



BERRY HEALTH BENEFITS SYMPOSIUM

The only conference focusing solely on berries & human health.

January 31 - February 2, 2023 | Tampa, FL - USA

Symposium Pre-Proceedings


Tuesday, January 31st, 2023

Westshore Ballroom

8:45am-9:00am | **Opening Remarks -** Chris Christian, *California Strawberry Commission*

Welcome - *Florida Department of Agriculture*

Berries & the Brain *(Pages 10-19)*

9:00am-9:15am | *Current Research Review.* Chair overview by Dr. Barbara Shukitt-Hale, USDA/Tufts University

9:15am-9:40am | *Effects of an Acute Wild Blueberry Intervention on Cognition, Mood and Vascular Function Across the Lifespan: the BluLife study* - Dr. Claire Williams, University of Reading

9:40am-10:05am | *Blueberry Supplementation in Midlife for Dementia Risk Reduction* - Dr. Robert Krikorian, University of Cincinnati

10:05am-10:30am | *Berries, Bioactive Nutrients and Alzheimer's Disease* - Dr. Puja Agarwal, Rush University Medical Center

10:30am-10:45am | **BREAK** - Sponsored by Aneberries *Las pequeñas frutas de un gran país*

10:45am-11:15am | *The Effects of Acute Raspberry Intake on the Relationship Between Enhanced Metabolic Control and Cognitive and Psychomotor Function* - Di Xiao, Illinois Institute of Technology

Berry Seminar Session *(Page 21)*

11:15am-12:00pm | *TODAY'S FOOD CONVERSATION: What Messages Should We Be Communicating About Berries?* - Amy Myrdal-Miller, Farmer's Daughter® Consulting, Inc.

12:00pm-1:15pm | **LUNCH** - Spaniard Terrace

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Berries & the Heart / Healthy Aging *(Pages 22-31)*

1:15pm-1:30pm | *Current Research Review.* Chair overview by Dr. Britt Burton-Freeman, Illinois Institute of Technology

1:30pm-1:55pm | *Impact of Blueberries on Vascular Endothelial Function in Postmenopausal Women: Clinical Impact and Possible Mechanisms* - Dr. Sarah Johnson, Colorado State University

1:55pm-2:20pm | *Metabolites Mediate the Vascular Effects of Dietary Blueberries* - Dr. Anandh Babu Pon Velayutham, University of Utah

2:20pm-2:45pm | *Cranberries and Cardiometabolic Health* - Dr. Ann Skulas-Ray, The University of Arizona

2:45pm-3:15pm | *Role of Dietary Berries in Glycemic Control and Insulin Resistance* - Dr. Arpita Basu, University of Nevada, Las Vegas

4:00pm-5:30pm | **Poster Presentations** - Westshore Ballroom - *(Pages 68-74)*

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Wednesday, February 1st, 2023

Westshore Ballroom

Berry Seminar Session *(Pages 32-33)*

9:00am-10:00am | **Berry Seminar Session** | Industry Panel - Broadening the Berry Basket with Berry Supplements, Christian G. Krueger, Complete Phytochemical Solutions, LLC, Melanie Bush, Artemis International, and Brenda Van Goethem, Nature's Way

Berries & the Skin *(Pages 34-43)*

10:00am-10:15am | *Current Research Review.* Chair overview by Dr. Mary Ann Lila, North Carolina State University

10:15am-10:40am | *Blueberry Extracts as a Novel Approach to Prevent Ozone-Induced Cutaneous Inflammasome Activation* - Dr. Giuseppe Valacchi, North Carolina State University

10:40am-10:55am | **BREAK** - sponsored by Wyman's

10:55am-11:20am | *Black Raspberries Mitigate DNFB-Induced Contact Hypersensitivity by Down-Regulating Dendritic Cell Activation and Inhibiting Mediators of Effector Responses* - Dr. Steve Oghumu, The Ohio State University

11:20am-11:45am | *Food and Skin Care Convergence: Natural and Sustainable Fruit-Derived Compounds to Prevent Skin Damage* - Dr. Roberta Hoskin, North Carolina State University

11:45am-12:10pm | *New Horizons for Skin Healthcare - Exploring the Colour and Bioactivity of Berry Anthocyanins and Related Structures* - Dr. Iva Fernandes, REQUIMTE-LAQV

12:15pm-1:30pm | **LUNCH** - Spaniard Terrace

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Berries & Gut Health / Gut Microflora *(Pages 44-53)*

1:30pm-1:45pm | *Current Research Review.* Chair overview by Dr. Jess Reed, University of Wisconsin-Madison

1:45pm-2:10pm | *The Gut Microbiome - Brain Connection: Variety is the Spice Brains Need* - Dr. Grant Canipe, The Chicago School of Professional Psychology

2:10pm-2:35pm | *California Strawberry Consumption Increased the Abundance of Gut Microorganisms Related to Lean Body Weight, Health and Longevity in Healthy Subjects* - Dr. Zahra Ezzat-Zadeh, David Geffen School of Medicine at UCLA

2:35pm-3:00pm | *Berry Consumption and the GUT Microbiome - Impacts on the Human Metabolome* - Dr. Colin Kay, North Carolina State University

3:00pm-3:25pm | *Dissecting the Impact of Anthocyanin and Residue Fractions of Black raspberries and Protocatechuic Acid, an Anthocyanin Gut Bacterial Metabolite, on Gut Microbiota Profiles* - Dr. Li-Shu Wang, Medical College of Wisconsin

3:25pm-3:35pm | **Jim Joseph Award Presentation**

3:35pm-4:15pm | Junior Investigator's Oral Presentations & Poster Session Awards *(Pages 54-56)*

Chemical Composition of Volatile Extracts from Blackberries, Black Raspberries, and Blueberries and Their Anti-Proliferative Effect on A549 Non-Small-Cell Lung Cancer Cells - Inah Gu, University of Arkansas

Cranberry-derived Extracellular Vesicles Decrease Whole-body Adiposity and Modulate Gut Microbiota Composition in a Mice Model of Diet-induced Obesity - Amélie Légaré, Université Laval

Phenolic Acids from Wild Blueberry Facilitate Wound Healing via Vascular Remodeling: A Novel Therapy for Clinical Wound Treatment - Tolu Esther Alaba, University of Maine

4:30pm-6:00pm | **Berry Supplements Reception**

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Thursday, February 2nd, 2023

Westshore Ballroom

Keynote Address:

Dr. Taylor Wallace
Think Healthy Group

Flavan-3-ols and Cardiometabolic Health - The First U.S. Based Guideline and Intake Recommendation for a Bioactive

Taylor C. Wallace, PhD, CFS, FACN, is Principal and CEO at the Think Healthy Group and a Professor in the Department of Nutrition and Food Studies at George Mason University. His academic research interests are in the area of nutritional interventions to promote health and prevent health and the onset of chronic disease. Dr. Wallace has a PhD an MS in Food Science and Nutrition from The Ohio State University and a BS in Food Science from the University of Kentucky. He operates the popular food and nutrition blog, www.DrTaylorWallace.com, is a member of Forbes Health Advisory Board, and a regular guest commentator in the mainstream media, regularly seen on NBC4 Washington and the Dr. Oz Show. He is a fellow of the American College of Nutrition and is the 2015 recipient of the Charles A. Regus Award, given by the American College of Nutrition for original research and innovation in the field of nutrition. Dr. Wallace is a Senior Fellow of the Center for Magnesium Education & Research, the Editor-in-chief of the Journal of the Dietary Supplements, Deputy Editor-in-chief of the Journal of the American College of Nutrition, Nutrition Section Editor of Annals of Medicine, the editor of seven academic textbooks, author of over 75 peer-reviewed manuscripts and book chapters, and author of the cookbook, Sizzling Science.

Talk Abstract | Developing recommended intakes or guidelines for dietary bioactive compounds is both beneficial and challenging. Nevertheless, with a rapidly growing body of human data reflecting benefits of intake that outweigh potential harms, establishment of such guidelines is likely influence overall health and longevity of the population while promoting a higher consumption of plant foods containing dietary bioactives. Acknowledging the growing body of research on flavan-3-ols, an Expert Panel within the Academy of Nutrition and Dietetics conducted a structured in-depth review of the current scientific literature surrounding flavan-3-ols and cardiometabolic outcomes, determined its suitability for making an intake recommendation, and developed a guideline that clinicians, policy-makers, public-health entities, and consumers can utilize. This presentation will give a sneak peak into the first draft guideline for a group of dietary bioactives (i.e., flavan-3-ols) and supporting data behind the proposed recommendation.

9:00am-9:45am | **Keynote Address:** Dr. Taylor Wallace

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Berry Special Topics, Food Technology & Chemistry *(Pages 58-67)*

9:45am-10:00am | *Current Research Review.* Chair overview by Dr. Amy B. Howell, Rutgers, the State University of New Jersey

10:00am-10:25am | *Berry Anthocyanins Uptake and Transport Through Human Gastric Epithelial (NCI-N87) Cells* - Dr. M. Mónica Giusti, The Ohio State University

10:25am-10:50am | *Black Currant and Digital Eye Strain: Findings from a Randomized, Double Blind, Placebo Controlled Clinical Trial* - Dr. Jessie Hawkins, Franklin Health Research

10:50am-11:05am | **BREAK** - sponsored by Wild Blueberries

11:05am-11:30am | *Blueberries and Bone Health* - Dr. Connie Weaver, Purdue University

11:30am-11:55am | *Anti-inflammatory Effect of Blackberry Phenolic and Volatile Extracts* - Dr. Luke Howard, University of Arkansas

12:00pm-1:00pm | **BOXED LUNCH PICK-UP & BREAK**

1:00pm-9:00pm | **Florida Berry Discovery Tour**

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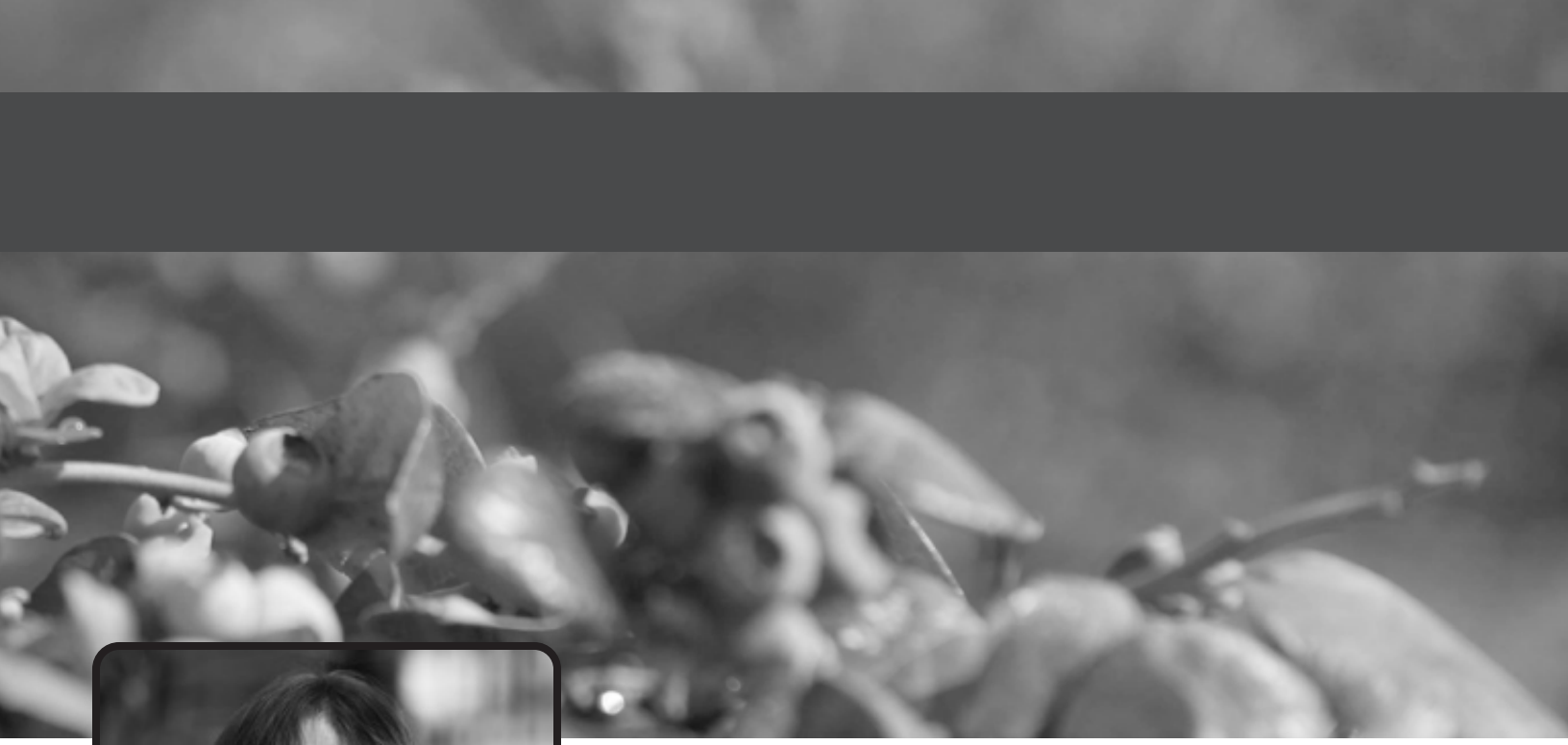
Tuesday, January 31st - Scientific Presentations

Berries & the Brain



Dr. Barbara Shukitt-Hale
USDA & Tufts University

Session Chair

Current Research Review

Dr. Barbara Shukitt-Hale is a USDA Staff Scientist in the Laboratory of Neuroscience and Aging, USDA-ARS, Human Nutrition Research Center on Aging (HNRCA) at Tufts University in Boston, MA. Additionally, she serves as an Affiliate Faculty member in the Psychology Department and a Visiting Scholar in the Friedman School of Nutrition Science and Policy at Tufts University. She received her Ph.D. in Experimental Psychology from Boston University in 1993.

In 1996, Dr. Shukitt-Hale was awarded the Glenn Post-Doctoral Award, presented by the American Aging Association. She is a member of the Society for Neuroscience and has served as a board member and secretary of the American Aging Association. Dr. Shukitt-Hale has been involved in research for almost 30 years, beginning when she was an undergraduate student at Boston University; this work earned her the Research Award, given at graduation to the best student researcher in the Psychology Department. Before coming to the HNRCA, she worked as a Research Psychologist in the Division of Health and Performance and as a Neuroscientist in the Military Performance and Neuroscience Division at the U.S. Army Research Institute of Environmental Medicine (USARIEM).

Dr. Shukitt-Hale's current work involves researching the behavioral and neurochemical effects of aging in rodents, specifically investigating motor and cognitive performance changes due to oxidative stress, using the free-radical theory of aging as a working model. Her work includes determining the factors responsible for age-related behavioral changes and possible amelioration of these effects with various nutritional treatments. Her work showing that a diet supplemented with blueberry extract could reverse functional age-related deficits in motor and cognitive behavior has had a tremendous impact in the popular press. She continues to research the mechanisms behind the berry fruit's positive effects, and has found that they 1) have direct effects on signaling to enhance neuronal communication, 2) have the ability to buffer against excess calcium, 3) enhance neuroprotective stress shock proteins, and 4) reduce stress signals and increase neurogenesis. She has published more than 166 articles and selected papers.

Dr. Claire Williams
University of Reading, UK

Professor Williams is Chair of Neuroscience in the School of Psychology & Clinical Language Sciences at the University of Reading, UK. She received her PhD in Psychology from the University of Reading in 2000.

Dr. Williams' research group, the Nutritional Psychology laboratory, investigates the health benefits of plant-derived chemicals. The main focus of her laboratory is the interplay between dietary intake and measures of psychological well-being such as cognitive performance, food preference, mood, and quality of life using a wide range of techniques (e.g. animal studies, randomised controlled trials, neuroimaging) and population groups (e.g., school-aged children, healthy adults, older adults, patients with mild cognitive impairment). The group have published a number of articles including a demonstration that improvements in spatial working memory induced by a high flavonoid diet can be linked to de novo protein synthesis in rat hippocampus, flavonoid supplementation is associated with increased cerebral blood perfusion in healthy older adults, and that single acute doses of blueberries can significantly improve memory and attention in children aged 8-10 years old. She has published more than eighty peer-reviewed research articles, five book chapters and is listed as an inventor on six international patent families, including 34 worldwide granted patents.

Effects of an Acute Wild Blueberry Intervention on Cognition, Mood and Vascular Function Across the Lifespan: the BluLife study

Authors: Claire M Williams[1], Sabine Hein[1,2], Eleanor Wood[1,2], Robin Mesnage[3], Filipe Fernandes[4], Lynne Bell[1], Ana Rodriguez-Mateos[2]

Affiliations:

1. School of Psychology & Clinical Language Sciences, University of Reading, Reading, UK
2. Department of Nutritional Sciences, King's College London, London, UK
3. Department of Medical and Molecular Genetics, King's College London, London, UK
4. Department of Medical Engineering and Physics, King's College Hospital NHS Foundation Trust, London, UK

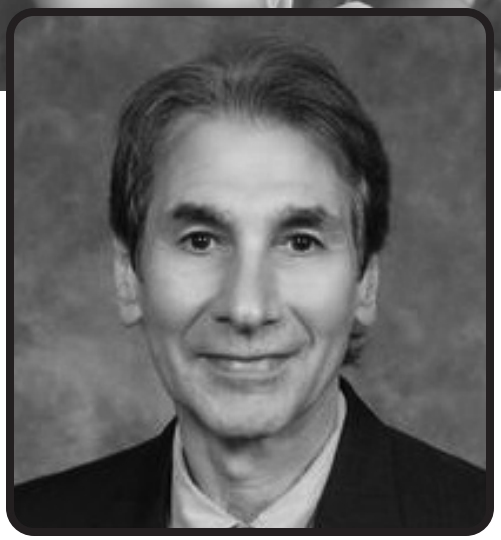
There is growing evidence suggesting blueberry (poly)phenols can improve vascular and cognitive function, subsequently reducing an individual's future risk of non-communicable diseases such as cardiovascular disease and dementia. However, whether this happens throughout all the stages of the life course, in different age groups including children and adolescents, is currently unknown. In this study we aim to investigate whether wild blueberry supplementation can lead to changes in cognitive function, mood and vascular function in a cohort of healthy people representative of the general population, from children to older adults.

A 2-arm, crossover, double blind RCT was conducted in 95 healthy individuals across 5 age groups (8-10, 14-18, 22-28, 40-50 and 65-80; n=~20 per group). The impact of wild blueberry (poly)phenols on a battery of tasks targeting cognitive function (Auditory Verbal Learning Tasks; AVLT, Corsi Blocks Task; CBT, and Task Switch Task; TST), mood, flow-mediated dilatation (FMD), active and resting CBF using transcranial doppler ultrasound, and blood pressure (BP) was assessed at baseline and 2 h after consumption of blueberry containing 133 mg anthocyanins (equivalent to 106 g fresh wild blueberries) or a macronutrient and micronutrient matched control drink (0 mg anthocyanins). Blood and 24 h urine samples were also collected to analyse (poly)phenol metabolites.

Linear mixed model analysis revealed significant cognitive benefits following WBB consumption relative to placebo, whereby WBB attenuated a decline in word acquisition on the AVLT, improved spatial working memory performance on the CBT and significantly lowered negative mood, all effects were seen irrespective of age group. Only executive function demonstrated an impact of age with improved accuracy and lower reaction times seen on the TST for children aged 8-10 years old only. Significant improvements in FMD were observed in all age groups apart from the 8-10 age group (ranging from 1.03%-1.55%) with a total increase in all ages of 1.15% following WBB consumption compared to control. In addition, improvements in FMD correlated with a total of 22 plasma and urinary metabolites, with the majority derivatives of Phenylpropanoic acids, Benzoic acids and Cinnamic acids. No changes were observed in CBF or BP following the WBB treatment.

Conclusion: Acute WBB intake improved cognitive function across the life-course and endothelial function in healthy individuals including adolescents through to older adults. These improvements correlate with acute increases in blueberry derived (poly)phenol metabolites suggesting that circulating metabolites may be directly linked with increases in endothelial function and cognition. If these effects remained over a longer period with regular consumption, blueberry (poly)phenols may reduce an individual's future risk of developing CVD and dementia, throughout the natural ageing process.

Keywords: Wild blueberry, polyphenol, cognition, vascular function, flow-mediated dilation, cerebral blood flow, nutrition, life-course



Dr. Robert Krikorian
University of Cincinnati

Dr. Robert Krikorian is Professor in the Department of Psychiatry & Behavioral Neuroscience and Director of the Cognitive Aging Program at the University of Cincinnati Academic Health Center. He earned BA and MA degrees in Philosophy from Boston University, MA and PhD degrees in Clinical Psychology from the University of Cincinnati and completed a fellowship in Clinical Neuropsychology in the departments of neurology and neurosurgery.

He chief interest is the influence of health conditions on cognitive decline with aging and risk for Alzheimer's disease. He directs a clinical program within the Department of Psychiatry that provides neurocognitive diagnostic services and lifestyle coaching and a research program investigating nutritional interventions to forestall cognitive aging and progression of neurodegeneration. His current research involves investigations of the effects of berry fruit supplementation and nutritional ketosis on cognitive function and metabolism in middle-aged individuals with increased risk for late-life dementia. Funding for his research has come from the NIH, from philanthropy, and from foundation and industry sources.

Blueberry Supplementation in Midlife for Dementia Risk Reduction

Authors: Robert Krikorian[1], Matthew Skelton[2], Suzanne S Summer[3], Marcelle D Shidler[1], Patrick G Sullivan[4]

Affiliations:

1. Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati Academic Health Center, Cincinnati, OH USA
2. Division of Neurology, Cincinnati Children's Research Foundation, Cincinnati, OH, USA
3. Bionutrition Core, Clinical Translational Research Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH USA
4. Spinal Cord & Brain Injury Research Center, University of Kentucky Chandler College of Medicine, Lexington, KY USA

Correspondence: Robert Krikorian PhD, Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati Academic Health Center, Cincinnati, OH 45267-0559, USA Email: robert.krikorian@uc.edu, Phone: 513 558-4224

BACKGROUND: Late-life dementia typically develops over a period of many years beginning in middle age. Prevalence of metabolic disturbance accelerates in middle age and is a prominent risk factor for dementia. Preliminary studies show that blueberry supplementation can improve cognitive performance and influence brain and metabolic function.

OBJECTIVE: To investigate the effects of blueberry supplementation on cognitive, metabolic, and anthropometric outcomes in middle-aged individuals with insulin resistance and elevated risk for late-life dementia.

METHODS: We enrolled overweight men and women, aged 50 to 65, with subjective cognitive decline. In a double blind, controlled, and randomized trial we investigated the effects of 12 weeks' daily blueberry supplementation with pre- and post-intervention assessment of cognitive, metabolic, and anthropometric outcomes and exploratory measures of mitochondrial function.

RESULTS: We observed improved performances for the blueberry group on measures of lexical access, $p = 0.003$, and memory interference, $p = 0.04$, indicating enhanced executive ability, and blueberry-treated participants reported reduced memory encoding difficulty in daily life activities, $p = 0.03$. The blueberry group also exhibited correction of peripheral hyperinsulinemia, $p = 0.04$, and a modest trend for enhanced mitochondrial uncoupling, $p = 0.11$.

CONCLUSIONS: The demonstration of cognitive and metabolic benefits in middle-aged individuals with insulin resistance and subjective cognitive decline suggests that ongoing blueberry supplementation can contribute to protection against cognitive decline when implemented early in at-risk individuals. Metabolic and bioenergetic mechanisms associated with anthocyanin actions may be contributing factors.

Keywords: blueberry supplementation; BMI; insulin resistance; cognition; dementia prevention

Dr. Puja Agarwal
Rush University Medical College

Dr. Puja Agarwal is a nutritional epidemiologist whose research focuses on nutrition and neurodegenerative diseases, primarily Alzheimer's and Parkinson's disease. She completed her Ph.D. in Human Nutrition at the University of Illinois at Chicago and a Post-doctoral research fellowship in nutritional epidemiology at Rush University Medical Center. Her primary interest is investigating the association of dietary patterns, specific foods including berries, green leafy, fish, and various nutrients and bioactive with cognition, motor function, and brain neuropathologies in older adults. California Strawberry Commission supported her work relating berry to brain health. Her current work is funded by the National Institute on Aging and philanthropic grants (Alzheimer's Association; Michael J Fox Foundation for Parkinson's Research; Consolidated Anti-Aging Foundation).

Berries, Bioactive Nutrients and Alzheimer's Disease

Authors: Puja Agarwal[1,2,3], Thomas M Holland[2], Bryan D James[1,2], Laurel L Cherian[5], Neelum T Aggarwal[1,5], David A Bennett[1], Julie A Schneider[1,5]

Affiliations:

1. Rush Alzheimer's Disease Center
2. Department of Internal Medicine
3. Department of Clinical Nutrition
4. Rush Institute of Healthy Aging
5. Department of Neurology; Rush University Medical Center, Chicago, IL

BACKGROUND: Alzheimer's disease (AD) is the most common neurodegenerative disorder and a significant public health concern of the increasing aging population. With limited available treatment, studying modifiable factors such as a diet rich in antioxidants and other essential nutrients is crucial. We earlier found berries rich in bioactive relate to better cognition and reduced Alzheimer's dementia risk.
OBJECTIVE: Examine berry and anthocyanidin intake association with the AD pathology and further assess how this may vary by APO- 4 allele and cognitive status.

METHODS: The study was conducted on 575 autopsied participants of the Rush Memory and Aging Project, with completed dietary data (assessed using a food frequency questionnaire) and neuropathological evaluations. Mean berry intake during the follow-up was assessed as a continuous variable and different anthocyanidin intakes were energy-adjusted and modeled in quartiles. Amyloid-beta load and phosphorylated-tau tangles were assessed using immunohistochemistry. Global AD pathology burden, a quantitative summary score of neurofibrillary tangles, and diffuse and neuritic plaques in multiple brain regions were also assessed.

RESULTS: Overall berry intake was not associated with AD pathology. In separate linear regression models adjusted for age at death, sex, education, APO- 4 status, vitamin E, and vitamin C, participants in the highest quartile of pelargonidin intake when compared to those in the lowest quartile, had less amyloid-beta load ((SE)=-0.293(0.14),p=0.04), phosphorylated-tau tangle ((SE)=-0.310,p=0.05) and lower trend for global AD pathology ((SE)=-0.083(0.04),p=0.06). Among APO- 4 non-carriers, higher strawberry ((SE)=-0.214(0.11), p=0.05) and pelargonidin (Q4 vs. Q1: (SE)=-0.401(0.16), p=0.01; p trend=0.01) intake was associated with fewer phosphorylated-tau tangles and no such association was observed in APO- 4 carriers. In sensitivity analysis, excluding participants with dementia or mild cognitive impairment at baseline strawberry (p=0.004) and pelargonidin (p trend=0.007) intake was associated with fewer phosphorylated-tau tangles.

CONCLUSIONS: Higher pelargonidin intake, a bioactive mostly present in berries, is associated with less Alzheimer's disease neuropathology, primarily phosphorylated-tau tangles.

Keywords: Alzheimer's Disease pathology, brain health, longitudinal dietary assessment, community-based older adults

Di Xiao
Illinois Institute of Technology

Di Xiao, PhD candidate, is a clinical nutrition research associate at the Center for Nutrition Research, Department of Food Science and Nutrition, Illinois Institute of Technology. Di Xiao's long term research interests involve the development of a comprehensive understanding of utilizing bioactive components in foods as preventive strategy of chronic disease, such as diabetes and Alzheimer disease. As a research scientist and PhD student working in Dr. Britt Burton-Freeman and Dr. Indika Edirisinghe's lab, her previous researches focused on understanding the health benefit of foods rich in dietary bioactive compounds, such as mango, watermelon and berries in at-risk populations, such as among adults with prediabetes, insulin resistant and metabolic syndrome. Di Xiao also extensively involved on variety of dietary fibers studies on postprandial glycemic response in healthy adults. Di Xiao's academic training and research experience resulted in several peer reviewed publications, as well as poster presentations at scientific meetings, such as Annual Experimental Biology and Annual Nutrition Science Meeting. Di Xiao's PhD project is on developing dietary strategies for healthy aging, involving understand and investigate the effect of modified ketogenic diet and berries on cardio-metabolic-vascular-cognitive health.

The Effects of Acute Raspberry Intake on the Relationship Between Enhanced Metabolic Control and Cognitive and Psychomotor Function

Authors: Di Xiao[1], Britt Burton-Freeman[1], Barbara Shukitt-Hale[2], Indika Edirisinghe[1]

Affiliations:

1. Center for Nutrition Research, Institution for Food Safety and Health, Illinois Institute of Technology, Chicago, IL,60616
2. United States Department of Agriculture/Agricultural Research Service, Human Nutrition Research Center on Aging (HNRCA) at Tufts University, 711 Washington Street, Boston, MA, 02111

Red raspberries (RRB) contain fibers and a unique combination of polyphenols with possible cardiovascular, neurovascular, and metabolic benefits. The objective of this study was to evaluate the effects of acute red raspberry intake on cardio-metabolic markers of postprandial substrate metabolism, vascular endothelial function, and cognition and fine motor function in older overweight/obese adults. Thirty six adults (Site1: n=30, age: 60 ± 4 years, BMI: 29.9 ± 3.0 kg m-2, Site 2: n=6, age: 64 ± 5 years, BMI: 31.0 ± 1.7 kg m-2, mean ± SD,) were randomized to the single-blinded, controlled, crossover trial. Participants consumed a high carbohydrate moderate fat breakfast (HCMF) meal containing 0 gram (control meal, 750 kcal) or 25 grams of freeze-dried RRB powder (1 cup fresh RRB equivalence, RRB meal, 752 kcal) on two occasions separated by 7 days washout period. Blood was collected at baseline, then again at 8 time points over 7.5 hours after test meals to determine glucose, insulin, triglyceride, and interleukin 6 (IL-6) concentrations. Flow-mediated dilation (FMD) was assessed at baseline and then at 2 and 5 hours post test meal (site1 only). Cognition and fine motor function were assessed at baseline and then at 2 and 6 hours following the meal through standardized assessments, including the following tests: Hopkins Verbal Learning Test, Digit Symbol Coding, Grooved Pegboard, Profile of Mood States, and The Cambridge Neuropsychological Test Automated Battery (CANTAB) tests (Paired Associates Learning, Spatial Working Memory and Rapid Visual Information Processing). A significant treatment * time interaction was observed for glucose (P= 0.0025) and insulin (P=0.0020) levels. Additionally, RRB significantly reduced the postprandial maximum concentration of glucose (P< 0.05), and insulin (P< 0.05), as well as the incremental area under the curve (iAUC) of insulin (P< 0.05). In CANTAB-Spatial working memory test, higher strategy scores (p<0.05) and less errors (p<0.05) were observed 6 hours post RRB meals compare to control meal. No significant treatment-related differences were observed for vascular function as measured by changes in %FMD, other metabolic markers, and the rest cognitive/behavior assessments test variables. Overall, acute RRB supplementation attenuated postprandial glycemia and improved the working memory after an HCMF meal challenge in a group of older overweight and obese individuals.

Keywords: red raspberry, cognitive, memory, metabolic control, FMD

TODAY'S FOOD CONVERSATION
What Messages Should We Be Communicating About Berries?

Talk Sponsored by:

WASHINGTON
AMERICA'S RASPBERRIES

Amy Myrdal-Miller
Farmer's Daughter® Consulting, Inc.

Amy Myrdal Miller, MS, RDN, FAND, is an award-winning dietitian, farmer's daughter, public speaker, author, and president of Farmer's Daughter® Consulting, Inc., an agriculture, food, and culinary communications firm.

Amy's career highlights include working for Fleishman Hillard's Agribusiness Practice, Dole Food Company, the California Walnut Board & Commission, and The Culinary Institute of America. Today, Amy works with a variety of clients across the food system, including seed companies, commodity boards, marketing orders, national brands, food start-ups, colleges, and restaurants. She become the retail nutrition marketing and foodservice partnership specialist for the Buy California Marketing Agreement and the CA GROWN® brand in April 2022.

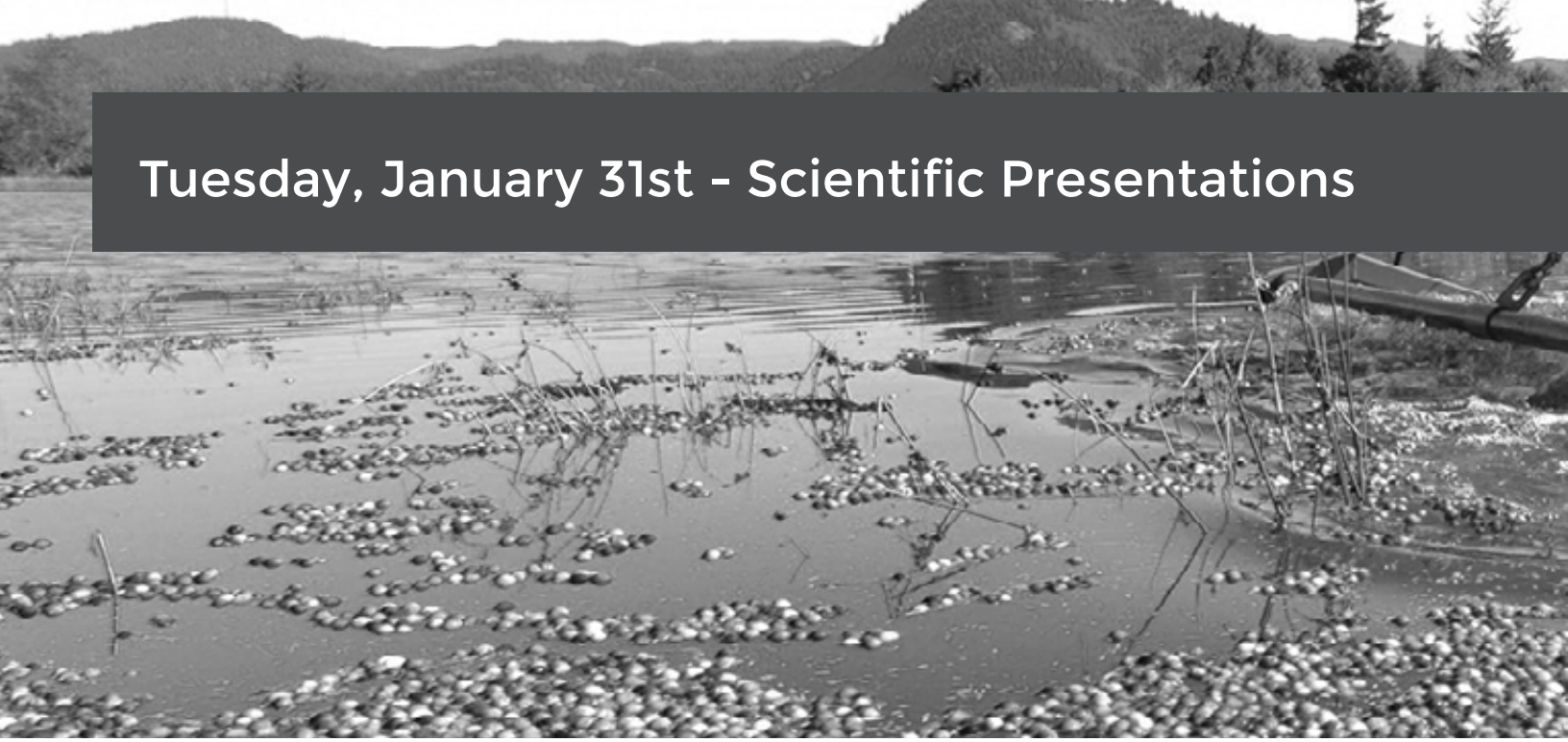
She is the co-author of Cooking á la Heart, a cookbook focused on plant-forward eating patterns that reduce inflammation and promote cardiovascular health that will be published February 1, 2023 by The Experiment Publishing, a division of Hachette Books.

Amy writes a monthly column on foodservice and flavor trends for Produce Business magazine. She has authored or co-authored ten papers in peer-reviewed journals and presented at more than 275 state, national, and international conferences the past 20 years, including giving the Lenna Frances Cooper Memorial Lecture at the Academy of Nutrition and Dietetics Food and Nutrition Conference in 2015 and presenting at the world-renowned Aspen Ideas Festival in 2017.

She is a member of the Academy of Nutrition and Dietetics, a former chair of the Food & Culinary Professionals DPG, a former president of the California Academy of Nutrition and Dietetics, and a board member of the Sacramento chapter of Les Dames d'Escoffier International.

Amy received her B.S. in dietetics from the University of California Davis, and her M.S. in nutrition communication from Tufts University School of Nutrition Science and Policy. She received the Tufts Nutrition Impact Award in 2014.

A farmer's daughter from North Dakota, today Amy and her husband Scott Miller live in Carmichael, California with "the interns" Violet Grey and Schroeder "the Shredder" Miller.



Tuesday, January 31st - Scientific Presentations

Berries & the Heart / Healthy Aging

Dr. Britt Burton-Freeman
Illinois Institute of Technology

Session Chair

Current Research Review

Britt Burton-Freeman, Ph.D., is the Director of the Institute for Food Safety and Health's (IFSH) Center for Nutrition Research and Associate Professor in Food Science and Nutrition and Biomedical Engineering at the Illinois Institute of Technology (IIT). She also holds a research nutritionist appointment in the department of Nutrition at UC Davis and is affiliated with the Institute for Translational Medicine at the University of Chicago.

Dr. Burton-Freeman's current research interests are in mitigating disease processes through dietary approaches focused on bioactive components of foods. Specific disease targets are cardiovascular, metabolic syndrome and obesity. Current work focuses on physiological effects and mechanistic underpinnings of polyphenols and novel carbohydrates, including their pharmaco-kinetic and -dynamic relationships in human biology to impact health status. The influence of food matrix, processing, host/microbiome characteristics and interactions are also being addressed.

As the Director for the Center for Nutrition Research at IIT/IFSH in conjunction with the National Center for Food Safety and Technology, she leads a nutrition and health initiative with food industry partners and government collaborators to provide critical science that supports policy, dietary recommendations and comprehensive innovative solutions linking nutrition and food safety to improve the health and quality of life of Americans. Recent work has focused on fiber definitions for labeling and perceptions/responses to key terms associated with health in low income populations.

Dr. Burton-Freeman is actively involved in multiple professional societies dedicated to health and disease abatement including the American Society for Nutrition, the Obesity Society, the American Chemical Society and the Institute of Food Technologist. Dr. Freeman publishes in various top Journals and is co Editor-in-Chief of Nutrition and Healthy Aging.

Dr. Burton-Freeman holds a BS in Dietetics from the California State University, Chico, a MS and PhD in Nutritional Biology from the University of California, Davis and completed a postdoctoral fellowship in the Department of Internal Medicine at University of California, Davis. Dr. Burton-Freeman has held professional appointments in academia and the biotechnology industry leading research programs and teams to deliver on basic and clinical science objectives.

Dr. Sarah A. Johnson
Colorado State University

Dr. Sarah A. Johnson, PhD, RDN is an Associate Professor, the Director of the Functional Foods & Human Health Laboratory, and the Director of the Didactic Program in Dietetics in the Department of Food Science and Human Nutrition at Colorado State University.

Dr. Johnson's research program aims to integrate multiple disciplines including nutrition, food, agriculture, and biomedical sciences to perform translational research studies focused on critically examining the efficacy and mechanisms by which functional foods, namely berries, improve cardiovascular disease risk factors and modulate vascular function in high-risk aging populations. Current work focuses on determining the clinical efficacy of blueberries and aronia berries in attenuating age-related vascular dysfunction, and underlying mechanisms responsible for clinical efficacy and physiological effects in general. Her research is funded through federal and industry sources, and she publishes in high-quality nutrition, food, and physiology journals.

Dr. Johnson is an Associate Editor for the journals Nutrition Research and Nutrition and Healthy Aging, and is an Editorial Board Member for the Journal of Nutritional Biochemistry, Nutrients, and the Journal of Medicinal Food. She has received honors and awards such as the Emerging Leaders Network Award from the Institute of Food Technologists, the Abbott Nutrition Award in Women's Health from the Academy, the Junior Faculty Author Award from the Research Dietetic Practice Group of the Academy of Nutrition and Dietetics, and the Clinical Emerging Leader Award from the Medical Nutrition Council of the American Society for Nutrition. She is actively involved in the American Society for Nutrition, the Academy of Nutrition and Dietetics, and the Institute of Food Technologists.

Dr. Johnson received a BS in Nutrition and Food Science/Dietetics from the University of Vermont, and an MS and PhD in Nutrition and Food Science from Florida State University, where she also completed a postdoctoral fellowship.

Impact of Blueberries on Vascular Endothelial Function in Postmenopausal Women: Clinical Impact and Possible Mechanisms

Authors: Emily K. Woolf[1], Janee D. Terwood[2], Nicole S. Litwin[1], Allegra R. Vazquez[1], Nathan B. Ketelhut[2], Kiri A. Michell[1], Brayden T. Smith[1], Lauren E. Grabos[1], Sylvia Y. Lee[1], Nancy Ghanem[1], Sangeeta Rao[3], Melanie Le Sayec[4], Ana Rodriguez-Mateos[4], Christopher L. Gentile[1], Tiffany L. Weir[1], Douglas R. Seals[5], Frank A. Dinenno[2], Sarah A. Johnson[1*]

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Previous research with blueberries strongly suggests their potential for reducing age-related cardiovascular disease (CVD). They are rich in (poly)phenols including flavonoids, phenolic acids, and pterostilbene. These compounds, and derivatives resulting from gut microbial and phase II metabolism, are known to attenuate oxidative stress and inflammation. We previously demonstrated that consumption of 22 g/day freeze-dried highbush blueberry powder (equivalent to ~1 cup fresh blueberries) for 8 weeks reduced blood pressure and systemic/peripheral arterial stiffness and increased circulating nitric oxide metabolites in postmenopausal women with pre- and stage 1-hypertension (HTN), suggestive of improvements in vascular endothelial function. Progressive impairments in oxidative stress-mediated endothelial function have been observed across the menopausal transition in human studies, which is linked to increased CVD risk. In a recent randomized, double-blind, placebo-controlled, parallel-arm trial, we evaluated the impact of consuming 22 g/day for 12 weeks of freeze-dried highbush blueberry powder on vascular endothelial function and possible mechanisms, as well as other measures of cardiovascular health, in postmenopausal women with elevated blood pressure or stage 1-HTN. Following 12 weeks of daily blueberry consumption, flow-mediated dilation (FMD) normalized to shear rate area under the curve (FMD/SRAUC; to control for inter-individual variability) was significantly increased compared to baseline, and changes from baseline to 12 weeks were significantly higher than the placebo group indicating an improvement in vascular endothelial function. There were no changes in endothelium-independent dilation confirming that improvements were endothelium-dependent. We also found that improvements in endothelial function were due, at least in part, to reductions in oxidative stress, and that plasma (poly)phenol metabolites related to flavonoid and gut microbial metabolism were increased following blueberry consumption, providing insight into physiological mechanisms. Certain (poly)phenol metabolites and endothelial cell protein expression markers were correlated with improvements in endothelial function. Other measures of cardiometabolic health, including blood pressure, were largely unchanged due to blueberry consumption. The underlying mechanisms contributing to improvements in vascular endothelial function cannot be determined at this time. With respect to blood pressure, the current findings do not support that blueberries exert antihypertensive effects in this population. However, considering our previous findings in this population demonstrating antihypertensive effects, and the mixed body of evidence surrounding blueberries and blood pressure such that about half demonstrated beneficial effects, further research is needed to better understand the antihypertensive effects of blueberries, and factors that can be modified and/or implemented to improve efficacy. Future human studies evaluating blueberry consumption that can provide further insight into physiological mechanisms is needed, as well research to understand factors contributing to inter-individual variability in clinical responses to support a precision nutrition approach. Overall, our data suggest that blueberries exert cardiovascular-protective effects, including beneficial effects on vascular endothelial function, in postmenopausal women with above-normal blood pressure.

Keywords: Anthocyanins, blueberry, cardiovascular disease, endothelial dysfunction, hypertension, (poly)phenols

Funding: This research was funded by the US Highbush Blueberry Council and the USDA National Institute of Food and Agriculture [grant no. 2020-67017-30833/project accession no. 1021875].

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Dr. Anandh Babu Pon Velayutham

The University of Utah

Dr. Anandh Babu Pon Velayutham is an Associate Professor in the Department of Nutrition and Integrative Physiology at the University of Utah. His research focuses on identifying novel dietary compounds for the prevention of vascular disease in diabetes and metabolic syndrome. His current research examines the vascular effects of blueberries and strawberries with special emphasis on the microbial metabolites of berry anthocyanins and the molecular signaling mechanisms involved. Dr. Velayutham's research aims to understand the causal association between dietary berries, gut microbiome and vascular health.

Metabolites Mediate the Vascular Effects of Dietary Blueberries

Human studies support the vascular effects of anthocyanins, one class of flavonoids widely found in berry fruits. Evidence indicates that intake of blueberry improves vascular function in healthy men, reduces blood pressure and improves arterial dysfunction in individuals with metabolic syndrome, hypertension and endothelial dysfunction. Anthocyanins are extensively metabolized by the gut microbiota in humans, suggesting their vascular benefits might be mediated by their circulating microbial metabolites. Gut microbiota metabolizes anthocyanins into more readily absorbable bioactive metabolites, and anthocyanins support the growth of microbes, indicating a two-way relationship between anthocyanins and microbiota. In our study, wild blueberry supplementation at a nutritional dose suppressed vascular inflammation, increased endothelium-dependent vasorelaxation, reduced arterial pressure, and increased beneficial gut microbes in diabetic mice. However, antibiotic treatment abolishes the beneficial vascular effects of blueberries, indicating the crucial role of gut microbes in mediating the bioactivities of dietary blueberries. Further, key blueberry metabolites ameliorated endothelial inflammation in endothelial cells isolated from diabetic individuals and improved lipotoxicity-induced endothelial inflammation and vascular dysfunction. Collectively, our study provides evidence that blueberry-derived microbial metabolites are responsible for the vascular beneficial effects of blueberries. Understanding and validating the bioactivities of blueberry will provide a solid scientific foundation for recommending dietary intake of blueberry to improve vascular health.

Keywords: Blueberry, Gut Microbes, Vascular Inflammation, Vascular Function, Diabetes, Blueberry Metabolites

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Dr. Ann Skulas-Ray
University of Arizona

Dr. Skulas-Ray is an Assistant Professor in the Department of Nutritional Sciences at the University of Arizona. Her research focuses on identifying and refining nutritional strategies for reducing chronic inflammation and cardiovascular disease risk. She specializes in human subjects intervention studies that investigate effects of omega-3 fatty acids and plant bioactives on lipids/lipoproteins, inflammation, insulin resistance, oxidative stress, brachial and central blood pressure, indices of arterial stiffness, and other cardiovascular disease risk factors. She has been an investigator on 16 clinical studies and has over 40 publications in the areas of inflammation, nutrition, and cardiovascular research, including 5 book chapters, 2 encyclopedia entries, and lead authorship of a National Advisory for the American Heart Association.

Cranberries and Cardiometabolic Health

Authors: Chesney K. Richter[1], Ann C. Skulas-Ray[1], Trent L. Gaugler[2], Stacey Meily[3], Kristina S. Petersen[4], and Penny M. Kris-Etherton[3]

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Emerging cardiovascular disease (CVD) risk factors, including central vascular function and HDL efflux, may be modifiable with food-based interventions such as cranberry juice. A randomized, placebo-controlled, crossover trial was conducted in middle-aged adults with overweight/obesity (n = 40; mean BMI: 28.7 ± 0.8 kg/m2; mean age: 47 ± 2 years) and elevated brachial blood pressure (mean systolic/diastolic BP: 124 ± 2/81 ± 1 mm Hg). Study participants consumed 500 mL/d of cranberry juice (~16 fl oz; 27% cranberry juice) or a matched placebo juice in a randomized order (8-week supplementation periods; 8-week compliance break), with blood samples and vascular measurements obtained at study entry and following each supplementation period. There was no significant treatment effect of cranberry juice supplementation on the primary endpoint of central systolic blood pressure or central or brachial diastolic pressure. Cranberry juice significantly reduced 24-h diastolic ambulatory BP by ~2 mm Hg compared to the placebo (p = 0.05) during daytime hours. Cranberry juice supplementation did not alter LDL-C but significantly changed the composition of the lipoprotein profile compared to the placebo, increasing the concentration of large LDL-C particles (+29.5 vs. -6.7 nmol/L; p = 0.02) and LDL size (+0.073 vs. -0.068 nm; p = 0.001). There was no effect of treatment on ex vivo HDL efflux in the total population, but exploratory subgroup analyses identified an interaction between BMI and global HDL efflux (p = 0.02), with greater effect of cranberry juice in participants who were overweight. Exploratory analyses indicate that baseline C-reactive protein (CRP) values may moderate treatment effects. In this population of adults with elevated blood pressure, cranberry juice supplementation had no significant effect on central systolic blood pressure but did have modest effects on 24-h diastolic ambulatory BP and the lipoprotein profile. Future studies are needed to verify these findings and the results of our exploratory analyses related to baseline health moderators.

Keywords: Cranberry, cardiovascular, biomarkers, clinical, cholesterol

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Dr. Arpita Basu
University of Nevada, Las Vegas

Associate Professor Dr. Basu's research focuses on understanding the health effects of dietary bioactive compounds, such as those found in tea, berries, and cocoa in modulating disease biomarkers in type 2 diabetes, hypertension, and cardiovascular diseases. She has conducted several clinical trials focused on these foods, beverages, and dietary supplements among adults with the metabolic syndrome, type 2 diabetes, and cardiovascular risks. Dr. Basu also has extensive research interests in diabetes and nutritional epidemiology and has published several reports about prospective associations of lipid and lipoprotein biomarkers, as well as of dietary patterns, with diabetes vascular complications. She has been published in more than 80 peer-reviewed journal articles and invited book chapters. Her research has been funded by federal and industrial agencies.

Dr. Basu earned her master's in food and nutrition from University of Calcutta India, her master's in public health with focus on epidemiology from University of South Florida, and her Ph.D. in nutrition from Texas Woman's University. She completed her postdoctoral fellowship in clinical nutrition at University of California Davis Medical Center. Dr. Basu has served on the editorial board of the Journal of Nutrition since 2012 and has received numerous research awards from the American Society for Nutrition and the American College of Nutrition for her research in dietary bioactive compounds in human health.

Role of Dietary Berries in Glycemic Control and Insulin Resistance

Dietary berries are a rich source of several nutrients and phytochemicals and in recent years, accumulating evidence suggests they can reduce risks of several chronic diseases, including type 2 diabetes (T2D). The objective of this presentation is to summarize and discuss the role of dietary berries on insulin resistance and biomarkers of T2D in human feeding studies. Commonly consumed berries, especially cranberries, blueberries, raspberries, and strawberries, ameliorate postprandial hyperglycemia and hyperinsulinemia in overweight or obese adults with insulin resistance, and in adults with the metabolic syndrome. To further explore the role of strawberries at a dietary feasible dose of 2.5 fresh strawberries per day for four weeks, we recently completed a RCT crossover study in adults with above optimal serum LDL-cholesterol, as well as having features of the metabolic syndrome. In this trial, 2.5 servings of strawberries decreased insulin resistance and fasting insulin and revealed a borderline decrease in serum LDL-cholesterol. Similar observations were also noted when pregnant women at high risk of gestational diabetes were given a daily dose of two cups of blueberries and 12g soluble fiber for 18 weeks; intervention improved postprandial blood glucose and C-reactive protein.

In non-acute long-term studies, these berries either alone, or in combination with other functional foods or dietary interventions, can improve glycemic and lipid profiles, blood pressure and surrogate markers of atherosclerosis. Since T2D represents a cluster of these cardiometabolic conditions, dietary berries can certainly help better manage diabetes-related metabolic health. Nevertheless, existing evidence, although sparse, suggests that berries have an emerging role in dietary strategies for the prevention of diabetes and its complications in adults.

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Berry Session: Industry Panel
Broadening the Berry Basket with Berry Supplements

Christian G. Krueger
CEO of Complete Phytochemical Solutions, LLC

Mr. Christian G. Krueger is the Chief Executive Officer and Co-Founder of Complete Phytochemical Solutions, LLC, a consulting and analytic service company that provides intellectual and technical expertise in phytochemistry that enables their clients to develop, manufacture and market high quality and efficacious botanical and food products for human and animal nutrition.

Mr. Krueger has a 25+ year career at the University of Wisconsin-Madison as a phytochemist specializing in the development, validation and harmonization of analytic methods. Christian has published over 70 peer-reviewed manuscripts and his expertise in natural product chemistry, understanding of supply chain management (growers, processors, formulators, and retail) and research experiences relating phytochemical structures to biologic function provides a unique skill set and background. He is a member on several Association of Official Analytic Chemists (AOAC) Expert Review Panels and works closely with the United State Pharmacopeia (USP) to develop monographs for Dietary Supplement Compendia. He is an invited Advisory Council Member for the School of Nutrition at the Southwest College of Naturopathic Medicine and Health Sciences (SCNM).

Brenda Van Goethem
Director of Quality Systems
Nature's Way®

Brenda Van Goethem is the Director of Quality Systems at Nature's Way®, a leader in the dietary supplement industry focusing on product innovation and quality. She has over 30 years of quality assurance and regulatory compliance management experience in the dietary supplement and food industries working for H.J. Heinz Company, Schreiber Foods, Michael Foods, and Enzymatic Therapy. In her current role, she leads the Quality Systems teams comprising of Quality Assurance, Quality Control, and Labeling Compliance. She ensures that all Nature's Way operations are compliant to applicable dietary supplement, food, and drug regulations. She is responsible for overseeing quality strategies in regards to supply quality, cGMP compliance, and analytical excellence.

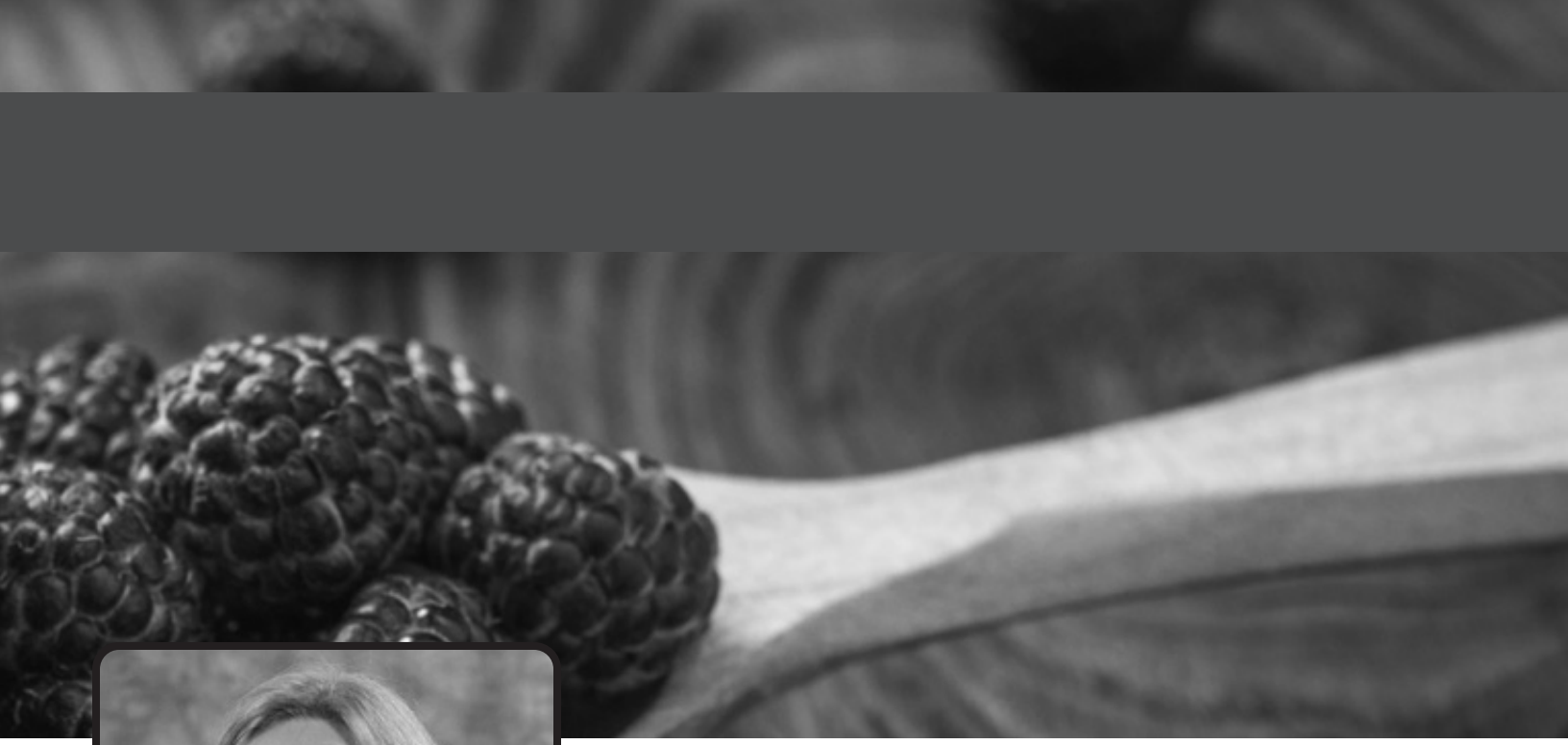
Melanie Bush
Vice President of Science and Research for Artemis International

Melanie Bush is the Vice President of Science and Research for Artemis International, a leading supplier of berry nutraceutical ingredients. She has been a part of the Artemis team for over 15 years and her management role spans several departments including Quality Assurance, Research & Development and Technical Sales Support. She coordinates and communicates new research on the health benefits of berries, and she is a regular contributor and writer for numerous industry publications.

She attended Purdue University-Fort Wayne on a full academic scholarship, where she earned both bachelor's and master's degrees in biology. While there she received multiple academic awards for her six years of immunology research on high anthocyanin berry extracts and their immune-enhancing and anti-cancer effects.

She is also currently an adjunct biology instructor at Trine University in Indiana and was previously recognized by Greater Fort Wayne Business Weekly as one of "Forty Under 40" for her service to both her work and her community.

Berries & the Skin



Mary Ann Lila, PhD
North Carolina State University

Session Chair

Current Research Review

Dr. Mary Ann Lila is a David H. Murdock Distinguished Professor and Director, Plants for Human Health Institute at North Carolina State University.

Over the past two decades, Dr. Lila's research has centered on bioactive phytochemical constituents, particularly polyphenolic/flavonoid phytoactives, their capacity to mitigate immunosuppression and inflammation, and the differential efficacies that these compounds exert in individual human subjects. The primary emphases in her team are (1) rigorous structural characterization of phytochemicals and metabolites (2) elucidation of phytochemical interactions that potentiate benefits for human health maintenance and allergy attenutation, (3) development of functional ingredients that stabilize the bioactive properties of these otherwise ephemeral constituents, (4) individualized responses of subjects to phytoactive agents (tentatively as a consequence of their differential intestinal microbiota profiles, which condition the production of active catabolites), and (5) interpretation of the bioavailability/bioaccessibility of plant-derived metabolites.

Dr. Giuseppe Valacchi
North Carolina State University

Dr. Giuseppe Valacchi is Professor in Regenerative Medicine at North Caroline State University and Professor in Physiology at the University of Ferrara, Italy. In addition, since 2008 he is Adjunct Professor at Kyung Hee, Dept. of Nutrition, Seoul, South Korea.

Dr. Valacchi's research has been focused in understanding the cellular and molecular mechanisms that define the tissues physio-pathological responses to altered redox homeostasis with special focus on cutaneous tissue. His group is the pioneer in understanding the skin responses to ozone challenge. He has won several awards among them the Entelligence Award from Actelion, Science and Education Award and recently, the Exposome grant.

In 2018 Dr. Valacchi was awarded with the "Doctorate Honoris Causa" in Biochemistry and Pharmacy from the University of Buenos Aires (rank n. 72 among the over 3,000 universities in the world) for his work in the redox biology field, and he is the recipient of the 2021 Clinical Research award from the SFRR-E.

Dr. Valacchi is author of more than 280 peer reviewed internationals papers (most of them related to the effect of pollution in target organs), 15 book chapters, one book. He has been invited speaker to more than 100 international conferences and organizer/Chair to over 50 international meetings.

Dr. Valacchi is the Associate Editor of several international journals among which is Mediators of Inflammation, Frontiers in Cellular Biochemistry, Journal of Complementary and Traditional Medicine, Biomed Research International (Dermatology Subjects), Oxidative Medicine and Cellular Longevity, Antioxidants; in addition he is member of the Editorial Board of several journals including Genes and Nutrition, Archives in Biophysics and Biochemistry, Frontiers in Inflammation Pharmacology, BioFactors, Cosmetics, Free Radicals in Biology and Medicine.

Blueberry Extracts as a Novel Approach to Prevent Ozone-Induced Cutaneous Inflammasome Activation

Authors: Giuseppe Valacchi, Erika Pambianchi, Francesca Ferrara, Alessandra Pecorelli, Brittany Woodby, Mary Grace, Jean-Philippe Therrien, Mary Ann Lila.

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BACKGROUND: The World Health Organization estimates that 7 million people die every year due to pollution exposure. Among the different pollutants to which living organism are exposed, ozone (O3) represents one of the most toxic. The skin is one of the main tissues exposed to the outdoor environment. Chronic exposure to outdoor stressors can alter cutaneous redox state resulting in the activation of inflammatory pathways. Recently, a new player in the inflammation mechanism was discovered: the multiprotein complex NLRP1 inflammasome, which has been shown to be also expressed in the skin. The topical application of natural compounds has been studied for the last 40 years as a possible approach to prevent and eventually cure skin conditions. Recently, the possibility to use blueberry (BB) extract to prevent pollution-induced skin toxicity has been of great interest in the cosmeceutical industry.

OBJECTIVE: In the present study we want to evaluate the eventual protective effect of BB extract against ozone induced cutaneous inflammasome activation.

METHODS: We analyzed the cutaneous protective effect of BB extract in several skin models: human keratinocytes (2D model), reconstitute human epidermis (3D models), and human skin explants (ex vivo).

RESULTS: we observed that in the different skin models used, BB extracts were able to enhance keratinocyte wound closure and normalize proliferation and migration responses previously altered by O3. In addition, pretreatment with BB extracts was able to prevent ozone-induced ROS production and inflammasome activation measured as NRLP1-ASC scaffold formation and also prevent the transcripts of key inflammasome players such as CASP1 and IL-18, suggesting that this approach as a possible new technology to prevent cutaneous pollution damage.

CONCLUSIONS: Our data support the hypothesis that BB extracts can effectively reduce skin inflammation and be a possible new technology against cutaneous pollution-induced damage.

Keywords: Inflammasome, pollution, ozone, topical, NLRP1

Dr. Steve Oghumu
The Ohio State University

Dr. Steve Oghumu is an Assistant Professor at the Ohio State University Wexner Medical Center, Department of Pathology. Research in their laboratory is focused on understanding the cellular and molecular mechanisms of oral carcinogenesis and oral cancer chemoprevention. They are developing a number of preclinical models that will enable them to fully explore the underlying mechanisms of oral cancer inhibition by dietary phytochemicals and other immunomodulatory compounds. Of particular interest to their research are the bioactive phytochemicals that are found in black raspberries. Their long term goal is to identify discrete significant mediators of oral carcinogenesis that can be exploited in preventive and/or therapeutic strategies to reduce the risk of oral cancer development.

Black Raspberries Mitigate DNFB-Induced Contact Hypersensitivity by Down-Regulating Dendritic Cell Activation and Inhibiting Mediators of Effector Responses

Contact hypersensitivity (CHS) is the most common occupational dermatological disease. Dendritic cells (DCs) mediate the sensitization stage of CHS, while T-cells facilitate the effector mechanisms that drive CHS. Black raspberry (Rubus occidentalis, BRB) and BRB phytochemicals possess immunomodulatory properties, but their dietary effects on CHS are unknown. We examined the effects of diets containing BRB and protocatechuic acid (PCA), on CHS using a model induced by 2,4-dinitrofluorobenze (DNFB). Mice were fed control diet or diets supplemented with BRB or PCA. In-vitro, bone-marrow derived DCs and RAW264.7 macrophages were treated with BRB extract and PCA. Mice fed BRB or PCA supplemented diets displayed decreased DNFB-induced ear swelling, marked by decreased splenic DC accumulation. BRB extract diminished DC maturation associated with reduced Cd80 expression and IL-12 secretion, and PCA reduced IL-12. Dietary supplementation with BRB and PCA induced differential decreases in IL-12-driven CHS mediators, including IFN- and IL-17 production by T-cells. BRB extracts and PCA directly attenuated CHS-promoting macrophage activity mediated by nitric oxide and IL-12. Our results demonstrate that BRB and PCA mitigate CHS pathology, providing a rationale for CHS alleviation via dietary supplementation with BRB or BRB derived anthocyanins.

Dr. Roberta Hoskin
North Carolina State University

Dr. Roberta Hoskin is a Senior Researcher Scholar in the Department of Food, Bioprocessing and Nutrition Sciences at the North Carolina State University's Plants for Human Health Research Institute. Dr. Hoskin's primary research interests are centered on technological strategies that promote, enhance, and preserve the health benefits of plant-derived phytochemicals, mainly polyphenolic/flavonoid bioactive compounds. She is particularly interested on the research and development of novel food ingredients and products using sustainable food sources, such as secondary streams of the food industry and underexploited dietary materials. Her green-chemistry approach aims to create high-quality ingredients containing physiologically relevant concentrations of stabilized phytoactives to provide sustainable, efficient and innovative solutions for the health-oriented industry.

Food and Skin Care Convergence: Natural and Sustainable Fruit-derived Compounds to Prevent Skin Damage

Berries are natural sources of health relevant phytonutrients with antioxidant, anti-inflammatory, antiaging and antimicrobial properties [1, 2, 3]. In addition, secondary streams of the fruit industry have proved to be particularly rich in the same health-promoting compounds found in fresh fruits and are now recognized as novel, environmentally friendly sources of biologically active key phytochemicals [4]. Target molecules extracted from berries or recovered from berry pomaces are prime sources of molecules with demonstrated biologically relevant activity not only to be used as ingredients in food formulations, but also to be incorporated into skin care products in lieu of synthetic chemicals that are currently used in the beauty industry [5].

Indeed, growing evidence shows berries as multifaceted natural sources of high value molecules for convergent food and skin care applications [6,7]. The demand for natural ingredients in cosmetics and skin care products is now in the “all natural” spotlight fueled by the current movement for cleaner, organic, green and sustainable products. Several well-established food industries are now interested in diversifying and expanding their fruit-derived portfolio of products marketed to the well-being and healthy market. This scenario creates opportunities and challenges to develop smart products with preserved natural phytoactives extracted from berry fruits and pomaces that deliver active molecules in an easy-to-handle, stable format using enhanced extraction and processing techniques [7, 8, 9]. Therefore, in this presentation, different strategies exploring the potential efficacy of berry-derived formulations designed to mitigate pollution-induced skin damage will be discussed. For this, the efficacy of berry extracts in preventing UV-induced oxidative stress, inflammation, and structural impairment of cutaneous tissue by quenching direct and indirect sources of oxidative stress will be assessed. The challenges associated with developing innovative products will also be addressed.

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Dr. Iva Fernandes
REQUIMTE/LAQV, University of Porto

Dr. Iva Fernandes has a degree in Biochemistry and a PhD in Chemistry (2012) obtained at the Faculty of Sciences of University of Porto (FCUP) under the topic hemi-synthesis, bioavailability and biological properties of anthocyanins and metabolites. In 2013, Dr. Fernandes started a postdoc to continue her research area on the development of methods to analyze and characterize polyphenols and metabolites in biological samples, synthesis of metabolically relevant metabolites and evaluation of their bioavailability, metabolism and biological activity, using in vitro models and human clinical trials.

At present, Dr. Fernandes is Invited Auxiliar Professor Scholar position at FCUP & IPP and a senior researcher in LAQV with expertise on understanding the bioavailability and biological properties of phytochemicals, particularly unravelling their mechanisms of action. Dr. Fernandes has published 67 papers, an h-index of 24 and has 5 book chapters. She participated in (inter)national conferences (49 posters & 36 oral) and invited talks at National Meeting of Blueberry Producers on 2021 and TEDx Move on 2021.

Dr. Fernandes has received 8 awards including 2 Fellows, best poster awards in Iberphenol – International Conference and International Conference on Polyphenols and Health, best oral presentation in Portuguese Association of Nutrition (APN) and wine and Science World Congress, Conference Grant by the “Polyphenols Group”, Nutrition Award by APN, Excellence award by “SuperBock Group”. Dr. Fernandes is responsible for a submitted patent, NPAT357. Dr. Fernandes was involved in the organization of: Global Women’s Breakfast, International Workshop Anthocyanins, National Meeting of the Portuguese Chemistry Society.

Dr. Fernandes is/was supervisor of 2 PhD, 5 MSc and several works of course completion of LSc/BSc. Dr. Fernandes is/was co-PI in project Winput and team member in 14 FCT/ANI/AGRO projects (BIOCORK, AGRO 386, VINE&WINE RESIDUES, Sino-Portuguese Program, VINOFLAVO, POLY4CD, NUTRALLERPHEN, FoodSmarTag, ANTHO4SKIN, MONET). Dr. Fernandes has collaborated with (inter)national research facilities (CENTI, CINTESIS/FMUP, IBeSa, Wuhan Polytechnic University, Nova Medical School, Northwest A&F University) and food companies (Superbock Group, Frulact & SONAE). She is a member of Collaborative Laboratory Colab4Food. She has served as Guest Editor for IJMS and Nutrients. Dr. Fernandes is reviewer of JAFQ, Food Chem, Mol Nutr Food Res, J Funct foods and member of examiner boards. Dr. Fernandes is leader of Wine and Health Work group of OENOVITI International Network and member of European Foundation for the Study of Diabetes. Recently, she has been involved in projects related with new anthocyanin derivatives for technological applications in the cosmetic industry and therapeutic applications.

New Horizons for Skin Healthcare – Exploring the Colour and Bioactivity of Berry Anthocyanins and Related Structures

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BACKGROUND: Human skin is commonly described as a particularly dynamic and complex environment, with a physiological balance continuously orchestrated by numerous internal and external factors. Intrinsic aging, exposure to UV radiation and skin pathogens are some of the key players that account for dermatological alterations and ailments.

OBJECTIVE: This study intended to explore the potential skin-health beneficial properties of molecules belonging to the anthocyanin family and prepare topical formulations enriched with them. Different types of emulsions were developed: oil/water and gel-in-oil emulsions, containing the natural dyes alone or in combination with a commercial chemical UV filter.

METHODS: Anthocyanins were extracted from blackberries and chemical transformed into anthocyanin derivatives. Inhibition of biofilm formation was assessed by the crystal violet assay and fluorescence microscopy. Quorum sensing (QS)-related genes were quantified by RT-qPCR and Galleria mellonella infection model was used to assess in vivo the effects. Cytotoxic and phototoxic effects towards human skin cells were evaluated by MTT assay and production of reactive oxygen species (ROS) was determined by DCFDA assay. Enzymatic inhibition was monitored spectrophotometrically. Compounds were further incorporated in two types of emulsions: oil-in-water and gel-in-oil emulsions. UV-vis spectrophotometry analysis was used for SPF estimation and interaction studies. Samples were characterized, regarding their rheological behavior, pH, droplet size distribution and microscopic appearance. Color variation upon different storage conditions was monitored at several timepoints by colorimetry.

RESULTS: Some of the tested compounds were found to: affect S. aureus and P. aeruginosa biofilm formation and carboxypyCy-3-glc in particular was shown to interfere with the expression of QS-related genes; exhibit UV-filter capacity, reduce ROS production in human skin cells and inhibit skin aging-related enzymes activity. Compounds were successfully incorporated in topical emulsions, yielding formulations with different and appealing colors. Very subtle color variations were observed in dark storage conditions, particularly in the gel-in-oil formulations. Interestingly, an interaction with the commercial chemical UV filter was detected which resulted in a strong increase of absorbance with notorious color intensification of the formulations and a deviation from the original color hue. A good complementarity between the absorbance spectrum of the anthocyanin and the filter was obtained.

CONCLUSIONS: Combination of bioactivities displayed by these compounds supports their usefulness as natural ingredients for skin health. Combination of their UV-absorptive properties and antioxidant activity would provide a dual function of photoprotection. Also, carboxypyCy-3-glc ability to strongly impair S. aureus biofilm formation could be interesting in the perspective of biofilm-associated cutaneous infections treatment, particularly those related to chronic infected wounds. Despite the susceptibility of these compounds to light and high temperature, when kept at dark conditions at room temperature, developed formulations exhibited good color retention. The new uncovered interaction between the natural dyes and the chemical filter offers the possibility of natural color diversification and the potential promotion of photostability of these molecules.

Keywords: anthocyanins; biofilms; cosmeceuticals; ECM; oxidative stress; photoprotection; pyranoanthocyanins; skin aging; topical formulations; UV-filter

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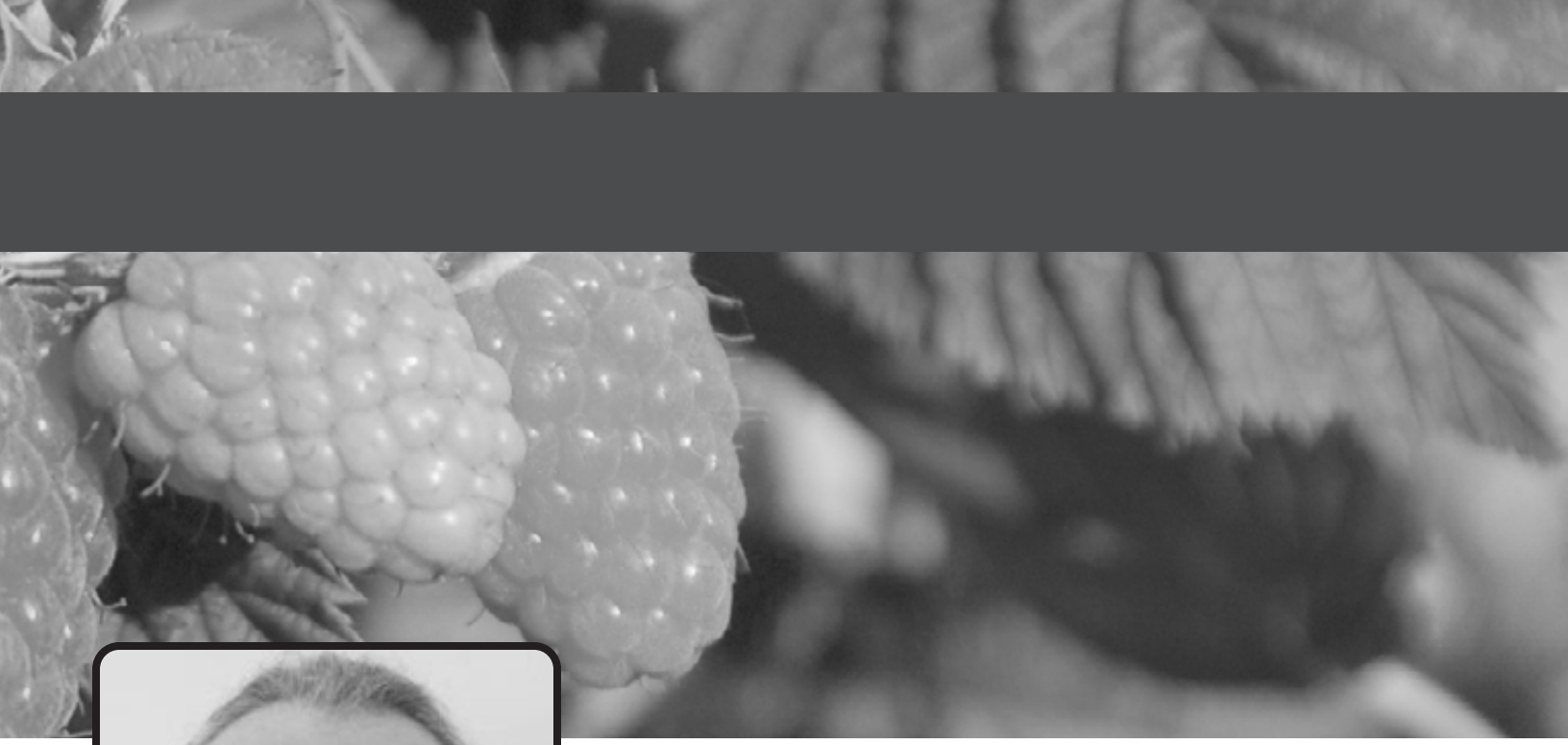
Berries & Gut Health / Gut Microflora



Dr. Jess Reed
University of Wisconsin-Madison

Session Chair

Current Research Review

Dr. Jess Reed is Professor of Animal Nutrition at the University of Wisconsin-Madison. He received a PhD from Cornell in 1983. His 33 years of research has focused on the effects of phytochemicals in foods and forages on human and animal health and nutrition, including 6 years at the International Livestock Center for Africa where he studied the phyochemistry of tropical legume forages.

Starting in 1996, he began researching the effects of flavonoids in foods on human health, including cardiovascular disease, urinary tract infections and cancer. Reed has over 100 research publications in his field and a successful research program funded through competitive grants from NIH and USDA along with collaborative projects with the food and nutritional supplements industry. Dr. Reed also maintains an active outreach program in agricultural development with project experience in 20 countries.

Dr. Grant Canipe
Chicago School of Professional Psychology

Dr. Canipe is a developmental cognitive neuroscientist and first-generation undergraduate and graduate student. He graduated with a B.S. in Psychology with honors from Appalachian State University before joining the Cheatham Lab at The University of North Carolina at Chapel Hill to pursue his Ph.D. in August 2013. During his graduate school training, he investigated fetal alcohol exposure before selecting a new topic for his dissertation – investigating nutrition and lifestyle factors that affect cognitive function in typically aging older adults.

Dr. Canipe's research interests lie in factors to prevent and reverse cognitive aging, particularly the impact of antioxidants and the gut microbiome.

In Fall 2020, he joined the Chicago School of Professional Psychology as an Assistant Professor. In his role at The Chicago School, he teaches courses for the PsyD program in Human Development, Cognitive Affective Bases of Behavior, Biological Bases of Behavior, Statistics, Research Methods, and Learning and Motivation. Dr. Canipe also serves as a Visiting Lecturer at UNC-Chapel Hill, teaching advanced research theory in psychology (a senior capstone course).

The Gut Microbiome – Brain Connection: Variety is the Spice Brains Need

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BACKGROUND: An individual's gut microflora can significantly influence gut-brain communication, brain function, and behavior. The gut-brain axis is a bidirectional signaling pathway between the gut's enteric nervous system to the brain's central nervous system. Interaction between these two systems occurs through the collaboration of neuronal, endocrine, and immune cells that transmit information along the Vagus nerve that can be directly and indirectly activated by microbial compounds. However, little research has been done to evaluate the gut-brain relation in non-clinical populations, with no previous studies, to our knowledge, in healthy older adults. Further, serious mental illness (SMI), disorders that cause significant functional impairment, may be treatable by influencing changes in gut microbiome composition.

OBJECTIVE: The objective was to describe the relation between microbiome diversity and cognitive abilities in a sample of older adults and propose a theoretical framework to improve mental health via gut microbiome composition changes.

METHODS: Sixty-three healthy older adults between 67 and 83 years of age provided a fecal sample and completed an electrophysiological brain imaging assessment (event-related potentials; ERP) and the Cambridge Neuropsychological Test Automated Battery (CANTAB). Electrophysiological and behavioral data were examined with respect to alpha diversity, a measure of the variety of species in the gut microbiome. Further, a literature review and meta-analysis were performed to explore the clinical implications of gut microbiome alterations on SMI.

RESULTS: There was an association between behavioral measures (paired-associate learning and spatial working memory from the CANTAB) and calculated alpha diversity of the gut microbiome, where poorer performance (indicative of cognitive dysfunction) predicted lower gut-microbiome diversity. In the ERP data, the minimum and mean amplitude of the negative deflection in the frontal cluster during the target condition of a detection task and during a passive oddball task significantly predicted alpha diversity. An additional review of the literature and a planned meta-analysis suggests that individuals with SMI have significantly less abundance in gut microbiome composition than those without, as increased microbiota diversity is associated with better health. Therefore, creating healthier (more diverse) gut microbiota samples for individuals with SMI can assist in promoting a variety of microorganisms needed to address dysbiosis and other adverse symptoms associated with the disease.

CONCLUSIONS: Greater diversity in the gut microflora is related to better cognitive abilities and likely improves mental health outcomes. Our results begin to bridge the gap in our understanding of the connection between behavior and the composition of the gut microbiome, commonly referred to as the gut-brain axis.

KEYWORDS: cognitive aging, gut microbiome, cognitive decline, electrophysiology, CANTAB, ERP, older adults

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Dr. Zahra Ezzat Zadeh
David Geffen School of Medicine at UCLA

Dr. Zahra Ezzat Zadeh is a clinical scientist with a PhD. in Nutrition and Food Sciences from Florida State University and a MS. in Nutrition, Metabolism and Genetics from University of Calgary in Alberta, Canada. She has completed her postdoctoral training at Cedars Sinai Diabetes and Obesity Research Institute in Beverly Hills and UCLA Center for Human Nutrition in Los Angeles. She is affiliated with Center for Human Nutrition at UCLA David Geffen School of Medicine were she conducted clinical trials investigating the functionality of food, metabolic inflammation and microbiome.

Dr. Ezzat Zadeh's research is focused on using dietary interventions to prevent and treat metabolic and/or chronic disease conditions. Her work involves investigating the role of bioactive components of foods on both whole body and tissue specific biochemical, physiological and metabolic regulation. Her novel research on inflammation and altered body composition during menopausal transition has received multiple awards and recognition. She is the recipient of The Canadian Institutes of Health Research (CIHR) award for her work on altered metabolism following high fat diet induced insulin resistant heart.

Beyond her research projects, Dr. Ezzat Zadeh is a Registered Dietitian Nutritionist (RDN); a member of US Academy of Nutrition and Dietetics and College of Dietitians of British Columbia in Canada. She is an expert in knowledge translation with years of experience in translating the latest findings in food and nutrition sciences into therapeutic diets to improve the quality of patient care and the treatment options available for people diagnosed with chronic disease conditions.

Strawberry Consumption Increased the Abundance of Gut Microorganisms Related to Lean Body Weight, Health and Longevity in Healthy Subjects

Authors: Adekeye, T[1], Tsakiroglou, P[3], Klimis-Zacas, D[1,2]

Zahra Ezzat-Zadeh[1], Susanne M. Henning[1], Jieping Yang[1], Shih Lung Woo[1], Ru-Po Lee[1], Jianjun Huang[1], Gail Thames[1], Irene Gilbuena[1], Chi-Hong Tseng[2], David Heber[1] and Zhaoping Li[1].

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The consumption of strawberries has shown promising health benefits in a number of clinical trials 1,2. For example, cardiovascular protection by decreasing LDL-cholesterol and benefits to patients with type II diabetes by lowering serum insulin have been reported 3. Strawberries provide a rich source of polyphenols and fiber 4. It was our hypothesis that foods high in polyphenols and fiber have prebiotic activity. This human intervention study aimed to determine if daily consumption of freeze-dried California strawberry powder (SBP) leads to changes in the intestinal microbiota, fecal cholesterol and bile acid (BA) microbial metabolites. Fifteen healthy adults consumed a beige diet+26 g of SBP for 4 weeks, followed by 2 weeks of beige diet only. Stool samples were collected at 0, 4, and 6 weeks. Fecal microbiota was analyzed by 16S rRNA sequencing; fecal cholesterol, BA, and microbial metabolites by gas chromatography. Confirming compliance, urine concentration of pelargonidin, urolithin A glucuronide and dimethylellagic acid glucuronide were present after 4 weeks of SBP consumption. Daily SBP altered the abundance of 24 operational taxonomic units (OTUs). Comparing week 4 to baseline the most significant increases were observed for one OTU from Firmicutes\Clostridia\ Christensenellaceae\NA, one OTU from Firmicutes\ Clostridia\Mogibacteriacea\NA, one OTU from Verrucomicrobia\ Verrucomicrobiaceae\Akkermansia\Muciniphila, one OTU from Actinobacteria\ Bifidobacteriaceae\Bifidobacterium\NA, and one OTU from Bacteroidetes\Bacteroidia\ Bacteroidaceae\Bacteroides and decrease of one OTU from Proteobacteria\ Betaproteobacteria\ Alcaligenaceae\Sutterella. Comparing week 4 to 6, we observed a reversal of the same OTUs from C Christensenellaceae, V muciniphilia and C Mogibacteriaceae. Fecal short chain fatty acids and most of the fecal markers including cholesterol, coprostanol, primary and secondary BAs were not changed significantly except for lithocholic acid, which was increased significantly at week 6 compared to baseline. In summary, SBP consumption increased the abundance of gut microorganisms related to lean body weight, health and longevity, and increased fecal lithocholic acid at week 6 in healthy study participants.

Keywords: Fecal bile acids; Fecal cholesterol; Human study; Microbiome; Strawberry.

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Dr. Colin D. Kay
North Carolina State University

Dr. Colin D. Kay is a professor of translational nutrition in the Department of Food, Bioprocessing and Nutrition Sciences at the North Carolina State University's Plants for Human Health Research Institute. Dr. Kay's research is centered on establishing the metabolism of dietary phytochemicals and the potential impact this has on their biological activity. His research core is focused on the development of qualitative and quantitative metabolomic MS/MS methodologies for establishing the contribution of dietary phytochemicals to the human metabolome. This work has led to the development of a food composition knowledge database (MetaboFood®) comprising chemical composition and metabolome data, including chemical, reaction, and pathway identifiers for supporting precision nutrition and health initiatives.

Berry Consumption and the GUT Microbiome – Impacts on the Human Metabolome

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Background. Berries are rich sources of dietary (poly)phenols and make an ideal 'model fruit' for studying the impact of (poly)phenol absorption and metabolism on health. Recent evidence indicates that gut microbes increase (poly)phenol bioavailability by modifying their structure to smaller, less polar molecules, which facilitate enhanced absorption {PMID:25182418; PMID:33350159}. However, there is extensive variability among individuals in their metabolism and elimination kinetics. It also remains unknown what microbes and microbial enzymes are responsible for this extensive metabolism. This differential metabolism suggests a strong interplay between gut microbial and human metabolic enzymes, although sex and age are also likely to play a role.

Objective. We have conducted multiple studies on short (postprandial) and long-term (1-6mo) berry consumption (blueberry, blackberry, strawberry, bilberry and blackcurrant) and will present our findings relative to observed relationships between the microbiome and human metabolome.

Methods & Results. Across these berry studies, anywhere from 14 to 28 small molecule (poly)phenol metabolites were significantly increased in the metabolomes of those consuming berries and found at concentrations far exceeding precursor flavonoids. Metabolite subclasses were consistent across studies, with metabolome shifts reported for multiple hydroxybenzoic, hydroxyphenylacetic, (hydroxy) phenylpropanoic, hydroxycinnamic, and hippuric acids. Interestingly, in a 6-month, multi-dose (0.5 or 1 cup) blueberry intervention {PMID:31136659} using shotgun metagenomics, meta-transcriptomics, and targeted metabolomics to profile fecal samples from 112 participants, we observed a substantial shift in serum and urinary polyphenol metabolites which correlated with chronic improvements in endothelial function and lipoproteins; Although we found no significant shifts in gut microbiome composition, significant effects were observed for 28 metabolites. The identified microbial enzymes associated with the metabolites include benzoate monooxygenases, decarboxylases, hydratases/lyases, O-demethylases and reductases {PMID:27899662}.

Further, in an acute study (24h) following consumption of a supplement rich in blackberries, 16 (poly)phenol metabolites showed either age, sex or age-by-sex effects. Adjusting the model for BMI had no impact on level of significance. Age differences were seen for total cumulative urinary excretion and elimination kinetics, whereas maximal plasma concentrations (tmax) were shifted across age groups by as much as 3-5h; suggesting studies hoping to correlate biological outcomes or biomarkers with peak blood concentrations will require blood draws across multiple time points for populations of diverse age groups. Analysis of the microbiome also indicated age was the biggest discriminator of (poly)phenol absorption and elimination. 21 taxa, 12 families, and 19 species of microbes displayed age differences. Again, hierarchical liner regression analysis revealed sex and BMI were not significant drivers of the associations observed.

Conclusion. In conclusion, it appears that multiple enzymes from a diversity of microbes are capable of metabolizing (poly)phenols, and age may be the most significant discriminator of metabolism and clearance differences.

Keywords: metabolism, kinetics, microbiome, (poly)phenols, microbial metabolites, age effects

Dr. Li-Shu Wang
Medical College of Wisconsin

Dr. Li-Shu Wang is an Associate Professor of Medicine, Medical College of Wisconsin. She received her Ph.D. in Veterinary Biosciences in the College of Veterinary Medicine at Ohio State University in June 2006. Dr. Wang's work from human clinical trials has been published in high-rank journals in cancer prevention such as Clinical Cancer Research, Carcinogenesis, Cancer Prevention Research, Cancer Immunology Research, Frontiers in Immunology, International Journal of Cancer, etc. Dr. Wang's expertise is in cancer biology and prevention in animals and humans.

The primary goal of Dr. Wang's research is to translate the findings from bench to bedside. Using bio-directed fractionation, Dr. Wang showed that the anthocyanins in black raspberries (BRBs) are essential for their chemopreventive effects. She provided evidence that the ellagitannins may be less critical. More importantly, she has evidence that BRBs cause demethylation of tumor suppressor genes in rodents and humans, leading to their enhanced expression in two human clinical trials. The protective effects of BRBs against human and mouse colorectal cancer (CRC) are associated, at least in part, with their hypomethylation activities. Loss of responses to berry treatment in humans may be due to decreased sensitivity to berry-induced DNA demethylation. Further, BRB intervention induces significant metabolic changes and affects energy generating pathways in CRC patients. Recently, Dr. Wang's laboratory is investigating the mechanisms of active metabolites from BRBs to influence colon and pancreatic cancer immunology through epigenetic modifications. The results from animal models of both cancer types indicate that berries dampen tumor-induced immune suppressive microenvironment by decreasing CD11b+ myeloid cells and boosting CD8+ T-cell and natural killer cells. To translate laboratory findings to clinics, currently, Dr. Wang's group is investigating the effects of BRBs on DNA methylation in patients with myelodysplastic syndrome (MDS). This pilot clinical trial aims to evaluate the hypomethylating properties of BRBs in MDS patients after three months of BRB supplementation.

Dissecting the Impact of Anthocyanin and Residue Fractions of Black raspberries and Protocatechuic Acid, an Anthocyanin Gut Bacterial Metabolite, on Gut Microbiota Profiles

Authors: Athena Dong[1], Chien-Wei Lin[2], Yi-Wen Huang[1], Kiyoko Oshima[3], Martha Yearsley[4], Xiao Chen[1], Jianhua Yu[5], Li-Shu Wang[1]

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Natural compounds can alter the diversity and composition of the gut microbiome, potentially benefiting our health. We previously demonstrated the chemopreventive effects of black raspberries (BRBs) in colorectal cancer associated with gut dysbiosis. We set out to investigate the impact of whole BRBs and their fractions on gut microbiota. We showed that anthocyanin and residue fractions of BRBs induced different changes in gut bacteria compared to whole BRBs. The abundance of specific microbial species known to have anti-inflammatory effects, such as Akkermansia and Desulfovibrio, was increased by whole BRBs and their residue. Further, butyrate-producing bacteria, e.g., Anaerostipes, were raised by whole BRBs. These results suggest that the residue fraction of BRBs induced similar fecal microbiota changes as the entire BRBs. The administration of protocatechuic acid (PCA), an anthocyanin gut bacterial metabolite, has been demonstrated to exert chemopreventive effects against colorectal cancer. We found that pro-inflammatory bacterial profiles were replaced with anti-inflammatory bacteria by whole BRBs and 500 ppm PCA, but not 1000 ppm PCA that drove a pro-inflammatory bacterial profile. Altogether, our results suggest that similar to whole BRBs, the residue fraction of BRBs and lower-dose of PCA can alter the gut microbiota to a more favorable profile that could significantly influence human health.

Keywords: Gut microbiome, black raspberries, anthocyanins, fiber, protocatechuic acid

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Inah Gu
PhD Student at the University of Arkansas

Inah is a PhD student in Food Science at University of Arkansas. She received her B.S. degree in Food Science and Nutrition from Pusan National University, South Korea, and her M.S. degree in Food Science from the University of Arkansas. She works with her advisor Dr.Sun-Ok Lee, focusing on how dietary phytochemicals and bioactive components in foods and natural extracts exert human health benefits. Inah's research aims to identify and fractionate bioactive components in different kinds of berries and investigate the effects of berry bioactive compounds in chronic inflammation. She is a member of the American Society for Nutrition, and Korean-American Scientists and Engineers Association.

Chemical Composition of Volatile Extracts from Blackberries, Black Raspberries, and Blueberries and Their Anti-Proliferative Effect on A549 Non-Small-Cell Lung Cancer Cells

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BACKGROUND: Berry volatiles are responsible for the aroma of berries. Berry volatiles has been recently reported to have an anti-inflammatory effect. However, there is still limited information available on the health-promoting activities of berry volatiles.

OBJECTIVE: The objectives of this study were to evaluate the chemical composition of volatile extracts from blackberries, black raspberries, and blueberries and to investigate the anti-proliferative effect of three berry volatile extracts on A549 non-small-cell lung cancer cells and their mechanism.

METHODS: The chemical composition of berry volatile extracts (BVEs) from blackberries, black raspberries, and blueberries were identified by using gas chromatography-mass spectrometry. A549 lung cancer cells were treated with three dilutions (2-, 4-, and 8-fold diluted) of three berry volatile extracts for 12, 24, and 48 h. The proliferation of A549 was measured by the MTS assay. Changes in the cell cycle and apoptosis were examined by using cell sorting analysis, flow cytometry, and cell death detection ELISA kit. The apoptotic mechanism was further investigated by western blot analysis.

RESULTS: Total volatiles in three berry volatile extracts were 1.6±0.2 - 3.2±0.1 mg/L. Among them, monoterpene was the most abundant compounds in all three BVEs. All two-fold diluted BVEs significantly inhibited the proliferation of A549 after 48 h by inducing apoptosis ($p<0.05$). Two-fold diluted BVEs treatment for 48 h also increased the cell population in G0/G1 phase (64.9-73.1%) compared to the control (60.3%). Flow cytometric quantification of apoptosis identified the most amount of early apoptotic cells in blackberry volatile extracts. Similarly, blackberry volatile extracts significantly inhibited the level of poly ADP-ribose polymerase (PARP), procaspase-9, and procaspase-3 compared to the control ($p<0.05$).

CONCLUSIONS: These findings showed that berry volatile extracts from blackberries, black raspberries, and blueberries have an anti-proliferative effect on lung cancer cells through apoptosis, suggesting that berry volatiles from three berries may have a potential impact on lung cancer.

KEYWORDS: Berry volatiles, chemical composition, anti-proliferative effect, apoptosis, lung cancer, blackberry, black raspberry, blueberry.

Amélie Légaré
PhD Student at Université Laval

Amélie is a first-year Ph.D. molecular medicine student at Université Laval working in Dr. André Marette's lab. She is particularly interested in studying extracellular communication between plants, gut microbiota, and us. Moreover, Amélie nurtures the desire to develop plant-derived treatment alternatives against widespread metabolic diseases, such as obesity and non-alcoholic fatty liver disease.

Cranberry-derived Extracellular Vesicles Decrease Whole-body Adiposity and Modulate Gut Microbiota Composition in a Mice Model of Diet-Induced Obesity

Authors: Légaré, A[1,2,3], Morissette, A[1,2,3], Dallaire,C[1], Morissette, J[1], Guèvremont, G[1], Varin, T[1,2], Pilon, G[1], Boucher, J[3,4], Chénard, V[4], Marette, A[1,2,3,4]

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4. Centre de recherche du CHU de Québec, Canada

BACKGROUND: Several studies, notably conducted by our team, have shown that cranberries can hinder metabolic disturbances related to obesity. Recently, it has been reported that fruit-derived vesicles can alleviate gut-associated diseases and modulate the gut microbiota composition, a key player in host metabolism.

OBJECTIVE: Therefore, the objective of this study was to evaluate the effects of cranberry-derived extracellular vesicles' (CranEVs) administration on metabolic health and gut microbiota composition in a mice model of diet-induced obesity.

METHODS: CranEVs were isolated from cranberries by ultracentrifugation and sucrose gradient. Then, vesicles were characterized by Nanoparticle Tracking Analysis and transmission electron microscopy. Male C57bl/6J mice were fed a high-fat high-sucrose diet for 10 weeks and gavaged daily either with PBS or CranEVs solution (1x108 particles/mL; n = 12 per group). Food intake and body weight were monitored biweekly. Feces were collected to assess changes in the gut microbiota by 16S rRNA sequencing. Triglyceride and cholesterol liver content were analyzed with commercial biochemical assays.

RESULTS: Despite similar energy intake, mice receiving CranEVs gained significantly less weight than controls, along with a whole-body reduction in adipose tissue weight. In the liver, a significant decrease in triglyceride and cholesterol content was observed in the mice given the extract. Moreover, 16S rRNA sequencing analysis revealed that Dubosiella, Coriobacteriaceae, and Eubacterium coprostanoligenes were relatively increased in the group receiving CranEVs compared to control mice. Interestingly, these bacteria have been associated with improved metabolic and hepatic health.

CONCLUSION: This project is the first to evaluate the metabolic effects of CranEVs. According to our findings, CranEVs reduce adiposity and hepatic lipid accumulation and thus may represent a promising approach for the treatment of obesity-related metabolic diseases, such as non-alcoholic fatty liver diseases.

KEYWORDS: Obesity, Hepatic health, Metabolism, Glucose homeostasis, Microbiota, Cranberry, Plantderived extracellular vesicles.

Tolu Esther Alaba
PhD Student at the University of Maine

Tolu is a graduate of Human Physiology with eight years of research and teaching experience from Nigeria. Tolu's B. Tech thesis was focused on the effect of exercise on vertical jump height in athletes such as baseball, volleyball, basketball and soccer players. In 2015, she published her MS thesis focused on the nutritional management of Alloxan-induced Diabetic Nephropathy. Overtime, she learned to combine molecular and nutritional interventions for effective management of Cardiovascular Diseases. Currently, she work at Klimis-Zacas' Lab to investigate molecular pathways involved in the nutritional management of wounds.

Phenolic Acids from Wild Blueberry Facilitate Wound Healing via Vascular Remodeling: A Novel Therapy for Clinical Wound Treatment

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BACKGROUND: Approximately $50 billion is spent annually on wound care in the USA, majorly due to chronic wounds, such as pressure and diabetic ulcers, resulting from deficient vascular remodeling necessary for healing. Previously, our lab reported significant angiogenesis in HUVEC cells when treated with the phenolic acid extract (PE) from wild blueberries (WB).

OBJECTIVE: This study aims to examine the vascular remodeling effects of PE from WB on wound healing pathways in a rat model.

METHODS: PE was extracted from WB by solid phase extraction and incorporated into a gel or cream. Fifty-six rats were divided into seven groups: control; cream alone; gel alone; gel+500 ug/ml PE; cream+500 ug/ml PE; gel+1000 ug/ml PE; and cream+1000 ug/ml PE. Dorsal wounds were created and treated with the above for six days. Wounds were photographed daily for wound closure analysis in ImageJ. Skin wound areas were excised and fixed for molecular and histological analyses. The wounds were stained with H&E, imaged with a microscope, and quantified for vascularization and collagen formation using Qu-path software. Vascular (Vegfa) and collagen (Col1a1) proteins were assessed by western blotting.

RESULTS: Compared to the control, we found 12% increase in wound closure with gel+500 ug/ml of PE. Molecular analysis showed a significant increase in Vegfa (<0.0001 p-values) and collagen proteins (0.0058 p-values), and histological analysis revealed a 20% increase in vascularization and organized collagen deposition with gel+500 ug/ml of PE compared to control.

CONCLUSIONS: Our results documented significant effect(s) of PE from WB as a natural, inexpensive wound healing product and provide new insights into the potential clinical benefits of PE treatment for patients with acute and chronic wounds.

KEY WORDS: Phenolic acids, Wild blueberry, Wound healing, Clinical wounds, Vascularization, Collagen deposition.

Notes

Berry Special Topics, Food Technology and Chemistry

Dr. Amy B. Howell

Rutgers, the State University of New Jersey

Session Chair

Current Research Review

Amy Howell is an Associate Research Scientist at the Marucci Center for Blueberry Cranberry Research. She has a background in plant science and pathology and her program targets utilizing cranberry for prevention and management of bacterial diseases, including urinary tract infections (UTIs), stomach ulcers, and periodontal disease. She is keen to have consumers utilize more natural alternative methods, such as cranberry for disease prevention in an effort to curb overuse of antibiotics and resistance development. Her primary research focus has been on isolating polyphenolic compounds from cranberry and determining their role in prevention of UTIs. She studies the pharmacokinetics and bioavailability of the structurally unique cranberry proanthocyanidins in an effort to determine site(s) of action and dose-response, as well as the influence of cranberry on enhancing the potency of antibiotics. She regularly collaborates in clinical trials on cranberry consumption and UTI prevention. Other projects include development of cranberry supplements for both human and canine urinary health, and anti-cancer, anti-viral and oral cavity health studies utilizing cranberry.

Howell is very involved in method development for powdered cranberry supplements, working closely with regulatory teams from AOAC and USP (US Pharmacopoeia) to determine standard methods for quantification of the bioactive compounds in cranberries. USP determines FDA-enforceable quality standards for drugs and dietary supplements. This is extremely important given the variability in efficacy and frequent adulteration of cranberry products.

Howell actively supports the cranberry and blueberry industries and trade associations by educating consumers and healthcare professionals through seminar presentations on health attributes of the fruits. She has travelled to over 20 countries on international trade missions to present the latest findings on health-related research. She regularly travels as part of a team to China and India under the Global Based Initiative (GBI), a program funded by USDA and the Foreign Agricultural Service to introduce cranberries overseas. She serves on the USDA-sanctioned US Highbush Blueberry Council as the Public Member, helping determine funding for health-related research on blueberries.

Dr. M. Mónica Giusti
The Ohio State University

Dr. M. Mónica Giusti, is a Professor at the Food Science and Technology Department. Dr. Giusti received a Food Engineer degree from the Universidad Nacional Agraria, Peru and Master's and Doctorate degrees in Food Science from Oregon State University.

Dr. Giusti's research is focused on the chemistry and functionality of flavonoids, with emphasis on anthocyanins. She has more than 100 peer-reviewed journal articles, 4 books and 8 patents. She is the recipient of multiple awards including the 2017 Educator Award from the North American Colleges and Teachers in Agriculture, the 2019 Cruess Award for excellence in Teaching from the Institute of Food Technologists, and the 2020 Senior Faculty Researcher of the Year from the FAES College, at the Ohio State University. Dr. Giusti is a member of the American Chemical Society, the Institute of Food Technologists (IFT) and the AOAC, and is a Fellow of the National Academy of Inventors.

Berry Anthocyanins Uptake and Transport Through Human Gastric Epithelial (NCI-N87) Cells

Authors: M. Monica Giusti [1*], Allison A Atnip[1]; Mark L. Failla[2], Joshua A Bomser[2], C. Chitchumroonchokchai[2], Gregory T. Sigurdson[1]

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Most berries are rich in anthocyanins pigments with reported antioxidant, anti-inflammatory, and anti-cancer activities. Anthocyanin activity may start when they get in contact with saliva in the oral cavity, with some studies suggesting absorption may occur in the stomach, where the acidic environment favors anthocyanin stability. The objective of this work was to investigate the uptake, trans-epithelial transport, and anti-inflammatory activity of anthocyanins by using the NCI-N87 gastric epithelial cell line. Chokeberry and grape were used as anthocyanin sources. Chokeberry, containing different cyanidin derivatives, was used to determine the effects of different sugar substitutions; red grape was used as a source of monoglucosylated derivatives of different aglycones. The absorption and uptake of anthocyanins was tested using the NCI-N87 cell line at different time points (between 0 and 3 hr), and at different concentrations (0–1500 uM), and pH (3.0, 5.0, 7.4). The NCI-N87 cells formed a coherent monolayer, stable ≤32 days post confluency, and the monolayer integrity was minimally affected when the pH of the apical chamber was adjusted to pH 3.0, 5.0, or 7.4. Anthocyanins were transported from the apical to basolateral side of NCI-N87 cells in time and dose dependent manners at 37 °C, but not at 0 °C, suggesting a facilitated process. Anthocyanin aglycone and sugar substitution affected the rate and efficiency of uptake and transport. Among cyanidin-glycosides, transport of cyanidin-3-arabinoside was the greatest, while uptake was highest for cyanidin-3-glucoside. The aglycone structure also affected uptake and transport. Anthocyanins bearing B-ring di-substitution, cyanidin-3-glucoside and peonidin-3-glucoside, were transported and taken up the most by cells. The rate of transport was non-linear, increasing over the 3 hr of treatment, especially with higher anthocyanin concentrations. This further suggests an active mechanism for the transport of anthocyanins across the NCI-N87 monolayer. Anthocyanin transport was affected by pH, with higher transport at pH 3.0, compared to pH 5.0 and 7.4. At apical pH 3.0, anthocyanins exerted anti-inflammatory properties by significantly attenuating IL-8 secretion when added to medium before, during, and after incubation with IL-1 . The NCI-N87 cell line was a physiologically relevant model for in vitro studies of the transport, uptake and anti-inflammatory activities of anthocyanins in gastric tissue. Our results suggest that anthocyanin absorption can occur in the stomach, impacted by anthocyanin structure and gastric pH.

Keywords: anthocyanins; gastric; stomach; uptake; NCI-N87 cell line; chokeberry, grapes

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Dr. Jessie Hawkins
Franklin Health Research

Dr. Jessie Hawkins brings over 20 years of experience in the integrative health field to her role as Executive Director of the Franklin Health Research & Education Center and its associated 501(c)(3) nonprofit research organization. She established FHR in 2005 as an independent educational center and has overseen its growth and transition to an academically focused contract research organization for the natural products and medical devices industries. Dr. Hawkins holds a Bachelor's Degree in Environmental Health, a Master's Degree in Health Promotion, and a PhD in Health Research, and has received post-graduate education from London School of Hygiene and Tropical Medicine (epidemiology) and Harvard Medical School (clinical research). She is widely published in the integrative health field, and frequently travels to present FHR's research findings at professional conferences worldwide.

Black Currant and Digital Eye Strain: Findings from a Randomized, Double Blind, Placebo Controlled Clinical Trial

Berries, such as blackcurrant, which are rich in anthocyanins have been shown to support general vision health (Yuri, 2019). While the mechanisms of action are not fully known, human studies have shown black currant to be successful in increasing ocular blood flow and returning endothelin-, an oxidizing agent that increases inflammatory cytokines, to normal levels (Ohguro, 2012, Yoshida, 2013, Kowalczyk, 2015).

Eye health is of particular importance due to lifestyle changes required by the COVID-19 pandemic. As routine activities, such as business meetings and education, have transitioned to an online setting, hours that were previously spent in a face-to-face environment have been replaced by contact through a digital screen. This increase in screen time has been shown to produce negative effects on vision and eye health (Alabdulkader, 2021).

Our research team conducted a randomized double blind, placebo controlled parallel clinical trial to evaluate the effects of blackcurrant supplementation on three domains of eye health. Sixty-one otherwise healthy women aged 30-59 years old who spent 6+ hours per day in front of a digital screen participated in the study, which was powered to detect a large effect size.

While baseline scores on all metrics of eye health were similar, participants who consumed CurrantCraft blackcurrant supplements for ten weeks experienced a significant reduction on the eye health domain which included symptoms such as blurred vision, double vision, and difficulty refocusing, as compared to the placebo group. The effect size of these benefits was extremely large.

This study provides evidence that ten weeks of supplementation with blackcurrant supports eye health, particularly during a period of time when exposure to digital screens is increased. As many of the pandemic-era habits, including increased screen time, are expected to continue after the pandemic, supplements which have the potential to protect from symptoms associated with these habits are important tools for future health.

Keywords: blackcurrant, cassis, Ribes nigrum, eye health, vision fatigue

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This research was funded by Artemis International.

Dr. Connie M. Weaver
San Diego State University

Dr. Weaver is a Distinguished Research Professor in Exercise and Nutritional Sciences at San Diego State University, San Diego, CA, Distinguished Professor Emerita of Nutrition Science at Purdue University, Indiana, and CEO of Weaver and Associates Consulting, LLC. She is an elected member of The National Academies of Science, Engineering, and Medicine since 2010. She is a fellow of the American Society for Nutrition, the Institute of Food Technologists, the American Heart Association, and the American Society of Bone and Mineral Research. She is a member of the Science Advisory Boards of FDA, the California Prune Board, California Walnut Board, and Produce for Better Health (PBH) Foundation. Dr. Weaver is past president of American Society for Nutrition.

Blueberries and Bone Health

Correspondence: Connie M. Weaver, Ph.D. School of Exercise and Nutritional Sciences 5500 Campanile Drive San Diego State University San Diego, CA 92182 765-412-2695

Background: Epidemiological studies have shown associations between polyphenol-rich fruit intake and bone health and preclinical studies have shown blueberries improve bone health.

Objective: To determine the variety and dose of blueberries that are effective in ameliorating age-related bone loss.

Methods: A multi-institutional team of investigators performed in vitro, preclinical and clinical studies on blueberry varieties that differed in anthocyanin profiles.

Results: Bioavailability of polyphenols varied across specific flavonoids. Host x dose interactions were observed in polyphenol metabolism and gut microbiome profiles. Sex differences in response to blueberry feeding occurred in recovery of sex-steroid deficiency-induced bone loss and by different mechanisms in a preclinical mouse model. Lower doses of blueberries were more effective in preventing bone calcium loss in OVX-rats and postmenopausal women. High doses of blueberry polyphenols as an extract were safe up to an equivalent of 10 g polyphenols per day.

Conclusions: Dietary blueberries 0.75 cups per day can protect against bone loss due to age-related sex-hormone deficiency

Keywords: Blueberries, polyphenols, anthocyanins, sex-steroid hormones, bone

Luke Howard, PhD
University of Arkansas

Dr. Howard received his B.S. degree in Horticulture from Purdue University, and his M.S. and Ph.D. degrees in Food Science from the University of Arkansas. He worked as an Analytical Chemist at the Dole Packaged Foods Research and Development Center for two years, and was an Assistant Professor in the Horticultural Sciences Department at Texas A&M University for five years. He has served on the faculty in the Department of Food Science at the University of Arkansas since 1997 (Associate Research Professor 1997-2002, Professor 2002-present).

His research program is focused on extraction and characterization of bioactive compounds in fresh and processed fruits and vegetables, with emphasis on berries. Dr. Howard has published over 120 scientific articles and five book chapters and has delivered over 90 presentations at scientific meetings. He is a Professional Member of the American Chemical Society.

Anti-inflammatory Effect of Blackberry Phenolic and Volatile Extracts

Authors: Luke Howard, Pauline Morin, John Tipton, Laura Lavefve, Cindi Brownmiller, Sun-Ok Lee, Inah Gu, Rohana Liyanage and Jackson O. Lay

The anti-inflammatory activity of blackberries has been attributed to phenolic compounds, especially anthocyanins. The present study hypothesized that volatiles could contribute to anti-inflammatory activity as well. The anti-inflammatory properties of three blackberry genotypes varying in total volatile and phenolic contents were assessed by measuring concentrations of nitric oxide (NO), interleukin-6 (IL-6) and tumor necrosis factor - (TNF-) within LPS-inflamed RAW264.7 murine macrophage cells after a preventive treatment of either a phenolic or a volatile extract. Extracts from blackberry genotypes A2528T, A2587T and Natchez had total phenolic contents of 4315, 3369 and 3680 µg/mL, respectively, and total volatile contents of 283, 852 and 444 ng/mL, respectively. Phenolic and volatile extracts of all genotypes significantly lowered the secretion of NO, IL-6 and TNF- in ranges varying between 20-42%, 34-60% and 28-73% inhibition, respectively. Volatile extracts exhibited greater anti-inflammatory properties than phenolic extracts, despite being present at much lower concentrations in the berries. Further research is needed to assess bioavailability and anti-inflammatory effect of blackberry volatiles in vivo.

Keywords: Anti-inflammatory, Blackberries, Cytokines, Inflammation, in vitro, Phenolics.

Poster Presentation Abstracts

Poster Session Chair

Barbara Shukkitt-Hale
USDA & Tufts University

The 2023 Berry Health Benefits Symposium is pleased to offer two ways for students of berry science to share their latest research findings. Graduate students and postdoctoral fellows were invited to submit abstracts for review and consideration for both Poster Presentations and Oral Presentations at this years symposium.

These Junior Investigators submitted original research relating to the symposium themes of berry biochemical composition, cardiovascular health, metabolism regulation, brain health, skin health and other health properties of berry fruit.

The following posters were selected for Poster Presentations and are viewable in the Westshore Ballroom. The abstracts for the 3 oral presentations are available on pages 54-56. The winner of the “Most Outstanding Poster” award will be announced at the beginning of the Junior Investigator Oral Presentations taking place in the afternoon on Wednesday, February 1st.

Wild blueberry and raspberry counteract intestinal cell monolayer permeability induced by a TNF-α inflammatory stimulus.

Authors: Mirko Marino[1]*, Samuele Venturi[1], Marco Rendine[1], Claudio Gardana[1], Dorothy Klimis-Zacas[2] Patrizia Riso[1], Marisa Porrini[1] and Cristian Del Bo'[1]

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BACKGROUND: The impairment of intestinal permeability (IP) leads to a low-grade systemic inflammation which represents a major risk for chronic diseases development. In the last years, several studies demonstrated a potential protective role of different dietary components on gut health.

OBJECTIVE: The aim of the present study was to evaluate the effect of a wild blueberry (WB) and raspberry (RB) powder on Caco-2 cell monolayer permeability and oxidative stress markers.

METHODS: Caco-2 cell monolayer permeability was evaluated by using Transwell® model, measuring transepithelial electrical resistance (TEER) and paracellular transport of FITC (Fluorescein isothiocyanate)-dextran in the absence or presence of TNF-α pro-inflammatory stimulus (10 ng/ml) and with or without the supplementation of WB and RB powders tested at different concentrations (1 mg/ml and 5 mg/ml) for 24 hours. The analysis of tight junction (TJ) proteins and oxidative stress markers was performed by the use of ELISA.

RESULTS: The treatments with WB (5 mg/ml) and RB (1 mg/ml and 5 mg/ml) powders were capable of counteracting the loss of Caco-2 cell barrier integrity induced by TNF-α, reported as increased values in TEER ($p<0.01$) and reduced values in FITC-dextran membrane passage ($p<0.01$). In addition, the TNF-α-induced Caco-2 treated with WB and RB powders showed an overexpression of claudin-1 protein levels ($p<0.01$), a protein involved in intestinal permeability. Finally, a significant reduction ($p<0.01$) in the levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), as marker of oxidative stress, was documented.

CONCLUSIONS: Our findings suggest a protective role of WB and RB powders on impaired intestinal permeability induced by the inflammatory process, potentially through the modulation of oxidative stress and TJ protein expression.

KEYWORDS: Berries; Polyphenols; Gut health; Inflammation; Intestinal permeability; Oxidative stress.

Atheroprotective Effects and Cellular Mechanisms of Blueberry Polyphenol Metabolites on Endothelial Function in Postmenopausal Women

Authors: Emily K. Woolf[1], Nicole S. Litwin[1], Janée D. Terwood[2], Allegra R. Vazquez[1], Sylvia Y. Lee[1], Nancy Ghanem[1], Sangeeta Rao[3], Melanie Le Sayec[4], Ana Rodriguez-Mateos[4], Anandh B.P. Velayutham[5], Christopher L. Gentile[6], Tiffany L. Weir[1], Douglas R. Seals[6], Frank A. Dinenno[2], Sarah A. Johnson[1]

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6. Department of Integrative Physiology, University of Colorado, Boulder, CO, USA

BACKGROUND: Blueberries, their polyphenols, and resulting metabolites may reduce cardiovascular disease (CVD) risk by improving oxidative stress- and inflammatory-mediated endothelial dysfunction, which is a central contributor to atherosclerotic CVD development. Postmenopausal women develop endothelial dysfunction largely due to decreased estrogen production which promotes oxidative stress and inflammation.

OBJECTIVE: In a randomized, double-blind, placebo-controlled, parallel-arm clinical trial, 22 g/day freeze-dried blueberry powder consumption for 12 weeks increased plasma polyphenol metabolites and improved endothelial function (brachial artery flow-mediated dilation) in estrogen-deficient postmenopausal women aged 45-65 years with above-normal blood pressure (n=43; n=32 for endothelial function) through reducing oxidative stress; however, exact mechanisms remain unknown. The aim of this study was to use a reverse translational approach from humans to cells to identify cellular mechanisms responsible for clinical improvements in endothelial function and the anti-atherogenic potential of blueberries.

METHODS: We leveraged human blood serum samples with or without blueberry polyphenol metabolites (treatment and control) collected in our clinical trial to perform ex vivo cell culture experiments. First, human aortic endothelial cells were cultured to 80-85% confluency and incubated with 15% human serum for 1 hour. Cells were then incubated with 200 μM of hydrogen peroxide for 24 hours to induce endothelial cell dysfunction and 1) stimulated with THP-1 cells (monocytes) to quantify binding affinity or 2) assessed for nitric oxide and peroxynitrite concentrations. Endothelial nitric oxide synthase, manganese superoxide dismutase, and NADPH oxidase gene expression will be measured.

RESULTS: Analyses are underway, and results will be presented at the symposium.

CONCLUSIONS: Results from this novel study will provide mechanistic insight on how blueberry polyphenol metabolites protect against endothelial dysfunction and atherosclerotic CVD risk in postmenopausal women with above-normal blood pressure.

KEYWORDS: endothelial cells, endothelial function, blueberry, oxidative stress, inflammation, atherosclerosis.

Funded by US Highbush Blueberry Council and the USDA

Characterization and Stability of a Formulated Mixed Berry Beverage (Red Raspberry and Strawberry) Over 3-year Storage

Authors: Yudai Huang, Morganne M Freeman, Indika Edirisinghe, Britt M Burton-Freeman, Amandeep K Sandhu*

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BACKGROUND: Strawberries are rich in pelargonidin-based anthocyanins, while red raspberries are rich in cyanidin-based anthocyanins. They also both contain ellagitannins and other (poly) phenolic compounds. These berries have been studied individually in previous research but not in a combined form. The effect of long-term storage on stability of (poly)phenols in the combined composite for clinical trials use has not been studied.

OBJECTIVES: This study aimed to formulate a mixed berry (MB) beverage (using freeze-dried strawberry and red raspberry powders with/without fructooligosaccharides) to deliver specified amounts of ellagitannins and anthocyanins for clinical trial use (ClinicalTrail.gov NCT04100200). The selected (poly)phenols in the MB beverage were characterized and evaluated for stability over time in freezer storage (-20°C).

METHOD: Freeze-dried strawberry and red raspberry powders were first analyzed separately on ultra-high performance liquid chromatography coupled with triple quadrupole (UHPLC-QQQ) to determine their (poly)phenols compositions. The MB beverage (made fresh from stored freeze-dried powders on each analysis) was extracted and analyzed annually on UHPLC-QQQ since 2020. Statistical differences among each year were tested using ANOVA (Microsoft Excel).

RESULT: The MB beverages were formulated containing 100 g water, 4 g sugar, 15 g strawberries and 17 g red raspberries freeze-dried powder to obtain cyanidin and pelargonidin anthocyanins in ~ 1:1 ratio and ~95 mg ellagitannins per cup MB beverage with/without 8 g fructooligosaccharides (FOS). FOS did not influence analysis so data were combined. Cyanidins ranged from 48.5-57.3 mg/beverage and pelargonidin compounds ranged from 48.2-52.4. Ellagintannims ranged from 70.6-128.6 mg/beverage. Stability of compounds were tested over the three years indicating that pelargonidins were stable ($P=0.60$) in freezer storage, but cyanidins and ellagitannins were reduced ($P<0.05$).

CONCLUSIONS: Freeze-dried berry powders stored continually at -20°C over 3 years can preserve the anthocyanins, especially pelargonidin, composition, which is ideal for multi-year clinical trials.

KEYWORDS: polyphenols, anthocyanins, ellagitannins, strawberries, red raspberries.

A Mixture of Berries Improves Cognitive Function, Metabolic Function and Alters the Gut Microbiota in C57Bl/6J Young Mice

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BACKGROUND: Previous studies have shown that supplementation with certain Nordic berries may improve memory in mice receiving high-fat diets. Emerging research has also demonstrated that brain health and cognitive function may be related to dynamic changes in the gut microbiota and metabolic function.

OBJECTIVE: In this study, a berry mixture of Nordic berries identified as having the potential to improve memory was supplemented to C57BL/6J young mice to investigate effects on cognition function as well as correlations to cardiometabolic parameters, brain markers, and gut microbiota composition.

METHODS: C57Bl/6J male mice at age of 8 weeks were given standard chow, high-fat diets (60%E fat), or high-fat diets supplemented with freeze-dried powder (20% dwb) of a mixture of Nordic berries and red grape juice for 18 weeks (n=12 animals/diet group). Different behaviour tests (Novel Object Recognition, T-maze, and Barnes maze) were conducted to measure effects on different aspects of cognitive function and blood plasma, cecum, and brain tissue were collected for further analyses.

RESULTS: The results show that supplementation with the berry mixture has beneficial effects on spatial memory, as seen by enhanced performance in T-maze and Barnes maze compared to the mice receiving HF-diet without berries. Body weight and fasting insulin levels tended to be improved by supplementation with the berry mixture Furthermore, the berry mixture has a great impact on shaping the gut microbiome profile.

CONCLUSIONS: The findings in this study demonstrate that the berry mixture diet improved the performance of mice affected by high fat-induced memory impairment, and induced alterations of the gut microbiota composition. The berry mixture diet might contribute to better weight management control as well as an improved fasting insulin profile, which may be associated with improved cognitive function.

KEYWORDS: berries, high-fat diet, cognitive function, gut microbiota, metabolic function, brain histology

Anti-inflammatory, Dermal Wound Repair Properties, and Chemical Composition of Industrially Processed and Non-processed, Purple and White Açaí Berries from the Brazilian Amazon

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BACKGROUND: It is known that wounds do not progress toward healing because it gets stalled in the inflammatory phase of wound healing. Nevertheless, the onset of uncontrolled inflammation, along with the presence of oxidative stress, could lead to the development of chronic inflammatory conditions. Natural products and substances derived popularly have been used for the healing of the wound due to their possession of anti-inflammatory, antibacterial, and antioxidant properties. Açaí, a berry-like native to the Amazon region of Brazil, is recognized for its health properties, antioxidant, and anti-inflammatory and for being consumed worldwide. However, it is still necessary to understand the molecular mechanisms of action and address the effects of industrial processing on this fruit.

OBJECTIVE: The comparative chemical and biological characterization of white and purple açaí (non-commercial and commercial), and investigate the effect of industrial processes on polyphenols content and bioactive effect.

METHODS: All samples were freeze-dried, ground into powder, and subjected to an extraction procedure. Spectrophotometric assays and chromatography techniques were used to differentiate the chemical composition, and the anti-inflammatory and wound-healing properties were analyzed in vitro using RAW 264.7 and HDFa cells.

RESULTS: Non-processed açaí was rich in total phenolics (TP) (18.9–58.8 mg g−1) and proanthocyanins (9.8–43.1 mg g−1). In comparison, the industrially processed samples lost substantial amounts of proanthocyanidins (> 83.2%), while the anthocyanins were enriched after processing (20-fold higher). TP in purple açaí (commercial) was higher than in white samples (non-commercial). The major anthocyanin compounds found in purple açaí were cyanidin-3-glucoside and cyanidin-3-rutinoside. Moreover, açaí presented significant levels of Ca, Mg, Mn, Fe, Zn, and Cu, in comparison with other berries. Non-processed açaí protect against early inflammation response in vitro by significantly inhibiting NO production and suppressing pro-inflammatory gene expression (IL-1 , cyclooxygenase-2, nitric oxide synthase, and IL-6). All the commercial and non-commercial samples potently inhibited the release of ROS in LPS-stimulated RAW 264.7. Furthermore, all the samples demonstrated the promotion of dermal wound repair due to the high levels of migration activity in HDFa cells.

CONCLUSIONS: All the açaí samples demonstrated anti-inflammatory response and promotion of dermal wound repair, which can be associated mainly with the high content of anthocyanins. After the industrial processing, the wound healing effect was retained. However the anti-inflammatory effect was diminished, suggesting that the processing technology needs to be improved to maintain the biological properties of açaí.

KEYWORDS: Açaí; wound healing; total polyphenol; antioxidant; elemental analysis.

Microencapsulation of Elderberry Juice and Pomace Extract to Produce Phytochemical-Rich Food Ingredients

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BACKGROUND: In recent years, there is a growing demand to consume functional foods, where beyond nutritional value, health benefits are also obtained. Elderberries are one of the richest sources of bioactive compounds and due to their health benefits, they have been used for various medicinal purposes.

OBJECTIVE: European elderberries have been extensively researched; however American cultivars remain largely underutilized. The chemistry of the two species is different; European elderberries have no acylated anthocyanins, while American elderberries contain more than 50% acylated anthocyanins and could be a better choice for processing. Owing to its perishability, there is a need to preserve these bioactive compounds-rich fruits. Because of the presence of heat-sensitive nutrients, spray-drying is one of the best choices to extend shelf life.

METHODS: Elderberry juice /pomace extract was homogenized with either SPI or tapioca starch and spray-dried at 120°C inlet temperature, 10mL/min feed flow, 100% aspirator. Spray- drying yield was determined and the obtained powder was analyzed for physicochemical (moisture, Aw, density, porosity, flowability, particle size, morphology, glass transition, color, hygroscopicity, solubility) and bioactive properties (total polyphenols, anthocyanin, proanthocyanidin). Further, an in-vitro gastrointestinal digestion model was used to study the bioaccessibility of these phytochemicals.

RESULTS: Aggregates produced with SPI showed comparably better physical properties. However, the morphology of tapioca aggregates was more uniform, ensuring better protection and retention of the active material. Although both SPI and tapioca exhibited good antioxidant capacity, tapioca significantly enhanced ($p<0.05$) the protection of TPC (42.01±1.01, 49.6±1.89 mg GAE/g sample), PAC (0.76±0.01, 2.86±0.03 mg PAC-B2/g sample), and anthocyanins (3380.22±41.75, 786.86±50.7 mg/100g) for juice and pomace. Nonetheless, in-vitro digestibility showed that SPI increased the bioaccessibility of elderberry juice, pomace extract, and powder compared to tapioca.

CONCLUSIONS: The results suggest that both SPI and tapioca can be used to produce elderberry powder with potential applications as functional ingredients.

KEYWORDS: American elderberry, pomace, spray drying, bioaccessibility, phytochemicals

Use of Blackberry Polyphenols as an Antioxidant Treatment in a Cell Model for Myotonic Dystrophy Type 1

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BACKGROUND: Myotonic dystrophy type 1 (DM1) is the most common adult muscular dystrophy. DM1 is caused by the expansion of an unstable CTG repeat located in the DMPK gene. The gene is transcribed into an RNA containing the CUG expansion which accumulates in the nucleus and is termed foci. These foci are involved in alteration of alternative splicing regulators affecting many different genes and trigger cellular alterations cause DM1 phenotype. One cellular modification associated to DM1 is oxidative stress (OS). Several OS markers were found to be higher in DM1 patients than in controls, suggesting a possible role for oxidative imbalance in the pathogenesis. OBJECTIVE: To evaluate the effect of blackberry polyphenols to counteract OS and the toxic effects of RNA in a cell model for myotonic dystrophy type 1.

METHODS: Different concentrations of a blackberry (Rubus adenotrichos) polyphenol extract were used to treat two DM1 cell models (MIO-M1-glia cells and SH-SY5Y- neuron cells) containing the CTG repeat expansion in a construct induced by adding doxocycline. To evaluate the decrease of OS, intracellular ROS and lipid peroxidation was measured using the fluorescent probes, and to evaluate the effect of blackberry in RNA-CUGexp toxic accumulation, the presence of foci was determined by FISH.

RESULTS: The blackberry extract mainly contain anthocyanins and ellagitannins. SH-SY5Y cell line treated with blackberry extract showed a significant dose-dependent decrease in intracellular ROS. Blackberry polyphenol concentrations of 16 ug/ml and 150 ug/ml reduced 25% and 65% DCFDA probe fluorescence. Also, for MIO-M1 cell line, a significant dose-dependent decrease in lipid peroxidation was observed due to blackberry extract treatment. Concentrations of 7.5 ug/ml and 30 ug/ml of blackberry polyphenols reduced 40% and 60% NAO fluorescence levels respectively. Additionally, in the MIO-M1 cell line, we observed that 55% of cells presented foci, but this was significantly reduced to 42% and 20% with blackberry polyphenols treatments of 7.5 ug/ml and 30 ug/ml respectively.

CONCLUSIONS: The blackberry antioxidants help counteract OS and the toxic effects of RNA in both DM1 cell models. This result provides preliminary scientific evidence that an antioxidants-based treatment could be beneficial for DM1. Although the main treatment for DM1 would not be based on antioxidants, using these compounds could reinforce the therapeutic strategy of DM1.

KEYWORDS: Rubus adenotrichos, Myotonic dystrophy type 1, polyphenols, DMPK gene, antioxidants, neurodegenerative disease

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