
Objective: Berries are high in flavonoids, especially anthocyanidins, and improve cognition in experimental studies. We prospectively evaluated whether greater long-term intakes of berries and flavonoids are associated with slower rates of cognitive decline in older women. Methods: Beginning in 1980, a semiquantitative food frequency questionnaire was administered every 4 years to Nurses' Health Study participants. In 1995–2001, we began measuring cognitive function in 16,010 participants, aged ≥70 years; follow-up assessments were conducted twice, at 2-year intervals. To ascertain long-term diet, we averaged dietary variables from 1980 through the initial cognitive interview. Using multivariate-adjusted, mixed linear regression, we estimated mean differences in slopes of cognitive decline by long-term berry and flavonoid intakes. Results: Greater intakes of blueberries and strawberries were associated with slower rates of cognitive decline (e.g., for a global score averaging all 6 cognitive tests, for blueberries: p-trend = 0.014 and mean difference = 0.04, 95% confidence interval [CI] = 0.01–0.07, comparing extreme categories of intake; for strawberries: p-trend = 0.022 and mean difference = 0.03, 95% CI = 0.00–0.06, comparing extreme categories of intake), after adjusting for multiple potential confounders. These effect estimates were equivalent to those we found for approximately 1.5 to 2.5 years of age in our cohort, indicating that berry intake appears to delay cognitive aging by up to 2.5 years. Additionally, in further supporting evidence, greater intakes of anthocyanidins and total flavonoids were associated with slower rates of cognitive decline (p-trends = 0.015 and 0.053, respectively, for the global score). Interpretation: Higher intake of flavonoids, particularly from berries, appears to reduce rates of cognitive decline in older adults. ANN NEUROL 2012


The objective of this study was to investigate the mechanisms by which total blueberry polyphenol extract (BPE) exerts its anti-inflammatory function on MC3T3-E1 preosteoblasts under inflammatory conditions. Cells were treated with BPE at concentrations of 0, 10, 100 μg/ml. After 24 h incubation, cells were stimulated with TNF-α (10 ng/ml) and IL-1 (10 ng/ml) individually or in combination for 24 and 48 hrs. Cells and supernatants were collected to assess NO production and for RNA extraction. Select gene expressions involved in bone cell differentiation were assessed using commercial cDNA array plates. BPE was able to suppress the increased NO production induced by either TNF-α or IL-1, suggesting the prevention of impaired osteoblastic differentiation. However, BPE had no significant effect on NO production when TNF-α and IL-1 were both
present. At the molecular level, BPE upregulated RANKL and IL-6 via the NF-B signaling pathway. In spite of this, BPE tended to increase gene expression of Runx2 and osterix, albeit not significantly. From these preliminary findings it can be suggested that BPE does not suppress bone turnover through osteoblast-mediated activity unlike in vivo findings.


Epidemiological studies have shown that populations who consume plant foods rich in polyphenols have lower incidence of chronic inflammatory diseases. These polyphenols have been shown to modulate the inflammatory response by inhibiting NO, TNF-α, and COX-2. The objective of this study is to investigate the extent to which blackberry and blueberry polyphenols modulate the production of NO, TNF-α, and expression of COX-2 in LPS-stimulated RAW 264.7 macrophages. Berry polyphenols were extracted using ethanol and total phenolics were quantified by Folin-Ciocalteu method. Macrophages were treated with different doses of polyphenols (0, 10, 100, 1000 μg/ml) 1 hr prior to stimulation with 10 ng/ml LPS for 6 hrs. Supernatants were collected to measure NO and TNF-α production and cells were harvested to assess COX-2 via western blot. Blackberry and blueberry polyphenol extracts contained 55.56 and 79.06 mg/g expressed as gallic acid equivalents, respectively. Blackberry polyphenol extract strongly inhibited NO production at doses of 10 and 100 μg/ml by 56 and 59%, respectively, without cytotoxicity whereas blueberry polyphenol extract had no effect on NO production. Thus far, these cell culture results indicate that polyphenol extracts from blackberry possess anti-inflammatory properties; however, these findings need to be confirmed in in vivo models.


Blueberries (BB) contain high levels of polyphenols. Among them, phenolic acids (PAs) have been recently suggested as a group of important bioactive compounds. Highbush BB (Vaccinium corymbosum) and lowbush "wild" BB (Vaccinium angustifolium) are two predominant species in North America. The first objective of this study is to systemically analyze and compare the profiles of PAs in these two species. Nine PAs were detected and quantified in both species by HPLC/MS; of these, five PAs were identified in BB for the first time. The total PA content of lowbush BB (4.90 mg/g, dry weight (DW)) is about 3.2 times higher than that of highbush BB (1.53 mg/g, DW). Chlorogenic acid is the most abundant PA in BB, at 4.87 mg/g DW and 1.12 mg/g DW in lowbush and highbush BB. Anti-inflammatory effects of polyphenol-rich extracts of the two BB species were evaluated by a SEAP reporter assay to measure NF-B activation.
An initial test using 10 μg/mL of extracts showed that lowbush and highbush BB inhibited LPS-induced NF-B activation by 30.7 % and 16.8 % (P<0.05), respectively. Our data indicated that the concentrations of phenolic acids in the two major BB species are very different. Lowbush BB polyphenols exhibited greater anti-inflammatory potential than those of highbush BB. The anti-inflammatory effects of polyphenols in BB warrant further investigation.


The study was conducted to elucidate the effects of blueberry(Vaccinium cyanococcus) supplementation on antioxidant enzyme activities in rat blood, skin and brain tissue. Forty-eight 10-week-old male Sprague-Dawley rats were assigned to four groups (n=12/group); no stress-normal diet(–CON), stress-normal diet(+CON), no stress-normal diet + 5% blueberry water(–BB), and stress-normal diet + 5% blueberry water(+BB). The +CON and +BB groups were given the stress during all experimental period and stress scheme was followed the chronic mild stress model. Body weight gain and feed efficiency ratio were decreased in given stress groups compared with non stress groups (p<0.05). Antioxidant activity levels in blueberry supplemented rats tended to increase compared to control groups. The stressed rats groups tended to have low antioxidant levels compared with unstressed rats groups. The superoxide dismutase(SOD) activity in serum and brain was not different among the treatments. The serum glutathione peroxidase activity was the highest in –BB group, but +BB group was lower than +CON(p<0.05). The skin SOD activity was significantly higher in blueberry supplementation groups than that of –CON and +CON groups. The skin catalase activity was higher in blueberry groups(p<0.05). From the findings, blueberry supplementation might provide the protection against oxidative stress induced by chronic stress.


Intake of anthocyanin-rich foods has been associated with a reduced risk of cardiovascular diseases. We recently reported that a nutritional supplementation with a bilberry anthocyanin-rich extract (BE) attenuates atherosclerotic lesion development in apolipoprotein E-deficient (apoE/) mice. However, the mechanism(s) of their preventive action are not completely understood. Anthocyanins may alter mRNA levels of genes related to atherosclerosis in cultured macrophages and endothelial cells, but in vivo studies remain scarce. The aim of the present study was to explore the in vivo mechanisms of action of the same bilberry extract, administered by supplementation at a nutritional level, in the aorta of apo E/ mice using a global transcriptomic approach. This study focused on the early stage of atherosclerosis development for better assessment
of BE action on initiation mechanisms of this pathology. After a two week period, plasma lipid and antioxidant capacity were evaluated and the global genomic analysis was carried out using pangenomic microarrays. BE supplementation significantly improved hypercholesterolemia whereas the plasmatic antioxidant status remained unchanged. Nutrigenomic analysis identified 1261 genes which expression was modulated by BE in the aorta. Bioinformatic analysis revealed that these genes are implicated in different cellular processes such as oxidative stress, inflammation, transendothelial migration and angiogenesis, processes associated with atherosclerosis development/protection. Some of the most significantly down-regulated genes included genes coding for AOX1, CYP2E1 or TXNIP implicated in the regulation of oxidative stress, JAM-A coding for adhesion molecules or VEGFR2 implicated in regulation of angiogenesis. Other genes were up-regulated, such as CRB3, CLDN14 or CDH4 potentially associated with increased cell-cell adhesion and decreased paracellular permeability. These results provide a global integrated view of the mechanisms involved in the preventive action of bilberry anthocyanin-rich extract against atherosclerosis.


ABSTRACT: BACKGROUND: Exercise-induced muscle damage (EIMD) is accompanied by localized oxidative stress / inflammation which, in the short-term at least, is associated with impaired muscular performance. Dietary antioxidants have been shown to reduce excessive oxidative stress; however, their effectiveness in facilitating recovery following EIMD is not clear. Blueberries demonstrate antioxidant and anti-inflammatory properties. In this study we examine the effect of New Zealand blueberries on EIMD after strenuous eccentric exercise. METHODS: In a randomized cross-over design, 10 females consumed a blueberry smoothie or placebo of a similar antioxidant capacity 5 and 10 hours prior to and then immediately, 12 and 36 hours after EIMD induced by 300 strenuous eccentric contractions of the quadriceps. Absolute peak and average peak torque across the knee, during concentric, isometric, and eccentric actions were measured. Blood biomarkers of oxidative stress, antioxidant capacity, and inflammation were assessed at 12, 36 and 60 hours post exercise. Data were analyzed using a two-way ANOVA. RESULTS: A significant (p < 0.001) decrease in isometric, concentric and eccentric torque was observed 12 hours following exercise in both treatment groups. During the 60 hour recovery period, a significant (p = 0.047) interaction effect was seen for peak isometric tension suggesting a faster rate of recovery in the blueberry intervention group. A similar trend was observed for concentric and eccentric strength. An increase in oxidative stress and inflammatory biomarkers was also observed in both treatment groups following EIMD. Although a faster rate of decrease in oxidative stress was observed in the blueberry group, it was not significant (p < 0.05) until 36 hours post-exercise and interestingly coincided with a gradual increase in plasma antioxidant capacity, whereas biomarkers for inflammation were still
elevated after 60 hours recovery. CONCLUSIONS: This study demonstrates that the ingestion of a blueberry smoothie prior to and after EIMD accelerates recovery of muscle peak isometric strength. This effect, although independent of the beverage’s inherent antioxidant capacity, appears to involve an up-regulation of adaptive processes, i.e. endogenous antioxidant processes, activated by the combined actions of the eccentric exercise and blueberry consumption. These findings may benefit the sporting community who should consider dietary interventions that specifically targets health and performance adaptation.


Blueberry possesses greater antioxidant capacity than most other fruits and vegetables. The present study investigated the lifespan-prolonging activity of blueberry extracts in fruit flies and explored its underlying mechanism. Results revealed that blueberry extracts at 5mg/ml in diet could significantly extend the mean lifespan of fruit flies by 10%, accompanied by up-regulating gene expression of superoxide dismutase (SOD), catalase (CAT) and Rpn11 and down-regulating Methuselah (MTH) gene. Intensive H(2)O(2) and Paraquat challenge tests showed that lifespan was only extended in Oregon-R wild type flies but not in SOD(n108) or Cat(n1) mutant strains. Chronic Paraquat exposure shortened the maximum survival time from 73 to 35days and decreased the climbing ability by 60% while blueberry extracts at 5mg/ml in diet could significantly increase the survival rate and partially restore the climbing ability with up-regulating SOD, CAT, and Rpn11. Furthermore, gustatory assay demonstrated that those changes were not due to the variation of food intake between the control and the experimental diet containing 5mg/ml blueberry extracts. It was therefore concluded that the lifespan-prolonging activity of blueberry extracts was at least partially associated with its interactions with MTH, Rpn11, and endogenous antioxidant enzymes SOD and CAT.


The occurrence of neurodegenerative disease substantially increases with age, which, in part, may be due to increased susceptibility to oxidative stress, inflammation and loss of autophagy (neuronal housekeeping). Polyphenols and fatty acids, abundant in berries (e.g., blueberry, strawberry, or acai fruit) and walnuts, have been shown to protect brain cells in culture and animals against oxidative stress/inflammation, with enhanced memory and cognitive function in animals. We have investigated whether feeding rats with blueberry- or strawberry-supplemented diets, followed by irradiation with high energy and charge (HZE) particles, a model for accelerated aging, would elicit any protective effects in the brain. HZE irradiation disrupted key proteins in the hippocampus
and striatum. Feeding animals with either berry diet, prior to irradiation, protected these brain regions against inflammation, oxidative stress and loss of autophagy. Moreover, autophagy activation was mediated by inhibiting the phosphorylation of mTOR and activating other proteins. Walnuts also elicited similar effects on the normal aging process when fed to aged animals. These molecular effects were further corroborated in vitro using BV2 microglia, HT22 neurons and E18 neuron-astrocyte cultures. This study extends molecular evidences for the health-promoting properties of berries and walnuts.


Despite the well-accepted notion of peri-natal origins of adult diseases, the factors and regulatory mechanisms underlying breast cancer development remain unclear. Diet is a highly modifiable determinant of breast cancer risk, and the effects of the in utero nutritional environment persist beyond fetal life. We investigated whether in utero/lactational exposure to blueberry (BB) via maternal diet alters the trajectory of Wnt1-induced mammary tumorigenesis in offspring. Wnt1 transgenic mice were exposed to maternal diets of casein (CAS; n=33) or blueberry-supplemented CAS (3% BB; n=28) from gestation day 4 until post-natal day 21. Offspring were then weaned to CAS and mammary tumor development was followed until age 8 months. While tumor incidence and latency were similar for both groups, tumor weight (by 2-fold, p=0.034) and growth rate (by 60%; p=0.008) were reduced in offspring of BB- versus CAS-fed dams. Tumors from the BB group had higher expression of tumor suppressors PTEN and E-cadherin and lower cyclin D1 and pro-apoptotic Bcl2 levels. Transcript levels for DNA methylation enzymes DNMT1 and EZH2 were higher in BB tumors. Serum levels of insulin and serum leptin/adiponectin ratio were lower for tumor-bearing BB than CAS offspring at sac. Our findings support a role for nutritional epigenetics in adult breast cancer outcome.


We previously demonstrated the protective effects of blueberry (BB) and black raspberry (BRB) supplemented at 2.5% dose in an ACI rat mammary tumor model. Here, we assessed a dose-related alteration in tumor indices with diet supplemented with 5% BB or BRB powder. The diet was well tolerated. Tumor palpation from 12 weeks revealed first tumor appearance by 84 days in the control group, that was delayed by 24 and 39 days with the BB and BRB diets, respectively (p = 0.04). Ellagic acid detected in the plasma of rats fed the BRB diet was in the range of 96.6-294.2 ng/mL. While the BB diet showed better efficacy in reducing mammary tissue proliferation and tumor burden, tumor latency was delayed efficiently by BRB. Furthermore, BB was effective in
downregulating CYP1A1 expression, while BRB downregulated ERalpha expression effectively. Distinct anticarcinogenic effects of the two berries correspond to their distinct phytochemical signatures.


There is considerable interest in the potential of a group of dietary-derived phytochemicals known as flavonoids in modulating neuronal function and thereby influencing memory, learning and cognitive function. The present review begins by detailing the molecular events that underlie the acquisition and consolidation of new memories in the brain in order to provide a critical background to understanding the impact of flavonoid-rich diets or pure flavonoids on memory. Data suggests that despite limited brain bioavailability, dietary supplementation with flavonoid-rich foods, such as blueberry, green tea and Ginkgo biloba lead to significant reversals of age-related deficits on spatial memory and learning. Furthermore, animal and cellular studies suggest that the mechanisms underpinning their ability to induce improvements in memory are linked to the potential of absorbed flavonoids and their metabolites to interact with and modulate critical signalling pathways, transcription factors and gene and/or protein expression which control memory and learning processes in the hippocampus; the brain structure where spatial learning occurs. Overall, current evidence suggests that human translation of these animal investigations are warranted, as are further studies, to better understand the precise cause-and-effect relationship between flavonoid intake and cognitive outputs.


RATIONALE: Flavonoid-rich foods have been shown to be able to reverse age-related cognitive deficits in memory and learning in both animals and humans. However, to date, there have been only a limited number of studies investigating the effects of flavonoid-rich foods on cognition in young/healthy animals. OBJECTIVES: The aim of this study was to investigate the effects of a blueberry-rich diet in young animals using a spatial working memory paradigm, the delayed non-match task, using an eight-arm radial maze. Furthermore, the mechanisms underlying such behavioural effects were investigated. RESULTS: We show that a 7-week supplementation with a blueberry diet (2 % w/w) improves the spatial memory performance of young rats (2 months old). Blueberry-fed animals also exhibited a faster rate of learning compared to those on the control diet. These behavioural outputs were accompanied by the activation of extracellular signal-related kinase (ERK1/2), increases in total cAMP-response element-binding protein (CREB) and elevated levels of pro- and mature brain-derived...
neurotrophic factor (BDNF) in the hippocampus. Changes in hippocampal CREB correlated well with memory performance. Further regional analysis of BDNF gene expression in the hippocampus revealed a specific increase in BDNF mRNA in the dentate gyrus and CA1 areas of hippocampi of blueberry-fed animals. CONCLUSIONS: The present study suggests that consumption of flavonoid-rich blueberries has a positive impact on spatial learning performance in young healthy animals, and these improvements are linked to the activation of ERK-CREB-BDNF pathway in the hippocampus.


This study investigates the ability of a wild blueberry (WB)-enriched diet to improve subclinical inflammatory status in the obese Zucker rat (OZR), an experimental model for the human metabolic syndrome. Twenty OZR and 20 lean controls (LZR) were fed either a control (C) or an 8% WB diet for 8 weeks. Blood levels of interleukin 6 (IL6), TNFα and adiponectin (APN) were significantly higher in OZR compared to LZR, independent of treatment. Within the OZR group, IL6 and TNFα were significantly lower in the WB group (219.3 ± 8.0 and 28.8 ± 0.8 pg/mL respectively) compared to controls (257.7 ± 7.7 and 38.7 ± 0.9 pg/mL), whereas APN levels were higher (20.7 ± 1.5 vs 17.0 ± 1.1 μg/mL). Expression of IL6, TNFα and NF-kB was significantly lower in the WB group of OZR both in the liver (–65%, –59% and –25% respectively) and the abdominal adipose tissue (–64%, –52% and –65%). Furthermore, expression of these genes was markedly increased in OZR on C diet compared to their lean controls, and this effect was almost completely reversed by the WB treatment. Liver expression of C-reactive protein significantly decreased in both groups following WB treatment (–16% in LZR and –25% in OZR). Expression of APN in the adipose tissue significantly increased following WB treatment in LZR (+25%), but not in OZR. In conclusion, results of this study suggest that WB consumption results in a markedly improved inflammatory status in the OZR.


BACKGROUND: Data from mechanistic studies support a beneficial effect of specific flavonoids on insulin sensitivity. However, few studies have evaluated the relation between intakes of different flavonoid subclasses and type 2 diabetes. OBJECTIVE: The objective was to evaluate whether dietary intakes of major flavonoid subclasses (ie, flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins) are associated with the risk of type 2 diabetes in US adults. DESIGN: We followed up a total of 70,359 women in the Nurses' Health Study (NHS; 1984-2008), 89,201 women in the NHS II (1991-2007), and 41,334 men in the Health Professionals Follow-Up Study (1986-2006) who were free of
diabetes, cardiovascular disease, and cancer at baseline. RESULTS: During 3,645,585 person-years of follow-up, we documented 12,611 incident cases of type 2 diabetes. Higher intakes of anthocyanins were significantly associated with a lower risk of type 2 diabetes (pooled HR for the 3 cohorts from a comparison of extreme quintiles: 0.85; 95% CI: 0.80, 0.91; P-trend < 0.001) after multivariate adjustment for age, BMI, and lifestyle and dietary factors. Consumption of anthocyanin-rich foods, particularly blueberries (pooled HR: 0.77 from a comparison of >/=2 servings/wk with <1 serving/mo; 95% CI: 0.68, 0.87; P-trend < 0.001) and apples/pears (pooled HR: 0.77 from a comparison of >/=5 servings/wk with <1 serving/mo; 95% CI: 0.65, 0.83; P-trend < 0.001), was also associated with a lower risk of type 2 diabetes. No significant associations were found for total flavonoid intake or other flavonoid subclasses. CONCLUSION: A higher consumption of anthocyanins and anthocyanin-rich fruit was associated with a lower risk of type 2 diabetes.


Experimental autoimmune encephalomyelitis (EAE) is an animal model of autoimmune disease that presents with pathological and clinical features similar to those of multiple sclerosis (MS) including inflammation and neurodegeneration. This study investigated whether blueberries, which possess immunomodulatory, anti-inflammatory, and neuroprotective properties, could provide protection in EAE. Dietary supplementation with 1% whole, freeze-dried blueberries reduced disease incidence by >50% in a chronic EAE model (p < 0.01). When blueberry-fed mice with EAE were compared with control-fed mice with EAE, blueberry-fed mice had significantly lower motor disability scores (p = 0.03) as well as significantly greater myelin preservation in the lumbar spinal cord (p = 0.04). In a relapsing-remitting EAE model, blueberry-supplemented mice showed improved cumulative and final motor scores compared to control diet-fed mice (p = 0.01 and 0.03, respectively). These data demonstrate that blueberry supplementation is beneficial in multiple EAE models, suggesting that blueberries, which are easily administered orally and well-tolerated, may provide benefit to MS patients.


Ovariectomy (OVX)-induced bone loss has been linked to increased bone turnover and higher bone matrix collagen degradation as the result of osteoclast activation. However, the role of degraded collagen matrix in the fate of resident bone-forming cells is unclear. In this report, we show that OVX-induced bone loss is associated with profound decreases in collagen 1 and Sirt1. This was accompanied by increases in expression and activity of the senescence marker
collagenase and expression of p16/p21 in bone. Feeding a diet supplemented with blueberries (BB) to pre-pubertal rats throughout development or only prior to puberty [postnatal day 21 (PND21) to PND34] prevents OVX-induced effects on expression of these molecules at PND68. In order to provide more evidence and gain a better understanding on the association between bone collagen matrix and resident bone cell fate, in vitro studies on the cellular senescence pathway using primary calvarial cells and three cell lines (ST2 cells, OB6, and MLO-Y4) were conducted. We found that senescence was inhibited by collagen in a dose-response manner. Treatment of cells with serum from OVX rats accelerated osteoblastic cell senescence pathways, but serum from BB-fed OVX rats had no effect. In the presence of low collagen or treatment with OVX rat serum, ST2 cells exhibited higher potential to differentiate into adipocytes. Finally, we demonstrated that bone cell senescence is associated with decreased Sirt1 expression and activated p53, p16, and p21. These results suggest that (1) a significant prevention of OVX-induced bone cell senescence from adult rats can occur after only 14 days consumption of a BB-containing diet immediately prior to puberty, and (2) the molecular mechanisms underlying this effect involves, at least in part, prevention of collagen degradation.