JOURNAL OF
AGRICULTURAL AND
FOOD CHEMISTRY

SYMPOSIUM

Berry Fruits: Compositional Elements, Biochemical Activities, and the Impact of Their Intake on Human Health, Performance, and Disease

NAVINDRA P. SEERAM[#]

Center for Human Nutrition, David Geffen School of Medicine, University of California, Los Angeles, California 90095

An overwhelming body of research has now firmly established that the dietary intake of berry fruits has a positive and profound impact on human health, performance, and disease. Berry fruits, which are commercially cultivated and commonly consumed in fresh and processed forms in North America, include blackberry (*Rubus* spp.), black raspberry (*Rubus occidentalis*), blueberry (*Vaccinium corymbosum*), cranberry (i.e., the American cranberry, *Vaccinium macrocarpon*, distinct from the European cranberry, *V. oxycoccus*), red raspberry (*Rubus idaeus*) and strawberry (*Fragaria* × *ananassa*). Other berry fruits, which are lesser known but consumed in the traditional diets of North American tribal communities, include chokecherry (*Prunus virginiana*), highbush cranberry (*Viburnum trilobum*), serviceberry (*Amelanchier alnifolia*), and silver buffaloberry (*Shepherdia argentea*). In addition, berry fruits such as arctic bramble (*Rubus articus*), bilberries (*Vaccinuim myrtillus*; also known as bog whortleberries), black currant (*Ribes nigrum*), boysenberries (*Rubus* spp.), cloudberries (*Rubus chamaemorus*), crowberries (*Empetrum nigrum*, *E. hermaphroditum*), elderberries (*Sambucus* spp.), gooseberry (*Ribes uva-crispa*), lingonberries (*Vaccinium vitis-idaea*), loganberry (*Rubus loganobaccus*), marionberries (*Rubus* spp.), Rowan berries (*Sorbus* spp.), and sea buckthorn (*Hippophae rhamnoides*), are also popularly consumed in other parts of the world. Recently, there has also been a surge in the consumption of exotic "berry-type" fruits such as the pomegranate (*Punica granatum*), goji berries (*Lycium barbarum*; also known as wolfberry), mangosteen (*Garcinia mangostana*), the Brazilian açaí berry (*Euterpe oleraceae*), and the Chilean maqui berry (*Aristotelia chilensis*). Given the wide consumption of berry fruits and their potential impact on human health and disease, conferences and symposia that target the latest scientific research (and, of equal importance, the dissemination of this information to the general public), on the chemistry and biological and physiological functions of these "superfoods" are necessary.

INTRODUCTION

The International Berry Health Benefits Symposium was initiated in 2005 (June 13–14, Corvallis, OR) and is a series of biennial conferences organized to investigate and explore the latest scientific research related to berry consumption and human health. The 2007 International Berry Health Benefits Symposium (June 11–12, Corvallis, OR) was sponsored by the Oregon Raspberry & Blackberry Commission, the Oregon Strawberry Commission, the California Strawberry Commission, the Washington Red Raspberry Commission, the Wild Blueberry Association of North America, the U.S. Highbush Blueberry Council, and the Cranberry Institute. The symposium comprised a multidisciplinary group of international participants from Asia, Europe, New Zealand, Mexico, and North and South Americas. Participants included berry growers; industrial whole foods, beverage, and botanical ingredient manufacturers and suppliers; basic scientists; and clinicians, dietitians, and other health-care personnel. From the discussions, it was apparent that the public has a growing interest in the potential human health benefits that may be imparted from the consumption of berry fruits.

The cluster of papers presented here is largely derived from presentations at the meeting. Discussions included scientific reviews and recent research progress made in identifying phytochemicals (plant chemicals) present in berry fruits and elucidating the cellular and molecular mechanisms of actions of these compounds. The bioavailability, metabolism, and tissue

[#] Present address: Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI 02881 (e-mail nseeram@mail.uri.edu).

10.1021/jf071988k CCC: $40.75
Published on Web 01/23/2008

distribution of berry phytochemicals (namely, phenolics) was the subject of several presentations. Some of the oral presentations were organized around selected chronic human diseases that show promise in being positively affected by berry consumption. These include heart health and cardiovascular disease, neurodegenerative and other diseases of aging, obesity, and also certain human cancers, such as esophageal and gastrointestinal cancers. In addition, the effects of berry consumption on symptoms of the metabolic syndrome and on human performance enhancement were also included as oral presentations.

Before specific presentations are discussed, it is useful to briefly reflect on berry phytochemicals and our understanding of how their chemistry influences their biological and physiological functions. Although many berry fruits contain micro- and macronutrients including vitamins, minerals, folate, and fiber, their various biological properties have been largely related to their high levels and wide diversity of phenolic-type phytochemicals. It is noteworthy that both lipophilic (minor) and hydrophilic (major) phytochemicals are found in berries, but it is the latter class that has been largely implicated in the bioactivities of these fruits. However, the complementary, additive, and/or synergistic effects resulting from multiple phytochemicals found in berry fruits are believed to be responsible for their wide range of observed biological properties rather than these effects being due to a single constituent alone.

Berry phenolics include flavonoids (anthocyanins, flavonols, and flavanols), tannins [condensed tannins (proanthocyanidins) and hydrolyzable tannins (ellagitannins and gallotannins)], stilbenoids, and phenolic acids (reviewed in ref *1*). Among berry phenolics, the anthocyanins (pigments that account for their attractive colors), are best studied and have a wide range of bioactivities including antioxidant, anticancer, and anti-inflammatory properties (*2–4*). However, advances in tannin/polyphenol research have increased our knowledge of the roles that these larger molecules play in human health (see ref *5*; Editorial for the Fourth Tannin Conference). The levels of a particular class of tannin molecule, that is, either condensed (proanthocyanidins) or hydrolyzable (ellagitannins) tannins, vary considerably among berries. In fact, among commonly consumed berries, blueberries and cranberries contain predominantly proanthocyanidins, whereas blackberries, black raspberries, red raspberries, and strawberries contain predominantly ellagitannins. Therefore, the class (and specific chemical structures) of tannins present in a particular berry type may contribute significantly to its unique biological properties. For example, the bacterial antiadhesive properties observed for the cranberry, which is apparently unique among berry fruits, is accounted for by its oligomeric proanthocyanidins, which possess an A-type structural linkage (*6*). Similarly, the distinct biological effects observed for blueberries (a proanthocyanidin-rich fruit) versus strawberries (an ellagitannin-rich fruit) on neuronal function and behavior in aging animals may be due to the effects of the individual classes of tannins in different regions of the brain (*7*). Shukitt-Hale et al. reported that aging rats on a strawberry diet had better protection against spatial deficits, probably because they were better able to retain place information (a hippocampally mediated behavior), whereas blueberry-fed animals had improved reversal learning, a behavior more dependent on intact striatal function (*7*). Evaluation of the tissue distribution of the respective berry tannins, and their metabolites, in separate brain regions of these animals is planned for future collaborative research (N. P. Seeram, J. Joseph, and B. Shukitt-Hale, personal communication). It is noteworthy that anthocyanins, from blueberries, have been previously reported to cross the blood−brain barrier of aged rats and localize in various brain regions, important for learning and memory (*8*).

Berry phenolics are best known for their ability to act as antioxidants, but the biological activities exerted by berry phytochemicals in vivo extend beyond antioxidation (reviewed in ref *9*). In fact, a large and growing body of evidence shows that berry phytochemicals regulate the activities of metabolizing enzymes; modulate nuclear receptors, gene expression, and subcellular signaling pathways; and repair DNA oxidative damage, etc. (*9, 10*). Although the multimechanistic actions of berry phytochemicals have been firmly established from in vitro studies, it has only been since the past decade that animal and human studies have significantly increased our knowledge of the bioavailability, metabolism, tissue distribution, and biological effects of these compounds in vivo. It should be noted that based on the current literature, it is widely accepted that berry phenolics are "poorly bioavailable" due to their relatively "low levels" in human circulation. However, berry phenolics are extensively metabolized and also further converted by colonic microflora into related molecules. These compounds may persist in vivo, accumulate in target tissues, and contribute significantly to the biological effects that have been observed for berry fruits. Finally, it is also noteworthy that the levels of berry phenolics in vivo may also be underestimated due to limitations in laboratory extraction procedures because these compounds may bind to proteins, etc., causing their extraction for chemical analyses to be difficult. Therefore, in conclusion, studies into the bioavailability and metabolism of berry phenolics are necessary, and the aforementioned points are critical in the overall examination of the role that berry phytochemicals play in the prevention and treatment of chronic human diseases.

PRESENTATIONS AT THE SYMPOSIUM

The first session on "Anthocyanins and Health" had *Michael Lefevre* from the Pennington Biomedical Research Center presenting the effects of berry anthocyanins on gene regulation and energy metabolism. *Tony K. McGhie* from the Horticulture and Food Research Institute (HortResearch, New Zealand) presented the in vitro and in vivo antioxidant properties of berry fruits.

In the session on "Cardiovascular Disease", *Giuseppe (Joe) Mazza* from Agriculture and Agri-Food (Canada) presented a review on anthocyanins and heart health. *Raika Koli* from the Biomarker Laboratory, National Public Health Institute KTL (Finland), provided an update on a current human study investigating the health effects of berry consumption in subjects at risk for cardiovascular disease. The presentation of *Jess D. Reed* from the University of Wisconsin, Madison, focused on cranberry proanthocyanidins and cardiovascular health.

In the session on "Obesity", *Tanaka Tsuda* from Chubu University (Japan) discussed the regulation of adipocyte function by berry anthocyanins and their potential for preventing the metabolic syndrome. *Ronald L. Prior* from the USDA-ARS Arkansas Nutrition Center, University of Arkansas, spoke on anthocyanin absorption, metabolism, and obesity.

In the "Cancer" session, *Gary Stoner* and *Laura Kresty*, both from The Ohio State University, discussed the prevention of gastrointestinal tract cancers with berries and the ability of cranberry extract to modulate signaling pathways in esophageal cancer cells, respectively.

In the "Berries and Performance" session, *Mary Ann Lila* from the University of Illinois reported on the performance-enhancing effects of berries traditionally consumed by North American tribal communities. *Wilhelmina Kalt* from Agriculture and Agri-Food (Canada) discussed the distribution of anthocyanins in body tissues of pigs after long-term blueberry feeding. *James A. Joseph* from the USDA Human Nutrition Research Center and Aging, Tufts University, spoke on the beneficial effects of berry fruits on behavioral and neuronal aging.

In the session on “Processing Effects”, *Luke Howard* from the University of Arkansas presented a paper on how berry polyphenolics change with processing.

In the final session on “Berry Phenolics: Composition and Health Effects”, *Riitta Puupponen-Pimiä* from the VTT Technical Research Center (Finland) presented on the in vivo and in vitro effects of therapeutically active berry compounds on human health. *Navindra P. Seeram* from the UCLA Center for Human Nutrition, School of Medicine, University of California, Los Angeles, discussed the bioavailability and bioactivity of strawberry phytochemicals in animals and human subjects. *Maurizio Battino* from the Universita Politecnica Delle Marche (Italy) reported the characterization of bioactive compounds from different strawberry cultivars and the role of these compounds on antioxidant capacity in vitro and in vivo. *Alan Crozier* from the University of Glasgow (Scotland) presented a paper on berry phenolics and their fate within the body after ingestion.

Finally, it should also be mentioned that *David Heber*, UCLA Center for Human Nutrition, School of Medicine, University of California, Los Angeles, presented the keynote dinner speech. His discussion, “What Color Is Your Berry?”, focused on how humans should move into the modern era of agriculture and nutrigenomics and take advantage of berries as sources of phytonutrients to stem the global epidemics of obesity and chronic disease.

FUTURE OPPORTUNITIES AND CHALLENGES FOR BERRY RESEARCH

There should be a strong emphasis on the interdisciplinary cross-fertilization of berry research conducted in the basic and clinical sciences to ultimately culminate in translational research (from laboratory to bedside). It is also imperative that the outcomes of these meetings be carefully and responsibly communicated to the general and lay public.

Although considerable progress has been made in understanding the role that berry phytochemicals play in affecting human health and disease, there are still important gaps in our knowledge concerning the biology and chemistry of these compounds. Future studies should be designed to enhance our knowledge of the intricate roles and functions that berry phytochemicals impart at the cellular and molecular levels. In addition, as research into the potential health benefits of berries continue in a postgenomic era, it will bring ever-increasing demands to observe and characterize variations within biological systems. Research focus on nutrigenomics (effects of nutrients on the genome, proteome, and metabolome) and nutrigenetics (effects of genetic variation on the interaction between diet and disease) will be essential. Future studies on the metabolomics of berry phenolics are necessary, and there should be renewed focus on evaluating whether metabolites formed in vivo accumulate within target tissues and exert biological effects therein. For example, it may be possible that on ingestion, metabolites including glucuronidated, sulfated, and methylated derivatives may act as “pro-drugs” within target tissue sites. In addition, the products formed from the action of colonic microflora on berry phenolics may also significantly contribute to health benefits that may result from berry consumption. Studies should also be conducted to evaluate whether the biological effects of berry phytochemicals are enhanced by the complex interactions of multiple components within the food matrix of a particular fruit compared to a single purified constituent or constituents. In addition, whether health benefits of berry fruits are enhanced through additive and/or synergistic interactions with phytochemicals from other foods should be examined. Finally, future berry research should also focus on studying gene−nutrient interactions and health outcomes to achieve individual dietary intervention strategies aimed at preventing chronic human diseases, improving quality of life, and promoting healthy aging.

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Received for review July 3, 2007. Accepted November 27, 2007.

JF071988K