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Impact of Berry Polyphenols on the Gut-Brain Axis

Tremendous progress has been made in characterizing the bidirectional interactions between the central nervous system and the gastrointestinal tract [1]. This concept of a microbiome–gut–brain axis suggests that modulation of the gut microbiota is a tractable approach for developing novel strategies for the regulation of overall brain function [2]. This is particularly relevant for an ageing population for which cognitive decline is a common symptom and can be a harbinger of the development of neurodegenerative conditions, such as dementia.

The wide variation in the gut microbiota between individuals is a result of modulations of many genetic, environmental and physiological factors though changes in dietary composition and diversity are considered the main drivers of the shifts in microbiome structure and activity [3]. Such findings argue in favour of an approach of modulating the microbiome and indirectly brain functions with dietary interventions containing defined nutrients and food bioactives designed to promote healthier ageing. Amongst those nutrients, polyphenols have been consistently reported to play a protective role against cognitive decline [4] and have the ability to modify the microbiome composition and metabolism [5]. Emerging evidence including studies in animal models [6] and a recent prospective clinical trial [7] showed that cranberries had an impact on gut microbiota. However, the impact of cranberries in modulating cognitive functions through the gut-brain axis has never been investigated.
Thus, the purpose of this presentation is to provide an overview of the gut-brain axis regulation, to discuss the regulation of cognitive functions and the gut microbiota by dietary polyphenols and to update on our recent intervention study aiming at investigating the impact of cranberries on the gut-brain axis. Potential molecular mechanisms of actions will also be discussed.

Keywords: Microbiome, polyphenols, cognition, cranberries, gut-brain axis

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The Effects of Berry Polyphenols on Cognitive Function in Adults in the Context of Other Plant Based Ingredients: An ILSI Europe Systematic Review

There is increasing interest in identifying natural products that can support the improvement of mental performance and/or prevent age-related cognitive decline. There is a wealth of published work supporting the cognitive benefits of specific plant-based compounds. However, a systematic review of the evidence for cognitive effects of plant-based ingredients from studies, which apply rigorous methodology, their mechanisms of action and the potential synergy between ingredients is lacking.

ILSI Europe has brought together experts in the field to form a Nutrition and Mental Performance expert group to assess 'plant-based ingredients and cognitive performance'. The expert group set out to summarise and evaluate the existing literature relating to key plant-based ingredients, alone and in combination, in order to critically evaluate the evidence for benefits to cognitive performance. The objective of this systematic review is to highlight the most effective ingredients and combinations thereof and to provide guidance on methodological considerations that may reduce inconsistencies in future research.

Nine plant based ingredient groups were included. These were amino acids including taurine and L-theanine, botanicals such as ginko biloba, ginseng, sage, lemon balm, wild oat extracts, acetyl L-carnitine, hypersine, vinpocetine, bacopa, pycnogenol, ashwagandha, curcumin and alpha-lipoeic acid, carotenoids, vitamins and minerals including Vitamin B, C and E and combinations thereof, phospholipids, omega 3 fatty acids, prebiotics and finally, polyphenols.

Inclusion criteria were applied such that studies that recruited healthy adults (age ≥ 20) of either sex, including pregnant women where the cognitive effects on their children (not preterm) were analysed, were included. Studies conducted in 3rd world countries (e.g. undernourished people or at risk for undernourishment) were also eligible to be included providing participants had no diagnosed disease. Furthermore, randomised controlled trials (RCT) of any duration (acute or chronic) that administered a plant-based ingredient of interest, delivered in any form e.g. liquid, gel capsule were included. For crossover studies, there was no restriction on the inclusion or length of wash-out period. Where a placebo was supplied with an additional ingredient, this same ingredient must have been administered with the active supplement. Follow-up studies following the intervention were also included. For parallel group studies to be included, randomisation to condition had to be stated within the article. However, for crossover trials, randomisation to treatment sequence was assumed to have taken place and therefore was not required to be stated explicitly within the article. Studies which included at least one standardised measure of cognitive performance for any cognitive domain were included. This could be either a primary or secondary endpoint. Studies that utilised a qualitative or subjective report as a measure of cognitive performance or assessed change in mood in the absence of an objective measure of cognitive performance were excluded. Five per cent of all studies per ingredient type returned by the search were independently assessed for eligibility. Each study was assessed for quality using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins et al., 2011). Risk of bias was performed by the original reviewer but confirmed by another, randomly allocated, reviewer. Embase (Embase Classic + Embase 1947) and PubMed electronic databases were searched with a final end date for inclusion of 10th July 2018.

With respect to polyphenols, the searches identified 16 studies of isoflavones and 12 studies of cocoa flavonols which met the inclusion criteria. Six studies of stilbenes (resveratrol) and 6 studies of nitrates (primarily beetroot) were also identified. There were 3 studies of flavanones which examined effects of orange juice.

In summary for polyphenols and berries in particular, the published literature included more reviews than well-controlled data papers. Few studies met the strict inclusion criteria, in part because the majority of studies were conducted in children (4 examined blueberries) or older adults with MCI (2 with blueberries, 1 with Concord Grape Juice, and 1 examined Cherry Juice). Effects of blueberries in older adults were examined in 4 included studies and examined alone or in combination with fish oil in 1 study. There were 3 studies of Concord grape juice (CGJ) included (2 acute and 1 chronic) and 1 CGJ study in older adults with MCI excluded. Two studies of blackcurrant juice, one of haskap berry and one study of plum juice were included. One study of cherry juice in older adults with dementia was excluded as was the only study of pomegranate juice which examined cognitive function postoperatively. The various studies did not show consistent effects on cognitive domains but varied in dose and duration. Those areas with consistent effects are discussed and common mechanisms considered. There are far fewer studies of berry anthocyanin based interventions than for other polyphenols and less than for other plant based ingredients such as micronutrients, amino acids and even ingredients such as L-theanine. This underlines the importance of further exploration of the potential benefits of berry polyphenols for cognitive function in carefully controlled randomised controlled designs with appropriate measures of cognitive function and appropriate methods of analysis applied.

Keywords: Cognition, flavonoids, memory, healthy adults, attention, executive function.

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Blueberry Anthocyanins and Proanthocyanins Improve Insulin Sensitivity in Diet-Induced Obese Mice Through Their Impact on the Gut Microbiota

Previous studies from our group and others have reported that polyphenol-rich extracts from various sources can prevent obesity and associated inflammatory and metabolic disorders in diet-induced obese mice and human subjects (1-7). However, the mechanisms underlying the beneficial effects of berry polyphenols remains poorly understood.

In the present study, we aimed to evaluate the effect of high-bush (HB) blueberry intake in a mouse model of obesity and associated metabolic diseases. This study was also designed to test whether anthocyanins (ANT) or proanthocyanins (PAC) found in HB blueberry could be involved in the modulation of body weight gain and metabolic homeostasis. We also aimed to demonstrate the role of the gut microbiota in the potential beneficial effects of HB blueberry extracts by using fecal microbiota transplantation (FMT). Our data show that both ANT and PAC extracts of HB blueberries improve insulin sensitivity in mice fed a high-fat and high sucrose (HFHS) diet promoting obesity. PAC-treated mice also showed increased leanness which was linked to greater physical activity. FMT studies further revealed that the improvement of insulin sensitivity by both HB blueberry ANT and PAC are linked to the modulation of the gut microbiota in HFHS-fed mice.

Keywords: Blueberry polyphenols, Microbiome, Microbiota, Obesity, Insulin resistance, Energy metabolism, Glucose metabolism

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Blueberries for Attenuating Age-Related Vascular Dysfunction: Evidence and Opportunities

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. Aging is the primary risk factor for CVD, in large part due to adverse modifications to the vasculature, particularly the arteries. During aging, adverse structural and functional changes in the arteries lead to the development of vascular dysfunction, namely vascular endothelial dysfunction and arterial stiffness. Age-related vascular dysfunction contributes to the development of atherosclerosis and hypertension (isolated systolic hypertension in particular), and can lead to stroke, myocardial infarction, and other adverse events including death. Mechanisms underlying vascular dysfunction with aging are complex and multifactorial, but reduced nitric oxide (NO) bioavailability secondary to excessive superoxide-driven oxidative stress and chronic inflammation is believed to be a central contributor. Numerous factors such as menopause, obesity, and metabolic syndrome can accelerate these processes and therefore vascular dysfunction in aging individuals, or cause premature development in others. Elevated blood pressure and hypertension (HTN) further perpetuate these processes leading to greater impairments in vascular function. Importantly, greater than two-thirds of the United States population has elevated blood pressure or stage 1-HTN.

Previous research with blueberries strongly suggests their potential for improving blood pressure, attenuating vascular dysfunction, and therefore reducing age-related CVD risk. Blueberries are rich in bioactive compounds 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 blueberry powder (equivalent to ~1 cup fresh blueberries) for 8 weeks reduced blood pressure and arterial stiffness and increased circulating NO metabolites in postmenopausal women with pre- and stage 1-HTN. However, mechanisms contributing to these effects remain unknown. Several other clinical trials have demonstrated improvements in vascular function and/or blood pressure, though findings have not been consistent likely due in part to baseline health status. Preclinical research has provided important insight into potential mechanisms of action. Altogether, previous research has laid important groundwork for current and future research investigating the impact of blueberry consumption on age-related vascular dysfunction.

Our laboratory is currently examining the efficacy of consuming 22 g/day of freeze-dried blueberry powder to improve endothelial function in postmenopausal women with elevated blood pressure or stage 1-HTN and baseline vascular endothelial dysfunction in a 12-week randomized, double-blind, placebo-controlled, parallel arm clinical trial. Assessments being performed will provide important mechanistic insight into the extent to which blueberries improve vascular endothelial function through reductions in oxidative stress and inflammation. We will also begin exploring the impact of blueberries (at the same dose) on blood pressure and vascular function in middle-aged/older men with elevated blood pressure or stage 1-HTN and baseline endothelial dysfunction in a 12-week randomized, double-blind, placebo-controlled, parallel arm clinical trial. At this relatively low dose, blueberries represent a practical, safe, well-accepted, and cost-effective therapy for the treatment of elevated blood pressure or HTN and vascular endothelial dysfunction in aging populations with a high-risk for developing CVD.

The Impact of Blueberries on Cardiometabolic Health in Participants with Metabolic Syndrome – Results From a 6-Month Trial

Although anthocyanin intake is associated with reduced cardiovascular disease risk in prospective studies, few long-term randomised controlled trials (RCT) have been conducted in individuals at elevated risk. Following ingestion, anthocyanins are extensively metabolised (by Phase I & II metabolism and the gut microbiome) with the gut microbiome likely playing a key metabolic role, catabolising unabsorbed constituents into smaller molecules such as phenolic and aromatic acids, which are also absorbed (1,2). For anthocyanins consumed in the diet, the parent compounds may not be responsible for bioactivity; instead this may be mediated by metabolites present in the systemic circulation (2,3). Data from limited available trials show that following berry or anthocyanin intake there is extensive variability in metabolite levels. This wide inter-individual variability in metabolism (15-99% of the ingested intake recovered as a wide range of urinary metabolites (1, 3-4) suggest that metabolism may be critical in explaining the differential responses in cardiovascular risk biomarkers observed in clinical trials (responders v non-responders) (5-7).

We recently completed a clinical trial to examine the effect of 6-month blueberry intake on clinically-relevant biomarkers of insulin resistance, vascular function, lipid status and anthocyanin metabolism in participants with metabolic syndrome (MetS) (8). In this double-blind, parallel RCT (n=115), we fed two dietary achievable blueberry intakes (equivalent to ½ /1 cup/d, fed as 13 g v 26 g freeze-dried blueberries daily containing 182 and 364 mg/d anthocyanins). Insulin resistance was assessed via HOMA-IR (primary endpoint) and confrmed by [6-6-2H2] glucose-labelled, 2-step hyperinsulinemic clamp (n=20). Clinically-relevant cardiometabolic endpoints (including fow mediated dilatation (FMD), blood pressure (BP), augmentation index (AIx), pulse wave velocity (PWV)) and anthocyanin metabolism (in urine and blood) were also assessed. Shot-gun sequencing analyses of the gut microbiome is ongoing.

We found that 1 cup improved endothelial function (FMD): [+1.45%, 95%CI: 0.83, 2.1; p<0.001]), AIx: [-2.24%, 95%CI: -3.97, -0.61; p=0.04]) and cyclic guanosine monophosphate concentrations ((cGMP): [+0.99 pmol/mL, 95%CI: -9.24, 11.2; p=0.04]). In statin non-users (n=71), elevated HDL-C [+0.08mmol/L; p=0.03], HDL particle (HDL-P) density [+0.48 n, x10-6; p=0.002) and Apo-A1 (+0.05 g/L; p=0.01) levels were observed following intervention. Concurrently, LC-MS/MS analysis confrmed associations between increased downstream anthocyanin metabolite levels and changes in measures of vascular health. The intervention had no effect on insulin resistance (assessed via HOMA-IR (primary endpoint) and confrmed (in n=20) by [6-6-2H2] glucose-labelled, 2-step hyperinsulinemic clamp), PWV or BP. The ½ cup intake had no effect on any biomarkers in this high risk group.

Despite no change in insulin resistance, we show for the frst time, clinically relevant changes in vascular function and underlying improvements in NO bioactivity and lipid status, following 1 cup/d of blueberries for 6-months. Blueberries should be included in dietary strategies aimed at improving individual and population heart health.

To understand the importance of metabolism, particularly microbiome-mediated biotransformation, in explaining the CV health effects of anthocyanins a combination of epidemiological studies and dietary intervention trials (acute and chronic) are needed. This will allow the identifcation of metabolites and microbial composition as intermediate biomarkers for dietary interventions and will be critical in identifying and validating biomarkers to employ to examine associations of bioavailable favonoids with CV health in prospective studies. Ultimately, detecting the infuence of anthocyanin intake on microbiota shifts and metabolism will strengthen the case for causality of anthocyanin-disease relationships.

Keywords: Blueberries, endothelial function, anthocyanins, gut microbiome, metabolic syndrome

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Dietary Berries, Insulin Resistance and Diabetes

According to the CDC, more than 30 million Americans (9.4% of US population) were estimated to have diabetes mellitus (DM) in 2015. This number is expected to double or triple by the year 2050. Pharmacologic interventions are costly and are associated with adverse side effects, thus nutritional therapy continues to play an important role in the prevention, development and treatment of this disease. Among various foods and beverages high in dietary bioactive compounds, colorful berries have been shown to play an important role in the management of hyperglycemia and diabetes-related vascular complications. In our previous studies in participants with pre-diabetes or the metabolic syndrome, supplementation of freeze-dried blueberries and strawberries were shown to improve blood pressure and surrogate markers of vascular dysfunction, but with no significant changes in blood glucose and/or insulin resistance. On the other hand, we observed a significant decrease in postprandial hyperglycemia and inflammation, when dietary cranberries or red raspberries were administered along with a high-fat breakfast meal in participants with type 2 diabetes. These clinical observations are further supported by experimental data on the role of berry bioactive compounds in improving glucose metabolism and glycemic control in animal models of type 2 diabetes. This presentation will provide an overview of clinical studies on the effects of dietary berries on glycemic control, and results from our ongoing studies on the effects of strawberries on insulin resistance and diabetes-related 'transcriptomics'.

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Anti-proliferative Activity of Berry Volatiles

Authors: Luke Howard, Cindi Brownmiller, & Sun-Ok Lee

Affiliation: Department of Food Science, University of Arkansas, Fayetteville, AR

Berries are rich source of phytochemicals, especially polyphenolics [1] that are thought to protect against a number of chronic diseases including various types of cancer, cardiovascular diseases, diabetes and obesity, metabolic syndrome, and digestive disorders [2]. Berries also contain volatile compounds comprising a complex mixture of monoterpenes, ketones, acids, esters, furans, aldehydes, alcohols and lactones that are responsible for the unique aromas of berries [3,4]. However, information is lacking on volatile composition of berries and their potential health benefits.

In this study we isolated phenolic and volatile fractions from fresh blueberries, blackberries, red raspberries, black raspberries, cranberries and strawberries. Black raspberries had the highest levels of total phenolics followed by cranberries, blueberries, blackberries, red raspberries, and strawberries. Blackberries had the highest levels of volatiles followed by black raspberries, strawberries, cranberries, red raspberries, and blueberries. Each berry contains a complex fingerprint of volatiles that impart unique aromas. Monoterpenes predominated in black and red raspberries, blueberries, cranberries, and strawberries, while acids predominated in blackberries. Phenolic and volatile fractions were evaluated for anti-proliferative activity using Caco-2 colon cancer cells at concentrations close to those found in fresh berries. The percentage inhibition of cell proliferation compared with the control for the phenolic fraction ranged from 3% for black raspberry to 58% for blueberry, whereas the values for the volatile fraction ranged from 5% for blackberry to 43% for black raspberry. The volatile fraction inhibited cellular proliferation much better than the phenolic fraction at 12 hr, whereas the phenolic fraction generally showed greater inhibition after 24 hr.

Berry volatiles showed comparable anti-proliferative activity as phenolics despite being present in the fruit at 300 to 2700-fold lower concentrations. In addition to impacting aroma of berries, volatile compounds may play an important role in health-promotion. More research is needed to determine the bioavailability and mechanisms responsible for anti-proliferative activity of berry volatiles.

Keywords: Anti-proliferation, Berries, Phenolics, Volatiles

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Comparison of Blueberry Extract vs. Blueberry Powder Confections: Exposure Analyzed by Targeted and Untargeted Metabolomics

Authors: Megan M. Kemski[1], Meredith R. Meyers[2], Yael Vodovotz[1], Ken M. Riedl[1], Matthias S. Klein[1]

Affiliation:

1. Department of Food Science and Technology, The Ohio State University, 2015 Fyffe Road, Columbus, OH 43210
1. Ocean Spray Cranberries, Inc. 1 Ocean Spray Drive, Lakeville-Middleboro, MA 02349

BACKGROUND: Blueberries are a rich source of bioactive flavonoids, mainly anthocyanins, that reach systemic circulation and can cross the blood-brain barrier. However, consumers would have to eat more than a cup of blueberries in order to consume an efficacious dose according to animal studies. It is unclear if anthocyanins from a phenolic extract of blueberries have similar bioavailability as from freeze-dried blueberries. Thus, our lab developed blueberry confections from concentrated blueberry extract (BE) and whole blueberry powder (BP) for use in a human dietary intervention.

OBJECTIVES: The objectives of this study were to compare the bioavailability of a single dose of anthocyanins from confections made with either BE or BP in the urine of 12 subjects using a cross-over design.

METHODS: A dietary intervention with blueberry confections was conducted for urinary uptake of anthocyanins and their metabolites in 12 human subjects. Confections were formulated with BP or BE (125mg anthocyanins/dose), sugar, jello, gelatin, citric acid, and water. Subjects followed a week wash-out period eliminating berries from their diet and a 24hr urine collection immediately followed by a single dose of one type of confection (6 pieces of BE or 4 pieces of BP confection) and another 24hr urine collection. A second washout was conducted with intervention using the alternate confection. Urine samples were tested in a targeted manner by mass spectrometry to determine anthocyanin metabolites and by NMR metabolomics with confirmation by mass spectrometry.

RESULTS/CONCLUSIONS: Anthocyanins were not detected in the 12 subject urines after the week-long washout. Following either intervention, all anthocyanins were found in all urines as well as glucuronide conjugates. Only 0.05% by weight of anthocyanins consumed were recovered in the urine samples and uptake varied among individuals more so than by confection type. NMR metabolomics revealed adipic acid, a component of commercial gelatin, as highly elevated in the confection groups.

KEYWORDS: Blueberry confections, Extract, Powder, Anthocyanins, Bioavailability, Metabolomics