19th Annual OXFORD ICSB April 8th - 11th 2019

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

Oxfor

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

CELEBRATING 25 YEARS OF DSHEA



The upcoming year's meeting will celebrate the 25th Anniversary of DSHEA (The Dietary Supplement Health and Education Act of 1994) by reviewing the history, confronting the issues, and discussing future aspects.

CONFERENCE AGENDA

- Daily Schedule
- Speaker Abstracts
- Speaker Bios

TITLE SPONSORSHIP PROVIDED BY:

YILING PHARMA DOTERRA



April 8, 2019

Dear Friends,

On behalf of the Organizing Committee, I would like to invite you to present at the 19th Annual International Conference on the Science of Botanicals (ICSB) to be held April 8th – 11th, 2019 in Oxford, Mississippi. The ICSB is organized by the National Center for Natural Products Research (NCNPR), University of Mississippi, and a FDA Center of Excellence.

The 19th ICSB will take on a special meaning in that it coincides with the 25th anniversary of the Dietary Supplements and Health and Education Act (DSHEA), the primary regulatory framework for dietary supplements and herbal products in the United States of America. 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. The conference with explore approaches for post market surveillance, risk and safety assessment, quality control and adverse event reporting for botanical dietary supplements and natural products, including regulatory perspectives from governments; manufacturers and trade associations.

You can find additional information regarding this conference at www.oxfordICSB.org. 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) supports this conference. Our co-sponsors: 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 (KSP) and the Japanese Society of Pharmacognosy (JSP).

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,

Oklas Chan

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





Organizing Committee

Sibyl Swift, Ph.D. Special Assistant, FDA, Office of Dietary Supplement Programs.

Ikhlas Khan, Ph.D. Director of FDA Program, The University of Mississippi.

Larry A. Walker, Ph.D. Emeritus 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, Reeves Group Consultations

K. Hüsnü C. Baser, Ph.D. Professor, Head of the Department of Pharmacognosy, Anadolu University, Eskisehir, Turkey.

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

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, Strategic Sourcing, Inc.

Craig Hopp, Ph.D. Program Officer, NCCAM, NIH

Jinwoong Kim, Ph.D. Seoul National University, South Korea.

A. Douglas Kinghorn, Ph.D., D.Sc. Jack L. Beal Professor and Chair, Ohio State University, College of Pharmacy.

Brigitte Kopp, PhD Professor of Pharmacognosy, Department of Pharmacognosy, University of Vienna, Austria. Amar Chittiboyina, Ph.D. Senior Research Scientist NCNPR, University of Mississippi

Robin J. Marles, Ph.D. Director, Bureau of Clinical Trials and Health Science NHPD, Health Products and Food Branch, Health Canada

James McChesney, Ph.D. Ironstone, Inc.

Dan Fabricant, Ph.D. Natural Products Association

Amy Roe, Ph.D., DABT The Procter & Gamble Company

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.

Daniel S. Marsman, DVM PhD Head, Product Safety, Global Product Stewardship P&G Health Care, Worldwide

Steven Musser, Ph.D. Director, Office of Regulatory Science, CFSAN, FDA.



DAY 1 (MONDAY, APRIL 8)

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

9:00-10:15 Opening Session - OCC Auditorium

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

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

Welcome and Introductory Remarks from Organizers

Ikhlas Khan, Director, National Center for Natural Products Research, University of Mississippi

SESSION 1: "25 Years of DSHEA: Historical Perspective"

Loren Israelsen, President, United Natural Products Alliance and Mark Blumenthal, Founder & Executive Director, American Botanical Council

10:15-10:30	Break
SESSION 2: "25 Moderator and	Years of Dietary Supplements Health and Education" - OCC Auditorium Session Chair: Robin Marles, Senior Scientific Advisor, Health Canada
10:30-10:45	Joe Betz, Acting Director, Office of Dietary Supplements, National Institute of Health
	"The NIH Office of Dietary Supplements: A Twenty-Five Year Retrospective"
10:45-11:00	Craig Hopp, Deputy Director, Division of Extramural Research, National Center for Complementary and
	Integrative Health, National Institutes of Health
	"NCCIH Turns 20: What Have We Learned? "
11:00-11:25	Tieraona LowDog, Integrative Medicine Concepts, LLC
	"25 Years of DSHEA: A Physician's Perspective "
11:25-11:50	Stephen Daniells, Editor-in-Chief, William Reed Business Media
	"An Editor's View of the Evolving Global Natural Products Marketplace"

11:50-12:00 Conference Photograph-Meet at OCC side patio across from Cedar Room Dining Hall

12:00-1:00

Lunch (OCC Cedar)

PANEL 1: "25 Years of DSHEA: Impact On Supply, Conservation and Sustainability, GACPS and Regulatory Compliance of Botanical Ingredients" - OCC Auditorium

Moderator and Session Chair: *Josef Brinckmann, Research Fellow, Medicinal Plants & Botanical Supply Chain, Traditional Medicinals, Inc. & Trish Flaster, Executive Director, Botanical Liaisons, LLC*

1:00-2:30

- Edward Fletcher, Director of Quality & Sustainability, Herbal Ingenuity
- **Rupa Das**, VP of Global Quality & Compliance, BI Nutraceuticals
- Josef Brinckmann, Research Fellow, Medicinal Plants & Botanical Supply Chain, Traditional Medicinals, Inc

SESSION 3: "International Perspectives On Botanical Research Part 1" - OCC Magnolia

Moderator and	i Session Chair: Shabana Khan, Principal Scientist, University of Mississippi
1:00-1:30	Ameenah GuribFakim, Professor, Founder, Ameenah Gurib-Fakim Foundation, Mauritius "African Traditional Knowledge as Source of Leads for Innovative Ingredients"
1:30-2:00	Carla Holandino Quaresma, Professor, Pharmacy College, Federal University of Rio de Janeiro "Therapeutic Potential of Natural Products: Research and Development"
2:00-2:30	Thomas Efferth, Professor, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University "Network Pharmacology and Precision Medicine for Cancer Therapy with Natural Products"
2:30-3:00	Break (30min)

PANEL 2: "Sports Nutrition: Its Genesis, Growth and Impact Under DSHEA" - OCC Auditorium Moderator and Session Chair: John Travis, Senior Research Scientist, NSF International

3:00-4:30

- **Patty Deuster,** Professor and Director, Consortium for Health and Military Performance, Department of Military and Emergency Medicine, Uniformed Services University
- Amy Eichner, Special Advisor on Drugs and Supplements, U.S. Anti-Doping Agency
- Joel Totoro, Director of Sports Science, Thorne Research
- John Travis, Senior Research Scientist, NSF International





DAY 1 (MONDAY, APRIL 8) Cont.

SESSION 4: "Natural Products Discovery and Development"- OCC Magnolia Moderator and Session Chair: Xing-Cong Li, Principal Scientist, University of Mississippi		
3:00-3:15	Susan Murch, Professor, University of British Columbia	
	"Breadfruit (Artocarpus altilis): An Example of the Potential of a Traditional Underutilized Crop for Modern	
	Foods, Cosmetics and Natural Health Products"	
3:15-3:30	Nirmal Pugh, Principal Scientist, University of Mississippi	
	"The Mushroom Microbiome: Significance of Microbial-Derived Components to The Macrophage Stimulatory	
	Activity of Edible Mushrooms"	
3:30-3:45	Jeffrey Langland, Research Department Chair, Southwest College of Naturopathic Medicine	
	"Controlling The Threat of Herpes and Ebola Viruses: The Mechanism of Action and Active Constituents of	
	Melissa officinalis"	
3:45-4:00	Jia-Wen Shou, Researcher, the Chinese University of Hong Kong	
	"Berberine Protects C17.2 Neural Stem Cells from Oxidative Damage And	
	Induces Their Neuronal Differentiation"	
4:00-4:15	Mohamed Albadry, Researcher, University of Mississippi	
	"Isolation, Structure Elucidation and Synthesis of Natural Products; Efficient Tools for Dealing with A Needle in	
	A Haystack"	

SESSION 5: "DSHEA at 25: Is The FDA Enforcing the Law or Is DSHEA Unenforceable?" - OCC Auditorium

4:30-5:15 Pieter Cohen, Associate Professor of Medicine, Harvard Medical School

6:00-8:00 pm Reception/Mixer Lyric 1006 Van Buren Ave, Oxford, MS 38655-Award Presentation: Outstanding Contribution in Natural Products Research

DAY 2 (TUESDAY, APRIL 9)

SESSION 6: "FDA and CFSAN Update On the Science and Regulation" - OCC Auditorium Moderator and Session Chair: Sibyl Swift, Special Assistant, Office of Dietary Supplement Programs/CFSAN, Food and Drug Administration

8:30-10:00

• Steven Tave, Director, Office of Dietary Supplement Programs, FDA, Center for Food and Safety & Applied Nutrition

"Regulating for The Next 25 Years"

- Gregory Noonan, Division Director, Center for Food Safety & Applied Nutrition "New Approaches to The Analysis and Regulation of Dietary Supplements"
- Jason Humbert, CDR, USPHS, Health Fraud, Office of Regulatory Affairs, FDA "Dietary Supplements That Contain Hidden, Harmful Ingredients Continue to Be a Public Health Concern"

10:00-10:30

Break

PANEL 3: "Perspectives On Twenty-Five Years of DSHEA and The Safety of Botanical Dietary Supplements" - OCC Auditorium Moderator and Session Chair: Rick Kingston, President, SafetyCall/UoM 10:30-12:00

10:30-12:00

- Victor Navarro, Medical Chair, Department of Digestive Diseases and Transplantation, Einstein Healthcare Network
- Dan Fabricant, President, Natural Products Association
- Tieraona Low Dog, Integrative Medicine Concepts, LLC
- Frank Jaksch, Co-founder, ChromaDex



DAY 2 (TUESDAY, APRIL 9) Continued

SESSION 7:" TCM Research and Development" - OCC Magnolia

Moderators and Session Chairs: Jinhui Dou, Vice Dean, Yiling Pharmaceuticals, Inc.

 10:30-11:00 De-an Guo, Professor, Shanghai Institute of Materia Media, Chinese Academy of Sciences "TCM Research: Challenges, Current Status and Future Perspectives"
 11:00-11:30 Hua Yang, Professor, China Pharmaceutical University "Synergistic Combination Discovery from Herbal Medicines for Myocardial Ischemia Reperfusion Injury"
 11:30-12:00 Wansheng Chen, Director of Department of Pharmacy, Changzheng Affiliated Hospital of Second Military Medical University

"Biosynthesis and Metabolic Regulation of Lignans in Isatis indigotica"

12:00-1:00

Lunch

PANEL 4: "Dietary Supplement Safety: A 25-Year Retrospective Assessment" - OCC Auditorium Moderator and Session Chair: Bill Gurley, Professor, University of Arkansas for Medical Sciences 1:00-2:30

- Shabana Khan, Principal Scientist, University of Mississippi
- Amy Roe, Product Safety & Regulatory Affairs, The Procter & Gamble Company
- Sibyl Swift, Special Assistant, Office of Dietary Supplement Programs/CFSAN, Food and Drug Administration
- Duffy MacKay, Senior Vice President, Scientific & Regulatory Affairs, CV Sciences CBD brand

SESSION 8: "Analytical Methodology" - OCC Magnolia

Moderators and Session Chairs: Bharathi Avula, Principal Scientist, University of Mississippi

1:00-1:20	Naren Meruva, Water Corporation
	"Real-Time Authentication of Botanicals by Direct Mass Spectrometry Using DART-MS and LiveID Analysis"
1:20-1:40	Maged Sharaf, Director of Scientific Business Development, Camag Scientific
	"Is It Ginkgo?"
1:40-2:00	Jimmy Yuk, Water Corporation
	"Accurate Compound Identification of Complex Traditional Herbal Medicine Using a Novel Mass Spectrometry Acquisition Method"
2:00-2:20	Cuiying Ma, Senior Scientific Liaison, U.S. Pharmacopeia
	"Quality Control of Botanicals with USP Botanical MonographsHPLC and HPTLC Identify Plant Products and Distinguish Closely Related Species"

2:30-3:00

Break (30min)

PANEL 5: "The Botanical Safety Consortium: A Cross-Sector Collaboration to Advance Botanical Safety Through Application of State-Of-The-Art Toxicological Science" - OCC Auditorium

Moderators and Session Chairs: Dan Marsman, Head, Product Safety and Regulatory Affairs, P&G Health Care; Stefan Gafner, Chief Science Officer, American Botanical Council; and Douglas MacKay, CV Sciences CBD brand

3:00-3:15	Cynthia Rider, Toxicologist, National Toxicology Program
	"What Is the Botanical Safety Consortium (BSC)?"
3:15-3:30	Amy Roe, Product Safety & Regulatory Affairs, The Procter & Gamble Company

- "Exploring Hepatotoxicity Using the Latest Toxicology Tools" 3:30-3:45 Joseph Dever, Manager, Regulatory Affairs, Product Safety
 - "Evaluating Systemic Toxicity Risk Using Alternative Approaches"
- 3:45-4:00 Sibyl Swift, Special Assistant, Office of Dietary Supplement Programs/CFSAN, Food and Drug Administration "BSC: Next Steps"
- 4:00–4:15 Dan Marsman, Head, Product Safety and Regulatory Affairs, P&G Health Care; Stefan Gafner, Chief Science Officer, American Botanical Council; and Douglas MacKay, CV Sciences CBD brand.
- 4:15-4:30 **Panel Discussion** with the BSC Steering Committee



DAY 2 (TUESDAY, APRIL 9) Continued

SESSION 9: "Natural Product Discovery and Development"- OCC Magnolia

Moderator and Session Chair: Samir Ross, Research Professor, University of Mississippi		
3:00-3:15	Rahul Pawar, Research Chemist, Office of Regulatory Science, FDA, Center for Food Safety & Applied Nutrition	
	"Analysis of Bitter Orange Containing Dietary Supplements by LC-MS/MS."	
3:15-3:30	Xing-Cong Li, Principal Scientist, University of Mississippi	
	"Exploring Antimicrobial Natural Products as Food Preservatives"	
3:30-3:45	Wilmer Perera, Ironstone Separations, Inc.	
	"Stevia rebaudiana and Its Tetracyclic Diterpene Glycosides as A Source of High-Potency Sweeteners."	
3:45-4:00	Lauren Erland, Department of Plant Agriculture, University of Guelph	
	"Melatonin in Diets and Dietary Supplements"	
4:00-4:15	Aihua Liu, Director of Research & Development, Dyad labs	
	"Fast, Sensitive and Comprehensive Assay to Quantify 112 Pesticide Residues in Botanical and Non-Botanical	
	Dietary Supplements Using LC/MS/MS and GC/MS/MS Coupled with QuECHERS Extraction Method"	
4:15-4:30	Sayeed Ahmad, Researcher, Jamia Hamdard University	
	"Metabolomic Analysis Of Unani And Ayurvedic Medicines For Scientific Validation Of Traditional Claims"	
5:30-8:00	Poster Session Chair: Amar Chittiboyina, University of Mississippi (OCC Oak)	
7:00 - 8:00	Dinner (OCC Cedar)	
	DAY 3 (WEDNESDAY, APRIL 10)	

SESSION 10: "Cannabis-derived Therapeutics: New Developments" - OCC Auditorium

Moderator and	I Session Chair: Larry Walker, Director Emeritus, University of Mississippi
8:15-8:40	Cassandra Taylor, Chemist, Science Staff, Immediate Office, Office of Pharmaceutical Quality/CDER, FDA
	"FDA Role in Regulation of Cannabis Products"
8:40-9:05	Tom Marcotte, Professor of Psychiatry, Co-Director, Center for Medicinal Cannabis Research, University of
	California, San Diego
	"The Changing Landscape in Medicinal Cannabis Research"
9:05-9:30	John Ingram, Children's Neurology, University of Mississippi Medical Center
	"Cannabis Extract for Drug Resistant Pediatric Epilepsy—What Have We Learned So Far"
9:30-9:55	Alice Mead, Vice President, U.S. Public Policy & Public Affairs, Greenwich Biosciences
	"How Cannabis-Derived Medications Go Through The FDA Approval Process"

10:00-10:30 Break

SESSION 11a: "Global Regulations of Herbal Medicines" OCC Auditorium Moderator and Session Chair: Michael Smith, Consultant, MJS Consulting 10:30-12:00

- Adam Gibson, Vice President, Public Affairs, Consumer Health Products Canada "The Challenges, Past and Future, Facing Canada's Approach to Natural Health Product Regulations"
- Armando Cáceres, Professor of University of San Carlos of Guatemala/Farmaya Natural Products Laboratories "Regulation of Natural Health Products in Latin America – Current Situation and Future Developments"
- Jon Wardle, Senior Lecturer in Public Health, University of Technology Sydney "Australian Regulatory Reforms for Traditional and Complementary Medicines: Challenges, Opportunities, And Lessons Learned"



DAY 3 (WEDNESDAY, APRIL 10) Continued

SESSION 11b: "Cannabis: Safety, Quality and Regulations" - OCC Magnolia

Moderator and	Session Chair: Mahmoud ElSohly, Research Professor, University of Mississippi
10:30-10:50	Igor Koturbash, Associate Professor and Vice-Chair, University of Arkansas for Medical Sciences
10:50-11:10	James Neal-Kababick, Director, Flora Research Laboratories, LLC
	"Novel Screening Method (SYNCAN) For 370 Synthetic Cannabinoids by Accurate Mass Q-TOF Mass Spectrometry"
11:10-11:30	Phil Wylie, Sr. Research Scientist, Agilent Technologies "Ensuring The Safety of Cannabis by Screening for Approved and Unapproved Pesticide Residues"
11:30-11:50	Tomas Sadilek, Director of Governmental Affairs, International Cannabis & Cannabinoids Institute "Low THC Products Regulation at European Level - Current Status and Its Future"

1.2.00	.1.00
12.00	T.00

Lunch (OCC Cedar)

PANEL 6: *"US Hemp over the Hump? Potential Impact of the Recent Farm Bill Legislation"-* OCC Auditorium Moderators and Session Chairs: Larry Walker, Director Emeritus, University of Mississippi & Trish Flaster, Executive Director, Botanical Liaisons, LLC

1:00-2:30

- Daniel Shortt, Attorney, Harris Bricken
- Roger Hayes, VP of Business Development, Green Remedy, Inc
- Courtney Moran, Attorney, Earth Law, LLC
- James N. Kababick, Director, Flora Research Laboratories

3:00-5:00	ICSB Yard Games and Crawfish Boil-OCC grounds

5:00-9:00 Dinner and Bowling and Arcade fun- Premier Lanes-204 Commonwealth Boulevard, Oxford, MS 38655

DAY 4, (THURSDAY, APRIL 11)

SESSION 12: "International Perspectives on Botanical Research part 2" - OCC Auditorium Moderator and Session Chair: Ryan Yates, Principal Scientist, University of Mississippi
8:30-9:00 Zhenhua Jia, Dean, Yiling Pharmaceutical "Further Development of Chinese Herbal Medicines Through Collaborations-The Yiling Pharmaceutical's Approach"
9:00-9:30 Ibrahim Jantan, Professor, School of Pharmacy, Faculty of Health and Medical Sciences, Taylor's University "Modulatory Effects of Medicinal Herbs On the Immune System and Their Potential as Sources of Immunomodulatory Dietary Supplements and Pharmaceuticals"
9:30-10:00 Mary Hardy, Wellness Works "The Effect of DSHEA On Clinical Research in Dietary Supplements"

PANEL 7: "Pharmacopeial Standards as Tools to Assure Botanical Quality" - OCC Auditorium

Moderator and Session Chair: Nandakumara Sarma, Director, United States Pharmacopeia

10:30-12:00

- Nandakumara Sarma, Director, Dietary Supplements and Herbal Medicines, United States Pharmacopeia
- Gabriel Giancaspro, Vice President-Science, Dietary Supplements and Herbal Medicines
- Ulrich Rose, Head of Division A, Deputy Head of European Pharmacopoeia Department (EPD), EDQM, Council of Europe
- Roy Upton, President, American Herbal Pharmacopoeia
- **G N Singh**, Secretary cum Scientific Director, Indian Pharmacopeia Commission
- Vivekanandan Kalaiselvan, Principal Scientific Officer, Indian Pharmacopoeia Commission, Government of India (Ministry of Health & Family Welfare)
- De-an Guo, Professor, Shanghai Institute of Materia Media, Chinese Academy of Sciences



DAY 4 (THURSDAY, APRIL 11) Continued

SESSION 13: "Botanical Characterization and Quality Assessment" - OCC Magnolia Moderator and Session Chair: Jing Li, Staff Fellow, FDA/CDER 10:30-10:50 Sara Handy, Research Biologist, Center for Food Safety & Applied Nutrition, Office of Regulatory Science, FDA "Genomic Approaches Used by FDA-CFSAN to Understand Botanical Challenges and The Expansion of GenometrackrCP" 10:50-11:10 Nicole Stevens, Research and Development Scientist, doTerra "Frontiers of Essential Oil Research" 11:10-11:30 Cody Beaumont, Sr. Director, QC & Analytical Services, doTerra "Essential Oil Chemical Biosynthesis" 11:30-11:50 Abidah Parveen, Researcher, University of Mississippi "Development of A Chemical Fingerprint as A Tool to Distinguish Closely Related Tinospora Species And Quantitation of Major Compounds" 12:10-1:10 Lunch

PANEL 8: "The Evolution of Analytical Approaches for Botanical Characterization" -OCC Auditorium Moderators and Session Chairs: Paula Brown, Director of Applied Research, BCIT & Holly Johnson, Chief Science Officer, American Herbal Products Association

1:00-2:30

- James Harnly, Research Leader, Food Composition and Methods Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, USDA
- Peter Harrington, Professor, Ohio University
- Wendy Applequist, Associate Curator, Missouri Botanical Garden
- **Tyler Daniels**, Scientist, Biotechnology, Thorne
- James Neal-Kababick, Director, Flora Research Laboratories, LLC

2:30-3:00

Break (30min)

PANEL 9: "Basic and Clinical Research On Botanical Natural Products Health Effects"- OCC Auditorium Moderator and Session Chair: Adam Kuszak, Director, National Institutes of Health

3:00-4:30

- Craig Hopp, Deputy Director, Division of Extramural Research, National Center for Complementary and Integrative Health, National Institutes of Health
- Suramya Waidyanatha, Chemistry and ADME Resources Group Leader, Program Operations Branch, Division of National Toxicology Program, National Institute of Environmental Health Sciences
- James Harnly, Research Leader, Food Composition and Methods Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, USDA
- Nicholas Oberlies, Patricia A. Sullivan Distinguished Professor of Chemistry, Department of Chemistry and Biochemistry, University of North Carolina at Greensboro Institutes of Health
- Adam Kuszak, Director, Analytical Methods and Reference Materials Program, Office of Dietary Supplements, National

Afternoon tour of NCNPR facilities or Medicinal Plant Garden

6:30

Closing Ceremony and Banquet (OCC Cedar) Registration is required and is available online and onsite

"25 YEARS OF DSHEA: HISTORICAL PERSPECTIVE"



Mr. Loren Israelsen is President of the United Natural Products Alliance (UNPA), a trade association of dietary supplement companies committed to safety, science and quality.

He has been deeply involved in the commercial and regulatory issues facing the global dietary supplement industry since 1980. On the commercial side, he served as general counsel and president of Nature's Way Products, Inc. He has also served as vice president/general counsel to the American Herbal Products Association, co-founder and counsel to the European American Phytomedicine Coalition (EAPC), founding member of IADSA, industry liaison to FDA's Expert Advisory Committee on Ephedra, industry advisor to the Office of Dietary Supplements (ODS), expert panel member on IFT's Functional Food Report (2005) and most recently sat as an expert panel member to the Department of Defense / RAND study on dietary supplement use among military personnel.

Mr. Israelsen has authored over 150 articles, book chapters and has lectured in over 30 countries on dietary supplement and functional food issues. He is the recipient of the NBJ Lifetime Achievement Award, the NNFA President's Award and the B.Y. Morrison Lecture and Medal. He was honored to be included in Natural Health Magazine's 30th Anniversary Hall of Fame and the New Hope Natural Media Hall of Fame. Mr. Israelsen was awarded the Mark Blumenthal Community Builder award in March of 2015.



"25 YEARS OF DSHEA: HISTORICAL PERSPECTIVE"



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.



"THE NIH OFFICE OF DIETARY SUPPLEMENTS: A TWENTY-FIVE YEAR RETROSPECTIVE"



Joseph M. Betz, PH.D., was appointed Acting Director of the Office of Dietary Supplements (ODS) in June of 2018. Dr. Betz joined ODS in 2002 as the first director of the Analytical Methods and Reference Materials (AMRM) program. As AMRM director, he oversaw several large intra- and extra-governmental initiatives with the goal of providing stakeholders with rugged, validated analytical methods and reference materials for measuring natural products in research, industrial, and regulatory settings.

Prior to joining ODS, Dr. Betz was vice president for scientific and technical affairs at the American Herbal Products Association (AHPA). Before serving at AHPA, Dr. Betz worked for 12 years as a research chemist in the Division of Natural Products at FDA's Center for Food Safety and Applied Nutrition.

Dr. Betz is an adjunct associate professor at the Georgetown University School of Medicine and, the Philadelphia College of Pharmacy and Science (now called the University of the Sciences, USciences). He is a member of the Board of Visitors of the Misher College of Arts and Sciences in the USciences. He is a member of the American Society of Pharmacognosy and a fellow of AOAC International. He also is chair of the Editorial Board for the Journal of AOAC International, a member of the United States Pharmacopeia's Expert Committee on Dietary Supplements and serves on expert scientific advisory committees for the governments of Canada and Hong Kong.

The author or co-author of over 100 peer-reviewed publications, Dr. Betz is the recipient of the American Botanical Council's first Norman R. Farnsworth Award, the American Herbal Product Association's Herbal Insight Award, AOAC International's Technical Division on Reference Materials (TDRM) Reference Material Achievement Award, and the American Society of Pharmacognosy's Varro E. Tyler. He was recognized by the NIH Office of the Director with an Honor Award for his contributions to the establishment and development of the ODS Vitamin D Standardization Program.

A native of Philadelphia Dr. Betz earned a B.Sc. degree in Biology at USciences and a M.Sc. in Marine and Environmental Science at C.W. Post/Long Island University. Dr. Betz earned a Ph.D. in Pharmacognosy at USciences.



"THE NIH OFFICE OF DIETARY SUPPLEMENTS: A TWENTY-FIVE YEAR RETROSPECTIVE"

<u>Betz JM</u>

NIH Office of Dietary Supplements, Bethesda, MD 20892, USA

The Dietary Supplement Health and Education Act (DSHEA) of 1994 amended the U.S. Federal Food, Drug, and Cosmetic Act. The DSHEA also amended the U.S. Public Health Service Act in order to establish the Office of Dietary Supplements (ODS) and place it within the National Institutes of Health (NIH). Passage of the DSHEA assured consumer access to supplements, defined dietary supplements as a special category of foods, laid out a regulatory framework enforced by the Food and Drug Administration (FDA), and provided a basis for creating and disseminating research to strengthen knowledge and understanding of dietary supplements.

As directed by Congress, ODS's mission to foster an enhanced quality of life and health for the U.S. population is achieved by providing resources for evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public. The ODS budget has grown over the years from a bit less that \$1 million in 1995 to about \$25 million in 2018. This amount is relatively modest by NIH standards, but ODS effectively leverages its resources with other parts of the NIH and with other collaborators to create a disproportionately large impact on our understanding of dietary supplements.

Over the past 25 years, ODS and its partners have created the NIH Centers for Advancing Research on Botanical and other Natural products (CARBON) program[1], the ODS Analytical Methods and Reference Materials Program[2], the ODS Evidence-based Review Program[3], the ODS Population Studies Program[4], and a brand new Biochemical Mediators of Resilience Program.

The Office has also created free public databases of dietary supplement labels[5] and ingredients[6], and a series of dietary supplement fact sheets[7]. Other research initiatives include creation and oversight of an international program for standardization of vitamin D metabolite measurements, support of measurement of total nutrient intake through the National Health and Nutrition Examination Survey and similar activities, a program for evaluation of the sufficiency of iodine intake, a program for studying nutrient biomarkers that includes collection and evaluation of information on intake, status, and associated health effects. Finally, the Office of Dietary Supplements co-funds dietary supplement grants with many other NIH Institutes and Centers. Last year's co-fund commitment was approximately \$14 million, about half of the total ODS budget.

Going forward, ODS will continue to pursue its Congressionally mandated mission by continuing successful programs and by creating new programs as emerging needs are identified.

[1] http://ods.od.nih.gov/Research/Dietary_Supplement_Research_Centers.aspx (accessed 1/07/19)

[2] http://ods.od.nih.gov/Research/AMRMProgramDescription.aspx (accessed 1/07/19)

[3] http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx (accessed 1/07/19)

[4] https://ods.od.nih.gov/Research/populationstudies.aspx (accessed 1/07/19)

[5] http://www.dsld.nlm.nih.gov/dsld/ (accessed 1/07/19)

[6] https://dietarysupplementdatabase.usda.nih.gov (accessed 1/07/19)

[7] http://ods.od.nih.gov/factsheets/list-all/ (accessed 1/07/19)

ODS Staff: Richard Bailen, LaVerne Brown, Cindy Davis, Abby Ershow, Claudia Faigen, Jaime Gahche, Adam Kuszak, Nancy Potischman, Barbara Sorkin, Anne Thurn. A special acknowledgement to my friend and mentor Paul Coates.



Craig Hopp, Deputy Director, Division of Extramural Research, National Center for Complementary and Integrative Health, National Institutes of Health

Dr. Hopp is Deputy Director of the Division of Extramural Research at NCCIH.

In addition to serving as Deputy Director, Dr. Hopp continues to oversee the administration of the product integrity policy. This involves evaluation of proposed study materials to ensure they are safe and properly characterized. He also focuses on large scale projects such as research on drug-natural product interactions, the Innovation and Technology research center, and the CARBON program. Dr. Hopp uses his expertise and experience in the field of natural products to help shape research priorities at NCCIH.

Dr. Hopp received his B.S. in chemistry from James Madison University in 1993 and his Ph.D. in pharmacognosy from Purdue University in 1997. As a postdoctoral researcher at Shaman Pharmaceuticals, he used his knowledge of indigenous cultures from around the world regarding medicinal plants to aid in the discovery of new pharmaceutical agents. While with Shaman Pharmaceuticals, Dr. Hopp discovered and obtained multiple patents on antihyperglycemic compounds. Subsequently, he worked at an herbal company, Phyto-Technologies, for 2 years where he was responsible for research and development on multiple herb formulas used in traditional Chinese medicine.

Prior to joining NCCIH, Dr. Hopp worked for AMRI, located outside of Seattle. There he was a senior research scientist responsible for the isolation and identification of compounds from a variety of natural sources with activity in a wide range of therapeutic targets.



"NCCIH TURNS 20: WHAT HAVE WE LEARNED?"

NCCIH was established in 1999 with a mandate to fund research on those practices considered outside the mainstream of western medicine. In the ensuing 20 years, NCCIH has supported a wide variety of research using many different complementary and integrative health approaches. Along the way we have learned a great deal about how best to support this research and how to get the most out of our investments. As a result, NCCIH has become much more thoughtful about how to fund clinical research as well as what sorts of biological outcomes are most relevant to our mission. This presentation will provide an overview focused on NCCIH investments in natural products research. This will include a retrospective of the clinical trials that were funded in our first 10 years, how those trials were perceived by various stakeholders, and how we have applied the lessons learned in our first two decades to our priorities for the future.





Tieraona LowDog, MD is a physician, author, and thought leader in integrative medicine. Her background in herbal medicine, midwifery, massage, and martial arts, made her a natural choice to lead the Fellowship program at the University of Arizona Center for Integrative Medicine, where she oversaw the training of more than 600 physicians and nurse practitioners. Tieraona is a leading expert in dietary supplements and botanical medicine, being honored with many awards from academia, public health, and industry throughout her 40-year career. A prolific scholar, she has authored/co-authored 52 peer-reviewed journal articles, written 22 chapters for medical textbooks, five books, including four with National Geographic; and was co-editor of Integrative Women's Health (Oxford University Press). She has chaired expert panels for supplement/botanical safety at the United States Pharmacopeia for the past twenty years. Tieraona been an invited speaker to more than 600 conferences, reaching more than 50,000 people every year with her message of integrative medicine, compassionate care, and deep ecology. She lives and practices outside of Santa Fe, New Mexico.



"25 YEARS OF DSHEA: A PHYSICIAN'S PERSPECTIVE "





Stephen Daniells is the Editor-in-Chief, North and South America of William Reed Business Media, which includes the marketleading publications NutraIngredients-USA and FoodNavigator-USA. Stephen obtained a 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 United Natural Products Alliance (UNPA), the International Probiotics Association (IPA), the Natural Health Products Research Society of Canada (NHPRS), CHFA West, and the Oxford International Conference on the Science of Botanicals (University of Mississippi). Stephen also acts as the editorial consultant and chair of William Reed's Probiota Americas event and the NutraIngredients-USA Sports Nutrition Summit. He lives in Chicago.



"AN EDITOR'S VIEW OF THE EVOLVING GLOBAL NATURAL PRODUCTS MARKETPLACE"

As we mark the 25th anniversary of the Dietary Supplement Health & Education Act (DSHEA) it's good to take a step back and look at some of the trends that are shaping the industry today.

Lines are blurring between the food and nutrition industries, while overlaps are growing between nutrition and cosmetics, and nutrition and pharma. Meteoric growth is being accompanied by increased scrutiny from the media and regulators into the supply chain, and greater demands from consumers for transparency around the safety and efficacy of these products.

With over a decade of reporting on the food and nutrition industries in multiple regions, Dr Stephen Daniells, Editor-in-Chief of the market leading trade publications NutraIngredients-USA and FoodNavigator-USA, will give his unique perspective on the current state of affairs for the industry and its consumers, and look at areas of innovation and opportunity for industry, researchers, and consumers.



<u>Panel Session Chair/Moderator</u>: Josef Brinckmann, Research Fellow, Medicinal Plants & Botanical Supply Chain, Traditional Medicinals, Inc. & Trish Flaster, Executive Director, Botanical Liaisons, LLC

Prior to October 1994 in the United States, botanical substances were regulated as ingredients of drug products, both over-thecounter (OTC) and prescription (Rx), or as components of food products. Most of the thousands of medicinal plant species in global commerce were not expressly permitted for use in food products. This fact, coupled with the reality that the U.S. Food and Drug Administration (FDA) had established panels to review all old drugs and establish new monographs, led to the eventual reclassification of most botanicals as non-monograph. Thus, by the early 1990's many botanicals had no safe harbor, as they were determined to be unlawful for use as components of both foods and drugs.

The tension caused by these facts is a backdrop, that leads to the U.S. Congress establishing a new regulatory framework, between food and drug, the Dietary Supplement Health and Education Act of 1994 (DSHEA). With the passage of DSHEA, most herbs of commerce, if intended for oral ingestion, became "old dietary ingredients" and could now be marketed with "nutrient content" or "structure function" claim statements. Botanicals intended for topical application were not protected by DSHEA however, and, for the most part, transitioned to use in non-drug cosmetic products, with the exception of a few that remained in the FDA monographs.

Post-DSHEA, the U.S. market for herbal supplements boomed and continues to grow. This paper examines the impacts of DSHEA, 25-years in, on the ever-increasing market demand for botanical ingredients, including legal and regulatory issues (state, federal, and international) affecting production, import, trade and use of botanical supplement ingredients, and the necessary developments of (a) quality management systems such as good agricultural and collection practices (GACPs) linked to good manufacturing practices (GMPs); (b) ingredient quality standards such as pharmacopoeial monographs that can serve as the basis of specifications for testing composition, identity, purity, and strength; (c) conservation status assessments of popular species, as many are obtained through wild-collection; and (d) standards (national and voluntary) for sustainable agriculture and wild collection practices in order to meet increasing market demand without detriment to biodiversity.





Edward J. Fletcher is the Director of Quality & Sustainability at Herbal Ingenuity. He has been in the botanical business and made his livelihood with plants for all his adult life. Therefore, he understands sustainability supports livelihoods in many ways.

The part of his job he enjoys the most is working with farmers, growers and suppliers around the world to educate and assist them in producing the best possible crop they can. He addresses all aspects of the process from propagation, cultivation, harvesting and post-harvest handling techniques for the chosen crop to achieve this. He has conducted research on different crops to improve their yields, marker constituents and overall quality through different techniques including Regulated Irrigation Deficit, Light Percentage Variances and Nutritional Input Impact Studies.

He is an active member of the American Herbal Products Associations (AHPA) and serves on the Board of Trustees as well as the current Chair of the Botanical Raw Materials Committee and a member of the Sustainability Committee. He sits on the Dietary Supplement General Chapters Expert Committee of the United States Pharmacopeia, other advisory panels and enjoys speaking and presenting at numerous Industry gatherings and is always more than happy to discuss any botanical questions you may have.





Rupa Das is the Vice President of Global Quality and Compliance at BI Nutraceuticals, one of the leading ingredient suppliers to the Dietary Supplement and Food & Beverage industries. She is charged with developing, implementing, and managing the quality assurance, quality control, and regulatory systems all four of BI's manufacturing facilities worldwide. During her time at BI, she has implemented the Identilok[®] program, an orthogonal trade-marked ID testing program, as well as a Global Supplier Qualification Program. BI's Global Supplier Qualification Program is one of the industry's most stringent quality programs that verifies and validates all stages of the supply chain from the farm to the shipping docks at BI. With more than 22 years of quality and regulatory compliance management experience in the dietary supplement and personal care product industries-, she has a unique understanding of the most pressing quality and regulatory challenges impacting the industry. She is a certified GMP auditor and SQF practitioner, and is involved at different levels with leading industry organizations. Prior to working in the Dietary Supplement industry she was a Chemistry lecturer at different California State Universities.



Josef A. Brinckmann, Research Fellow, Medicinal Plants & Botanical Supply Chain, Traditional Medicinals, Inc., Sebastopol, California

Working in the medicinal plant sector since 1979, Brinckmann presently serves as 'Research Fellow, Medicinal Plants and Botanical Supply Chain' for Traditional Medicinals, Inc. (Sebastopol, CA), a manufacturer of herbal medicinal products. He received the 2013 Herbal Insight Award of the American Herbal Products Association (AHPA), the 2016 Champion Award of the American Botanical Council (ABC), and in 2016 was conferred an honorary degree of 'Doctor of Humane Letters in Healing and Sustainability *honoris causa*' from the California Institute of Integral Studies (CIIS) and American College of Traditional Chinese Medicine.

Presently serving in his third 5-year term (since 2005) with the United States Pharmacopoeia (USP), Brinckmann is an elected member of the 'Botanical Dietary Supplements and Herbal Medicines Expert Committee,' and of the 'DSHM Nomenclature Joint Sub-Committee.' Since 2006, he has also served the American Herbal Pharmacopoeia (AHP) as an advisor on commercial sources & handling, as contributing writer of international regulatory status sections of the AHP monographs, and editorial board member of the AHP Herbal QRS (Quality, Research, Safety) Bulletin.

With the American Botanical Council (ABC), Brinckmann has served as an Advisory Board member since 2005, and in 2019 became an Advisory Group Member of the newly established Sustainable Herbs Program. He is a member of the Medicinal Plant Specialist Group, International Union for Conservation of Nature (IUCN) Species Survival Commission, and serves as Vice Chair of the Board of Trustees of the FairWild Foundation, a Switzerland-based non-profit standards setting organization for the sustainable wild collection of medicinal and aromatic plants. Since 1996, Brinckmann has been a member of the American Herbal Products Association (AHPA) Botanical Raw Materials and Standards Committees, and has joined the newly established Sustainability Subcommittee.

Brinckmann serves as an editorial board member of the Journal of Alternative and Complementary Medicine and of the World Journal of Traditional Chinese Medicine, and as contributing editor of HerbalGram Journal of the American Botanical Council (ABC).





Ameenah Gurib-Fakim earnt a BSc Chemistry (University of Surrey, UK) and PhD (University of Exeter, UK). She spent her entire academic career studying the medicinal and aromatic plants of Mauritius and also of the Indian Ocean creating the first ever database and has published extensively in this area. Author of 28 books and research papers, she translated her academic research work into an enterprise CIDP Research and Innovation, specialising in the production of innovative ingredients for the food, cosmetic and pharma sectors as well as validating traditional knowledge for novel innovative products. She has participated in several international conferences and lectured across the world.



"AFRICAN TRADITIONAL KNOWLEDGE AS A SOURCE OF LEADS FOR INNOVATIVE INGREDIENTS"

The African continent has an estimated over 216 M ha of closed forest area and houses 40-45.000 higher plant species with huge untapped potential. Africa contributes 25% of the global pool of plant genetic resources currently being traded. While over 5.000 plants are used medicinally, few have been described and studied. This gross under-utilisation is further challenged with massive loss of biodiversity averaging 1% as opposed to a global 0.6%.

In spite of these challenges, Africa traditional knowledge has helped to contribute to the world's leading commercial medicinal plants, albeit on the low side (83 out of the 1100). Among them are the following: Madagascan Periwinkle (Catharanthus roseus), Devil's Claw (Harpagophytum procrumbens), Rauwolfia (Rauwolfia vomitoria) amongst others which have been explored for their medicinal value. On the cosmetic side, Shea butter (Vitteleria paradoxa) as well as the oil of the Baobab (Adansonia digitata), Rooibos extract (Aspalathus linearis) Honey bush (Cyclopia sp.) are fast becoming the hallmark of the continent. With so much potential and diversity, why is African 'absent' on the international scene. It is becoming increasingly clear that the potential for the business is enormous. Research works are increasingly pointing to this huge untapped potential. This presentation will present some of the recent results from the standpoint of standardized herbal extracts; novel essential oils from the local flora, as well as new leads for for the pharma and cosmetic industries.





Carla Holandino Quaresma is a Full Professor of the Federal University of Rio de Janeiro.

She received her B.SC Pharmacy (02/1992) in Pharmacy from Pharmacy College, Federal University of Rio de Janeiro, UFRJ, Brazil, her M.Sc. (03/1994) in Biophysics from Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, UFRJ, Brazil, her Specialization (M.Sc. equivalent) (01/2003) in Immunoparasitology from Instituto Hanhemanniano do Brasil, Federal University of Rio de Janeiro, UNIRIO, Brazil, her Ph.D in Science (12/2000) Biophysics from Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, UFRJ, Brazil, and her Post-Doc (07/2018) in Anticancer Natural Products at Bern University and Society Cancer Research, Arleisheim, Switzerland

Positions and Employment

Complete List of	f Published Work in My Bibliography: http://lattes.cnpq.br/7921071460655010	
2018 to date	Director of Brazilian Consortium of Integrative Medicine	
	Switzerland (Head: Prof Dr. Stephan Baumgartner)	
2017-2018	Postdoctoral Research Associate at the Dept. Basic Research, Society for Cancer Research, Arlesheim,	
2019 to date	Full Professor at Pharmacy College, Federal University of Rio de Janeiro, Brazil	



"THERAPEUTIC POTENTIAL OF NATURAL PRODUCTS: RESEARCH AND DEVELOPMENT"

Prof. Carla Holandino Quaresma, PhD

In complementary medicine, extracts from different plants have been used in the treatment of several diseases, such as cancer, AIDS, tuberculosis, anxiety, among others. Nowadays, the market of herbal medicines moves a large part of the financial and economic resources in the world. In this context, it is very important to elucidate the phytochemical profile of the plants' extracts in order to increase the pharmacologic uses of these promising natural substances. Our work will discuss and explore the confluence of current research topics related to natural products, with focus in the chronic diseases, specially cancer because it is still a challenge for medicine.

Plants' extracts exert effects through multiple keylock models and the production of secondary metabolites (diterpenes, triterpenes, steroids, flavonoids, ellagitannins) is directly related to the therapeutic potential of these natural products. To evaluate extract composition, phytochemical analyses can be performed, based on HPLC analysis, for example. Currently, the ultra-high resolution and accuracy of mass spectrometry, allow the identification of complex plant mixtures without prior extraction or separation steps. Besides, the use of multivariate statistical analysis using Partial Least Square Discriminant Analysis (PLS-DA), applied in metabolomics studies, enables analyses of complex mixtures at the molecular level. An in-depth characterization of the compounds responsible for this chemical discrimination is currently performed to better understand their importance for the bioactivity of vegetal extracts. All of these aspects will be discussed in order to highlight the promising therapeutic potential of natural substances.

Prof. Carla Holandino Quaresma, PhD, Full Professor at Pharmacy College, Federal University of Rio de Janeiro

Correspondence address: Federal University of Rio de Janeiro, Health Sciences Center, Pharmacy College, Underground B, Rooms11, 34, Zip code: 21941-902. Rio de Janeiro, Brazil. Mobile phone: +55 21 99725-7775; Email address: cholandino@gmail.com or cholandino@pharma.ufrj.br





Professor Dr. Prof. h. c. mult. Thomas Efferth is chair of the Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany. He is biologist by training (Technical University of Darmstadt, Germany). His doctoral thesis was completed at the German Cancer Research Center (DKFZ), Heidelberg, Germany (1990). Dr. Efferth was awarded the Ludolf-Krehl-Prize of the Southwest German Association for Medicine (1991), the Willmar-Schwabe-Award of the German Society for Medicinal Plant Research (2006), the citizen medal of the City of Heidelberg, Germany (2008), the CESAR Award for Translational Oncology (2011), the SCENTEDdrop Award on medicinal and flagrant herbs (2015), and the *Qihuang* International Award of the Chinese Association of Chinese Medicine (2017). Since 2018, he is full member of the World Academy of Sciences.

He headed a research group for Pharmaceutical Biology at DKFZ (2005-2009) and was adjunct professor (apl.) at the University of Heidelberg (2007-2009). In 2009, he took over the Chair of Pharmaceutical Biology (full professorship) at the Johannes Gutenberg University, Mainz. Furthermore, he is honorary professor at the Northeast Forestry University, Harbin, and at the Zhejiang Chinese Medical University, Hangzhou, China. Moreover, he is visiting professor at the Zhejiang University of Science and Technology, Hangzhou, China and honorary adjunct professor at the Chinese University Hong Kong.

Thomas Efferth has published 560 PubMed-listed papers and in peer-reviewed journals in the field of cancer research, pharmacology, and natural products (Hirsch-factor: 74; citation rate: 23,000; acc. Google Scholar) and a textbook on 'Molecular Pharmacology and Toxicology' (Springer Publisher; 2006). He holds 7 patents. The scientific results were communicated in over 250 oral presentation and invited lectures and over 180 poster presentations at national and international conferences and meetings. He is editor-in-chief of Phytomedicine as well as co-editor, associate editor and editorial board member of several scientific journals and scientific advisory board member of the German Pharmaceutical Society and several other institutions. Eight of his former lab members promoted to leading academic positions (1 vice-president, 1 full professor, 6 associate/assistant professors).

The focus of Dr. Efferth's research is on tumor pharmacology, network pharmacology, and the development of novel options for treatment and diagnosis of cancer. A major topic is research on chemical entities from natural sources:

1. Network pharmacological and bioinformatic approaches to unravel modes of actions of synthetic and natural compounds with activity against otherwise drug-resistant tumors (basic research)

2. Predictive and prognostic markers for personalized cancer medicine (translational research)



"NETWORK PHARMACOLOGY AND PRECISION MEDICINE FOR CANCER THERAPY WITH NATURAL PRODUCTS"

<u>Efferth T</u>¹

¹ Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, johannes gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany. E-mail: <u>efferth@uni-mainz.de</u>

To combat complex systemic diseases that harbor robust biological networks such as cancer, single target intervention is proved to be ineffective. In such cases, network pharmacology approaches are highly useful, because they differ from conventional drug discovery by addressing the ability of drugs to target numerous proteins or networks involved in a disease. Pleiotropic natural products are one of the promising strategies due to their multi-targeting and due to lower side effects. In this review, we discuss the application of network pharmacology for cancer drug discovery. We provide an overview of the current state of knowledge on network pharmacology, focus on different technical approaches and implications for cancer therapy (*e.g.* polypharmacology and synthetic lethality), and illustrate the therapeutic potential with selected examples from herbal mixtures, medicinal herbs and isolated phytochemicals. Finally, we present future perspectives on their plausible applications for diagnosis and therapy of cancer.

Selected papers:

Kadioglu O...., Efferth T. Biochem Pharmacol. 2014;87:399-409; Zhao Q,, Efferth T. Int J Cancer. 2015 ;137(6):1446-56; Panossian A,, Efferth T. Phytomedicine. 2015;22:981-92; Saeed M,, Efferth T. J Nutr Biochem. 2015;26:44-56.; Kadioglu O,, Efferth T. Arch Toxicol. 2016;90:575-88; Poornima P,, Efferth T. Pharmacol Res. 2016;111:290-302; Efferth T et al. Oncotarget. 2017;8:50284-50304; Hong C,, Efferth T. Sci Rep. 2017;7:11551; Hamdoun S, ..., Efferth T. Biochem Pharmacol. 2017;146:63-73; Efferth T. Semin Cancer Biol. 2017;46:65-83; Efferth T, Paul, NW. Lancet Planet Health. 2017;1:e301-e303



Panel Moderator & Session Chair: John Travis

Sports nutrition did not exist as a product category when the Dietary Supplement Health and Education Act (DSHEA) was signed into law in 1994. By 2017, market researchers estimated the market was worth more than \$44 billion. At their genesis, sports nutrition products were a niche market for the bodybuilding gym rat. Today, soccer moms are downing protein shakes while carting their kids around town. We also remember a time when "Andro" and "GHB" were marketed as supplements, which today is anathema. How has this rapid and enormous growth impacted the supplement industry and its consumers? Our distinguished panelists, representing the spectrum of stakeholders in the sports nutrition industry, invite you to discuss the successes and failures we have had along the way, and how we can responsibly grow the industry while conscientiously serving its consumers.





Patricia A. Deuster, PhD, MPH, is a Professor in the Department of Military and Emergency Medicine at the Uniformed Services University of the Health Sciences (USU) in Bethesda, Maryland and Director for the Consortium for Health and Military Performance (CHAMP), the Defense Center of Excellence for Human Performance Optimization. She obtained an AB in Mathematics and Computer Science and MA in Education and Physical Education from the College of William and Mary, a PhD in Nutritional Sciences and Physiology from the University of Maryland, and a MPH with an emphasis in public health and epidemiology from USU.

Dr. Deuster chairs the Department of Defense (DoD) Dietary Supplement Subcommittee, is a member of the DoD Food and Nutrition Subcommittee, serves on the DoD Human Performance Optimization Committee, the VA/DoD Health Executive Committee Women's Health Work Group, the DoD Nutrition Committee, and the DoD Population Health Working Group. She also oversees the DoD Operational Supplement Safety (OPSS) program. She is a Fellow of the American College of Sports Medicine, a Certified Nutrition Specialist, and has over 250 peer-reviewed papers and numerous book chapters and books relating to human performance with a focus on health, nutrition, dietary supplements, and total force fitness. She has conducted research in the area of sports and warrior nutrition and performance for over 35 years. Visit the CHAMP Human Performance Resource Center (hprc-online.org) and Operation Supplement Safety (OPSS.org) websites. Dr. Deuster is a member of the Order of Military Medical Merit and received the Special Operations Medical Researcher Award from the Special Operations Medical Association in 2014.

She was the author of the first U.S. Navy SEAL Nutrition Guide sponsored by U.S. Special Operations Command and was commissioned in 2006 to update the nutrition guide for the United States Special Operations Commands (USSOCOM). Dr. Deuster has been a tennis professional, nationally ranked marathoner, qualifier for the First Women's Olympic Marathon Trials, triathlete, skydiver with over 100 jumps, and world-wide scuba diver.





Amy Eichner, has a bachelor's in psychology from the University of Minnesota and a PhD in Medical Science with a focus Neuroscience from the Australian National University. She has done postdoctoral studies at Harvard University and Massachusetts General Hospital before moving to the field of health product regulation. In 2008 she became the Senior Biocompatibility Scientist at the Therapeutic Goods Administration in Australia where she ran the Biocompatibility of Medical Devices Laboratory. In 2009 she became the Manager of the Drug Reference Department at the US Anti-Doping Agency in Colorado Springs. Since 2011, she has been the Special Advisor on Drugs and Dietary Supplements at the US Anti-Doping Agency where she manages GlobalDRO.com, a web-based tool to determine the status of medications in sport. She also manages Supplement411.org and the High Risk List (a list of dietary supplements that contain, or claim to contain substances prohibited in sport), develops educational materials, and monitors trends and risks in the use and availability of various dietary supplements and alternative medicines.





Joel Totoro is a Registered Dietitian with over a decade experience in trauma and sports nutrition. Prior to joining Thorne, he served 3 years as sport dietitian for the University of Michigan and 8 years at the New England Patriots, where he was the first full time sports dietitian in pro-sports. Totoro is also an original member for the Collegiate and Professional Sports Dietitians Association where he served 4 years as an elected member of the Board of Directors.





John Travis has more than 20 years of experience as an analytical chemist specializing in the analysis of dietary supplements. As Senior Research Scientist at global public health organization NSF International, Travis analyzes hundreds of dietary supplement products each year for various contaminants, emerging drugs and harmful compounds.

Utilizing a variety of analytical techniques, he has developed and validated analytical methods for the analysis of dietary supplements. He was instrumental in the development of the screening methods used for the NSF International Certified for Sport[®] program, which now screens products for more than 270 banned substances on the World Anti-Doping Agency list. Travis is currently involved with the analysis of pharmaceutical agents and illicit drugs, stimulants and other prohibited substances as both adulterants and contaminants in dietary supplements and functional foods, co-authoring scientific papers on ingredients of concern in dietary supplements.



"BREADFRUIT (ARTOCARPUS ALTILIS): AN EXAMPLE OF THE POTENTIAL OF A TRADITIONAL UNDERUTILIZED CROP FOR MODERN FOODS, COSMETICS AND NATURAL HEALTH PRODUCTS"

Murch SJ¹

¹Chemistry, University of British Columbia, Kelowna, British Columbia, Canada, V1V 1V7

To keep up with population growth, production of staple foods will have to increase by about 50% to around 3 billion tonnes annually before 2050. Maize, wheat and rice provide 60% of the world's food energy intake but these are high-input crops requiring annual replanting and chemical management. Allergies to wheat and corn are increasing. Underutilized crops offer the opportunity for low-input, sustainable, nutrient dense staple food for food security and modern food products. Breadfruit (*Artocarpus altilis* (Parkinson) Fosberg) is a traditional staple crop of the Pacific listed as a priority underutilized crop on Annex 1 of the International Treaty on Plant Genetic Resources for Food and Agriculture. The availability of breadfruit as a sustainable staple food has been limited by difficulties with propagation and distribution of the trees. Our research program developed *in vitro* mass propagation and *ex vitro* acclimatization methods to provide breadfruit trees for food security projects in the tropics. Each tree produces >400 kg of fresh fruit that can be eaten boiled, baked, or fried; made into chips; fermented into beer or vodka; dried and ground into gluten free flour and prepared other ways. Breadfruit flour has a lower glycaemic index and is a good source of complete protein containing all of the essential amino acids required for human health. Numerous secondary products can be made from breadfruit trees including insect repellents and cosmetics. Underutilized crops like breadfruit are an untapped resource for sustainable food production, new product development and food security in the future.



"THE MUSHROOM MICROBIOME: SIGNIFICANCE OF MICROBIAL-DERIVED COMPONENTS TO THE MACROPHAGE STIMULATORY ACTIVITY OF EDIBLE MUSHROOMS"

Pugh ND¹, Zhang J¹& Pasco DS^{1,2}

¹National Center for Natural Products Research, ²Department of BioMolecular Sciences, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University MS 38677, USA.

Both water-soluble and water-insoluble beta glucans are thought to contribute to the *in vitro* macrophage stimulatory activity exhibited by edible mushrooms and that these components are synthesized by the mushrooms. However, preparations of these macromolecules often contain residual/trace components from other classes that could contribute to or account for the detected activity. A growing body of evidence supports the theory that the microbiome of plants and mushrooms produce potent activators of pathogen recognition receptors which are principal contributors to the stimulation of macrophages. We have previously reported that the *in vitro* macrophage stimulatory activity of the water-soluble components from 13 different types of edible mushrooms is predominantly due to Toll-like receptor (TLR) agonists such as LPS and other bacterial components originating from the naturally occurring microbial communities within these materials. In our current research we evaluated whether these 13 mushrooms contain water-insoluble/particulate beta glucans that activate the dectin-1b signaling pathway. Dectin-1b-dependent activity was found to vary dramatically between mushroom samples and preliminary data suggests that this activity is derived from endophytic yeast. In agreement with the literature, we also found that co-stimulation of macrophages with bacterial components (TLR2 or TLR4 agonists) and particulate beta glucan (dectin-1b agonist) results in a synergistic enhancement of *in vitro* cytokine production. Taken together, these findings indicate that the *in vitro* macrophage activating potential of edible mushroom is due to the collaborative interaction of water-soluble TLR agonists (derived from microbiome bacteria) and water-insoluble particulate beta glucans (derived from microbiome bacteria) and water-insoluble particulate beta glucans (derived from microbiome bacteria) and water-insoluble particulate beta glucans (derived from microbiome bacteria) and water-insoluble particulate beta glucans (derived from m

This research was partly funded by the USDA, ARS Specific Cooperative Agreement No. 58-6060-6-015.


"CONTROLLING THE THREAT OF HERPES AND EBOLA VIRUSES: THE MECHANISM OF ACTION AND ACTIVE CONSTITUENTS OF MELISSA OFFICINALIS"

Langland, J.O.^{1,2}

¹Center for Integrative Naturopathic Medicine, Southwest College of Naturopathic Medicine, Tempe, Arizona, USA 85282

²Biodesign Institute, Arizona State University, Tempe, Arizona, USA 85287

Herpes simplex virus 1 (HSV1) is the primary cause of herpes labialis, or 'cold sores', in humans. HSV1 infection can also lead to blindness, encephalitis and is potentially involved in the development of Alzheimer's disease. Drugs like acyclovir and its derivatives are available for treatment, but with increased use, the development of resistance to these drugs is increasing. Extracts of the botanical, *Melissa officinalis*, have historically been used for the treatment of herpes virus infections. Our studies confirm the antiviral activity of this botanical and further characterize the mechanism of action related to interaction of botanical constituents with specific viral glycoproteins on the HSV1 virion leading to inhibition of binding to cells. *Melissa officinalis* was shown to inhibit other alpha herpes viruses as well as having inhibitory activity against other viruses, including Ebola virus. Isolation of the active compound(s) in *Melissa officinalis* identified organic compounds with a caffeoyl moiety, including caffeic acid and rosmarinic acid. However, commercially synthesized caffeic acid and rosmarinic acid did not demonstrate any anti-viral activity. The activity of these compounds was dependent upon chelation with a metal ion where the antiviral activity of caffeic acid increased upwards of 100-fold by the addition of cations, such as Fe3+, and anionic molecules, such as molybdate and phosphate. Cellular toxicity tests of the caffeic acid chelates demonstrated low toxicities. The caffeic acid chelates target an extra-cellular process, they might be able to be combined with existing medications, such as acyclovir, to achieve greater viral control.



"BERBERINE PROTECTS C17.2 NEURAL STEM CELLS FROM OXIDATIVE DAMAGE AND INDUCES THEIR NEURONAL DIFFERENTIATION"

Jia-Wen Shou, Chun-Kai Cheung, Pang-Chui Shaw

LDS YYC R & D Centre for Chinese Medicine and School of Life Sciences,The Chinese University of Hong Kong, Hong Kong

Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons. Neurodegenerative diseases have been regarded as world-wide burden due to the dramatic increase of life span. The oxidative stress has been suggested as one of the common etiology in various neurodegenerative diseases. It is therefore necessary to find the effective medicines that can protect against oxidative damage and induce neurogenesis.

Berberine has been shown beneficial effects in various neurodegenerative and neuropsychiatric disorders. We hypothesized berberine could protect C17.2 neural stem cells from 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH)-induced oxidative damage and then promote neuronal differentiation.

Results showed that berberine was able to protect C17.2 neural stem cells from AAPH-induced oxidative damage. It lowered the cellular reactive oxygen species (ROS) level in C17.2 cells via NRF1/2-NQO1-HO1 pathway. It also down-regulated the apoptotic factor- caspase 3 and Bax and the anti-apoptotic factor- Bcl2. After AAPH damage, berberine-protected C17.2 cells were recovered for two days. Berberine could increase C17.2 cell viability via up-regulating ERK and pERK expression in this recovery period. Then cells were kept cultured for another week in differentiation medium with/without berberine. Berberine promoted C17.2 cell to differentiate into neurons and the differentiation mechanism involved the activation of WNT/b -catenin pathway as well as the upregulation of pro-neural factors like ASCL1, Neurog1, NeuroD2 and DCX.

Our work provides scientific evidence to support the use of berberine as anti-neurodegeneration medicine.

J.W. Shou was supported by the Hong Kong PhD Fellowship Scheme (PF15-16899).



"ISOLATION, STRUCTURE ELUCIDATION AND SYNTHESIS OF NATURAL PRODUCTS; EFFICIENT TOOLS FOR DEALING WITH A NEEDLE IN A HAYSTACK"

Mohamed A. Albadry

Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Cairo 11371, Egypt and National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University, MS 38677, USA

Natural products are essential players in the drug discovery process; however, the limited natural supply of material is a challenge. The low yields for certain metabolites hamper their complete structure assignment and/or biological evaluation. Chemical synthesis is a substitute tactic to deliver suï-fcient quantities of these metabolites for future studies, but before the synthesis is carried out, a complete structural characterization of the relevant compounds is necessary.

Different chromatographic techniques have been used to accomplish the isolation of 12 peptides from the kahalalide family from the marine alga *Bryopsis pennata*. By utilizing a combination of molecular modeling techniques, integrated NOESY measurements, and amide protons' temperature coefficient calculations, the assignment of the absolute configuration of the final stereogenic center in kahalalide Y was achieved.

Karlotoxins are a group of marine-derived polyketides which have been isolated from the dinoflagellate *Karlodinium veneficum* in minute quantities. Chemical synthesis is thus essential to produce sufficient quantities of KmTx 5 for future evaluations. The synthetic strategy utilized to synthesize the polyol chain of karlotoxin 5 (C₁-C₁₇) consists of iterative chain elongation protocol entailing three-steps of catalytic hydrogenation of alkene and hydrogenolysis of benzyl ether with Pd/C, Dess-Martin Periodinane oxidation of alcohol to aldehyde, and Julia-Kocienski olefination.

Mesembrine is an alkaloid previously isolated from some *Sceletium* species. Mesembrine has some challenging chemical features such as a cis-3a-aryloctahydroindole moiety with *syn* configuration at two bridgehead stereogenic centers. The desired stereogenic center at carbon 3a was created early in the synthesis followed by carbene insertion and intramolecular aldol reactions to complete the aryloctahydroindole scaffold.

Rubia cordifolia is a widely used plant in the traditional Chinese medicine for the treatment of several ailments. *Rubia*-derived cyclic peptides have attracted considerable attention for their potential antitumor activity *in vitro* and *in vivo*, in addition to their characteristic bicyclic structure incorporating the isodityrosine moiety.





Dr. Pieter Cohen, a graduate of Yale School of Medicine, is an Associate Professor of Medicine at Harvard Medical School and a practicing internist at Cambridge Health Alliance (Somerville, Massachusetts) who routinely recommends dietary supplements to his patients. His area of research is the safety of dietary supplements. Along with analytic chemistry colleagues he has spent the last decade exploring the boundaries between drugs and supplements. His work has been published in the *New England Journal of Medicine, JAMA, JAMA Internal Medicine, American Journal of Public Health* and *Annals of Internal Medicine*.



"DSHEA AT 25: IS THE FDA ENFORCING THE LAW OR IS DSHEA UNENFORCEABLE?"

Dr. Pieter Cohen will review recent research examining the enforcement of DSHEA by the US Food and Drug Administration and the implications for the safety of dietary supplements. He will discuss the effectiveness of the agency's actions to remove novel ephedra replacements from supplements, the FDA's ability to ensure safe levels of pharmacologically active substances in supplements and the efficacy of the FDA's recalls of supplements adulterated with pharmaceutical drugs. How these research findings can provide evidence to support future thoughtful policy and regulatory changes will be explored. Additional background information is available in his recent article "The FDA and Adulterated Supplements—Dereliction of Duty" (JAMA Netw Open, 2018:1(6), e183329).





Steven Tave is the Director of the Office of Dietary Supplement Programs (ODSP) in FDA's Center for Food Safety and Applied Nutrition (CFSAN). He was named ODSP's first permanent Director in November 2016 after serving as Acting Director beginning in March 2016. Previously, Steve was the Acting Director of the Office of Unapproved New Drugs and Labeling Compliance in CDER's Office of Compliance, where he led a multidisciplinary staff with responsibility for operations and regulatory actions with respect to misbranded and unapproved new drugs, including compounded drugs, fraudulent drugs, homeopathic drugs, marketed unapproved drugs, and over-the-counter drugs. Steve began his career as an attorney and practiced law for almost 15 years, both as a litigator in FDA's Office of Chief Counsel and in the private sector. He received his law degree from the University of Virginia School of Law and his bachelor's degree from Northwestern University.



"REGULATING FOR THE NEXT 25 YEARS"





Dr. Gregory Noonan joined the US Food and Drug Administration in 2002 and is currently the Director of the Division of Bioanalytical Chemistry (DBC) in the Office of Regulatory Science. The Division of Bioanalytical Chemistry contains over 35 scientists performing research and developing analytical methods in numerous subject areas, including, toxic elements analysis, immunodiagnostic and DNA-based allergen detection, radionuclides, pesticide analysis, mycotoxin analysis, dietary supplements and botanicals, nutritional ingredients and cosmetics. Prior to becoming Director, Dr. Noonan was a Research Chemist in the Method Development Branch of the Division of Analytical Chemistry. His research focused on developing methods for the determination of food additives, including indirect additives, and process induced contaminants. Dr. Noonan also serves as the US Delegate to the Codex Committee on Methods of Analysis and Sampling (CCMAS), where he chairs the Working Group on the Endorsement of Methods. Dr. Noonan received his PhD in Chemistry from Michigan State University in 1996. After graduation he worked for the Diagnostic Division of Abbott Laboratories, where he developed diagnostic immunoassays for Hepatitis A, B and C and HIV. After leaving Abbott Laboratories and prior to joining the FDA, he was a postdoctoral fellow in the Civil and Environmental Engineering department of the Massachusetts Institute of Technology, where he studied the fate and transport of polar, water soluble environmental contaminants.



"NEW APPROACHES TO THE ANALYSIS AND REGULATION OF DIETARY SUPPLEMENTS"

In the 25 years that the Dietary Supplement Health and Education Act (DSHEA) has been law, there have been tremendous changes and advances in the field of Analytical Chemistry. Some, such as inductively coupled plasma-mass spectrometry have been valuable incremental advances while others, such as the wide use electrospray ionization have transformed the methods and approaches for analyzing dietary supplements. A brief review of these and other methods, shows that developments in electronics, computing and informatics clearly play a role in these advances. Based on our past experience in instrumental analysis and current research in areas of elemental analysis, high resolution mass spectrometry, allergen detection and next generation sequencing, we hope to continue to advance the methods and tools used in the analysis and regulation of dietary supplements. In this presentation I will highlight current work in these four areas of method/data development that we believe can be used to help manufacturers, distributors and regulators improve and monitor the safety and reliability of dietary supplements.





Jason Humbert is a Captain in the U.S. Public Health Service and the Director of the Health Fraud Branch in FDA's Office of Regulatory Affairs. Captain Humbert served in the U.S. Army before joining the Public Health Service. He earned a bachelor's degree in Nursing and a master's degree in professional studies focusing on homeland security and public health preparedness. Most recently, Captain Humbert completed a graduate program focused on cyber investigations and dark web targeting and analysis with an emphasis on FDA-regulated products. Captain Humbert has presented his experiences on health fraud to consumers, media, industry, academia, healthcare providers and regulatory agencies in the U.S. and abroad.



"DIETARY SUPPLEMENTS THAT CONTAIN HIDDEN, HARMFUL INGREDIENTS CONTINUE TO BE A PUBLIC HEALTH CONCERN"

Products marketed as dietary supplements that contain hidden, harmful ingredients continue to be a public health concern. The U.S. Food and Drug Administration receives consumer complaints and adverse event reports involving these "tainted products." As the marketplace for dietary supplements has evolved, so has the marketplace for the illegal sale of these adulterated products which contain ingredients ranging from prescription drugs to controlled substances to chemicals not intended for human consumption. The agency maintains a database for tainted products and posts consumer notifications when FDA laboratories find the presence of hidden ingredients in these products. Enforcement actions involving manufacturers and distributors of tainted products range from advisory actions to criminal prosecutions, but the nature of this marketplace presents considerable challenges for the agency. The goal of this presentation is to increase awareness of this public health issue, provide an overview of the steps FDA is taking to protect consumers from tainted products, and provide resources about tainted products and the means which the public can report issues related to these types of products.



<u>Panel Session Chair/Moderator</u>: Rick Kingston, PharmD, SafetyCall International & University of Minnesota, College of Pharmacy & University of Mississippi College of Pharmacy/National Center for Natural Product Research

It's been 25 years since the passage of DSHEA and although much has changed regarding regulatory and industry efforts to improve the quality and ultimately the safety of dietary supplements there continues to be questions related to existing data or regulatory gaps and what more can or should be done to ensure patient safety. Arguably, the biggest safety issue facing the natural product industry since passage of DSHEA involved ephedra. At the time, industry was unable to institute self-regulatory practices to deal with the risks associated with one of the most prominent botanicals in commerce. Subsequent to FDA action to remove ephedra from the dietary supplement market, industry reacted in a responsible manner and called for passage of mandatory adverse event monitoring and reporting of serious adverse events to FDA. With the passage of the Dietary Supplement and Nonprescription Drug Consumer Protection Act (DSNDCPA) of 2006, a framework for enhanced safety and oversight by regulators was launched which included record keeping, data archiving, establishment of policies and procedures related to AE management and documentation, and timely submissions of required AEs directly to the Agency. After passage of adverse event legislation, implementation of cGMPs allowed for closer scrutiny of supplement manufacturing practices by FDA which further enhanced product quality and consumer safety. Despite these industry and regulatory initiatives, clinicians and other stakeholders have questioned whether enough is being done to protect consumers. Reports of serious liver injury involving various botanical containing dietary supplements continue to appear in the literature and other professional venues and published studies describing emergency room visits involving dietary supplements have led to further questions regarding supplement safety. Lastly, the emergence of dietary supplements containing CBD, an ingredient the FDA has labeled as an unapproved dietary ingredient have raised questions of whether the Agency has the resources or ability to adequately carry out its statutory authority and oversight of the dietary supplement market. Independent of whether CBD should be granted a pathway to legal status as an accepted dietary ingredient, how are current CBD containing dietary supplements being monitored for quality and safety?

What has gone right since the passage of DSHEA, what are the outstanding safety issues, data gaps and potential solutions. As to whether or not there are real or clinically relevant safety concerns a panel of medical, regulatory and industry experts will provide their perspectives.





Dr. 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 obtained fellowship training in Gastroenterology, Hepatology, and Hepatobiliary Endoscopy at Yale University. 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.

In 2002, Dr. Navarro assumed a 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. 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. In 2016, Dr. Navarro became the founding medical chair of the Department of Digestive Disease and Transplantation for the Einstein Healthcare Network; in this position, he oversees Divisions of Hepatology, Gastroenterology, Transplant and Hepatobiliary Surgery.

As a mentor, Dr. Navarro has been directly responsible for the scholarly and clinical training of many young and mid-career health professionals and academicians. Dr. Navarro's chief sources of research funding are the National Institutes of Health as an investigator for the U.S. Drug Induced Liver Injury Network (DILIN), and the Patient Centered Outcomes Research Institute for his study of Palliative Care in Patients with End Stage Liver Disease.





Dan Fabricant





Tieraona LowDog, MD is a physician, author, and thought leader in integrative medicine. Her background in herbal medicine, midwifery, massage, and martial arts, made her a natural choice to lead the Fellowship program at the University of Arizona Center for Integrative Medicine, where she oversaw the training of more than 600 physicians and nurse practitioners. Tieraona is a leading expert in dietary supplements and botanical medicine, being honored with many awards from academia, public health, and industry throughout her 40-year career. A prolific scholar, she has authored/co-authored 52 peer-reviewed journal articles, written 22 chapters for medical textbooks, five books, including four with National Geographic; and was co-editor of Integrative Women's Health (Oxford University Press). She has chaired expert panels for supplement/botanical safety at the United States Pharmacopeia for the past twenty years. Tieraona been an invited speaker to more than 600 conferences, reaching more than 50,000 people every year with her message of integrative medicine, compassionate care, and deep ecology. She lives and practices outside of Santa Fe, New Mexico.





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 *Executive Chairman*. 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.

Built on this platform of science, ChromaDex (NASDAQ: CDXC) has been transformed into an integrated, global nutraceutical company devoted to improving the way people age. ChromaDex scientists partner with leading universities and research institutions worldwide to uncover the full potential of NAD and identify and develop novel, science-based ingredients. Its flagship ingredient, NIAGEN[®] nicotinamide riboside, sold directly to consumers as TRU NIAGEN[®], is backed with clinical and scientific research, as well as extensive IP protection. TRU NIAGEN[®] is helping the world AGE BETTER[®].

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 25 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 Botanical Council Directors Circle and the NSF Joint Committee for Dietary Supplements. He also serves on the board of directors for the Natural Products Association(NPA). 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.





Dr. De-an Guo serves as director of the Shanghai Research Center for TCM Modernization at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. He received his Ph.D. Degree of Pharmacognosy at Beijing Medical University in 1990. He engaged in his postdoctoral research at the Department of Chemistry and Biochemistry, Texas Tech University, (1993-1996). His major research interest is focused on the standardization and modernization of Chinese herbal medicines. He has received a number of international, national and ministerial awards such as National Natural Science Award, Norman Farnsworth Excellence in Botanical Research Award, etc. He is currently the president of GP-TCM Research Association (London) and chair or expert committee members of Chinese Pharmacopoeia, United States Pharmacopoeia and European Pharmacopoeia. At present, he is Editor-in-chief, vice editor or editorial board member of 18 international journals. To date, he has published 560 papers including 380 SCI articles with over 6000 SCI citations.



"TCM RESEARCH: CHALLENGES, CURRENT STATUS AND FUTURE PERSPECTIVES"

De-an Guo, National Engineering Laboratory for TCM Standardization Technology, Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P.R. China; Email: <u>daguo@simm.ac.cn</u>

Traditional Chinese medicine is an extremely complex system, which contains hundreds or even thousands of chemical components in one herb, not to say compound formulas composed of several or tens of herbs. This generates extreme difficulty to clarify its chemical composition, which is the fundamental basis for the research of quality control, mechanism, pharmacological and toxicological actions, new drug discovery, etc. Acknowledging to the new analytical technique advancement, comprehensive analysis for traditional Chinese medicines and other herbal medicines becomes feasible. The challenges TCM research faces, and progress achieved were briefly summarized. Special attention was focused on our dedicated research on herbal analysis and quality control by employing state-of-art techniques, such as UPLC, 2DLC, HRLC-MS to facilitate the elaboration of holistic quality control standards of herbal complex systems. Several typical herbs were exemplified by using this approach as Panax species, Tumeric, Uncaria species, etc. Based on the comprehensive analysis results, holistic quality standard of TCM complex systems was elaborated. This quality control approach was effectively applied to assure the herbal quality in the entire supply and production chain from seedling, cultivation, processing, manufacturing, to the finished products. The strategy and key factors of holistic standard were established and the quality monographs of a number of CHM herbs were elaborated and adopted by the mainstream Pharmacopoeias. It can be concluded that with the new development of analytical techniques, more and more chemical components in the complex herbal system will be clarified to facilitate their quality control and clarification of therapeutic substances, which hence guarantees the quality of CHM.

Keywords: Holistic Quality Control; Chinese herbal medicines; Pharmacopoeia Standards



Dr. Hua Yang is Full Professor at State Key Laboratory of Natural Medicines, School of Traditional Chinese Pharmacy, China Pharmaceutical University (Nanjing, China) and assistant director of Department of Pharmacognosy. Dr. Yang's research focused on discovering bioactive components of herbal medicines and exploring their mechanism.



"SYNERGISTIC COMBINATION DISCOVERY FROM HERBAL MEDICINES FOR MYOCARDIAL ISCHEMIA REPERFUSION INJURY"

The multi-faceted pathogenesis are involved in the disease progression, which making the diseases more intricate to be handled. In this regard, the appropriate therapeutic strategy may require the combination of additive or synergistic multi-target therapies. Herbal medicines have played an important role in the treatment of disease for thousands of years, and receive increasing attention worldwide. The therapeutic mode of phyto-therapy, principally based on combined actions of multiple components, could provide a directive source for the rapid discovery of synergistic combination for the treatment of complex diseases. As a case, we identified two synergistic compounds from *Salvia miltiorrhiza*, dihydrotanshinone I (DT) and protocatechuic aldehyde (PCA). Combinatorial and sequential application of DT and PCA, but not the reverse, exhibited powerful cardioprotective effects, much better than that when both compounds were applied alone, against I/R injury in rats.





Dr. Wan-Sheng Chen, Professor and Director, Professor of Pharmacognosy, Department of Pharmacy, Shanghai Changzheng Hospital, 415 Fengyang Road, Shanghai 200003, Research and Development Center of Chinese Medicine Resources and Biotechnology, Shanghai University of Traditional Chinese Medicine, 3528 Jinke Road, Shanghai 201203, PR CHINA

Born in 1968, Ph.D, Prof. Wansheng Chen is now director of Department of Pharmacy, Changzheng Hospital, Second Military Medical University, he is also the director of Research and Development Center of Chinese Medicine Resources and Biotechnology, Shanghai University of Traditional Chinese Medicine. He is a member of 11th China Pharmacopoeia Committee, vice chairman of the Special Committee of TCM Pharmaceutical Analysis WFCMF, chairman of the Shanghai Society for Plant Physiology, etc. Prof. Chen mainly focuses on the bioactive secondary metabolites in traditional herbal medicinal plants and quality control of TCM. During the past 5 years, he presides 12 research projects, had published 87 SCI papers as corresponding author. He obtained the support of Science Fund for National Distinguished Young Scholars in 2013. He was commended as the Shanghai Excellent Academic Leader in 2009.



"BIOSYNTHESIS AND METABOLIC REGULATION OF LIGNANS IN ISATIS INDIGOTICA"

Wansheng Chen

Research and Development Center of Chinese Medicine Resources and Biotechnology, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

Isatis indigotica is a widely used herb for the clinical treatment of colds, fever, and influenza in Traditional Chinese Medicine. Lignans, such as lariciresinol and its derivatives, have been identified as effective antiviral ingredients of I. indigotica. A molecular description of lignan biosynthesis in Isatis indigotica displaying its synthetic characteristics and regulatory mechanism is of great importance for the improvement of the production of this class of active compounds. In our study, I. indigotica hairy roots elicited by methyl jasmonate were used as a source of systematic variation for exploring the metabolic/transcriptional changes and candidate genes that might play key roles in lignan biosynthesis. Integrated analysis of transcriptome and metabolome profiling identified 17 hub genes for the regulation of lignans, providing a pool of candidates for genetic improvement of I. indigotica. Further gene functional study demonstrated the analysis is robust and genes identified via this process are worthy of validation. A large number of lignan biosynthetic genes were subsequently intensively investigated, including transcription factor family libHLHs, liAP2/ERFs, liWRKYs, and a series of lariciresinol biosynthetic pathway genes such as liPAL (DQ115905), liC4H (GU014562), Ii4CL (GU937875), IiCCR (GQ872418), IiCAD (GU937874), IiC3H (JF826963), IiCCoAOMT (DQ115904), and IiPLR (JF264893), as well as liDirs family. Knowledge-based metabolic engineering strategies were thereby performed for genetic regulation of lignans. Overexpression of IPLR1 significantly enhanced lariciresinol accumulation in I. indigotica hairy roots with the content of 353.9 µg/g DW, which was ~6.3-fold more than the wild type. Transgenic I. indigotica overexpressing AP2/ERF transcription factor *li*049 produced 425.60 µg/g lariciresinol with an 8.3-fold increase compared with the wild type production. Transcription factor *li*WRKY34 overexpression not only greatly boosted lariciresinol production (400.4 µg/g DW), but also regulated root development and stress tolerance of Isatis indigotica. In conclusion, our study provides new insights into lignan biosynthesis as well as potential targets for genetic improvement of I. indigotica, also gives a methodological reference for the study of TCM Quality-Design.



Panel Moderator and Session Chair: Bill Gurley-Safety Khan SI1, Roe AL2, Swift S3, MacKay D4, Gurley BJ5

1National Center for Natural Product Research, School of Pharmacy, University of Mississippi, MS 38677, USA; 2The Procter & Gamble Company, Cincinnati, OH 45202, USA; 3Center for Food Safety and Applied Nutrition, U.S. Food & Drug Administration, College Park, MD 20740, USA; 4Council for Responsible Nutrition, Washington, DC 20036, USA; 5University of Arkansas for Medical Sciences, College of Pharmacy, Department of Pharmaceutical Sciences, Little Rock, AR 72205, USA

Passage of the Dietary Supplement Health & Education Act (DSHEA) in 1994 ushered in a new category of consumer products known as dietary supplements (DS). DSHEA's definition of a dietary supplement encompasses a wide variety of products from multivitamins and single-ingredient botanical extracts, to "proprietary blends" of multiple botanical extracts and/or vitamins and minerals. Almost from their inception, safety concerns regarding certain categories of "proprietary blends" have plagued the DS industry. Most notable of these involved Ephedra-containing DS, whose questionable safety record led to their removal from the U.S. market in 2004 by the FDA after a 10-year period of public outcry and legal wrangling. Since that time other "proprietary blends" have come under scrutiny by the medical community for potential adverse health effects. While the vast majority of DS appear to have excellent safety profiles, others remain doubtful. Over the course of 25 years, much has changed in the DS industry. Today, thanks to internet marketing and easy access to a global supply chain, the once fledgling DS industry is now a multi-billion-dollar entity supplying tens of thousands of DS to the world market. The rapid evolution of the DS industry has brought with it a host of new concerns (e.g., adulteration, contamination, misbranding, drug interactions, toxicity from ill-advised proprietary blends, and others). The question now is, does DSHEA's approach to safety, as written in its original form, remain a reasonable expectation for the DS industry, the FDA, and the consuming public? This panel will discuss DSHEA's applicability in today's rapidly evolving DS domain and examine what steps, if any, are necessary to render it more effective from a safety perspective.





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

Dr. Khan has a special interest in characterizing ADME properties, pharmacokinetics and drug interaction potential of botanical dietary supplements and their safety especially when used in combination with other botanicals or pharmaceutical drugs which are the substrates of drug metabolizing enzymes and transporters. Her research interest also includes pharmacological properties of natural products in relation to cancer, inflammation and metabolic disorder.

She has published more than 200 papers in peer reviewed journals in the areas of natural products drug discovery, pharmacology, pharmacokinetics and drug interactions.

She has been a member of American Society of Pharmacognosy for fifteen years.





Dr. Amy Roe 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. 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 (Co-chair), SOT Regulatory & Safety Evaluation Specialty Section (Vice-President), and an NIH/NCCIH Expert Advisory Panel. 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.





Sibyl Swift, Ph.D., is a special assistant within the U.S. Food and Drug Administration's (FDA) Office of Dietary Supplement Programs. In this role, Dr. Swift works on special projects related to dietary supplements, including coordinating the Office's research agenda. She also uses her research experience to review dietary ingredient safety. Dr. Swift is a co-chair of the Botanical Safety Consortium, a collaboration between scientists from government agencies, such as FDA and the National Toxicology Program, as well as from academia and industry.

Before joining FDA, Dr. Swift was a research biochemist in the Department of Defense at the Armed Forces Radiobiology Research Institute. While at this facility, she collaborated with fellow investigators to create a novel model of polytrauma and also explored the efficacy of vitamin E isomers as radiation countermeasures. She completed a postdoctoral fellowship at the Uniformed Services University of the Health Sciences (USUHS) in a neuroendocrinology laboratory where she directed a Defense Medical Research and Development Program-funded grant exploring a novel method of inducing traumatic brain injury and its effect on stress response. Dr. Swift earned her Ph.D. in nutrition and M.S. in physiology at Texas A&M University. She is currently a member of the American Society for Nutrition and serves as an adjunct faculty member at USUHS in the Department of Military Emergency Medicine.





Douglas 'Duffy' MacKay, N.D., is senior vice president, scientific and regulatory affairs for the Council for Responsible Nutrition (CRN). Dr. MacKay oversees CRN's science and regulatory affairs department, ensuring that the association's scientific, policy and legislative positions are based on credible scientific rationale. His expertise combines practical knowledge of industry regulation and scientific product development with hands-on experience as a medical practitioner. He is a licensed naturopathic doctor. Prior to joining CRN, Dr. MacKay spent eight years working as a medical and nutrition expert for two companies in the dietary supplement industry, including four years as an executive with Nordic Naturals, where he was in charge of clinical research. He previously served as Technical Advisor for Thorne Research. Dr. MacKay has published articles in peer-reviewed journals, and serves on the Editorial Board of the peer-reviewed publications: the *Journal of Alternative and Complementary Medicine, Integrative Medicine: A Clinician's Journal, Current Topics in Nutraceutical Research*, and the official publication of the American Association of Naturopathic Physicians, *Natural Medicine Journal*. Dr. MacKay serves on the Advisory Board for the American Botanical Council, the NSF International Joint Committee on Dietary Supplements, the National Institute of Standards Technology/National Institutes of Health, Dietary Supplement Laboratory Quality Assurance Program, and Nutritional Outlook. He is also Chair of the Steering Committee for the SIDI Work Group. Dr. MacKay earned his undergraduate degree from the University of California, Santa Cruz, and his N.D. from the National College of Naturopathic Medicine in Portland, Oregon.



"REAL-TIME AUTHENTICATION OF BOTANICALS BY DIRECT MASS SPECTROMETRY USING DART-MS AND LIVEID ANALYSIS"

Sara Stead¹, Kari Organtini² and Naren Meruva²

¹ Waters Corporation, Stamford Avenue, Altrincham Road, SK9 4AX Wilmslow UK

² Waters Corporation, Milford MA 01757

This study investigates the potential for the implementation of direct mass spectrometry using DART QDA with LiveID as the solution for the rapid authentication of high value botanical ingredients and products with minimal sample preparation. Food, beverages and botanicals of higher commercial value are frequently subject to fraudulent practice. Analytical methods are required for process control, quality assurance and flavor formulation monitoring. Analysis of the characteristic profiles of such high value products can be conducted using extraction followed by chromatography for authenticity purposes. Such methods are time-consuming and there is a need for rapid, qualitative testing to keep pace with industry requirements. DART produces relatively simple mass spectra in positive and negative ionization mode. The mass spectral features are used to generate a multivariate model using a combination of principal component analysis (PCA) for data dimension reduction and linear discriminant analysis (LDA) for class discrimination to distinguish between samples of different processing and production types. Data from real-time authentication of herbs and spices (cinnamon), palm oil and beverages will be presented.



"IS IT GINKGO?"

Débora Frommenwiler¹, Eike Reich¹ & <u>Maged H.M. Sharaf²</u> ¹CAMAG Laboratory, 4132 Muttenz, Switzerland. ²CAMAG Scientific Inc., Wilmington, NC 28401, USA

As part of Exercise O of the Dietary Supplement Laboratory Quality Assurance Program (DSQAP), participants were invited to test the identity of samples labeled as ginkgo using various methods available to them, including microscopy, DNA testing, HPLC, HPTLC, etc. Participants were requested to investigate if gingko was present in the samples, the type of plant part(s), and to list any other significant components and their approximate amounts. This presentation will summarize the HPTLC results obtained at CAMAG Laboratory for those samples.

DSQAP is a program of the National Institute of Standards and Technology (NIST) in collaboration with the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). The program's intercomparison exercises, data reports, and workshops are designed to provide participants with the tools to evaluate their dietary supplement analytical methodology.





"ACCURATE COMPOUND IDENTIFICATION OF COMPLEX TRADITIONAL HERBAL MEDICINE USING A NOVEL MASS SPECTROMETRY ACQUISITION METHOD"

Jimmy Yuk1, Giorgis Isaac1, Lee Gethings2, Rob Plumb1 and Rudolf Bauer3 1Waters Corporation, Milford, MA, USA; 2Waters Corporation, Wilmslow, UK; 3Department of Pharmacognosy, University of Graz, Graz, Austria Yu Ping Feng San (YPFS) is a three herbs TCM formulation. The LC-MS data generated from such multiple herbs contain fragments from co-eluting multiple precursor ions. This makes the fragment data more complex and hence difficult to make correct compound identification. Here we describe the application of a novel data independent acquisition (DIA) approach called SONARâ, ¢ for improved spectral clarity and confident compound identification from a complex samples such as TCM. SONARâ, ¢ utilizes a low resolution quadrupole mass filter, which is scanned continuously and both precursor and MS/MS data are acquired. Data was also collected for comparison purposes using a traditional DIA method such as MSe which provides both precursor and fragment ion information but without a resolving quadrupole. From the results, the specificity of SONARâ, ¢ provides cleaner precursor and fragment ion spectra compared to the traditional DIA acquisition method. As an example, the identification of prim-O-glucosylcimifugin acquired using a traditional DIA and SONARâ,,¢ was compared. When using the traditional DIA there are multiple co-eluting compounds which could confound the structural analysis. The presence of these co-eluting precursor ions with prim-O-glucosylcimifugin provided a high complexity with 97 high energy fragment ions, making compound identification very complex and challenging. On the other hand when the data is acquired using SONARâ, ¢, cleaner precursor and fragment ion spectra were generated. The selected narrow precursor mass window from SONARTM provided specific fragment ions and contains only the parent ions prim-Oglucosylcimifugin [M+H] + and [M+Na]+. Eight clean relevant fragment ions generated only from the parent ion prim-Oglucosylcimifugin which leads to correct and confident compound identification. The specificity of SONARâ, ¢ provides cleaner precursor and high energy fragment ion spectra, which results in confident compound identification.



"QUALITY CONTROL OF BOTANICALS WITH USP BOTANICAL MONOGRAPHS--HPLC AND HPTLC IDENTIFY PLANT PRODUCTS AND DISTINGUISH CLOSELY RELATED SPECIES"

<u>Cuiying Ma</u>, Gabriel I. Giancaspro

Department of Dietary Supplements and Herbal Medicines, Science Division U.S. Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852, USA

Quality control of botanicals used in dietary supplements and herbal medicines presents major challenges due to the complexity of the articles. Problems are often encountered in identifying botanical products and distinguishing between closely related species. The botanical monographs in *United States Pharmacopeia* (*USP*) and the *Herbal Medicines Compendium* (*HMC*) define appropriate quality for botanical dietary supplements and herbal medicines, with science-based standards that include multiple interrelated tests to provide a full characterization for each article in terms of its identity, purity, and content.

The multiple tests included in each monograph complement each other to provide an appropriate pharmacopeial quality characterization for the botanicals used as herbal medicines and dietary supplements. The USP botanical monographs provide detailed specifications for identity, content of bioactive constituents or quality markers, and limits of contaminants, adulterants, and potentially toxic substances. Additional requirements such as labeling and packaging further contribute to the quality of these products. Selective chromatographic procedures, such as high-performance liquid chromatography (HPLC) and high-performance thin-layer chromatography (HPTLC), are powerful methods to identify plant products and distinguish closely related species.

Botanical microscopic and macroscopic descriptions can distinguish some closely related species, for example the three *Coptis* species. However, macroscopic cannot be used with powders and neither both macroscopic and microscopic methods can be used to identify plant extracts. Chromatographic profiling of secondary metabolites by HPLC and HPTLC can identify plant powders and plant extracts, and distinguish closely related species with high selectivity. Description of an HPLC characteristic fingerprint involves of relative peak intensity or quantitative assessment of content ratios of the constituents to be tested, in addition to peak location through relative retention times in a "Chromatographic Window". Determination of the total content of a class of secondary metabolites provides a surrogate measurement for strength in botanical articles. Supporting data used to generate selective identification tests are presented for roots and rhizomes of *Rhodiola rosea* and *R. crenulata* by HPTLC; Chrysanthemum Flower and Wild Chrysanthemum Flower by HPLC, and Dong Quai Root and Sichuan Lovage Rhizomes by HPLC. HPLC determination of total content of flavonol glycosides of Japanese Sophora Flower is used to illustrate a test for "Assay" and the content ratios contributing to the identity of the plant in botanical monographs.

The following organizations contributed for developing methods used in aforementioned USP monographs: (1) Department of Pharmaceutical Analysis, Shenyang Pharmaceutical University, Shenyang, China. (2) Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China; (3) State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing, China.



Panel Moderator and Session Chair: **Dan Marsman**, Head, Product Safety and Regulatory Affairs, P&G Health Care; **Stefan Gafner**, Chief Science Officer, American Botanical Council; and **Douglas MacKay**, CV Sciences CBD brand

Authors: Swift SN¹, Dever J², Gafner S³, MacKay D⁴, Marsman DS⁵, Rider CV⁶

¹Office of Dietary Supplement Programs/CFSAN, Food and Drug Administration, College Park MD, ²Nutrilite Health Institute, Amway Corporation, Ada, MI, ³American Botanical Council, Austin, TX, ⁴Council for Responsible Nutrition, Washington, DC. ⁵P&G Health Care, Cincinnati OH, ⁶Toxicology Branch, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Millions of people consume botanical dietary supplements with continued growth in the industry expected. However, current regulatory guidance in the United States emphasizes a botanical safety framework that relies on history of safe use and traditional animal testing paradigms with virtually no utilization of in vitro and in silico approaches. Today there are thousands of botanical products that combine unique botanical ingredients, which makes it difficult to establish history of safe use for unique dietary supplements. Botanicals themselves are naturally complex and may be subject to contamination and adulteration. The 1994 Dietary Supplement Health and Education Act provides the statutory basis for regulating the safety of botanical dietary supplements and mandates that manufacturers ensure the safety of their products with the FDA bearing enforcement responsibility. Data supporting safe history of human use often provides the best indication of an ingredient's safety but is not always available or sufficient. Animal studies are the current standard for assessing toxicity, but the number, complexity and variable nature of botanicals precludes their use as a pragmatic solution. Established in vitro and in silico approaches offer promise for bridging the gap, however there are numerous uncertainties in the appropriate application of these methodologies. The convergence of these factors calls for the development of a pragmatic strategy for evaluating the safety of botanicals. The Botanical Safety Consortium is a collaboration between scientists in industry, government and academia formed with the goal of providing a sound scientific basis for integrating existing data with the latest toxicology tools to evaluate botanical safety. Chemical characterization of complex botanical products and identification of fit-for-purpose assays for evaluating genotoxicity, hepatotoxicity, developmental and reproductive toxicity, cardiotoxicity, and repeat-dose, systemic toxicity are key areas to be explored by the Consortium. A botanical library containing ingredients with known in vivo toxicity, from animal studies or reports of adverse events, will be created and evaluated as part of the recommended battery of assays. Results from the Consortium will be shared through a publicly available database and recommendations published in the peer-reviewed literature. The Botanical Safety Consortium aims to enhance the botanical safety toolkit and bring clarity to botanical safety assessments for manufacturers and regulators of botanical ingredients. This session will outline the regulatory and safety challenges, fundamental developments and gaps from the botanical safety sciences, and key next steps of the consortium.





Cynthia Rider, PhD, DABT, 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, and industrial chemicals. 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 received her B.S. from Tulane University in Environmental Studies and Biology and her Ph.D. from North Carolina State University in Environmental Toxicology. She completed post-doctoral training in the Reproductive Toxicology Branch of the National Health and Environmental Effects Research Laboratory, U. S. Environmental Protection Agency and the Nicholas School of the Environment at Duke University.

Recent botanical publications:

Roe, A., Dever, J. T., Gafner, S., Marsman, D. S., **Rider, C. V.** & Swift, S. 2019. The Botanical Safety Consortium – A Roundtable Discussion. Applied In Vitro Toxicology. (ahead of print)

Catlin, N.R., Collins, B.J., Auerbach, S.S., Ferguson, S.S., Harnly, J.M., Gennings, C., Waidyanatha, S., Rice, G.E., Smith-Roe, S.L., Witt, K.L., **Rider C.V.** 2018. How similar is similar enough? A sufficient similarity case study with *Ginkgo biloba* extract. Food Chem. Toxicol. 118: 328-339.

Shipkowski, K.A., Betz, J.M., Birnbaum, L.S., Bucher, J.R., Coates, P.M., Hopp, D.C., MacKay, D., Oketch-Rabah H., Walker, N.J., Welch, C., **Rider, C.V.** 2018. Naturally complex: Perspectives and challenges associated with Botanical Dietary Supplement Safety assessment. Food Chem. Toxicol. 118: 963-971.





Dr. Amy Roe 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. 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 (Co-chair), SOT Regulatory & Safety Evaluation Specialty Section (Vice-President), and an NIH/NCCIH Expert Advisory Panel. 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.





Dr. Joseph Dever is the Manager of Global Product Safety for Amway Corporation, manufacturer of Nutrilite[™] and Artistry[™] brand products. He leads a team of toxicologists responsible for botanical and cosmetic product risk assessments with special emphasis on the use and acceptance of alternative methods for safety testing in global regulatory frameworks. He received a Bachelor of Arts (B.A.) degree in Biology from Luther College in Decorah, IA in 2001 and a Ph.D. in Molecular and Environmental Toxicology from the University of Wisconsin-Madison in 2008. He has been a Diplomate of the American Board of Toxicology since 2012 and has published numerous research and review articles as well as a book chapter in the areas of nutrition and toxicology.





Sibyl Swift, Ph.D., is a special assistant within the U.S. Food and Drug Administration's (FDA) Office of Dietary Supplement Programs. In this role, Dr. Swift works on special projects related to dietary supplements, including coordinating the Office's research agenda. She also uses her research experience to review dietary ingredient safety. Dr. Swift is a co-chair of the Botanical Safety Consortium, a collaboration between scientists from government agencies, such as FDA and the National Toxicology Program, as well as from academia and industry.

Before joining FDA, Dr. Swift was a research biochemist in the Department of Defense at the Armed Forces Radiobiology Research Institute. While at this facility, she collaborated with fellow investigators to create a novel model of polytrauma and also explored the efficacy of vitamin E isomers as radiation countermeasures. She completed a postdoctoral fellowship at the Uniformed Services University of the Health Sciences (USUHS) in a neuroendocrinology laboratory where she directed a Defense Medical Research and Development Program-funded grant exploring a novel method of inducing traumatic brain injury and its effect on stress response. Dr. Swift earned her Ph.D. in nutrition and M.S. in physiology at Texas A&M University. She is currently a member of the American Society for Nutrition and serves as an adjunct faculty member at USUHS in the Department of Military Emergency Medicine.


"THE BOTANICAL SAFETY CONSORTIUM: A CROSS-SECTOR COLLABORATION TO ADVANCE BOTANICAL SAFETY THROUGH APPLICATION OF STATE-OF-THE-ART TOXICOLOGICAL SCIENCE"



Dr. Daniel S. Marsman leads and manages worldwide Product Safety for P&G Health Care. His previous positions over 20+ years at P&G have included toxicological pathologist, research scientist (carcinogenesis), and global safety/regulatory affairs manager for P&G's Household, Baby, Feminine, Family, and Pet Care businesses. Dr. Marsman received his PhD from the Dept. of Pathology, College of Human Medicine, UNC-Chapel Hill, and did toxicology training as a postdoctoral fellow at CIIT (Research Triangle Park, NC). His 'One Health' interdisciplinary career began as a veterinary scientist (Michigan State Univ.) with medical parasitology investigations (funded by the WHO) in Khartoum, Sudan. He previously served as pathologist and study scientist for NIH (National Institute of Environmental Health Sciences), and as Head of Study Design for the NIH/NTP chronic toxicity/carcinogenicity testing program. He is dual-boarded in toxicology (DABT) and animal welfare (DACAW) and has published and consulted extensively in the fields of botanical ingredient and drug safety, toxicology, pathology, animal welfare and animal alternatives. His collaborative contributions on technical and policy committees have spanned numerous professional, governmental, NGO and trade associations. Recent external positions include charter diplomate of the American College of Animal Welfare, council member for the National Academy of Science/ILAR, Chair of the Board of Directors for the Council for Responsible Nutrition, International, and member of the Steering Team for the recently formed Botanical Safety Consortium.



"THE BOTANICAL SAFETY CONSORTIUM: A CROSS-SECTOR COLLABORATION TO ADVANCE BOTANICAL SAFETY THROUGH APPLICATION OF STATE-OF-THE-ART TOXICOLOGICAL SCIENCE"



Stefan Gafner, PhD, American Botanical Council, the organization's first-ever Chief Science Officer. 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).

Highlights of Dr. Gafner's impressive career include the discovery of dozens of new natural products, the development of more than 40 methods for the identification and authentication of herbal extracts, and the validation of methods for more than 20 over-the-counter drug ingredients for consumer products.

He has participated as an expert peer reviewer for many respected scientific journals including *Phytochemistry*, *Planta Medica*, *Journal of AOAC INTERNATIONAL*, *Journal of Agricultural and Food Chemistry*, and the *Journal of Natural Products*, and he co-chaired the organization of the American Society of Pharmacognosy's 48th annual meeting.



"THE BOTANICAL SAFETY CONSORTIUM: A CROSS-SECTOR COLLABORATION TO ADVANCE BOTANICAL SAFETY THROUGH APPLICATION OF STATE-OF-THE-ART TOXICOLOGICAL SCIENCE"



Douglas 'Duffy' MacKay, N.D., is senior vice president, scientific and regulatory affairs for the Council for Responsible Nutrition (CRN). Dr. MacKay oversees CRN's science and regulatory affairs department, ensuring that the association's scientific, policy and legislative positions are based on credible scientific rationale. His expertise combines practical knowledge of industry regulation and scientific product development with hands-on experience as a medical practitioner. He is a licensed naturopathic doctor. Prior to joining CRN, Dr. MacKay spent eight years working as a medical and nutrition expert for two companies in the dietary supplement industry, including four years as an executive with Nordic Naturals, where he was in charge of clinical research. He previously served as Technical Advisor for Thorne Research. Dr. MacKay has published articles in peer-reviewed journals, and serves on the Editorial Board of the peer-reviewed publications: the *Journal of Alternative and Complementary Medicine, Integrative Medicine: A Clinician's Journal, Current Topics in Nutraceutical Research*, and the official publication of the American Association of Naturopathic Physicians, *Natural Medicine Journal*. Dr. MacKay serves on the Advisory Board for the American Botanical Council, the NSF International Joint Committee on Dietary Supplements, the National Institute of Standards Technology/National Institutes of Health, Dietary Supplement Laboratory Quality Assurance Program, and Nutritional Outlook. He is also Chair of the Steering Committee for the SIDI Work Group. Dr. MacKay earned his undergraduate degree from the University of California, Santa Cruz, and his N.D. from the National College of Naturopathic Medicine in Portland, Oregon.



"ANALYSIS OF BITTER ORANGE CONTAINING DIETARY SUPPLEMENTS BY LC-MS/MS"

Pawar, RS and Sagi, S

Office of Regulatory Science, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, College Park, MD, USA

Citrus aurantium, commonly known as bitter orange, is a popular dietary supplement ingredient sold worldwide. Bitter orange supplements are sold primarily as weight management and sports performance products and gained popularity after Ephedra products were banned in the US market. These products are formulated with bitter orange extracts that are standardized for their synephrine content, the primary amine of bitter orange, typically 4-6% of the extract, but concentrations up to 95% have been reported. Synephrine is known to exhibit adverse cardiovascular effects, especially in the presence of caffeine. Several synthetic derivatives of bitter orange compounds, whose effects in humans are not known, have also been reported in dietary supplements. In the current work, an LC-MS/MS method was established to quantify synephrine, octopamine, 4-hydroxyephrine, etilefrine, deterenol, phenylephrine, hordenine, and N-methyltyramine in dietary supplements. The method was validated and was found to have acceptable sensitivity, accuracy, and reproducibility. A survey of 62 products was conducted to measure the amounts of these amines in bitter orange containing products sold in the US market. These products were labelled to contain bitter orange peel, extract, or its amines. Some of the products were found to contain high amounts of these amines.



"EXPLORING ANTIMICROBIAL NATURAL PRODUCTS AS FOOD PRESERVATIVES"

Xing-Cong Li, Siddharth K. Tripathi, Ikhlas A. Khan

National Center for Natural Product Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, Mississippi 38677, United States;

Food preservatives are utilized to prolong the shelf life of food products due to their antimicrobial and/or antioxidant properties. They play an important role in ensuring the quality and convenience of life to a healthy living. Current food preservatives have been used for decades and have many drawbacks. To address the need for the development of safer food preservatives, we have established an in vitro antimicrobial assay panel to screen natural product extracts derived from plants, marine organisms, and microbes. We have also evaluated many small-molecule antimicrobial natural products that are available in the National Center for Natural Product Research Repository. Salient results and potential issues will be discussed in this presentation.

This work was supported by the USDA Agricultural Research Service Specific Cooperative Agreement No. 58-6060-6-015.



"STEVIA REBAUDIANA AND ITS TETRACYCLIC DITERPENE GLYCOSIDES AS A SOURCE OF HIGH-POTENCY SWEETENERS"

<u>Perera WH</u>¹, Rodenburg DL¹, Alves K¹, Ghiviriga I², Carvalho R³, Ramsaroop T¹, Wiggers FT⁴, Hufford CD⁴, Ibrahim MA⁴, Muhammad I⁴, Avula B⁴, Khan IA^{4,5} & McChesney JD¹.

¹ Ironstone Separations, Inc., Etta, MS 38627, USA

² Department of Chemistry, University of Florida, FL 32611, USA

³ Universidade Federal de Mato Grosso do Sul, 79070-900 Campo Grande-MS, Brazil

⁴ National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences. University of Mississippi, MS 38677, USA.

⁵ Department of Pharmacognosy, School of Pharmacy, University of Mississippi, MS 38677, USA

Stevia rebaudiana (Bertoni) Bertoni is a perennial shrub of the botanical family Asteraceae that grows up to 1 m tall. The plant is native to Brazil and Paraguay, where the leaves have been used by indigenous peoples of both countries for their sweet taste. It is now recognized that the diterpene glycosides with an *ent*-kaurene skeleton are the sweet principles. The United States Food and Drug Administration granted *generally recognized as safe* (*GRAS*) regulatory acceptance to rebaudioside A in 2008, and to steviol glycosides in 2010. Increased interest in non-caloric natural sweeteners has generated significant attention to glycosides from *S. rebaudiana*. Herein, is presented the processing strategy used to remove major steviol glycosides and the scale up of the purification process of minor steviol glycosides using large-scale normal phase high-performance and reversed-phase chromatographies at relative low cost. Due to the slight structural differences of steviol glycosides. co-elution is very common in a single high-performance liquid chromatographic method. Therefore, different high-performance liquid analytical techniques were developed to better verify the identity of a known or new target analyte in fractions rich in steviol glycosides. In addition, two approaches (chemical modification/reversed-phase high-performance liquid chromatography and electrospray ionization quadrupole time-of-flight tandem mass spectrometry) are also described as an aid for structure elucidation of new steviol glycosides. Combining the processing strategy and described isolation approaches with 1D and 2D NMR experiments several minor natural and chemically modified tetracyclic diterpene glycosides were unambiguously elucidated and described for the first time.



"MELATONIN IN DIETS AND DIETARY SUPPLEMENTS"

Erland LAE¹, Saxena PK¹, & Murch SJ²

- 1. ¹Department of Plant Agriculture, University of Guelph, Guelph, Ontario, Canada, N1G 2W1
- 2. ²Chemistry, University of British Columbia, Kelowna, British Columbia, Canada, V1V 1V7

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine neurotransmitter produced by the pineal gland and involved in sleep, regulation of circadian rhythms, and neurological health. In 1997, we reported that 3 plants used as natural products to treat neurological ailments contained relatively high levels of the human neurohormone melatonin. At the time, melatonin had only been found in plants in 2 nutritional studies of food products but over the last 20 years, melatonin has been identified in almost every plant family and in many of the plants we consume as a normal part of a daily diet. Some examples of plants that contain significant quantities of melatonin include onions, garlic, asparagus, pineapple, banana, rice, ginger, cherries, grapes, walnuts, cranberries, wine, coffee, tea, beer, medicinal plants and herbal supplements. Cooking and other food preparations decrease melatonin content, so the highest levels tend to be in fresh fruits, vegetables and unprocessed foods. Based on Canada's Food Guide, a standard diet contains about 200-300 µg/day of plant melatonin but could be as high as 3 mg/day with the addition of high melatonin foods like chocolate, nuts, and wine. Plant-based melatonin supplements formulated from concentrated extracts of cranberry and wine grapes are sold in European and North American markets. In the U.S.A. and Canada, melatonin tablets are sold as non-prescription supplements but in the E.U. melatonin is sold as a prescription drug with a label dose of 1, 3, 5 or 10 mg/tablet. Plant melatonin in foods and supplements could have direct impacts on circadian rhythms, insomnia, jet lag, anxiety and psychosis as well as recently hypothesized roles of dietary melatonin in complex diseases such as cancer, cardiovascular disease and neurodegenerative disease. Therefore, the dietary intake of melatonin, the composition of melatonin supplements and the impacts on human health and chronic disease warrant further investigation.



Financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC), the Gosling Research Institute for Plant Preservation and the Canadian Foundation for Innovation is gratefully acknowledged.



"FAST, SENSITIVE AND COMPREHENSIVE ASSAY TO QUANTIFY 112 PESTICIDE RESIDUES IN BOTANICAL AND NON-BOTANICAL DIETARY SUPPLEMENTS USING LC/MS/MS AND GC/MS/MS COUPLED WITH QUECHERS EXTRACTION

Liu A, Taylor D & Carter S, 1945 S, Fremont Dr. | Salt Lake City, UT 84104

Vitamin B_{12} has a key role in the normal functioning of the brain and nervous system with different forms including cyanocobalamin (cB_{12}), methylcobalamin (mB_{12}), adenosylcobalamin (cobamamide) and hydroxocobalamin (hB_{12}). The mB_{12} , cB_{12} and cobamamide are three natural forms of B_{12} , while cB_{12} is a synthetic form. Due to B_{12} 's special chemical structures and low amount in supplement, to the best of our knowledge, there is no published ultra-sensitive LC/MS/MS method to quantitate these B_{12} in finished goods. Thus, AOAC has called combo quantitative method to measure vitamin B_{12} in dietary supplement. Here, we report an ultra-sensitive, simple and specific LC-MS/MS assay for cB_{12} , mB_{12} and cobamamide in protein and non-protein dietary supplements.

Around 2 grams of protein or non-protein sample containing B_{12} and internal standard (IS) was extracted by diluent composed of water/methanol, followed by filtration with 0.45 μ m membrane filter. Extracts were injected for analysis on Shimadzu Nexera UPLC system with a Synergi Hydro-RP column at 40 °C and water/methanol as needle wash solvent under external needle wash mode. The mobile phase is consisted of formic acid, water and acetonitrile using a shallow gradient for 6 mins with 0.400 mL/min. A Sciex TSQ 5500 was used for quantitation with positive ions formed in the ESI mode. MRM transitions m/z 678.6 \rightarrow 358.9, 673.6 \rightarrow 665.6, 791.4 \rightarrow 665.7 and 669.5 \rightarrow 400.8 were monitored for cB12, mB12, cobamamide and IS, respectively.

The molecular weights of cB12, mB12, cobamamide and IS are 1355.4, 1344.4, 1579.6 and 1399.4 g/mol, respectively, while the mass range of Sciex TSQ 5500 is only 50-1250 m/z. Thus, instead of molecular weight ions, the proper fragmentations of B₁₂ are monitored as Q1 in MRM. Due to B₁₂ contains a Corrin ring with various attached side-groups, it is relatively challenging to form the fragmentation in ion source under MRM mode. Different fragments were investigated during method development and the one with the fewest interferences was selected for both the analytes and IS. Various columns and mobile phases were screened to achieve symmetrical peaks, and a Synergi Hydro-RP column with mobile phases composed of formic acid, water and acetonitrile provided optimal chromatography. Column carryover was initially observed; however, it was minimized under external needle wash mode. The stability study indicated that B₁₂ is very sensitive to the light and temperature, so extraction under yellow light and reduced temperature was applied to prevent instability issue. For non-protein dietary supplements, there is no significant matrix effect, and the standard calibrators could be prepared in the diluent directly. However, the matrix effect was observed in the protein dietary supplement, and the standard calibrators prepared protein supplement placebo was used to successfully compensate matrix effect. The sensitive combo B12 assay was successfully developed and fully validated for intra-day and interday precision and accuracy, selectivity/specificity, various stability conditions and recovery. The intra- and inter-day accuracy (% bias) at all QC levels for both protein and non-protein dietary supplement met the acceptance criteria (CV% ≤15%).

The validated method has been successfully applied into analysis of various supplemental products. It was noticed that the B12 contents in these products varies widely. For some products with large serving size, above validated range (2.00-200 ng/mL) is not sensitive enough. Further method development was conducted to establish a lower curve of 0.100-1.00 ng/mL. This lower curve is being under validation.



"METABOLOMIC ANALYSIS OF UNANI AND AYURVEDIC MEDICINES FOR SCIENTIFIC VALIDATION OF TRADITIONAL CLAIMS"

<u>Sayeed Ahmad</u>, Bioactive Natural Product Laboratory, Department of Pharmacognosy and Phytochemistry, School of Pharmaceutical Education and Research, Jamia Hamdard (Hamdard University), New Delhi, India-110062

Metabolomics is a modern omic-technique aims to characterize & analyze the phytochemicals, metabolites & garnered extensive interest in the research community, especially in traditional medicine or TM where maximum components of dosage form are unknown. The application of metabolomics was introduced in TM to promote identification of bioactive compounds & to insure quality of traditional Unani medicines.

Quality control of Unani TM continues to be a challenge & restricts its development throughout the world. The fingerprint analysis technique has been introduced & accepted as a strategy for assessing consistency between batches of TM. Metabolic fingerprinting of Unani & Ayurvedic medicines can be used for both qualitative & quantitative analysis. Several analytical methods have been published for the analysis of multiple markers of single herb but the main difficulties are the lack of an analytical method for scientifically evaluating the complex chromatograms of traditional formulations having multi-herbs & processed by multi-step technologies. Advances in mass spectrometry (MS) based platforms like GC-MS & LC-MS, helped in separation & identification of several metabolites.

Unani & Ayurvedic medicines are composed of more than one herb. The quality & content of the metabolites are highly variable depending on geographical origins, climate, cultivation, & the growth stage when harvested. The therapeutic effect of them are based on the synergic effect of their complex components, which is unique & different from western medicine.

There is insufficient data on traditional Indian medicines due to the lack of modern & scientific approaches for standardization. All the metabolites present in them are neither bioavailable nor bioactive & hence, in vivo pattern recognition is an important aspect, to identify the bioactive metabolites. Various chromatographic & hyphenated techniques are for quality control analysis to identify the bioactive compounds, to elucidate the mechanism & to validate the traditional claims. Thus, utilization of metabolomic approaches for exploring therapeutic efficacy, clarifying possible mechanisms of action, & modernization of traditional dosage forms followed by evaluation of quality of Indian medicines are need of present scenario to make them globally acceptable



"FDA ROLE IN REGULATION OF CANNABIS PRODUCTS"



Cassandra Taylor, Ph.D. is a Chemist at U.S. Food and Drug Administration within the Center for Drug Evaluation and Research (CDER) and is a member of the Botanical Review Team (BRT) which resides in the Science Staff (SRS) within the Immediate Office of the Office of Pharmaceutical Quality (OPQ/IO). She received her B.S. in Chemistry with a minor in Forensics from St. Francis University in Loretto, PA (2005), and her Ph.D. in Analytical Chemistry from the University of Maryland in College Park, MD (2014) under the guidance of Dr. Alice Mignerey. She conducted her graduate research work on anthocyanin extraction, isolation and identification from purple pepper foliage under the mentorship of Dr. John Stommel at the U.S. Department of Agriculture, Agricultural Research Services, Beltsville Agricultural Research Center, Plant Science Institute, Genetic Improvement of Fruits and Vegetables Laboratory (USDA/ARS/BARC/PSI/GIFVL). Cassie worked for Eurofins Scientific, Nutrition Analysis Center (Des Moines, IA) for 3 years where she initiated startup and develop improvement to juice authenticity analysis in the United States for Eurofins. She joined FDA in December 2014 as a member of BRT within the Science Staff (SRS) of OPQ/IO. Cassie is an active member of BRT and SRS, which is an efficient, agile, and flexible rapid response team that coordinates the intersection between science, review, and policy in OPQ while serving as in-house consultants on science. She works in collaboration with her BRT colleagues, who collective serve as an expert resource for CDER on all botanical issues.



"FDA ROLE IN REGULATION OF CANNABIS PRODUCTS"

19th Annual | April 8th – 11th, 2019



Dr. Thomas D. Marcotte is Professor of Psychiatry at the University of California, San Diego, and Co-Director of the UC Center for Medicinal Cannabis Research (<u>www.cmcr.ucsd.edu</u>), which has conducted clinical trials of cannabis for almost 20 years, and has an active, ongoing portfolio exploring the effects of cannabinoids (plant-based, synthetic) in various medical/psychiatric conditions. He is currently the principal investigator on studies addressing cannabis for the treatment of pain, and the effects of acute cannabis use on driving performance. He has previously been co-investigator on numerous cannabis studies addressing pain and spasticity in multiple sclerosis. He has also served as the Center Manager of the HIV Neurobehavioral Research Center, Co-Director of CHARTER (a national multi-site study of the CNS impact of treatments for HIV), and Director of Mental Health for the UCSD HIV Clinic. Dr. Marcotte has been on on the editorial boards of Neuropsychology and the Journal of the International Neuropsychological Society.



"CANNABIS-DERIVED THERAPEUTICS: NEW DEVELOPMENTS"

Dr. Marcotte will review recent findings regarding the potential for cannabis and cannabinoids to treat various medical conditions, as well as the potential side effects and safety concerns regarding cannabis as medicine. He will also address current barriers to cannabis research, and changes taking place in the regulatory landscape.





Dr. Brad Ingram is a 2001 graduate of the University of Mississippi and a 2005 graduate of the University of Mississippi Medical Center. He completed 2 residencies at the University of Mississippi Medical Center, one in Pediatrics and one in Pediatric Neurology, and was Chief Resident for both. He subsequently pursued a fellowship in Pediatric Epilepsy at the Cleveland Clinic, and is now Associate Professor of Pediatrics, Director of the Pediatric Comprehensive Epilepsy Program, and Assistant Dean of Graduate Medical Education. He is Principal Investigator of the Cannabidiol (CBD) Cannabis Extract Oral Solution for Drug Resistant Pediatric Epilepsy trial at the University of Mississippi Medical Center.



"CANNABIS-DERIVED THERAPEUTICS: NEW DEVELOPMENTS"





Alice P. Mead, J.D., LL.M received her Juris Doctor degree from University of Santa Clara School of Law and her Master of Law degree from Yale. She served for twelve years as an in-house counsel to the California Medical Association (CMA), one of the largest state medical associations in the country. Prior to that time, Ms. Mead was a litigation associate at a global law firm and an Assistant Professor of Law at Arizona State University College of Law, where she taught courses in constitutional law. Since 1999 she has served as Vice President, U.S. Public Policy and Public Affairs, for GW Pharmaceuticals (and its U.S. subsidiary, Greenwich Biosciences), one of the first companies in the world to develop cannabis-derived medications as prescription products in adherence to modern scientific and regulatory standards for pharmaceutical products. She focuses on domestic and international drug control laws and policy issues.



"HOW CANNABIS-DERIVED MEDICATIONS GO THROUGH THE FDA APPROVAL PROCESS"

Securing approval from the Food and Drug Administration (FDA) is difficult for any investigational medication, but the challenges are even greater for products derived from botanical materials. In addition, there are additional hurdles and requirements for products containing substances that may affect the central nervous system (CNS). Strict control of the conditions of cultivation and harvest of the botanical starting material is the essential first step. Multiple quality control steps, specifications (agreed to by FDA), and batch-to-batch consistency are required at each point along the way as the botanical raw material moves through various stages into a finished drug product. Since cannabis is classified in Schedule I of the Controlled Substances Act, special federal and state license and security requirements apply. Because cannabinoids have CNS activity, a full battery of abuse potential studies must be conducted. Upon FDA approval, a new cannabinoid product must be rescheduled under both state and federal law before it can be dispensed by pharmacies.





Adam Gibson is the Vice President of Public Affairs for Consumer Health Products Canada, the industry association representing companies that make evidence-based over-the-counter medicines and natural health products. Before joining industry, Adam worked for over 17 years within the Canadian federal government. His government roles have included those of Associate Director, Clinical Trials, Therapeutic Products Directorate (pharmaceuticals), Executive Director of the Food Directorate, and Director General, for the Natural and Non-Prescription Health Products Directorate all within Health Canada's Health Products Food Branch. In addition to his regulatory work, Adam has a rich history of collaboration and partnerships with domestic and international organizations including governments, health professionals, academia, industry and NGOs.



"NATURAL HEALTH PRODUCT REGULATIONS"

In 2004, the Canadian government introduced the Natural Health Product Regulations. These laws were based on 53 recommendations from a parliamentary standing committee on health and included the creation of a responsible government body that was then called the Natural Health Products Directorate within Health Canada. The Canadian parliament gave this new directorate the following mission: "The mission of the NHPD is to ensure that all Canadians have ready access to natural health products that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity."

As a former Director General of the Natural Health Products Directorate, Adam Gibson will reflect on the past 15 years of this program; the impact it has had on the Canadian market, successes, challenges and unintended consequences. Health Canada is now advancing consultations on a new strategy for all self-care products, including natural health products. This talk will cover the current state of the Canadian regulatory scheme touching on how well it appears to be performing with modern day influences including e-commerce, and intersections with Canada's Cannabis Act.





Armando Cáceres, Chemical Biologist, Faculty of Chemical Sciences and Pharmacy, University of San Carlos (USAC), Guatemala. Specialization in Immunology at Universities of Wisconsin, Laussane, Brasilia and del Valle (Colombia). Training in Pharmacognosy in USAC and Kitasato University, Japan, and phytopharmaceutical technology, Fluminense Federal University, Brazil. Retired Professor of Immunology, Immunopathology and Hematology (undergraduate) and Phytotherapy and Biological Medicine (graduate), USAC. Professor of Integrative Medicine and Phytototherapy, Galileo University, and Phytomedicine, San Pablo University, Guatemala. Experience as Coordinator or Director of several national and international project for research, production and utilization of medicinal plants and natural products. Founder and Research Director at Farmaya Natural Products Laboratories. Granted with research projects from national (CONCYT, DIGI and IIQB) and international (WHO, GTZ, IDRC, UNIDO, JICA, OAS, NIH, DED and CYTED) organizations. Has received several national and international awards, mainly José Capote Díaz Award (Panamerican Federation of Pharmacy and Biochemistry), Science and Technology Medal 1998 and University Medal 2000 and 2011. Author of more than 300 scientific papers, presentations and specialized books on the multidisciplinary approach of natural products. Organizer of more than 80 national and international scientific events, as well as technological transfer to enterprises, NGOs and community groups. Reviewer for 15 scientific journals and editor in two journals. Member of several international associations.



"REGULATION OF NATURAL HEALTH PRODUCTS IN LATIN AMERICA – CURRENT SITUATION AND FUTURE DEVELOPMENTS"

Armando Cáceres, Universidad de San Carlos de Guatemala Laboratorios de Productos Naturales Farmaya (<u>acaceres@farmaya.net</u>)

By the end of XX Century it was evident that there was an increasing demand and acceptation on natural health products (NHP) in Latin America, but the regulation, good manufacturing practices and quality issues were limited. A regionwide survey on the legislation of NHP in 1999 demonstrated high heterogeneity about the definition of the object of regulation and the requirements for registration and commercialization, suggesting the need for harmonization actions. Due to regulation by regions, at least three regional setting can be identified: Andean pact, South Cone and Central American common market. In the particular field of NHP this regional regulation is the tendency, contributing to more efficient harmonization. Nevertheless since early XXI century a dramatic change towards the inclusion of NHP in the concept of traditional, alternative or complementary medicine has conducted the regulation developments in the region leading to the modern concept of integrative medicine. This presentation will review briefly the main developments in regulation of NHP and integrative medicine in the Latin American countries. Concluding remark will identify the current situation and future developments.





Associate Professor Jon Wardle has clinical backgrounds in nursing and naturopathy and heads the Regulatory, Legislative and Policy Stream at the Australian Research Centre in Complementary and Integrative Medicine, Faculty of Health, University of Technology Sydney, where he holds a prestigious Australian National Health and Medical Research Council Research Translation Fellowship. In addition to his clinical qualifications, Jon also has postgraduate qualifications in public health (including a doctorate from the University of Queensland), law and health economics and holds visiting positions at the Schools of Medicine at University of Washington and Boston University. Jon has published more than 100 peer-reviewed journal articles and over 20 academic book chapters. Jon works on the editorial board of eight international academic journals, including serving as the Editor-in-Chief of the journals International Journal of Naturopathic Medicine and Advances in Integrative Medicine. Jon is also co-editor of Clinical Naturopathy: an Evidence-Based Guide to Practice, published by Churchill Livingstone now used as a core naturopathic teaching text in over a dozen countries. Jon is actively involved in research and policy at the interface of public health and traditional medicines. Jon is co-convener of the Public Health Association of Australia's Research Advisory Committee as well as the PHAA's Complementary Medicine Special Interest Group, is part of the American Public Health Association Integrative Health Section Policy Committee, and he has led several World Federation of Public Health Association initiatives on traditional medicines. Jon currently serves as Secretary-General of the World Naturopathic Federation, an organisation that represents naturopathic medicine at international organisations such as the World Health Organization. Jon has worked on traditional medicine, public health and primary health care policy and regulatory initiatives with numerous governments, non-government organisations and international bodies. Jon is passionate about both protecting and embracing tradition knowledge and fostering innovative research, and believes that by combining both can optimal public health outcomes be achieved.



"AUSTRALIAN REGULATORY REFORMS FOR TRADITIONAL AND COMPLEMENTARY MEDICINES: CHALLENGES, OPPORTUNITIES, AND LESSONS LEARNED"

Recent regulatory reforms around traditional and complementary medicines and amendments to the Therapeutic Goods Act 1989 - aimed at improving patient access to new medicines in a timely manner and encouraging industry innovation – transform the way in which therapeutic goods will be regulated in Australia. This includes stricter enforcement of advertising claims, but also allows the ability for some products to use higher level claims and gain market exclusivity for traditional and complementary medicines via a "third-listing pathway". Specificity clauses also allow for better intellectual property protections for product sponsors. These reforms are expected to drive innovation and research in the complementary medicines sector, as well as offer consumers a more informed indication of natural product effectiveness. These reforms also potentially open opportunities for international sponsors to pilot innovative and research-led natural health products in a climate of market exclusivity. Other reforms (highlighted previously) – such as the allowance of traditional medicine claims and the use of de novo and overseas regulator evidence – have had significant transformation during the implementation phase, and the challenges and the opportunities for product sponsors in Australia and overseas, and examine the lessons learned during the implementation of the largest reforms the natural health products sector has seen in recent decades, and what this means for product manufacturers, users and suppliers in Australia and internationally.



"HEPATOTOXICITY OF CANNABIDIOL IN THE MOUSE MODEL"

Ewing LE^{1,2}, Skinner CM^{1,4}, Elsohly MA^{5,6,7}, Gurley BJ^{3,4}, Koturbash I^{1,4}

¹Department of Environmental and Occupational Health ²Department of Pharmacology and Toxicology, ³Department of Pharmaceutical Sciences, ⁴Center for Dietary Supplements Research, University of Arkansas for Medical Sciences, Little Rock, AR; ⁵ National Center for Natural Products Research and ⁶Department of Pharmaceutic and Drug Delivery, School of Pharmacy, University of Mississippi, University, MS and ⁷ElSohly Laboratories, Inc. (ELI), Oxford, MS

Cannabidiol (CBD) is a non-psychotropic ingredient of Cannabis sativa and is a major component of EPIDIOLEX®, the drug designed for treatment of epileptic seizures. Utilization of CBD progressively increased in the last year due to the increased availability of CBD to the general public together with aggressive marketing that advertises CBD for management of migraine and other painassociated conditions. Emerging evidence, however, indicates that CBD poses a risk for hepatotoxicity. The goal of this study was to investigate the hepatotoxic potential of CBD delivered with sesame oil to the 8-week-old male B6C3F1 mice. Animals were gavaged with allometrically scaled mouse equivalent doses (MED) of either 0, 20, 60, or 200 mg/kg of CBD (acute toxicity, 24 h) or with daily doses of 0, 5, 15, or 50 mg/kg for 10 days. In both studies, CBD exhibited clear evidence of hepatotoxicity. Specifically, in the acute toxicity study, besides increases in the liver-to-body weight (LBW) ratio, gavaging mice with 200 mg/kg of CBD resulted in increased plasma concentrations of ALT and AST and spiking (~20-fold) levels of total bilirubin. In the sub-acute study, 50 % of mice gavaged with 50 mg/kg developed severe toxicity exhibited as tremor and lethargic condition between days 3 and 4 (after 2 or 3 doses of CBD). Similarly to the acute toxicity study, CBD caused increases in LBW ratio, ALT and AST as well as spiking levels of total bilirubin at 50 mg/kg dose. Hepatotoxicity gene expression array revealed over 50 genes that were differentially regulated in the livers of mice gavaged with CBD. Further analysis highlighted involvement of genes associated with response to oxidative stress and lipid metabolism as well as a number of cytochromes responsible for metabolism of common drugs (i.e., acetaminophen, phenobarbital) and ethanol. In conclusion, gavaging mice with clinically-relevant MED of CBD was clearly evidenced by signatures of hepatotoxicity. Increased serum concentrations of ALT and AST, paralleled by spiking levels of bilirubin suggest possibly cholestatic nature of liver injury. Furthermore, involvement of numerous pathways associated with lipid metabolism as well drugs metabolism and toxicity raises serious concerns regarding the safety of CBD.



"NOVEL SCREENING METHOD (SYNCAN) FOR 370 SYNTHETIC CANNABINOIDS BY ACCURATE MASS Q-TOF MASS SPECTROMETRY"

Neal-Kababick, James¹, Prozy, Pierce¹ ¹Flora Research Laboratories, LLC, Grants Pass, OR, 97526-3900, USA

Synthetic cannabinoids such as JWH-018 and HU-210 have been identified in products marketed as herbal incense blends which are in fact, clandestine products sold with the intention of being consumed as drugs. With the emerging CBD market, there have been reports of synthetic cannabinoid adulteration into vaping products. We present a novel screening method (SYNCAN Panel) for 370 synthetic cannabinoids utilizing an 18 minute separation on a rapid resolution liquid chromatography (RRLC) C18 column coupled to an accurate mass quadrupole-time of flight mass spectrometry (AM-QTOF-MS) detector. Data is analyzed using a Personal Compound Database Library (PCDL). The method offers rapid separation, a large panel of compounds, automated data analysis and the ability to detect novel clandestine synthetic cannabinoids. Analysis of CBD vaping liquids sold in the US market revealed several adulterated products containing different synthetic cannabinoids. This method has been adopted as part of the ICCT (International Center for Cannabis Therapy) qualification screening for North American entities seeking ICCT Certification.



"Ensuring the Safety of Cannabis by Screening for Approved and Unapproved Pesticide Residues"

Wylie PL and Westland J

Agilent Technologies, 2850 Centerville Rd., Wilmington DE 19808

With the use of medicinal and recreational cannabis becoming legal in Canada, Uruguay and many US states, there is an increased need to test cannabis products to ensure their safety. Pesticide residues on the plant material are of concern because cannabis can be ingested or smoked or extracted and concentrated for use in everything from food and beverages to tinctures and suppositories. Many jurisdictions that have legalized cannabis require testing for pesticide residues. For example, California, Oregon and Canada have lists of 66, 59, and 95 pesticides, respectively, that must be targeted by analysts. Unfortunately, some growers use pesticides that are not on lists of acceptable compounds for which maximum residue limits (MRLs) have been set. Product recalls are common, companies have gone out of business and occasionally someone is fined or even jailed for misuse of pesticides. On top of this, the unregulated black market for cannabis is still much bigger than the legal market. Many of the illegal growers use pesticides carelessly and leave unknown levels of sometimes illegal pesticides on the plant material.

Typically, laboratories test for pesticide residues on cannabis using gas chromatography and liquid chromatography with tandem quadrupole detectors (GC/TQ and LC/TQ). These instruments are extremely sensitive and are very selective in the multiple reaction monitoring (MRM) mode. However, they can only find those pesticides that are on the target list. Other pesticides and environmental contaminants will be missed.

Clandestine cannabis growers often use illegal pesticides and rodenticides at their grow sites. For example, carbofuran, an insecticide that is banned for use in the US was found at 78% of the eradicated illegal grow sites in 2017. This highly toxic pesticide would be missed by typical laboratory testing procedures. In this presentation we describe a procedure to test for over 1000 GC-amenable pesticides and environmental contaminants using an Agilent 8890/7250 GC quadrupole time-of-flight mass spectrometer (GC/Q-TOF) together with the Agilent Pesticides and Environmental Contaminants (P&EP) Personal Compound Database and Library (PCDL). The procedure is qualitative in nature, but quantification is possible when standards are available.

The authors would like to acknowledge Drs. M. ElSohly, M. Wang, M. Radwan, C. Majumdar and I. Khan for their help in the initial stages of this project and for providing samples for analysis.



"LOW THC PRODUCTS REGULATION AT EUROPEAN LEVEL - CURENT STATUS AND ITS FUTURE"

Tomas Sadilek joined the ICCI in the position of Director of Government Affairs. He brings with him extensive experience from the Office of the Government of the Czech Republic in the field of Legal and Illegal Drugs. Tomas represented the Czech Republic in all drug-related meetings in the United Nations institutions (Vienna, New York). Furthermore, he represented the Czech Republic in meetings in the EU area, Eastern Partnership countries area, occasionally the US; these being related to UN meetings, Council of the EU meetings and Council of Europe meetings

Hemp products and its reguation in European Union. I would like to also talk about regulation at the national level and provide guidance to understand the whole problematic from the perspective of food, food supplement and cosmetics.



Panel Moderators and Session Chairs: Larry Walker & Trish Flaster

There has been an explosion of interest in recent years in consumer products derived from cannabis (*Cannabis sativa* L.) and its components, including cannabidiol (CBD). An increasing variety of products are marketed in many states, and sold nationally via a number of channels, many of them based on the position that the "Farm Bill" allows exclusion of these products from Controlled Substance Act restrictions. The December 2018 Farm Bill (formally, the Agriculture Improvement Act of 2018) more explicitly codified a new definition of "hemp" – defined as cannabis and cannabis derivatives with low (no more than 0.3 percent dry weight) concentrations of THC. This is widely viewed as removing, once and for all, the CSA restrictions on the marketing of hemp-derived products. However, some potential ambiguities in these definitions still need to be resolved, and the implementation of these provisions in different states will entail development of "state plans" and approval by the U.S. Department of Agriculture and the Attorney General. The quality of some of the FDA will be critical in the marketing of any hemp/CBD-based consumer products – certainly with regard to permitted labeling, and perhaps more. The recent approval of the prescription drug Epidiolex^R (CBD) - for certain forms of intractable childhood epilepsy – will certainly be raised in FDA deliberations. This panel will explore these questions, with panelists addressing relevant issues, and audience participation in a "town hall" format.



Daniel Shortt, Attorney, Harris Bricken



Roger Hayes lives and breathes business development. Being a start-up junkie for over twenty years, Roger has utilized his talents for fact finding, truth telling, connecting talented people, and distribution channels across various consumer driven markets, including healthcare and wellness, prescription drug abuse prevention and most recently, hemp and hemp derived cannabinoids. He was born and raised in Kentucky where he attended the University of Kentucky.

Vice President Of Business Development, Green Remedy, Jun 2018 - Present

Green Remedy Inc. is a company founded in 2014. Being vertically integrated, Green Remedy will grow close to 500 acres of hemp on its Kentucky owned farms this year and process hemp extracted products through its 52,000 square feet of facilities in Louisville, KY. We are true Kentuckians and have been a part of the Kentucky farm family for many years. Our top priority is to produce and process the best quality U.S. grown hemp to be used in CBD nutritional & hemp food products. Our primary focus is on clean, safe, and efficient Supercritical CO2 extractions, which is proven to be the best and safest way to extract botanical compounds for products that can be used around the world.

Chief Operating Officer, Alternative Health Solutions, Jan 2014 – Mar 2017

Alternative Health Solutions brought a unique approach to the delivery of health care by partnering with employers to provide primary care and wellness programs. The model focuses on much more than "sick care". The belief at AHS was that a fully integrated, patient centric model is the only way to greatly effect population health. I was very fortunate to find the best people for the tasks at hand, as we built this great startup brand. My responsibilities included:

1. Spearhead the development, communication and implementation of Care Center growth strategies and processes that will streamline patient centered care;

2. Motivate and lead a high performance management and support team; attract, recruit and retain people who fit our culture first and a position second.

3. Communicate areas of strength, progress, opportunities to improve, financial status, and future growth with Board and Investors.





Courtney N. Moran, LL.M. founding principal of EARTH Law, LLC and chief legislative strategist for Agricultural Hemp Solutions, LLC is the leading expert on U.S. hemp law championing legal policy for sustainable *Cannabis* hemp agribusiness development. Courtney's article, *Industrial Hemp: Canada Exports, United States Imports* was published by the Fordham Environmental Law Review. She successfully lobbies for the Oregon Industrial Hemp Farmers Association passing legislation protecting Oregon hemp agricultural interests. She has also authored and strategically guided the passage and implementation of legislation establishing the hemp programs for the states of South Carolina, Wisconsin, Alaska, and most recently Missouri. Courtney successfully litigated the landmark cases *KaB, LLC v USPIS*, MLB 18-39 (2018) and *RNF, LLC v USPIS*, MLB 18-113 (2018) establishing precedent for the shipment of hemp, specifically hemp-derived CBD and viable hemp seeds, through the US Postal Service. Courtney worked closely with the offices of Senator Ron Wyden and Senate Majority Leader Mitch McConnell in drafting the Hemp Farming Act of 2018 (S. 2667), the language of which was included in the 2018 federal Farm Bill, the Agriculture Improvement Act of 2018, providing for full federal hemp legalization.

Courtney currently serves on the Oregon State Bar Cannabis Law Section Executive Committee, as Second Vice Chair on the national NORML Board of Directors, on the InterNational Cannabis Bar Association Board of Directors, on the national Hemp Industries Association Board of Directors, and as President of the regional Pacific Northwest Hemp Industries Association. Courtney was voted by the HIA membership as the 2018 Hemp Industries Association Advocate of the Year!





James Neal-Kababick is the founder and Director of Flora Research Laboratories, LLC (FRL) which specializes in the research and analysis of botanicals, dietary supplements and related compounds. For many years he served as an adjunct faculty at Bastyr University where he taught botanical drug identification by microscopy and thin layer chromatography. He continues to provide education in dietary supplement quality control testing to students of the Botanical Medicine Department through their field learning program. In addition to his work at the private research lab and university, he serves on multiple expert committees for AOAC, USP, NIH, AHPA, and others. Currently, his work is focused on the utilization of modern analytical technologies in the investigation of dietary supplements and other agricultural products. He is the pioneer of the field called "Phytoforensic Science." Phytoforensic Science involves utilizing numerous technologies from microscopy to mass spectrometry to detect adulteration and contamination in the global food supply chain with a special focus on dietary supplements. He has developed and presented the Standardized Phytoforensic Approach (SPA) as well as the Crossover Analytical Technique (CAT) to address strategic approaches to clandestine adulteration and DNA identity issues respectively. In 2010 James was named "Fellow of AOAC." Fellow of AOAC is awarded to scientists for meritorious service to the scientific society and their field of science. It is the second highest honor the organization bestows upon scientists. James is also a renowned expert in the detection of clandestine pharmaceutical adulteration of dietary supplements. He developed expanded screening panels for PDE-5 inhibitors (ED drugs), weight loss drugs, steroids and synthetic cannabinoids (SYNCAN panel). He appeared on the Dr. Oz Show to help educate consumers about the growing clandestine adulteration problem with tainted dietary supplements. He is the vice-chair of the USP<2251> Screening for Undeclared Drugs and Drug Analogs (SUDDA) Expert Committee joining experts globally to apply the phytoforensic approach to address methodology approaches for investigating clandestine adulteration of dietary supplements. He also serves on the 2015-2020 USP Non-Botanical Dietary Supplement Expert Committee, the USP Joint Standard Settings Subcommittee, the Joint Subcommittee on Modern Analytical Methods, the USP Dietary Protein Expert Committee, and the USP Dietary Supplement Compendium Revision Committee as well as serving as a USP Recruitment Ambassador. Currently, his collaborations include development of databases and spectral libraries for rapid identification of botanicals, compounds and clandestine drugs as well as presenting lecture series and teaching hands on training courses in the phytoforensic sciences. He is the coauthor of several papers related to dietary supplement adulteration, chemical profiling of botanicals, and collaborative studies and was the co developer of the AOAC Validation of Dietary Supplement Analytical Methods, Validation of Quantitative Chemical Test Methods and BSI-NIH funded Method Development and Validation of Dietary Supplement Analytical Test Methods training courses which he taught for many years. James routinely assists various federal agencies in collaborations including the various FDA field offices, the FDA Office of Criminal Investigation, the FDA Forensic Chemistry Center, US Department of Justice, US Customs and Border Enforcement as well as the DEA, BATFE and various state agencies throughout the country. He currently serves as an expert witness for the United States Department of Justice and various state justice departments.





"FURTHER DEVELOPMENT OF CHINESE HERBAL MEDICINES THROUGH COLLABORATIONS-THE YILING PHARMACEUTICAL'S APPROACH"

Zhenhua Jia, Dean, Yiling Pharmaceutical





Dr. Ibrahim Jantan is a Professor in Medicinal and Natural Products Chemistry at Taylor's University, Malaysia since 1 August 2018. He graduated from University of Mansoura, Egypt with BPharm (Hons) degree in 1981, obtained his MSc in Medicinal Chemistry from University of Minnesota, USA in 1985 and his PhD degree in Natural Products Chemistry from the University of Malaya in 1993. Prior to his present position, he was with Universiti Kebangsaan Malaysia (UKM) from 1996-2018. He was the founding Dean of the Faculty of Pharmacy, UKM from 2008 to 2015 after being the Head of Pharmacy Department, UKM from 1998-2007. He is currently the President of the Malaysian Natural Products Society, member of the Malaysian Herbal Council, board member of Asian Association School of Pharmacy and Malaysian Focal Point for Medicinal Plants of Malaysia for Indian Ocean Rim Association. Recently he was appointed as Research Advisor of Nan Yang Academy of Sciences (Singapore). He has more than 30 years of research experiences in natural products and medicinal chemistry and pharmacological activities of natural products. His research interests are identification of natural bioactive compounds, their derivatives and analogues as chemical leads for specific therapeutic efficacy (cardiovascular protective, immunomodulatory, anti-inflammatory, PAF antagonist & antimicrobial activities) leading to the development of new drug candidates against complex and challenging drug targets prior to clinical trials. He has supervised 22 PhD & 23 MSc. students. He has published over 180 papers in ISIindexed journals, 73 papers in proceedings, 2 books and 5 chapters in books. He was recipients of many awards including Medicine Srinakharinwirot University (MEDSWU) Honorable Award 2010, Thailand, Prof. Dr. A. Hisham Endowment Award, India and Distinguished Researcher Award 2013, Universiti Kebangsaan Malaysia Medical Center.



"MODULATORY EFFECTS OF MEDICINAL HERBS ON THE IMMUNE SYSTEM AND THEIR POTENTIAL AS SOURCES OF IMMUNOMODULATORY DIETARY SUPPLEMENTS AND PHARMACEUTICALS"

<u>I. Jantan</u>

School of Pharmacy, Faculty of Health and Medical Sciences, Taylor's University, Lakeside campus, No. 1, Jalan Taylors, 47500 Subang Jaya, Selangor, Malaysia

The phagocyte-microbe interactions in the immune system is a defense mechanism but when excessively or inappropriately deployed can harm host tissues and participate in the development of different non-immune and immune chronic inflammatory diseases such as autoimmune problems, allergies, some rheumatoid disorders, cancers and others. Immunodrugs include organic synthetics, biological agents such as cytokines and antibodies acting on single targets or pathways have been used to treat immune-related diseases but with limited success. Most of immunostimulants and immunosuppressants in clinical use are the cytotoxic drugs which possess serious side effects. There is a growing interest to use herbal medicines as multi-component agents to modulate the complex immune system in the prevention of infections rather than treating the immune-related diseases. Many therapeutic effects of plant extracts have been suggested to be due to their wide array of immunomodulatory effects and influence on the immune system of the human body. Phytochemicals such as flavonoids, polysaccharides, lactones, alkaloids, diterpenoids and glycosides have been reported to be responsible for plants immunomodulating properties. Thus the search for natural products of plant origin as potential sources of potent and safe immunomodulatory dietary supplements and pharmaceuticals is gaining much major research interest. In this paper, the use of integrated and multi-target approach to discover herbal extracts and their immunomodulating principles will be presented. Several medicinal herbs including Phyllanthus amarus, Tinospora crispa and Zingiber zerumbet which are used in traditional medicine to treat microbial and viral infections, fever, allergy and various inflammatory conditions were selected to study their effects on different components of the immune system; in humoral and cellular immune functions which include specific actions on immune cells, effector mechanisms, inhibition of nitric oxide and reactive oxygen species production, secretion of inflammatory cytokines, lymphocytes proliferation, signaling pathways in macrophage cells, and phagocytic activities.

Acknowledgements: Financial support for this research from the Ministry of Agriculture and Agro-Based Industry (grant no. NH1014D020) is greatly acknowledged.





Dr. Mary Hardy, board certified in internal medicine and a specialist in botanical and integrative medicine, has actively combined complementary and alternative therapies with traditional Western medicine for over thirty years in both her clinical practice and research projects. After completing her undergraduate studies at Vassar College, she returned to her hometown, New Orleans, to attend medical school at Louisiana State University. She completed her internship and residency in Internal Medicine at Tufts New England Medical Center.

In 1998, Dr. Hardy founded the Integrative Medicine Clinic at Cedars-Sinai and participated in a NCCAM funded research project that evaluated the barriers and facilitators of Integrative Medicine practice based on her clinic. She also has extensive experience in evaluating the evidence base for the efficacy and safety of complementary/ integrative medicine as part of her work as a research associate at the RAND Corporation.

Over her five years at RAND, Dr. Hardy was the co-principle investigator in a number of systematic reviews of complementary and alternative medicine (CAM) topics conducted in the Evidence Based Practice Center at RAND. Her projects there, sponsored by the National Center for Complementary and Alternative Medicine, included assessing data for the safety of ephedra as well as the efficacy and safety of alternative cancer practices. She has served on and chaired several United States Pharmacopeia (USP) expert committees examining the safety of selected dietary supplements and chaired the USP committee, Dietary Supplements Safety Modeling Expert Panel. She has also served for years on the External Advisory Council for the Natural Product Directorate for the Canadian Ministry of Health assessing scientific issues pertinent to regulatory issues and serving as an expert in natural products risk assessment and clinical trial design.

She has also helped to establish the Integrative Medicine Health and Wellness Program at the Venice Family Clinic, the largest free clinic in the United States and served as the Co-director of that program. Dr. Hardy was co-director for the successful multidisciplinary clinical program for the management of chronic pain that has been established as a result of her team's efforts.

Dr. Hardy has recently completed a popular book for Readers Digest entitled Best Remedies and serves on a number of editorial and scientific advisory boards including the American Botanical Council, Evidence Based Complementary and Alternative Medicine, Phytomedicine and Integrative Medicine: A Clinicians Journal.

Dr. Hardy is recognized as an authority on integrative medicine and herbal/natural products by organizations such as the Office of Dietary Supplements, the California Medical Board, the Canadian government, the United States Pharmacopeia, American Medical Association, the American Pharmaceutical Association, National Geographic, CBS, NBC, Discovery Channel and the Los Angeles Times.

Dr. Hardy's current research interests include reviewing the evidence for the safety and efficacy of natural therapies, especially botanicals as well as conducting clinical trials of dietary supplements and lifestyle choices to reduce toxicity and to improve outcomes of conventional cancer treatment. She also has a long-standing interest in patients who have shown exceptional responses during cancer care.


"THE EFFECT OF DSHEA ON CLINICAL RESEARCH IN DIETARY SUPPLEMENTS"



Panel Moderator and Session Chair: Nandakumara Sarma

DSHEA provided a path for the use of botanicals and botanically-derived products as dietary supplements. Botanicals are amongst the fastest growing segments of the dietary supplements in US, and new regulations since 1994 in countries such as Canada, India, China, Korea and Brazil provided path for their use as health supplements. These regulations variously recognize the national and international pharmacopeias as a source for voluntary or mandatory quality standards. The global supply chain and the adoption of several botanicals that were traditionally used as medicines as foods or dietary supplements around the world present challenges in ensuring the quality of the ingredients and products. Harmonization of national standards could also help in providing validated analytical methods and promote public health and global commerce. This session will focus on the past, present and future for pharmacopeial approaches to botanical standard-setting, and to explore the new areas where the pharmacopeial standards can play an important role. The session is also expected to provide a forum for the industry and regulators to share their experience in using the pharmacopeial standards, and to identify the industry needs and priorities.

Discussion topics:

Science basis for pharmacopeial standard-setting

Transparent methods to meet regulatory needs

Potential for prospective harmonization

Global supply chain and commerce – implications for pharmacopeial standards

Current industry needs and priorities

New technologies in pharmacopeial standards





Dr. Nandakumara (Nandu) Sarma is the Director for the Dietary Supplements and Herbal Medicines program at US Pharmacopeia (USP) responsible for strategy and external stakeholder engagement for new and innovative projects, working with global stakeholders and expert volunteers in the development of quality standards (monographs and general chapters) for dietary supplements and herbal medicines that are published in the USP *Dietary Supplements Compendium* (<u>http://www.usp.org/dietary-supplements/overview</u>) and the *Herbal Medicine Compendium* (<u>http://hmc.usp.org/</u>).

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 includes isolation and analysis of active components of botanicals and their biologic activity. He published more than 25 scientific articles in peer-reviewed journals. Dr. Sarma holds a Pharmacist degree and a Ph.D. in pharmaceutical sciences (pharmacognosy) from Banaras Hindu University, India.





Dr. Gabriel Giancaspro is the Vice President, Science—Dietary Supplements and Herbal Medicines, for USP. His department provides staff support to Expert Committees responsible for setting USP's standards for dietary supplements, herbal medicines, and food ingredients.

Previously, he was the Director for Dietary Supplements in the Documentary Standards Division at USP responsible for the development of monographs and general chapters for botanical and non-botanical dietary supplements, safety evaluations, performance standards, and the publication of the USP Dietary Supplements Compendium.

Before joining USP, Dr. Giancaspro's teaching and research experience included medicinal chemistry, drug analysis, and drug stability at the Pharmacy School at the University of Buenos Aires. He also has extensive industrial experience as the former Technical Director of Rigecin, Schwabe-Argentina and Kampel-Martian, in charge of Regulatory Affairs, Analytical Research and Development, and Quality Control of parenterals, herbal medicines, and oncological medicines.

Dr. Giancaspro holds a Pharmacist degree and a Ph.D. in pharmaceutical sciences (medicinal chemistry) from the University of Buenos Aires, Argentina.





Dr. Ulrich Rose is pharmacist by training and obtained his PhD in pharmaceutical chemistry in 1985. Before joining the EDQM in 1991 he was assistant professor and lecturer for pharmaceutical analysis and physico-chemistry at the University of Mainz in Germany.

Until 2011 he was responsible for the establishment and monitoring of Ph. Eur. reference standards in the European Pharmacopoeia laboratory. Moreover, he was involved in the elaboration and revision of Ph. Eur. monographs. After that he became co-ordinator and auditor for EDQM's Mutual Joint Audit program. Within this function he audited the Official Medicines Control Laboratories in and sometimes outside Europe. Since 2014 he is head of division A and deputy head of the European Pharmacopoeia department where he is overlooking the monograph work on chemically defined substances, herbals, finished products and general methods and is involved in the international harmonisation of pharmacopoeias.





Roy Upton, RH, DipAyu, is the founder, executive director, and editor of the American Herbal Pharmacopoeia (AHP). Roy is also co-founder and past president, of the American Herbalists Guild (AHG), and serves on botanical expert advisory committees of AOAC International, the American Botanical Council, NSF International, and the Lloyd Library and Museum.

Roy has been working and practicing professionally as an herbalist since 1981. He's trained in Ayurvedic, traditional Chinese, and Western herbal medicine, and he's also studied and worked extensively with Native American and Caribbean ethnobotanical traditions. As an integral part of his work as an herbalist, Roy spends a great deal of time defending the rights of people to access herbal medicines and to see herbal medicine integrated into the fabric of both our homes and health care systems.

In addition, Roy is the directorupton for the California-based herbal supplements company Planetary Herbals, is a member of the Standards Committee of the American Herbal Products Association, and is an internationally recognized lecturer and author of numerous popular and peer-reviewed scientific publications.





Dr G N Singh obtained his doctorate degree in Pharmaceutical Sciences from the Indian Institute of Technology, Banaras Hindu University in 1987 and MBA from University of Hull, UK, in 1997. A man of humble beginnings, he is an epitome of stellar leadership, grit, determination and commitment to the tasks assigned.

Dr Singh's experience in the field of manufacturing, quality and regulatory affairs of medicinal products has been immense. He has been instrumental in the creation of Indian Pharmacopoeia Commission (IPC) in the year 2009 and working as its founder Secretary-cum-Scientific Director till date. For the last decade he has been discharging the duties as Chief Scientific and Executive Officer of IPC.

His dynamism has helped place IPC on a sound pedestal this day. He has also made significant contributions in matters related to the quality, safety and rational use of medicines. In fact his pioneering efforts led to the global recognition of Indian Pharmacopoeia standards and National Formulary of India has been recognized as a guidance book for rational use of medicines in the country. Also, the PharmacovigilanceProgramme of India has caught up the imagination of the country's healthcare system with its expansion pan-India that it has been recognized by WHO-Geneva as its Collaborating Centre.

In 2012 Dr G N Singh was appointed as the Drugs Controller General (India) where he implemented several landmark reforms in the drug regulatory system of the country, including establishing transparency in clinical trial process, successful completion of WHO-National Regulatory Authority assessment, implementation of e-governance in drug approval process, strengthening of pharmacovigilance system in the country, bringing in medical devices under the regulation, materiovigilance, and creation of a separate class of drugs in the form of phytopharmaceuticals under the Drugs and Cosmetics Act, 1940 and Rules thereunder.

Dr Singh has been a member of Research Councils ofprestigious Institutes like CDRI-Lucknow, IIIM-Jammu. He is member of the Academic Council of DPSRU-New Delhi and JSS University-Mysore. Dr Singh is also on the expert panel of various national and international bodies to guide on standardization and regulation issues in the area of drugs and pharmaceuticals. He has been an expert member of WHO Expert Committee on Standardization at Geneva since 2012.

Dr G N Singh has the vision and zeal to be the perfect interphase among industry, academia, national healthcare institutions, and the public at large to see India as a guiding light in the field of global health system with immaculate standards of pharmacovigilance.





DR. V. KALAISELVAN, *Principal Scientific Officer, Indian Pharmacopoeia Commission (IPC), Ministry of Health & Family Welfare, Government of India,* Sector 23, Rajnagar, Ghaziabad, U.P, 201 002.

Dr. Kalaiselvan, received his under graduate and post graduate degree in Pharmacy from the Tamil Nadu Dr. MGR Medical University Chennai and Ph. D from University of Delhi. He has 20 years of multitude experience in the pharmaceutical sector such as academic, pre clinical and clinical research, Pharmacovigilance and drugs standards setting.

Currently, as Principal Scientific officer at IPC is responsible to protect and promote quality standards, safety and rational use of drugs. He is also working towards establishing Materiovigilance Programme of India to monitor the safety of medical devices. His responsibilities also includes to work with WHO – country office (India), HQ Geneva and South East Asia Regional Office to strengthen medical products quality and safety monitoring system in India and other WHO member countries

He has proved his ability to establish a robust system of Pharmacovigilance Programme of India (PvPI) which has been recognized by the WHO as a collaborating centre. He has instrumental in forging partnership with public health programmes, QCI, CSIR labs, academic institutions, CDSCO, WHO etc in enhancing the outreach of IPC services.

He has authored five books apart from published 72 research/review article in peer reviewed journals. He has been the recipient of fellowship from DST and AICTE to pursue research projects. He has organized numerous national and international level training programmes for the professionals of pharmaceutical industries, academics, hospitals and regulatory authorities to enhance the knowledge, practice and compliance of Pharmacovigilance/Pharmacopoeial standards.





Dr. De-an Guo serves as director of the Shanghai Research Center for TCM Modernization at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences. He received his Ph.D. Degree of Pharmacognosy at Beijing Medical University in 1990. He engaged in his postdoctoral research at the Department of Chemistry and Biochemistry, Texas Tech University, (1993-1996). His major research interest is focused on the standardization and modernization of Chinese herbal medicines. He has received a number of international, national and ministerial awards such as National Natural Science Award, Norman Farnsworth Excellence in Botanical Research Award, etc. He is currently the president of GP-TCM Research Association (London) and chair or expert committee members of Chinese Pharmacopoeia, United States Pharmacopoeia and European Pharmacopoeia. At present, he is Editor-in-chief, vice editor or editorial board member of 18 international journals. To date, he has published 560 papers including 380 SCI articles with over 6000 SCI citations.





Sara Handy obtained her Ph.D. in Oceanography at the University of Delaware in 2007, working under the direction of Dr. David Hutchins. For her dissertation work, she focused on DNA based identification of harmful algal species. In 2007, she started a postdoctoral position the University of Maryland with Dr. Charles Delwiche in the department of Cell Biology and Molecular Genetics on the evolution of dinoflagellates. In 2009, she began her work at the U.S. Food and Drug Administration in the Center for Food Safety and Applied Nutrition, where she could combine her DNA background with her understanding of phylogenetic tools. As a Research Biologist in the Office of Regulatory Science, she now works to develop and evaluate genomic methods to identify plant and animal species in foods and dietary supplements. She was a key contributor for "Out of the Box" Health and Human Services Innovates award recognizing innovations representing a new methodology, approach or technology for addressing a difficult problem relevant to HHS. She has authored or coauthored 40 manuscripts primarily focused on DNA based identification methods.



"GENOMIC APPROACHES USED BY FDA-CFSAN TO UNDERSTAND BOTANICAL CHALLENGES AND THE EXPANSION OF GENOMETRACKRCP"

Sara M. Handy¹, Brittany M. Ott¹, Alexandra Greenbaum¹, Amanda M. Windsor¹ and Jun Wen²

1. Center for Food Safety and Applied Nutrition, Office of Regulatory Science, U.S. Food and Drug Administration, College Park, MD, USA

2. Department of Botany, National Museum of Natural History, Smithsonian Institution, Washington D.C., USA

DNA based analyses that target genome differences have become a powerful and sometimes controversial tool in identifying species in raw and finished food products and dietary supplements. Due to the ever-increasing variety of plant and animal species being traded in commerce around the world, proper species identification is proving to be a critical component of the FDA's mission of assuring US consumers that the food they eat is both safe and accurately labeled. Many different chemical techniques have been used to monitor authenticity of supplements and more recently DNA-based tools have been included. Since 2014, the U.S. Food and Drug Administration (FDA) has been developing a publicly available reference library of annotated chloroplast genome sequences and whole genome shotgun raw reads (GenomeTrakrCP, NCBI Bioproject: PRJNA325670) from authenticated specimen. This initiative aims to facilitate traceability and accurate ingredient identification in response to consumer's demands for more transparency and accountability from the food supply and concerns about labeling and food allergies. The library includes a wide swath of plant groups with a focus on those found in foods and dietary supplements as well as known toxin producers, common contaminants, adulterants and their close relatives. These data have facilitated development of simplified assays used to screen food samples for targeted species (e.g., pine nut) at FDA-Center for Food Safety and Applied Nutrition. The raw shotgun reads are also now being utilized and evaluated to ascertain their use for identifying plant samples.





Nicole Stevens has been conducting research with essential oils for more than 20 years. She has worked in quality control laboratories in the nutraceutical industry as well as academic research laboratories at the University of Utah and the University of Nevada Las Vegas Cancer Research Institute. In addition to research, she has taught courses in chemistry and biochemistry at Brigham Young University – Idaho and University of Nevada Las Vegas. Currently she serves as Director of Clinical Research and Essential Oil Formulation at doTERRA International in Pleasant Grove, Utah, USA.

Nicole holds a Bachelor of Arts degree in Technical Writing and a Master of Science degree in Botany and Integrative Biology from Brigham Young University. She is a PhD candidate in Biochemistry and Molecular Biology from the University of Miami. Her main research field is essential oil biochemistry relating to human therapeutic application.



"FRONTIERS IN ESSENTIAL OIL RESEARCH"

Over the past two decades, essential oil research continues to gain attention as an important avenue in industries ranging from food to perfume, from forestry to medicine. Much research focuses on cell culture in the laboratory. This is an important foundation but only the beginning. This discussion will highlight some current technologies that are being used to segue into larger, human clinical studies, as well as showcase some new technologies that we hope will enhance our understanding of the field.





Dr. Cody Beaumont, Ph.D. has been with doTERRA since April 2015 and currently oversees R&D and all internal analytical laboratory testing and Quality Control activities for doTERRA. He has over 15 years of analytical experience including method development, validation, stability programs, analytical and laboratory process improvements in a both dietary supplement and pharmaceutical industries. Dr. Beaumont has extensive experience designing and building high quality analytical laboratories, and managing day to day analytical needs. Dr. Beaumont is an experienced scientific director in the health-wellness and fitness industry who is skilled in formulation through pharmacokinetics, method development, pharmaceutical research, and technical writing. Dr. Beaumont holds a Ph.D. in Medicinal Chemistry from the University of Michigan-Ann Arbor, has published research on essentials and holds memberships in American Chemical Society (ACS) and Association of Official Analytical Chemists (AOAC).



"ESSENTIAL OIL CHEMICAL BIOSYNTHESIS"

Essential oil components produced naturally in plants have a distinct and characteristic biosynthetic process for creation that provides consistent pathways for characterization and quality assessment. These chemical biomarkers produced naturally can further be used for species identification and aid in determination of potential adulteration. This discussion will focus on a select few popular essential oils and their biosynthetic chemical processes that lead to a detailed quality review through authentication and show how these biomarker ratios of chemical constituents are used by doTERRA to assess adulteration.



"DEVELOPMENT OF A CHEMICAL FINGERPRINT AS A TOOL TO DISTINGUISH CLOSELY RELATED TINOSPORA SPECIES AND QUANTITATION OF MAJOR COMPOUNDS"

Abidah Parveen^{1,2,3}, Omer Fantoukh^{1,2}, Yan-Hong Wang², Zulfiqar Ali², Vijayasankar Raman², Ikhlas A. Khan^{1,2}

¹Department of Biomolecular Sciences, Division of Pharmacognosy, ²National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, MS, 38677, USA, ³Department of Pharmaceutical Sciences, Abbottabad University of Science and Technology, Havelian, Abbottabad District, KPK, Pakistan

Tinospora species and their dietary supplement products are available to consumers through internet sources, the species look alike morphologically and substitution is also practiced. In the present study, a rapid, sensitive and reproducible method was established using ultra-high-performance liquid chromatography coupled with photodiode array and single quadrupole electrospray mass spectrometry detectors to perform qualitative and quantitative analysis. The developed method used several marker constituents to achieve decisiveness in not only identifying but also differentiating *T. crispa* from *T. sinensis* and other closely related *Tinospora* species. The validated method enabled quantitative determination of ten compounds including a flavonoid, two alkaloids, an amide and six diterpenoids in different *Tinospora* species and related products by UHPLC-UV and further confirmed by MS. The established method was fully validated in terms of linearity, sensitivity, precision, repeatability as well as recovery and successfully applied to the analysis of various *Tinospora* plant samples and dietary supplements.

This study was supported by Science Based Authentication of Dietary Supplements and Botanical Dietary Supplement Research funded by the Food and Drug Administration grant #2U01FD004246-06. Fulbright Graduate Scholarship Program and United States Educational Foundation of Pakistan (USEFP) are acknowledged for financial support.



Panel Moderator and Session Chair: Paula Brown, Director of Applied Research, BCIT & Holly Johnson, Chief Science Officer, American Herbal Products Association

Paula N. Brown¹, Holly E. Johnson²

¹BC Institute of Technology ²American Herbal Products Association

The need to evolve determinants of quality for botanical products is spurred by the increasing consumer market demand, changes in regulatory requirements, destabilized supply chains, innovations in product formulation and novel delivery formats. Government initiatives to increase the availability of validated analytical methods and botanical reference material have led to the publication of numerous validation studies in scientific journals. Analytical techniques and priority methods are influenced by the need for fast-screening techniques, the limited availability of reference material, market value, and the prevalence of contaminants in botanical supplements. Single laboratory and collaborative validation studies are structured to confirm a method's ruggedness and fit for purpose. While performance characteristics and statistical protocols followed throughout a validation study vary with the source of guidelines, most apply to quantitative, not qualitative methods. There remains a need to address how qualitative methods for establishing identity specifications can be validated and how to statistically power these studies with reference materials.

We gratefully acknowledge the panel participants: Wendy Applequist (Mobot), Tyler Daniels (Thorne), James Harnly (USDA), Peter de B. Harrington (Ohio University), James Neal-Kababick (Flora Research Laboratories), and Darryl Sullivan (Eurofins).





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 chemical fingerprinting and metabolomics of foods and botanical supplements. His personal research interest is the development of chemometric methods for 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.





Peter Harrington, Professor, Ohio University, After graduating with a degree in Chemistry, Peter worked for Nabisco as a flavor chemist where he became interested in analytical chemistry, chemometrics, and the forensic analyses of foods. After working for 2 years, he pursued doctoral research in analytical chemistry and machine learning under Tom Isenhour at the University of North Carolina-Chapel Hill. Afterwards, he held a research assistant professor appointment at the Colorado School of Mines where he developed algorithms and software for the detection of pathogenic bacteria by pyrolysis-mass spectrometry. In 1989, he began his career at OHIO University. His research combines the areas of chemometric, forensic, metabolomic, and proteomic analysis. Professor Harrington founded the Center of Intelligent Chemical Instrumentation in 1992 to foster automated chemical instruments and assumed the role of Director in 2002. In 2015, he was recognized as a Fellow of the American Academy of Forensic Sciences. In 2016, he earned the Ohio University College of Arts and Sciences Award for Excellence in Research. He is interested in self-optimizing chemometric algorithms and has devised many chemometric methods; the fuzzy rule-building expert systems (FuRES), the fuzzy optimal associative memories (FOAMs), principal component-orthogonal signal correction (PC-OSC), bootstrapped Latin partitions (BLP), analysis of variance principal component analysis (ANOVA-PCA), super partial least squares (sPLS), support vector machine trees (SVMTrees) and super support vector regression (sSVR). He seeks new collaborations with many groups and government agencies on combining state-of-the-art methods in machine learning and artificial intelligence to solving problems in analytical chemistry.





Wendy L. Applequist is a native of Illinois who received a B.S. in biology from the University of Illinois at Urbana-Champaign and a Ph.D. in plant systematics from Iowa State University. She has worked at the Missouri Botanical Garden since 2000 and is now an associate curator in the William L. Brown Center, the Garden's economic botany and ethnobotany department. Applequist is the author of a manual on morphological identification of medicinal plants, and her research interests include the taxonomy, identification and quality control, and chemical variability of medicinal plants. She also manages natural products discovery programs, conducts research on the taxonomy of the flora of Madagascar, and serves as Secretary of the international Nomenclature Committee for Vascular Plants.





Tyler Daniels, MS, Senior Scientist, Thorne, began his career in Thorne's Microbiology Laboratory in 2011 before moving into more broad Quality role shortly thereafter. There, he led the refinement of the company's ingredient quality standards and the subsequent integration of them into the specification portfolio. In this role, he drove solutions to quality issues that arose with botanical dietary ingredients, solving the root causes of them and resourcing ingredients as necessary. Included in those endeavors were the construction of 2nd generation DNA sequencing methodology toward identity in herbs of commerce. In his present position as Senior Scientist, Tyler has placed special expertise on understanding the global herbal marketplace including the appropriate fit that genetic testing has within it. His vision for the next generation of quality with herbal dietary supplements involves sourcing plants rather than powders, enabling supplement companies to have the oversight that is required to build quality into herbal products.

Alongside his role at Thorne, Tyler has an appointment as a Geneticist with the Biotechnology company Onegevity, where he integrates genomic data into a multi-omics platform for human medicine. He graduated from Washington State University with his MS in Animal Sciences in 2009.





James Neal-Kababick is the founder and Director of Flora Research Laboratories, LLC (FRL) which specializes in the research and analysis of botanicals, dietary supplements and related compounds. For many years he served as an adjunct faculty at Bastyr University where he taught botanical drug identification by microscopy and thin layer chromatography. He continues to provide education in dietary supplement quality control testing to students of the Botanical Medicine Department through their field learning program. In addition to his work at the private research lab and university, he serves on multiple expert committees for AOAC, USP, NIH, AHPA, and others. Currently, his work is focused on the utilization of modern analytical technologies in the investigation of dietary supplements and other agricultural products. He is the pioneer of the field called "Phytoforensic Science." Phytoforensic Science involves utilizing numerous technologies from microscopy to mass spectrometry to detect adulteration and contamination in the global food supply chain with a special focus on dietary supplements. He has developed and presented the Standardized Phytoforensic Approach (SPA) as well as the Crossover Analytical Technique (CAT) to address strategic approaches to clandestine adulteration and DNA identity issues respectively. In 2010 James was named "Fellow of AOAC." Fellow of AOAC is awarded to scientists for meritorious service to the scientific society and their field of science. It is the second highest honor the organization bestows upon scientists. James is also a renowned expert in the detection of clandestine pharmaceutical adulteration of dietary supplements. He developed expanded screening panels for PDE-5 inhibitors (ED drugs), weight loss drugs, steroids and synthetic cannabinoids (SYNCAN panel). He appeared on the Dr. Oz Show to help educate consumers about the growing clandestine adulteration problem with tainted dietary supplements. He is the vice-chair of the USP<2251> Screening for Undeclared Drugs and Drug Analogs (SUDDA) Expert Committee joining experts globally to apply the phytoforensic approach to address methodology approaches for investigating clandestine adulteration of dietary supplements. He also serves on the 2015-2020 USP Non-Botanical Dietary Supplement Expert Committee, the USP Joint Standard Settings Subcommittee, the Joint Subcommittee on Modern Analytical Methods, the USP Dietary Protein Expert Committee, and the USP Dietary Supplement Compendium Revision Committee as well as serving as a USP Recruitment Ambassador. Currently, his collaborations include development of databases and spectral libraries for rapid identification of botanicals, compounds and clandestine drugs as well as presenting lecture series and teaching hands on training courses in the phytoforensic sciences. He is the coauthor of several papers related to dietary supplement adulteration, chemical profiling of botanicals, and collaborative studies and was the co developer of the AOAC Validation of Dietary Supplement Analytical Methods, Validation of Quantitative Chemical Test Methods and BSI-NIH funded Method Development and Validation of Dietary Supplement Analytical Test Methods training courses which he taught for many years. James routinely assists various federal agencies in collaborations including the various FDA field offices, the FDA Office of Criminal Investigation, the FDA Forensic Chemistry Center, US Department of Justice, US Customs and Border Enforcement as well as the DEA, BATFE and various state agencies throughout the country. He currently serves as an expert witness for the United States Department of Justice and various state justice departments.



Panel Moderator and Session Chair: Adam Kuszak

This 90-minute session will provide a brief historical summary of biomedical research on the health effects of botanical natural products, including development of analytical methodology and tools for the characterization of clinical interventions and investigation of the metabolism and mechanisms of action causing specific biological outcomes. An expert panel will discuss the progression and milestones of basic and clinical botanical research over the past 25 years of the Dietary Supplement Health and Education Act, as well as share their views for where efforts need to be prioritized in method development, reference standards for metabolic profiles and/or bioactivities, and research training and education.





Craig Hopp, Deputy Director, Division of Extramural Research, National Center for Complementary and Integrative Health, National Institutes of Health. Dr. Hopp is Deputy Director of the Division of Extramural Research at NCCIH.

In addition to serving as Deputy Director, Dr. Hopp continues to oversee the administration of the product integrity policy. This involves evaluation of proposed study materials to ensure they are safe and properly characterized. He also focuses on large scale projects such as research on drug-natural product interactions, the Innovation and Technology research center, and the CARBON program. Dr. Hopp uses his expertise and experience in the field of natural products to help shape research priorities at NCCIH.

Dr. Hopp received his B.S. in chemistry from James Madison University in 1993 and his Ph.D. in pharmacognosy from Purdue University in 1997. As a postdoctoral researcher at Shaman Pharmaceuticals, he used his knowledge of indigenous cultures from around the world regarding medicinal plants to aid in the discovery of new pharmaceutical agents. While with Shaman Pharmaceuticals, Dr. Hopp discovered and obtained multiple patents on antihyperglycemic compounds. Subsequently, he worked at an herbal company, Phyto-Technologies, for 2 years where he was responsible for research and development on multiple herb formulas used in traditional Chinese medicine.

Prior to joining NCCIH, Dr. Hopp worked for AMRI, located outside of Seattle. There he was a senior research scientist responsible for the isolation and identification of compounds from a variety of natural sources with activity in a wide range of therapeutic targets.





Suramya Waidyanatha, Division of the National Toxicology Program, National Institute of Environmental Health Sciences

Education

Ph. D. 1991 Analytical Chemistry, University of Maine, MEM.S. 1987 Biochemistry, University of Illinois at Chicago, Chicago, ILB. Sc. (Honors) 1984 Chemistry, University of Colombo, Sri Lanka

Current Employment

2012-Present	Discipline Leader for Chemistry, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC
2010-Present	Group Leader, Chemistry and Absorption, Distribution, Metabolism and Excretion (ADME) Resources Group (CARG), Program Operations Branch, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC
2008-Present	Discipline Leader for ADME, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC
2008-Present	Project Officer/Contracting Officer's Technical Representative (COTR)/Contracting Officer's Representative (COR), Division of the National Toxicology Program, National Institute of Environmental Health Sciences, National Institute of Health, Research Triangle Park, NC
2008-present	Visiting Scholar, Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

Professional Organizations: Society of Toxicology, American Society for Mass Spectrometry, International Society for the Study of Xenobiotics, American Chemical Society, North Carolina Section of the American Chemical Society, RTP Drug Metabolism Discussion Group





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 chemical fingerprinting and metabolomics of foods and botanical supplements. His personal research interest is the development of chemometric methods for 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.





Nicholas Oberlies, Patricia A. Sullivan Distinguished Professor of Chemistry, Department of Chemistry and Biochemistry, University of North Carolina at Greensboro. Nick leads an energetic lab full of researchers (typically 20 people, ranging from undergraduate to both MS and PhD level graduate students, to postdocs and senior scientists). On a daily basis, his lab strives to purify compounds from nature, and then determine the structures of these chemical entities. In short, their goal is to uncover the chemistry of nature, with the larger goal of discovering compounds that benefit humankind, often in the form of anticancer, antibiotic, and other drug leads.

Nick received his B.S. in Chemistry from Miami University (1992) and his Ph.D. in Medicinal Chemistry and Pharmacognosy from Purdue University (1997), where he studied under Professor Jerry L. McLaughlin. He then spent a year as a postdoctoral chemist at American Cyanamid, where he investigated leads with insecticidal, herbicidal, and fungicidal properties from natural sources. In 1998, he joined Research Triangle Institute, specifically to be mentored by Dr. Mansukh Wani and the now late, Dr. Monroe Wall, who are the co-discoverers of taxol and camptothecin, two front line agents in the fight against cancer. He rose through the ranks of RTI and eventually directed the Natural Products Laboratory. In 2009, he moved his group to the Department of Chemistry & Biochemistry at the University of North Carolina at Greensboro, which has a relatively new Ph.D. program in Medicinal Biochemistry that has an emphasis in natural products chemistry. There he leads a multidisciplinary effort to characterize and develop new chemical entities from natural sources. Over the past fifteen years, his lab has worked to profile fungi for anticancer leads. His lab also has a wealth of experience in the characterization of herbal remedies, with a focus on insuring the safety and quality of various herbal preparations.





Adam Kuszak, Director, is an analyst in the National Institutes of Health (NIH) Office of Dietary Supplements (ODS), and Assistant Director of the ODS Analytical Methods and Reference Materials Program. Dr. Kuszak works with stakeholders involved in research, industry, and regulatory affairs to support scientific resource development and promote biomedical research on the mechanisms and health effects of dietary supplements and natural products. In addition, he works with ODS staff on several initiatives including the Dietary Supplement Label Database and the development of ODS dietary supplement Fact Sheets for health professionals. 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.

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 completed his postdoctoral training at the National Institute of Diabetes and Digestive and Kidney Diseases, and first joined the ODS as an American Association for the Advancement of Science (AAAS) Science & Technology Policy Fellow in 2014.



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