.



Development of a Reference Standard Library of Chloroplast Genome Sequences, GenomeTrakrCP

Sara M. Handy¹, Ning Zhang¹, Padmini Ramachandran¹, Jun Wen², Andrea R. Ottesen¹, Ruth E. Timme¹

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In 2015, the total sales of herbal dietary supplements in the United States reached \$6.92 billion, a 7.5% increase from the year before, and demand for botanicals have increased for 12 consecutive years. Many different chemical techniques have been used to monitor authenticity of supplements and more recently DNA based tools have been included. Since questions have been raised about traditional DNA barcoding especially for processed products and closely related species, developing methods targeting smaller diagnostic regions and reference libraries for rapid species identification of plants in foods and dietary supplements would be useful and complementary to chemical methods. In the past, the United States Food and Drug Administration (FDA) has been able to develop species specific assays targeting plant species of interest by utilizing chloroplast genome sequences. Presented here are the details for FDA's whole chloroplast genome sequencing effort and database, known as GenomeTrakrCP. Targeted species include plants found in foods and dietary supplements as well as plants known as toxin producers. Additionally, contaminants or adulterants and closely related species to these targeted species were sequenced. All data will be publically available through a bioproject in GenBank, e.g., PRJNA325670 derived from authenticated specimens and fully annotated. Currently there are 40 complete chloroplast genomes in the database from authenticated specimens. These data can be used by FDA and other government agencies, industry and any other researcher as complete chloroplast genomes or to design species specific assays to target plant species of interest.



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Natalia Ivanova, received her Ph.D. in Molecular Biology from Lomonosov Moscow State University in 1998. Natalia has joined Prof. Hebert's group at the University of Guelph in 2004, soon after inception of DNA Barcoding concept, and contributed to transition from an academic lab to a largest DNA Barcoding facility in the world processing 1M specimens per year. She considers herself an application specialist with a very simple strategy: design – implement – maintain. Her recent track record in methods development includes integration of robotic liquid handling stations, DNA extraction protocols for high-throughput automated environment, room temperature DNA storage and shipment, express DNA barcoding protocols, and development of QA/QC procedures utilizing control panels. She is currently involved in the following research projects: 384-well automated pipeline for HTS sample processing, SPRI-based methods for DNA purification, minimizing PCR bias in NGS workflows, detection and monitoring of toxigenic algal blooms in Great Lakes, biomonitoring of vertebrates in water and soil using eDNA, metabarcoding of insects in bulk samples, and authentication of food and Natural Health Products using NGS.



Embracing and Understanding Biocomplexity of Herbal Supplements

Natalia V. Ivanova, Maria L. Kuzmina, Thomas W. A. Braukmann, Alex V. Borisenko and Evgeny V. Zakharov,
Centre for Biodiversity Genomics, Biodiversity Institute of Ontario, University of Guelph, Guelph, Ontario,
Canada

Recent advances in DNA-based authentication have enabled fast and sensitive detection of DNA sources in herbal supplements. This is now utilized by some manufacturers for quality assurance of raw plant materials, final products, and contamination control during production. One of the common approaches, DNA barcoding, heavily relies on Sanger sequencing. However, stochastic amplification of multiple DNA sources that are often present even in single-source supplements renders Sanger results non-interpretable or non-reproducible, hence indicating strong need for NGS-based methods. While advances in NGS technology enable rapid and sensitive detection of DNA in complex mixtures, such results should be interpreted from a biocomplexity perspective. Aside from intended or non-intended substitution, possible cross-contamination with trace plant or fungal DNA can occur at any stage during growing, harvesting, manufacturing, handling or laboratory analysis of plant material. Detection of such non-target DNA is not necessarily indicative of technological flaws or deliberate adulteration and such results should be interpreted with caution. Diversity of fungi in herbal supplements is determined by a combination of pathogenic, saprophytic, endophytic and mycorrhizal fungi naturally associated with live plant material, and strains involved in the fermentation during manufacturing of bioactive components. Although this entire spectrum can be easily detected by NGS, interpretation of test results should focus on potential mycotoxin-producing fungi and human pathogens. While embracing this biocomplexity we are developing SNP-based diagnostic systems for selected species of interest by targeting multiple variable regions in chloroplast and nuclear DNA and propose NGS-facilitated detection method as a standardized tool for authentication of herbal supplements. Because manufacturing of extracts leads to DNA degradation or loss, quality control should utilize synergetic approach targeting both bioactive components (HPLC-MS) and DNA.



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David L. Erickson is the founder and CEO of DNA4 Technologies LLC, a biotechnology company in Baltimore, Maryland (USA), focused on developing new methods for the identification of natural products. In particular, David oversees the development of computational tools that leverage Next Generation Sequencing to accurately identify and quantify natural product content in commercial products. Before founding DNA4 Technologies, David was a ORISE Fellow at the Food and Drug Administrations' Center for Food Safety and Nutrition as well as having served as a biologist at the Smithsonian Institution's National Museum of Natural History where he developed laboratory and analysis methods related to DNA barcoding. While at the Smithsonian Institution David contributed to over 50 peer reviewed publications, many of which have been seminal in the development of DNA barcodes and their application in a range of scientific endeavors. Before his work at the Smithsonian, David was a Fellow in Quantitative Genetics at the University of Maryland, and in ancient DNA analysis of agricultural species at the Smithsonian Institution. David received his PhD in Botany from there University of Georgia where he was funded under a NSF Fellowship in Mechanisms of Plant Molecular Evolution, and where his love of plants and genetics merged and from which he has never looked back.



Meta-Genomic analysis of dietary supplement authenticity and complexity

David L. Erickson, Ph.D., DNA4 Technologies LLC, bwtech@umbc Research and Technology Park, Baltimore, MD

Modern genomic tools have revolutionized health sciences and pharmacology. These tools include the massively parallel sequencing technologies (termed NGS) that enable the capture of entire genome sequences at low cost. A parallel branch of innovation has been in the bioinformatic analyses of these massive DNA sequence data sets. In our presentation, we introduce a new bioinformatic tool called Genome-ID and demonstrate how it can be used to correctly identify the species contents of commercial dietary supplements, while removing many of the biases implicit in traditional DNA barcode approaches. Genome-ID uses inexpensively obtained NGS data as input and uses entire genomes (chloroplast and mitochondria) as the references. We provide examples of analysis from three sources: in-silico data from GenBank, experimental mixtures of known quantities of plant material, and from direct sequencing of commercial dietary supplements. We show how we can utilize Genome-ID to correctly identify and quantify species mixtures, as well as reduce the incidence of false positive identifications. At each stage we compare how traditional DNA barcoding approaches compare with Genome-ID. Lastly, we introduce an open access web-accessible portal that allows for implementation of the Genome-ID algorithm



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Philip Wylie is a Senior Applications Chemist for Agilent Technologies in Wilmington, Delaware, USA where he specializes in developing GC, GC/MS, GC/MS/MS and

GC/Q-TOF techniques for food safety analysis. He received his BA degree in Chemistry from Grinnell College (Iowa) and his Ph.D. in Organic Chemistry from the University of California, Davis. Before joining Hewlett-Packard Company (now Agilent) in 1984, he taught chemistry for nine years at the University of California, Davis; the University of Kansas; and Bates College in Maine. Recently, Dr. Wylie has focused on developing methods for the analysis of pesticide residues in food and on building collaborations with Agilent customers. He is the developer of Agilent's retention time locked databases for pesticide and indoor air analysis. Dr. Wylie holds four patents, has authored more than 70 journal articles and Application Notes. In recent years, he has lectured in 37 countries on five continents.



Analysis of Cannabis for Pesticide Residues by GC/Q-TOF

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19808¹, National Center for Natural Products Research, University of Mississippi, USA², Department of
Pharmaceutics and Drug Delivery, School of Pharmacy, University of Mississippi, USA³, ElSohly Laboratory Inc.⁴

As of the November 2016 election, 29 states have approved the use of medical cannabis and eight states, representing 65 million people, have approved recreational use by adults. Canada allows medical use and is on a path to full legalization. Because the US government still classifies cannabis as a schedule 1 drug, all legislation controlling the growing, testing and use of cannabis products is done at the state level. There is no uniformity in the regulations and their enforcement. Pesticide use on cannabis plants is very controversial, but is loosely regulated in most states. It is clear that pesticide residue testing is important for a product that may be eaten or inhaled. This paper describes the analysis of cannabis extracts for pesticide residues using an accurate mass high resolution GC/Q-TOF. Chromatograms are analyzed by applying an “all ions” approach using a personal compound database and library (PCDL) containing about 850 pesticide exact mass spectra. The software screens for all compounds in the PCDL in just a couple of minutes. Standards are only needed for those pesticides that are found and need to be quantified. This approach has also been used to identify pesticide residues in food and herbal extracts.



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Dr. Yan-Hong Wang is a principal scientist at the National Center for Natural Products Research, University of Mississippi. He has been conducting analytical/bio-analytical research of medicinal plants and related products (dietary supplements) in the center. Dr. Wang has extensive experience in analytical chemistry especially in liquid chromatography (LC) and mass spectrometry (MS) and expertise on methods development and validation using HPLC/UHPLC coupled with different detectors, such as PDA, ELSD, MS, and tandem mass. In addition, he has more than 26 years hand-on experience in natural products chemistry in the fields of isolation, purification and structural elucidation of active constituents from natural sources. Dr. Wang has teaching experience for the instruction of graduate students' course and lab training for the people having different backgrounds.



Chemical Analysis and Adulterant Characterization of Eleutherococcus senticosus and Ci-Wu-Jia Tea by UHPLC-UV-MS Using Novel Informatics Platform

Wang Y-H¹, Meng YH^{1,2}, Zhai CM^{1,2}, Avula B¹, Wang M¹, Yuk J³, Isaac G³, Smith K³, Khan IA^{1,4}, ¹National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, The University of Mississippi, University, MS 38677, USA, ²School of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin, 150040, P.R.China, ³Waters Corporation, MA 01757, USA, ⁴Department of BioMolecular Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA

Eleutherococcus senticosus (syn. *Acanthopanax senticosus*) species of the Araliaceae family is native to Northeastern Asia and commonly known as Siberian ginseng and ci-wu-jia or eleuthero. Ci-wu-jia tea is made from tender leaf of *E. senticosus* following the procedure of green tea preparation. Triterpenoid saponins, lignans, coumarins, organic acids, and flavonoids have been identified from different parts of *E. senticosus* by LC-UV and LC-MS [1,2]. The Natural Products Application Solution with UNIFI can be a sensitive and accurate-mass analytical platform integrated with fit-for-purpose workflows that merge UHPLC and QToF MS data. It provides an intuitive workflow encompasses data processing, characterization and identification of potential marker compounds, visualization, and reporting.

With the aim of developing a quality assurance and adulterant assessment strategy in foods and dietary supplements, an UHPLC-UV-MS method was developed to analyze total of 24 samples that included 13 authentic *E. senticosus* leaf samples and 11 ci-wu-jia tea products. Data mining was investigated using UNIFI platform with workflows of library development, key markers confirmation, and adulterants identification. The created library contains 243 compounds reported from the genus of *Eleutherococcus* and catechins from green tea. Out of 11 tea products, three tea samples were adulterated with green tea. The present work will explore the strategy of determination of marker compounds and adulterants from *E. senticosus* and ci-wu-jia tea products along with MS/MS characterization of key makers of *E. senticosus*.

Acknowledgements: This research is supported in part by "Science Based Authentication of Botanical Ingredients" funded by the Food and Drug Administration grant number 2U01FD004246-06, the United States Department of Agriculture, Agricultural Research Service, Specific Cooperative Agreement No. 58-6060-6-015.

References: [1] Sun H., Liu J., et al., (2016) *J Sep Sci* 39: 496-502. [2] Zhang X., Zhou X., et al., (2016) *J Chromatogr Sci* 54: 574-582.



Assoc. Prof. Krystyna Skalicka-Woźniak (PhD, DSc) studied pharmacy at the Medical University of Lublin, Poland and received her Master's degree in 2002. She completed her PhD in pharmacognosy with Prof. Kazimierz Głowniak in 2008 at the Medical University, and her dissertation was awarded with a Prime Minister Award for the best Doctoral Dissertation. Since 2010 she has been the Head of The Medicinal Plant Unit in Lublin. After habilitation in 2015, she was appointed as an Assoc. Prof. at the Medical University of Lublin. She has received several awards for her research, including one for Outstanding Young Scientists for a period of three years or The Ministry of Health for outstanding achievements. She has published more than 80 scientific papers, mostly in international journals. Her research interests include the discovery of bioactive compounds in plants, and the optimization of modern extraction and chromatographic techniques. The focus of her work for the past few years was the application of counter-current chromatography (CCC) for the isolation of natural products, particularly coumarins and terpenoids, and their biological evaluation for antimicrobial, antiviral, anticancer, spasmolytic, apoptotic, and antioxidant activities, as well as for Central Nervous System activity (epilepsy, anxiety and memory-related behavior). Her experience with CCC was acquired through a training period in a world-leading research center, the Brunel Institute of Bioengineering at Brunel University in London, and she is currently the leading practitioner of the applications of this technique in Poland. She is currently serving as a Subject Editor of the journal *Phytochemistry Letters* (Elsevier).



What power can liquids provide in separation – the case of counter-current chromatography?

Krystyna Skalicka-Woźniak, Department of Pharmacognosy with Medicinal Plant Unit, Medical University of Lublin, 1 Chodzki Str, 20-093 Lublin, Poland

In recent years, counter-current chromatography (CCC) has been broadly applied for the separation and purification of chemical compounds in complex matrices due to its unique advantages. CCC is a liquid–liquid partition chromatography process where both the mobile and stationary phases are liquids. The method is rapid and easy to scale up from analytical to a preparative, industrial scale. It also utilizes no solid support, and can be used for compounds with vastly different polarities, thus it is considered as one of the most efficient and economical separation techniques worldwide.

Due to these advantages, CCC has been broadly applied for the separation and purification of major and minor constituents in complex matrices, some of which can be used as quality standards essential for monitoring quality control of herbal drugs. Additionally, reproducibility of the process ensures sufficient quantity of even minor compounds required for full chemical structure elucidation and bioactivity studies.

In this presentation, several applications of this technique applied to the isolation of natural products will be highlighted including targeted purification, bioactivity-guided fractionation, followed by in vitro biological screening. The recent application of CCC as a novel method for the rapid and efficient purification of mono- and sesquiterpenes from essential oils.

Acknowledgments:

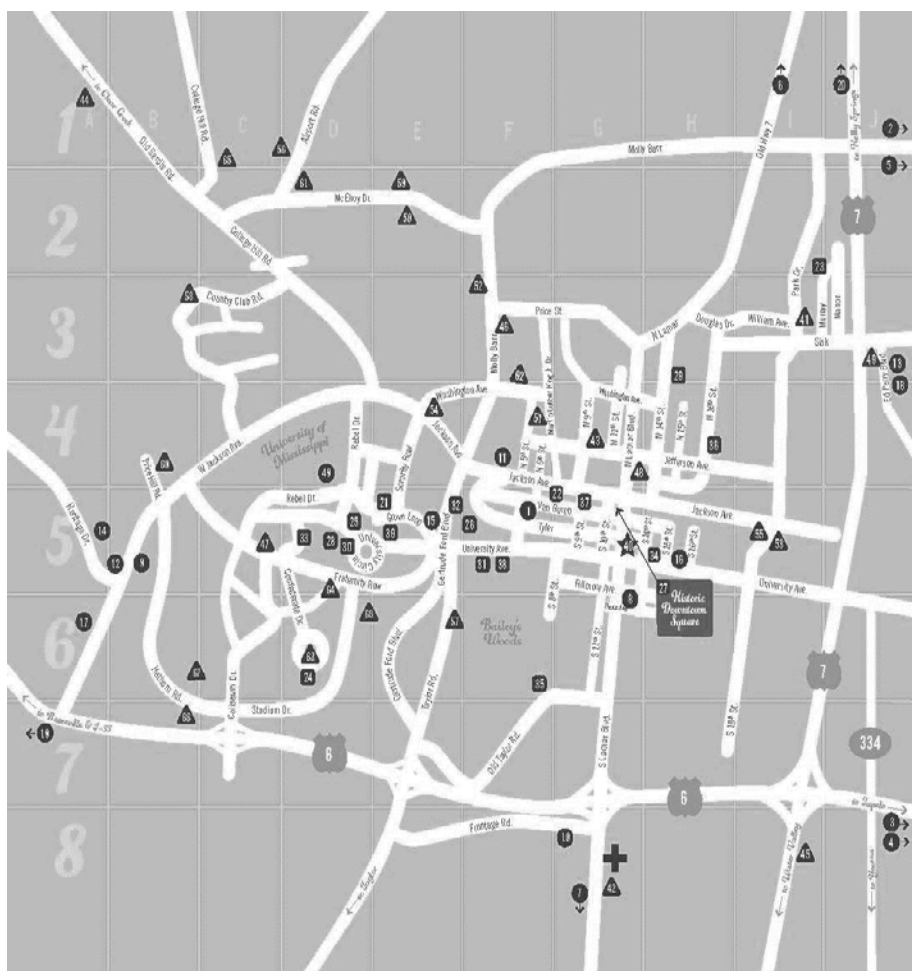
The work was financed from grant No 4/POLTUR-1/2016.



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- 21 BARNARD OBSERVATORY /
Center for the Study of
Southern Culture (E5)
- 22 Burns-Betty Church (G5)
- 23 Cedar Oaks (J2)
- 24 Confederate Monument &
Cemetery (D6)
- 25 Fulton Chapel (D5)
- 26 Gertrude C. Ford Performing
Arts Center (F5)
- 27 Historic Downtown Square (G5)
- 28 J.D. Williams Library (D4)
- 29 L.Q.C. Lamar House (H3)
- 30 Lyman/Civil Rights
Monument (D5)
- 31 Memory House (F5)
- 32 Oxford Depot (E5)
- 33 Pains-Yates Chapel (D5)
- 34 The Powerhouse Community
Arts Center (H5)
- 35 Rowan Oak (F6)
- 36 Saint Peter's Episcopal (H4)
- 37 Saint Peter's Episcopal
Church (G5)
- 38 University Museum /
Walton-Young House (F5)
- 39 Ventress Hall (F5)
- 40 Visitors
Center (G5)

AREA CAMPGROUNDS

- 19 JOHN KYLE STATE PARK
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Hunting, fishing, hiking and
boating in nearby Sandi-
s-Reservoir and Holly Springs
National Forest (A7)
- 20 WALL DOONEY STATE PARK
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Cabins, camping, fishing
and picnicking (J1)

Attractions

- 21 Barnard Observatory /
Center for the Study of
Southern Culture (E5)
- 22 Burns-Betty Church (G5)
- 23 Cedar Oaks (J2)
- 24 Confederate Monument &
Cemetery (D6)
- 25 Fulton Chapel (D5)
- 26 Gertrude C. Ford Performing
Arts Center (F5)
- 27 Historic Downtown Square (G5)
- 28 J.D. Williams Library (D4)
- 29 L.Q.C. Lamar House (H3)
- 30 Lyman/Civil Rights
Monument (D5)
- 31 Memory House (F5)
- 32 Oxford Depot (E5)
- 33 Pains-Yates Chapel (D5)
- 34 The Powerhouse Community
Arts Center (H5)
- 35 Rowan Oak (F6)
- 36 Saint Peter's Episcopal (H4)
- 37 Saint Peter's Episcopal
Church (G5)
- 38 University Museum /
Walton-Young House (F5)
- 39 Ventress Hall (F5)
- 40 Visitors
Center (G5)
- 41 Arent Park (J3)
- 42 Baptist Memorial Hospital-North
Mississippi (G8)
- 43 Barksdale Reading Institute at
Isom Place (G4)
- 44 FNC Park (A1)
- 45 Grand Oaks Golf Course (B8)
- 46 Oxford Activity Center
John L. Leake Tennis Courts (F3)
- 47 John M. Palmer/Mitchell
Stadium Tennis Center (G4)
- 48 Lafayette County Chancery
Building (G4)
- 49 Oxford Conference Center (J3)
- 50 Oxford Electric Department (E2)
- 51 Oxford Middle School (F4)
- 52 Oxford Police Department (F3)
- 53 Oxford Skate Park (I5)
- 54 Oxford-Lafayette County
Chamber of Commerce /
Economic Development
Foundation / Retiree Attraction
Program (E4)
- 55 Oxford-Lafayette County
Public Library (I5)
- 56 Oxford-University Airport (C1)
- 57 Oxford-University Stadium &
Swagoe Field (E8)
- 58 Patricia C. Lamar Park (B3)
- 59 Post Office (E2)
- 60 Price Hill Park (B4)
- 61 Soccer / Softball Complex (D2)
- 62 Stone Park & Recreation (F4)
- 63 Tad Smith Coliseum (D6)
- 64 Turner Center (D5)
- 65 University Golf Course (C1)
- 66 University Soccer Fields (B7)
- 67 University Softball Fields (B6)
- 68 Vaughn-Hammingway
Stadium (D6)