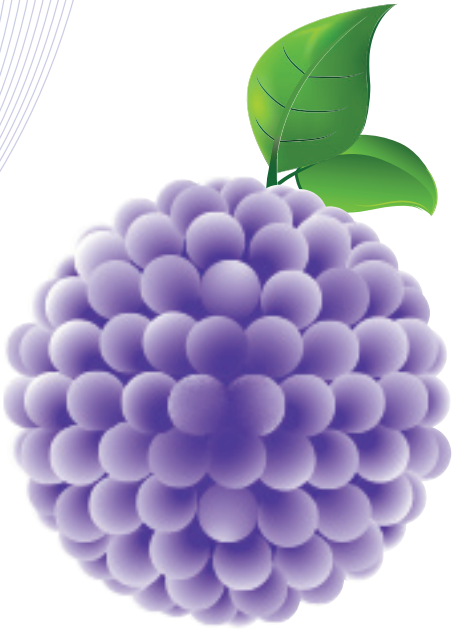

lab-berry™

Blueberry 4% Anthocyanins Extract

White Paper

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1. SUMMARY // ABSTRACT

Used as both a food and medicine among Native Americans, blueberries provide a range of bioactive principles with anthocyanins being predominant. Pharmacological activities include antioxidant, anti-inflammatory, cardioprotective, neuroprotective (cognitive enhancement), hepatoprotective, antibacterial, chemoprevention, UTI protective, and vision protective. Pre-clinical and clinical studies on blueberry have been conducted, with human clinical studies demonstrating efficacy in reducing oxidative stress and inflammation in a variety of situations, improving various parameters of cardiovascular health (reducing blood pressure, improving endothelial function, increasing nitric oxide levels), improving memory performance, reducing DNA damage, improving insulin sensitivity, and hastening the recovery of visual acuity after photobleaching. The Green Labs LLC offers Lab-Berry™ , a 100% blueberry fruit extract, standardized to 4% anthocyanins and manufactured using a proprietary process and environmentally-responsible extraction method that applies heat and pressure to water to lower its polarity, causing it to behave like an organic solvent in terms of its ability to dissolve valuable plant compounds without the numerous drawbacks associated with the use of organic solvents.

2. HISTORICAL USE

Blueberry has an extensive history of use as both a food and medicine among Native Americans.[1] Many early European settlers in the United States recorded the native peoples' use of blueberries. In 1615, Samuel de Champlain, the founder of Quebec, was the first to record that Algonquin women dried "blues" in the sun, preparing a kind of bread from pounded, sifted cornmeal, mixed with boiled, mashed beans, and then added the dried blueberries. He described the blueberries as providing "manna in winter" when other food was scarce.

Later, Henry David Thoreau wrote a manuscript entitled Wild Fruits, in which he researched and referenced more than 20 written citations on native peoples' use of blueberries, or whortleberries, as he called them. He indicated that they were a major Native American food source and that various parts of the plant were used for medicinal purposes. Other researchers reported that, among the intended applications, blueberry plant parts were used for purification of the blood, treating colic in infants, inducing labor, and as a diuretic.[2]

Until 1911, blueberries were picked from the wild or from wild bushes that were replanted elsewhere. The domestication of the blueberry as a crop started in 1908 when U.S. Department of Agriculture scientist, Frederick Coville, began studying wild blueberries and seeking out superior plants for breeding. He subsequently made the first successful crosses of several blueberry varieties still popular today for their important traits such as size and flavor. [3] [4]

3. CHEMISTRY

Research[5] [6] has demonstrated that the major bioactive principles in blueberry are anthocyanins (anthocyanidins, or phenolic aglycone, conjugated with sugar), chlorogenic acid, citric acid, arbutin, myricetin, flavonids, alpha-linolenic acid, pterostilbene, resveratrol, and vitamins. It is the anythocyanins that have been shown to provide the most significant medicinal activities associated with blueberries. Furthermore, after oral administration anthocyanins can pass through blood-brain barrier and thus appear in various organs including the brain.[7]

Surprisingly, research suggests that anthocyanins from blue- berry have low levels of absorption[8]—although pronounced health effects still occur despite low absorption.[9] This low absorption, however, can be easily mitigated. Other research has demonstrated almost three times greater absorption of anthocyanins from blueberry when consumed together with protein containing foods which appear to protect anthocyanins during transit through upper digestive tract.[10] Conversely, consumption of blueberry with milk was found to impair its in-vivo antioxidant properties and reduce the absorption of caffeic acid from blueberry.[11]

4. PHARMACOLOGICAL ACTIVITY // MECHANISM OF ACTIONS

The anthocyanins in blueberry offer a range of pharmacological activities with distinct mechanisms of action. These include the following:

Pharmacological activity	Mechanism of action
Antioxidant	Inhibition of prostaglandin E2[12]
	Decrease in oxidative stress and mitochondrial apoptosis in retinal cells[13]
	Alleviating the hyperoxia-induced redistribution of antioxidants between tissues.[14]
	High binding properties with human serum albumin[15]
	Reduction in functional central nervous system deficits[16]
	Improved red blood cell resistance to reactive oxygen species (ROS)[17]
	Improved cellular defense against DNA damage[18]
Anti-inflammatory	Inhibition of prostaglandin E2[19]
	Nutrigenomic induced reduction in gene expression of interleukin-1beta.[20]
	Increased anti-inflammatory cytokines[21]
	Microbial metabolism of blueberry phenolics in the colon[22]
Cardioprotective	Modulation of peripheral arterial dysfunction induced by acute cigarette smoking[23]
	Improvement in endothelial function[24]
	Increased nitric oxide production resulting in reduction in blood pressure and arterial stiffness[25]
	Reduction in lipid hydroperoxides[26]
	Increased flow-mediated dilation, resulting in improved vascular function[27]
	Decreased plasma oxidized LDL and serum malondialdehyde and hydroxynonenal concentrations[28]
	Reduced augmentation index*, aortic systolic pressures and diastolic pressures[29]
Neuroprotective (cognitive enhancement)	Reversed age-related deficits in several neuronal and behavioral parameters[30]
	Reversed age-induced declines in beta-adrenergic receptor function in cerebellar neurons[31]
	Reduced amyloid β-aggregation[32]
	Mitigated undesirable microglial response toward fibrillar amyloid β[33]
Hepatoprotective	Inhibited oleic acid-induced hepatic steatosis[34]
Antibacterial	Chelation of iron, resulting in antibacterial activity against the periodontopathogenic bacterium Fusobacterium nucleatum[35]
Chemoprevention	Impaired angiogenesis (vascular endothelial growth factor plays a crucial role for the vascularization of tumors)[36]
	Stimulated apoptosis of human cancer cells[37]
	Inhibiting cancer cell proliferation and act as cell antiinvasive factors[38]
	Diminished estrogen-mediated mammary tumorigenesis[39]
	Inhibited the induction of ornithine decarboxylase (ODC), the rate-limiting en-zyme in polyamine synthesis[40]
	Inhibited growth and metastatic potential of breast cancer cells[41] through mod-ulation of the phosphatidylinositol 3-kinase pathway[42]
UTI protection	Reduced E. coli adhesion to cells of urinary tract[43 44]
Vision protection	Hastened the recovery of visual acuity after photobleaching[45]
	Improved visual function by increasing rhodopsin[46]

5. PRECLINICAL RESEARCH

Oxidative stress

The aim of this study[47] was to investigate the cytoprotective role of blueberries on human retinal cells since the retina is located in a highly oxygenated environment and is therefore particularly susceptible to oxidative damage. After blueberry extract was incubated on a human retinal cell line, oxidative stress was induced with tert-butylhydroperoxide (tBHP).* Results showed that blueberry protected cells against tBHP-induced cytotoxicity, increased cell viability, decreased oxidative stress and mitochondrial apoptosis. The authors noted that blueberry seemed to be a potent antioxidant and could be easily added to food to prevent or limit ocular pathologies induced by oxidative stress.

In an in-vitro study,[48] berry extracts, characterized for their phenolic content, were prepared from bilberries and blueberries. The antioxidant activity of each extract was examined at the cellular level using the cellular antioxidant activity assay (CAA) in different cell lines. Results demonstrated that anthocyanins had intracellular antioxidant activity if applied at very low concentrations thereby providing a rationale for their health protecting effects in spite of their unfavorable pharmacokinetic proper- ties.

A combination in-vitro and in-vivo study[49] was conducted to investigate the potential antioxidant properties of blueberry polyphenolics to resistance to reactive oxygen species (ROS) in red blood cells (RBC). Results showed that incubation with anthocyanins or hydroxycinnamic acids (HCA) significantly enhanced RBC resistance to ROS production. Following oral supplementation, this protection was also observed, although only anthocyanins were found to afford protection at a significant level.

Inflammation

The effects of an anthocyanin rich blueberry fruit extract were studied[50] on the inflammatory prostaglandin E2 (PGE2) produced by endothelial cells. When stimulated by lipopolysaccharide, the production of PGE2 by endothelial cells were increased two fold. The blueberry extract, however, inhibited such action keeping the production of PGE2 at normal levels. This study indicated that anthocyanin rich fruit extract from Blueberry inhibit PGE2 produced by endothelial cells, demonstrating anti-inflammatory and antioxidant activity.

The inhibitory effect of blueberry's main on inflammatory response was investigated[51] in endothelial

** An organic peroxide widely used in a variety of oxidation processes.*

cells. Results demonstrated that the anthocyanins inhibited tumor necrosis factor-alpha (TNF-α) induced increases of monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) production. The data suggested that the anti-inflammation mechanism was mediated by the nuclear factor-kappa B (NF-κB) pathway. The researchers concluded that blueberry is good resource of anti- inflammatory anthocyanins, which can be promising molecules for the development of nutraceuticals to prevent chronic inflammation in many diseases.

Cardiovascular

To examine the efficacy of an aqueous wild blueberry extract and five blueberry polyphenol fractions on an in-vitro[52] model of heart disease, adult rat cardiomyocytes (heart muscle cells) were pretreated with extract and fractions, and then exposed to norepinephrine (NE). The results were that four of five blue- berry fractions prevented cell death and cardiomyocyte hyper- trophy. Total phenolic fractions prevented NE-induced increases in oxidative stress, nuclear condensation, calpain activity and lowering of SOD and CAT activities. Reduced contractile function was also significantly improved with blueberry fraction pretreatment. In conclusion, blueberry polyphenols prevent NE- induced cardiomyocyte hypertrophy and cell death.

Cognitive health

In a review[53] on blueberries and neuronal aging, Shukitt-Hale presents evidence that consumption of blueberries may help “forestall or even reverse age-related neuronal deficits, as well as their subsequent behavioral manifestations, in order to in- crease healthy aging.” The research presented suggests that the polyphenolic compounds found in blueberries exert their beneficial effects by lowering oxidative stress and inflammation and/or by altering the signaling involved in neuronal communication. In either case, these interventions may help protect against age-related deficits in cognitive and motor function.

In a study[54] on rats, an attempt was made to determine if using diets supplemented with blueberry extract, strawberry extract, vitamin E or spinach for six weeks would protect against exposure to oxidative stress and accelerated neuronal aging. Results indicated that these diets were effective in preventing oxidative stress-induced decrements in several parameters (e.g., nerve growth factor decreases), suggesting that although there may be increases in oxidative stress vulnerability in aging, phytochemicals present in antioxidant-rich foods may be beneficial in reducing or retarding the functional central nervous system deficits seen in aging or oxidative insult.

Subsequently, the same group of researchers conducted a follow-up study[55] which demonstrated that blueberry extract, strawberry extract or spinach fed to rats for eight weeks were also effective in reversing age-related deficits in several neuronal and behavioral parameters including motor behavioral performance. The researchers noted that these findings suggest the phytochemicals present in these antioxidant-rich foods may be beneficial in reversing the course of neuronal and behavioral aging. Likewise, Bickford et al[56] reported that diets supplemented with blueberry, strawberry or spinach reversed age-induced declines in beta-adrenergic receptor function in GABAergic neurons located in the cerebellum.

Alzheimer's Disease (AD) is the most common age-related dementia. The aggregation of amyloid-beta (Aβ) into fibrillary amyloid plaques is a key pathological event in the development of the disease, and microglial proinflammatory activation is widely known to cause neuronal and synaptic damage that correlates with cognitive impairment in AD. Researchers found that supplementation with blueberry extract in mice significantly enhanced microglial clearance of Aβ, inhibited aggregation of Aβ, and suppresses microglial activation.[57]

DNA Damage

Since metabolites of estradiol, an estrogen hormone, can cause oxidative DNA damage in rats, a study[58] was conducted in which rats were fed a standard laboratory diet or diets supplemented with 0.5% each of mixed berries (strawberry, blueberry, blackberry, and red and black raspberry), blueberry alone (BB; 2.5%), or ellagic acid (EA; 400 ppm) from 2 weeks prior to and up to 12 week of treatment with estradiol. Results showed that, compared to a control group, estradiol significantly increased markers for DNA damage. Conversely, this damage was significantly reduced by the BB diet ($P < 0.001$).and the EA diet ($P < 0.001$), while mixed berries were ineffective.

Mammary cancer/tumors

An anthocyanin extract from blueberry (extract I) and an anthocyanin-pyruvic acid adduct extract (extract II) were tested on two breast cancer cell lines (MDA-MB-231 and MCF7). In both cell lines, extracts I and II significantly reduced cell proliferation at 250 µg/mL, after 24 h of cell incubation. Both extracts demonstrated significant anti invasive potential in both cell lines. In conclusion, blueberry anthocyanins and the respective anthocyanin-pyruvic acid adducts demonstrated anticancer properties by inhibiting cancer cell proliferation and by acting as cell anti invasive factors and chemoinhibitors.[59]

To investigate efficacy of dietary berries and ellagic acid to re- duce estrogen-mediated mammary tumorigenesis, a study[60] was conducted using female rats who received implants of estradiol (resulting in mammary tumor development) and fed a standard laboratory diet or a diet supplemented with either powdered blueberry (n = 19) and black raspberry (n = 19) or ellagic acid (n = 22) at 400 ppm. Compared with the control group ellagic acid reduced the tumor volume by 75% ($P < 0.005$) and tumor multiplicity by 44% ($P < 0.05$). Black raspberry and blue- berry also reduced tumor volume significantly by > 69-40%.

This study[61] investigated the chemopreventive activity of blue- berry extract in triple-negative breast cancer cell lines in vitro and in vivo. Blueberry decreased cell proliferation in cell lines, and decreased metastatic potential. Likewise, tumor weight and proliferation were decreased in blueberry-treated mice. Immunohistochemical analysis of tumors from blueberry-fed mice showed decreased activation of AKT and p65 NFkappaB signaling proteins.

In a follow-up study,[62] the same researchers tested 2 doses of whole blueberry powder, 5 and 10% (wt:wt) in the diet, against MDA-MB-231 mammary tumor growth in female nude mice. Results showed that tumor volume was 75% lower in mice fed the 5% blueberry diet and 60% lower in mice fed the 10% blue- berry diet than in control mice ($P \leq 0.05$). Tumor cell proliferation also was lower in the 5 and 10% blueberry-fed mice compared to control mice ($P \leq 0.05$). Gene analysis of tumor tissues from the 5% BB-fed mice revealed significantly altered expression of genes important to inflammation, cancer, and metastasis. A second study tested the ability of the 5% blueberry diet to inhibit metastasis in vivo. Results showed that 5% blueberry-fed mice developed 70% fewer liver metastases ($P = 0.04$) and 25% fewer lymph node metastases ($P = 0.09$) compared to control mice.

6. CLINICAL RESEARCH

Oxidative stress

To determine whether consumption of blueberries could reduce post-meal oxidation when consumed with a typical high-carbohydrate, low-fat breakfast, a cross-over controlled study[63] was conducted in which participants (n=14) received each of the three treatments over 3 weeks:
1) high blueberry dose (75 g)
2) a low blueberry dose (35 g)
3) a control

Results showed that the mean serum ORAC (a measure of antioxidant activity) was significantly higher in the 75 g group than in the control group 2 hours following breakfast and there was a significant reduction in serum lipoprotein oxidation 3 hours following breakfast for both blueberry doses. In summary, a practically consumable quantity of blueberries (75 g) can provide statistically significant oxidative protection in vivo after a high-carbohydrate, low-fat breakfast.

Lab-Berry™ equivalency: 2.14 g

In a randomized, controlled study,[64] 20 chronic smokers consumed 250 g blueberries daily for three weeks or acute fruit ingestion of 250 g blueberries to examine the effect on various parameters, including lipid hydroperoxides (LH) as measures of oxidative stress. The results were that LH were significantly reduced ($P<0.001$) by daily blueberry consumption, but not affected by acute ingestion. The authors indicated that this finding could be one way in which fruit consumption contributes to prevention of cardiovascular disease.
Lab-Berry™ Blueberry 4 equivalency: 7.14 g

Inflammation

Since strenuous exercise acutely generates oxidative stress and an inflammatory state, a randomized, controlled study[65] was conducted to examine whether 250 g of blueberries per day for 6 weeks and 375 g given one hour prior to 2.5 hours of running at about 72% maximal oxygen consumption, counters oxidative stress, inflammation, and immune changes in 25 well- trained subjects. After randomization, subjects were assigned to blueberry (n=13) or control (n=12) groups. Results showed that that daily blueberry consumption for 6 weeks increased NK cell counts, and acute ingestion reduced oxidative stress and increases anti-inflammatory cytokines.

Lab-Berry ™ equivalency: 7.14 g

In obesity, oxidative stress and inflammation are prevalent and have been reported as being major mechanisms underlying obesity-related co-morbidities. To determine the effects of blue- berry consumption on biological antioxidant potential and inflammation markers, a study[66] was conducted on a population of 24 overweight and obese children (8–13 years). The children were divided into three groups, in which they consumed 375 g/ week of fresh blueberries, blueberry purée, or no blueberries (control). The results showed a higher increase in antioxidant levels in the group that ate

fresh berries than in the group that ate purée**, while the control group's biological antioxidant potential values decreased over the eight weeks of the study. Consumption of blueberries, hence antioxidant intake, appeared to have a positive effect on markers of inflammation and oxidative stress in overweight and obese patients during childhood.

Lab-Berry™ equivalency: 10.74 g

To determine whether specifically formulated botanical mixtures with blueberry can reduce inflammation in individuals with genetic variations that predispose to over expression of interleukin-1beta (IL-1beta, a mediator of the inflammatory response) and early heart disease, a 12-week randomized, placebo-controlled study[67] was conducted in which healthy adults with elevated C-reactive protein (CRP) were assigned to genetic groups based on being positive (IL1(Pos), n=39) or negative (IL1(Neg), n=40) for the at-risk IL-1 gene variations. Subjects were then randomized to placebo or the botanical formulation which included rose hips extract (1200 mg/d), blueberry powder (330 mg/d), blackberry powder (165 mg/d), and grapevine extract (40 mg/d).

Results showed that L-1beta gene expression by stimulated peripheral blood mononuclear cells was significantly lower than at baseline and significantly lower than placebo in IL1(Pos) and IL1(Neg) subjects using the botanical formulation, and the IL-1beta gene expression treatment effects were greater in IL1(Pos) than in IL1(Neg) subjects. In addition, significantly more IL1(Pos) subjects achieved a reduction in CRP with the botanical mixture than with placebo.

Cardiovascular health

Given that cigarette smoking causes oxidative stress, hyper- tension and endothelial dysfunction, a 3-armed randomized- controlled study[68] investigated the effect of a single serving of fresh-frozen blueberry intake on peripheral arterial function and arterial stiffness in 16 young male smokers. The experimental conditions consisted of smoking treatment (one cigarette), blueberry treatment (300 g of blueberry) + smoking, and control treatment (300 mL of water with sugar) + smoking. Each treatment was separated by one week of wash-out period. Results demonstrated that smoking impaired the blood pressure, heart rate and peripheral arterial function. Blueberry consumption counteracted the impairment of the reactive hyperemia index (a measure for endothelial function) induced by smoking ($p<0.01$), improved the Framingham reactive hyperemia index ($p<0.0001$), and reduced the increase of systolic blood pres- sure ($p < 0.05$) after cigarette smoking.

Lab-Berry™ Blueberry 4 equivalency: 8.57 g

A double-blind and placebo-controlled study[69] was conducted to assess certain cardiovascular parameters, including endothelial function, in 44

*** Researchers noted that the purée may have been susceptible to oxidation processes caused by the preparation and the time between preparation and consumption.*

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adults with metabolic syndrome. Subjects were randomized to receive a blueberry (n=23) or placebo (n=21) smoothie twice daily for six weeks. Those in the blue- berry group consumed a total of 45 g/day freeze-dried blueberry powder (providing 580.6 mg anthocyanins). Results showed that the mean change in resting endothelial function, expressed as reactive hyperemia index (RHI), was improved significantly more in the group consuming the blueberries versus the placebo group (p=0.024). Even after adjusting for confounding factors, the blueberry group still had a greater improvement in endothelial function when compared to their counterpart (p=0.0023). In conclusion, 73% of participants in the blueberry powder group experienced improvements in endothelial function, while 61% of the placebo displayed a decrease in endothelial function.

Lab-Berry™ equivalency: 14.52 g

A 8-week, randomized, double-blind, placebo-controlled clinical trial[70] was conducted to examine the effects of daily blueberry consumption for 8 weeks on blood pressure and arterial stiffness in 48 postmenopausal women with pre- and stage 1-hypertension. Participants were randomly assigned to receive either 22 g freeze-dried blueberry powder (providing about 284 mg anthocyanins)or 22 g control powder. After 8 weeks, there were significant reductions in systolic blood pressure and diastolic blood pressure (P<0.01) and brachial-ankle pulse wave velocity used to assess arterial stiffness (P<0.01) com- pared to baseline levels, whereas there were no changes in the group receiving the control powder. In addition, nitric oxide levels were greater (P<0.01) in the blueberry powder group at 8 weeks compared with baseline values, whereas there were no changes in the control group. In conclusion, daily blueberry consumption reduced blood pressure and arterial stiffness which, in part, may be due to increased nitric oxide production.

Lab-Berry™ equivalency: 7.1 g

Two randomized, controlled, double-blind, crossover human- intervention trials[71] were conducted with 21 healthy men to investigate the impact of various amounts of blueberry poly- phenol intake or a control on endothelial function in and assess potential mechanisms of action. Results demonstrated significant increases in flow-mediated dilation (FMD) at 1-2 and 6 hours after consumption of blueberry polyphenols. No significant intake-dependence was observed between 766 and 1791 mg (the total anthocyanin content of drinks ranged between 129 and 727 mg). However, at 1 hour after consumption, FMD increased dose dependently to ≤766 mg total blueberry polyphenol intake, after which FMD plateaued. Increases in FMD were closely linked to increases in circulating metabolites and by decreases in neutrophil NADPH oxidase activity at 1-2 and 6 hours. In conclusion, blueberry intake acutely improved vascular function in healthy men in a time- and intake-dependent manner. These benefits may be mechanistically linked to the actions of circulating phenolic metabolites on neutrophil NADPH oxidase activity.

Lab-Berry™ equivalency: 3.23 g

An 8-week, randomized, controlled trial[72] was conducted to ex- amine the effects of blueberry supplementation on features of metabolic syndrome and lipid peroxidation in 48, middle-aged obese men and women. The blueberry supplement consisted of a beverage with 50 g freeze-dried blueberries (equivalent to about 350 g fresh blueberries) consumed three times daily. The control beverage provided equivalent amounts of fluids. Results showed that decreases in systolic and diastolic blood pressures were greater in the blueberry-supplemented group (- 6 and -4%, respectively) than in controls (- 1.5 and - 1.2%) ($P<0.05$). The decreases in plasma oxidized LDL and serum malondialdehyde and hydroxynonenal concentrations were also greater in the blueberry group (- 28 and - 17%, respectively) than in the control group (- 9 and - 9%) ($P<0.01$). In conclusion, blueberries may improve selected features of metabolic syndrome and related cardiovascular risk factors at dietary achievable doses.

In a 6-week, randomized, placebo-controlled trial,[73] twenty-five men and postmenopausal women aged 18 to 50 years consumed whole blueberry powder (equivalent to 250 g berries daily) to investigate the effects on natural killer (NK) cells, augmentation index (a measure of wave reflection and arterial stiffness), aortic systolic pressures and other parameters. Results showed that augmentation index and aortic systolic pressures were significantly decreased in the blueberry group (treatment effect, $P=0.024$ and $P=0.046$, respectively). In addition, absolute NK cells were increased in the blueberry group (time, $P=0.001$ and interaction, $P=0.012$). Nine subjects with prehypertensive pressures (≥120/80 mm Hg, respectively) were examined as a subset and exhibited significant reductions in diastolic pressure ($P=0.038$) in the blueberry group. In conclusion, blueberry ingestion for 6 weeks increased NK cells and reduces augmentation index and aortic systolic pressures in sedentary males and females.

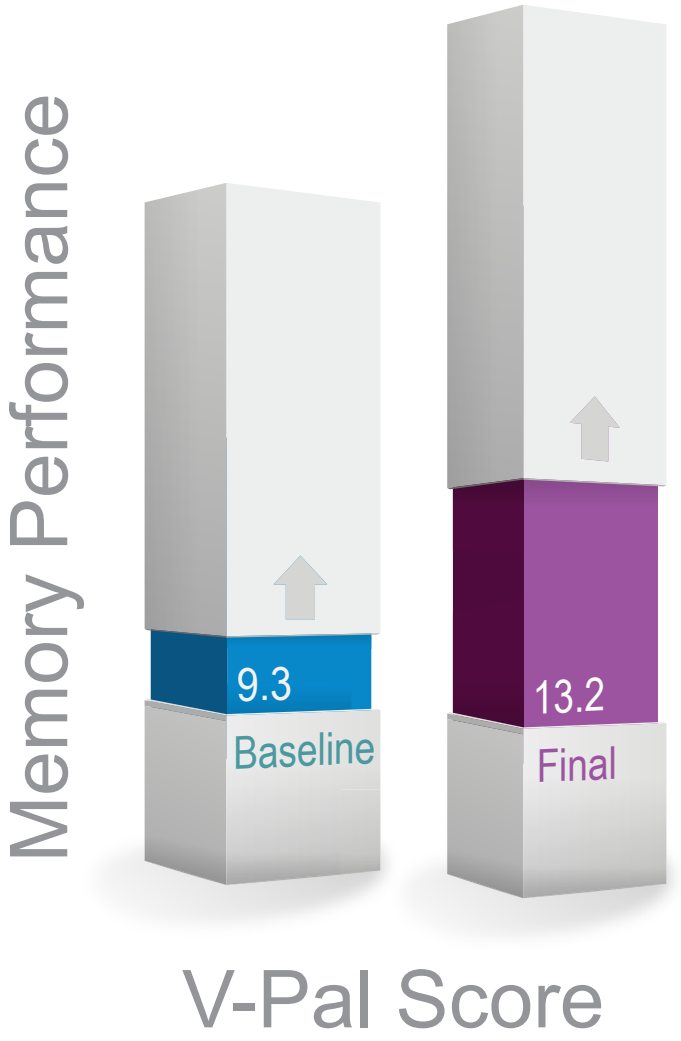
Lab-Berry™ Blueberry 4 equivalency: 7.14 g

Cognitive health

Given that blueberries contain polyphenolic compounds, prominently anthocyanins, shown to exert antioxidant and anti- inflammatory effects and help increase neuronal signaling in brain centers, mediating memory function, a 12-week study[74] was conducted to investigate the effects of daily consumption of wild blueberry juice in nine older adults with early memory changes. Individuals weighing 54 to 64 kg were prescribed 444 mL/day, those weighing between 65 and 76 kg consumed 532 mL/day, and those weighing between 77 and 91 kg consumed 621 mL/day. Results demonstrated improved paired associate learning (p = 0.009) and word list recall (p = 0.04), in addition to trends suggesting reduced depressive symptoms (p = 0.08) and lower glucose levels (p = 0.10).

Researchers compared the memory performances of the blue- berry subjects with a demographically matched sample who consumed a berry placebo beverage in a companion trial of identical design and observed comparable results for paired associate learning. In conclusion, the findings suggest that blue- berry supplementation can confer neurocognitive benefit.

Memory Performances for Blueberry Juice



Juice Consumed	Anthocyanin Content	Lab-Berry ™
444 mL / Day	99.59 mg	2.49 g
532 mL / Day	119.33 mg	2.98 g
621 mL / Day	139.29 mg	3.48 g

According to Reque et al,[75] whole blueberry juice provides 22.43mg anthocyanins per 100 mL. The following table shows the amount of anthocyanins that the subjects would have obtained based upon the amount of blueberry juice consumed, and the Lab-BerryTM Blueberry equivalency:

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DNA Damage

The free radical theory of aging maintains that age-associated disorders are a consequence of oxidative stress and reactive oxygen species that damage the structure of the genome. Like- wise, damage to DNA can accumulate as chemically "silent" errors in repair—insertions, deletions, substitutions, transpositions, and inversions in DNA sequences—that affect the expression and structure of proteins.76 Blueberries may help re- duce damage to DNA.

To investigate the effect of one portion (300 g) of blueberries on selected markers of oxidative stress and antioxidant protection (endogenous and oxidatively induced DNA damage), a randomized, controlled, cross-over study[77] was conducted in ten young volunteers. Before and after consumption (at 1, 2, and 24 hours), blood samples were collected. Results showed that blueberries significantly reduced ($P < .01$) hydrogen per- oxide-induced DNA damage (-18%) one hour after blueberry consumption compared to control. Researchers concluded that one portion of blueberries improved cell antioxidant defense against DNA damage.

Lab-Berry™ equivalency: 8.87 g

Another 6-week, placebo-controlled, cross-over study[78] in 18 male volunteers (ages 47.8 ± 9.7 years) found that 25 g freeze- dried wild blueberry powder, providing 375 mg of anthocyanins, significantly reduced the levels of endogenously oxidized DNA bases ($p \leq 0.01$) and the levels of hydrogen peroxide-induced DNA damage ($p \leq 0.01$), while no effect was found with the placebo.

Lab-Berry™ equivalency: 10.74 g

Insulin sensitivity

A 6-week, double-blinded, randomized, and placebo-controlled clinical study[79] was conducted to evaluate the effect of daily dietary supplementation with 45 g freeze-dried blueberries on whole-body insulin sensitivity in 32 obese, nondiabetic, and insulin-resistant men and women. Based on the compositional analysis, the 45 g of blueberry powder contained 1462 mg of total phenolics, 668 mg of anthocyanins. Both groups were instructed to maintain their body weight. Results showed that the average change in insulin sensitivity improved more in the blueberry group than in the placebo group ($P = 0.04$). Insulin sensitivity was enhanced in the blueberry group at the end of the study without significant changes in adiposity, energy intake, and inflammatory biomarkers. In conclusion, daily dietary supplementation with freeze-dried blueberry powder improved insulin sensitivity in obese, nondiabetic, and insulin-resistant participants.

Lab-Berry™ equivalency: 16.7 g

Vision

Two human trials[80] investigated blueberry anthocyanin effects on vision recovery after retinal

photobleaching.*** In a 3-week trial (n = 72), two anthocyanin doses (271 and 7.11 mg cyani- din 3-glucoside equivalents), and placebo were use. A 12-week trial (n = 59) tested one dose (346 mg) and placebo. In both trials anthocyanin consumption hastened the recovery of visual acuity after photobleaching. In the 3-week trial both anthocyanin doses were effective (P = 0.014), and in the 12-week trial recovery was improved at 8 weeks (P = 0.027) and 12 weeks (P = 0.030).

*** Loss of color by a pigment (such as rhodopsin) when illuminated.

Lab-Berry™ equivalency: 6.78-8.65 g

7. GOVERNMENTAL MONOGRAPHS

Health Canada's Natural Health Product monograph on blue- berry[81] indicates that its use or purpose was to provide a source of antioxidants, and acceptable pharmaceutical dosage forms included, but were not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets. Further- more, the actual blueberry material could include dry, non-standardized extracts and standardized extracts providing up to 20 g Quantity Crude Equivalent (QCE), per day and up to 150 g fresh fruit, per day. The monograph also indicated that there were no known contraindications or adverse reactions associated with the use of blueberry.

8. CONTRAINDICATIONS & PRECAUTIONS

According to Natural Medicines Comprehensive Database,[82] there are no reported adverse reactions associated with the consumption of blueberries. In addition blueberries are safe when consumed in amounts commonly found in foods.[83]

9. DRUG INTERACTIONS

Henley et al[84] conducted a study to evaluate the possibility of drug interactions involving blueberry juice (BBJ) and substrate drugs whose clearance is dependent on cytochromes P4503A (CYP3A) and P4502C9 (CYP2C9). As a result, the researchers concluded that there was "no evidence for concern about clinically important pharmacokinetic drug interactions of BBJ with substrate drugs metabolized by CYP3A or CYP2C9."

10. LAB-BERRY™ and THE GREEN LABS

At The Green Labs LLC, we are proud to offer the developed an advanced method for bioactive extraction to manufacture Lab-Berry™. The proprietary core technology used to extract Lab-Berry™ yields clean ingredients in an earth-friendly manner. Lab-Berry™ employs an environmentally-responsible extraction method that applies heat and pressure to water to lower its polarity, causing it to behave like an organic solvent in terms of its ability to dissolve valuable plant compounds without the numerous drawbacks associated with the use of organic solvents. This process redefines clean and green while delivering superior bio- actives.

Lab-Berry™ is a 100% pure plant extract—free from any carriers or trace solvents. Water soluble and standardized for the concentration of the bioactives, Lab-Berry™ meets the industry's requirements for a clean label offering. The advantages of similar herbal materials prepared using the same technology as in Lab-Berry™ includes:

- **Clean ingredients** – Follows an earth-friendly process that produces organic solvent-free ingredients in concentrated form.
- **Workplace safe** – Minimizes risk to employee health and safety by eliminating the use of hazardous organic solvents that require environmentally-intensive operations, complicated safe-handling procedures, and specialized hazardous waste management processes.
- **Less energy and waste** – Consumes less energy than traditional extraction methods. Its by-products are non-toxic and easily composted or disposed of without harm to the environment.
- **Optimal compound recovery** – Effectively isolates and extracts bioactives previously considered non-recoverable or uneconomic by conventional means.

The Green Labs®

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USA

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11. PRODUCT SPECIFICATIONS

(including amount required to support claims)

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lab-berry™

Specification Sheet

Product Name :	lab-berry ™ : Blueberry 4% Anthocyanins Extract	**Country of Origin:**	Canada
Latin name:	*Vaccinium corymbosum*	**Solvent**	Water (Low Polarity)
Lot #	Available on CofA	**Part used:**	Fruit

Item	Specifications	Test Method
Chemical Physical Analysis		
Appearance	Fine Powder	Organoleptic
Color	Dark Blue	Organoleptic
Flavor	Characteristic	Organoleptic
Odor	Characteristic	Organoleptic
Moisture	≤ 5%	AACC
Mesh Size	80 Mesh	USP
Residual Organic Solvents	None	
Heavy Metal Analysis		
Total Heavy Metals	≤ 5 ppm	ICP-MS
Lead	≤ 3 ppm	ICP-MS
Arsenic	≤ 1 ppm	ICP-MS
Cadmium	≤ 1 ppm	ICP-MS
Mercury	≤ 0.10 ppm	ICP-MS
Microbiology Analysis		
Total Plate Count	≤ 100 CFU/g	USP
Yeast & Molds	≤ 100 CFU/g	USP
E. Coli	Negative	USP
Salmonella	Negative	USP
Staphylococcus	Negative	USP
Assay		
Anthocyanins	≥ 4%	AOAC
Total Polyphenols	≥ 18%	FC / Spec

Product Packaging: Polyethylene 25 Kg bag with cardboard box/drum

Handling / Storage : Store in full sealed containers in cool dry place . Avoid sunlight and strong heat: Below 25°C and 60%RH

12. SUGGESTED STRUCTURE/FUNCTION CLAIMS

(based upon human research)

These are suggested structure/function claims. Please vet them through your own legal and regulatory counsel:

- May help reduce oxidative stress.*[63-64]
- May help reduce temporary inflammation associated with physical overexertion.* [65]
- Supports a healthy cardiovascular system.* [68-73]
- May help support healthy blood pressure levels already within normal ranges. [68, 70, 72-73]
- May help support normal endothelial function.* [69]
- May help promote the production of nitric oxide levels.*[70]
- May help support healthy memory performance.* [74]
- May help reducing DNA damage.* [76-77]
- May help support healthy insulin sensitivity.* [78]
- May support healthy visual acuity.* [79]

13. SUGGESTED LISTING WITHIN A SUPPLEMENT FACTS BOX

Supplement Facts
Serving Size: 1 capsule

	Amount Per Serving	% Daily Value
Blueberry Fruit 35: 1	500 mg	*

* Daily Value not established

Supplement Facts
Serving Size: 1 teaspoon

	Amount Per Serving	% Daily Value
Blueberry Fruit 35: 1	5 g	*

* Daily Value not established

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14. REFERENCES

1. Grubinger V. Health and History of Highbush Blueberries. University of Vermont Extension. June 1998. Retrieved September 3, 2015 from http://www.uvm.edu/vtvegandberry/factsheets/blueberrie.html.
2. Hummer KE. Manna in Winter: Indigenous Americans, Huckleberries, and Blueberries. HortScience. 2013; 48(4): 413-17.
3. Grubinger V. Health and History of Highbush Blueberries. University of Vermont Extension. June 1998. Retrieved September 3, 2015 from http://www.uvm.edu/vtvegandberry/factsheets/blueberrie.html.
4. Shukitt-Hale B. Blueberries and Neuronal Aging. Gerontology 2012;58:518–523.
5. Yang H, Jiang Y. [Research progress of bioactive constituents, absorption, metabolism, and neuroprotective effects from blueberry]. [Article in Chinese] Wei Sheng Yan Jiu. 2010 Jul;39(4):525-8.
6. Chen CF , Li YD, Xu Z. [Chemical principles and bioactivities of blueberry]. [Article in Chinese] Yao Xue Xue Bao. 2010 Apr;45(4):422-9.
7. Chen CF , Li YD, Xu Z. [Chemical principles and bioactivities of blueberry]. [Article in Chinese] Yao Xue Xue Bao. 2010 Apr;45(4):422-9.
8. Wu X, Cao G, Prior RL. Absorption and metabolism of anthocyanins in elderly women after consumption of elderberry or blueberry. J Nutr. 2002 Jul;132(7):1865-71.
9. Bornsek SM , Ziberna L, Polak T, Vanzo A, Ulrih NP, Abram V, Tramer F, Passamonti S. Bilberry and blueberry anthocyanins act as powerful intracellular antioxidants in mammalian cells. Food Chem. 2012 Oct 15;1 34(4):1878-84.
10. Ribnicky DM, Roopchand DE, Oren A, Grace M, Poulev A, Lila MA, Havenaar R, Raskin I. Effects of a high fat meal matrix and protein complexation on the bioaccessibility of blueberry anthocyanins using the TNO gastrointestinal model (TIM-1). Food Chem. 2014 January 1; 142: 349–357.
11. Serafini M, Testa MF, Villaño D, Pecorari M, van Wieren K, Azzini E, Brambilla A, Maiani G. Antioxidant activity of blueberry fruit is impaired by association with milk. Free Radic Biol Med. 2009 Mar 15;46(6):769-74.
12. Han GL , Li CM, Mazza G, Yang XG. [Effect of anthocyanin rich fruit extract on PGE2 produced by endothelial cells]. [Article in Chinese] Wei Sheng Yan Jiu. 2005 Sep;34(5):581-4.
13. Dutot M , Rambaux L, Warnet JM, Rat P. [Oxidative stress modulation using polyphenol-rich blueberries: application on a human retinal cell model]. [Article in French] J Fr Ophtalmol. 2008 Dec;31(10):975-80.
14. Cao G, Shukitt-Hale B, Bickford PC, Joseph JA, McEwen J, Prior RL. Hyperoxia-induced changes in antioxidant capacity and the effect of dietary antioxidants. J Appl Physiol (1985). 1999 Jun;86(6):1817-22.

15. Namiesnik J, Vearasilp K, Nemirovski A, Leontowicz H, Leontowicz M, Pasko P, Martinez-Ayala AL, González-Aguilar GA, Suhaj M, Gorinstein S. In vitro studies on the relationship between the antioxidant activities of some berry extracts and their binding properties to serum albumin. Appl Biochem Biotechnol. 2014 Mar;172(6):2849-65.
16. Joseph JA, Denisova N, Fisher D, Shukitt-Hale B, Bickford P, Prior R, Cao G. Membrane and receptor modifications of oxidative stress vulnerability in aging. Nutritional considerations. Ann N Y Acad Sci. 1998 Nov 20;854:268-76.
17. Youdim KA, Shukitt-Hale B, MacKinnon S, Kalt W, Joseph JA. Polyphenolics enhance red blood cell resistance to oxidative stress: in vitro and in vivo. Biochim Biophys Acta. 2000 Sep 1;1523(1):117-22.
18. Del Bó C, Riso P, Campolo J, Møller P, Loft S, Klimis-Zacas D, Brambilla A, Rizzolo A, Porrini M. A single portion of blueberry (Vaccinium corymbosum L) improves protection against DNA damage but not vascular function in healthy male volunteers. Nutr Res. 2013 Mar;33(3):220-7.
19. Han GL , Li CM, Mazza G, Yang XG. [Effect of anthocyanin rich fruit extract on PGE2 produced by endothelial cells]. [Article in Chinese] Wei Sheng Yan Jiu. 2005 Sep;34(5):581-4.
20. Kornman K , Rogus J, Roh-Schmidt H, Krempin D, Davies AJ, Grann K, Randolph RK. Interleukin-1 genotype-selective inhibition of inflammatory mediators by a botanical: a nutrigenetics proof of concept. Nutrition. 2007 Nov-Dec;23(11-12):844-52.
21. McAnulty LS, Nieman DC, Dumke CL, Shooter LA, Henson DA, Utter AC, Milne G, McAnulty SR. Effect of blueberry ingestion on natural killer cell counts, oxidative stress, and inflammation prior to and after 2.5 h of running. Appl Physiol Nutr Metab. 2011 Dec;36(6):976-84.
22. Russell WR, Labat A, Scobbie L, Duncan SH. Availability of blueberry phenolics for microbial metabolism in the colon and the potential inflammatory implications. Mol Nutr Food Res. 2007 Jun;51(6):726-31.
23. Del Bo' C , Porrini M, Fracassetti D, Campolo J, Klimis-Zacas D, Riso P. A single serving of blueberry (V. corymbosum) modulates peripheral arterial dysfunction induced by acute cigarette smoking in young volunteers: a randomized-controlled trial. Food Funct. 2014 Dec;5(12):3107-16.
24. Stull AJ, Cash KC, Champagne CM, Gupta AK, Boston R, Beyl RA, Johnson WD, Cefalu WT. Blueberries improve endothelial function, but not blood pressure, in adults with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial. Nutrients. 2015 May 27;7(6):4107-23.
25. Johnson SA, Figueroa A, Navaei N, Wong A, Kalfon R, Ormsbee LT, Feresin RG, Elam ML, Hooshmand S, Payton ME, Arjmandi BH.Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and stage 1-hypertension: a randomized, double-blind, placebo-controlled clinical trial. J Acad Nutr Diet. 2015 Mar;115(3):369-77.

26. McAnulty SR, McAnulty LS, Morrow JD, Khardouni D, Shooter L, Monk J, Gross S, Brown V. Effect of daily fruit ingestion on angiotensin converting enzyme activity, blood pressure, and oxidative stress in chronic smokers. Free Radic Res. 2005 Nov;39(11):1241-8.
27. Rodriguez-Mateos A, Rendeiro C, Bergillos-Meca T, Tabatabaee S, George TW, Heiss C, Spencer JP. Intake and time dependence of blueberry flavonoid-induced improvements in vascular function: a randomized, controlled, double-blind, crossover intervention study with mechanistic insights into biological activity. Am J Clin Nutr. 2013 Nov;98(5):1179-91.
28. Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, Aston CE, Lyons TJ. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. J Nutr. 2010 Sep;140(9):1582-7.
29. McAnulty LS, Collier SR, Landram MJ, Whittaker DS, Isaacs SE, Klemka JM, Cheek SL, Arms JC,
30. McAnulty SR. Six weeks daily ingestion of whole blueberry powder increases natural killer cell counts and reduces arterial stiffness in sedentary males and females. Nutr Res. 2014 Jul;34(7):577-84.
31. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci. 1999 Sep 15;19(18):8114-21.
32. Bickford PC , Gould T, Briederick L, Chadman K, Pollock A, Young D, Shukitt-Hale B, Joseph J. Antioxidant-rich diets improve cerebellar physiology and motor learning in aged rats. Brain Res. 2000 Jun 2;866(1-2):211-7.
33. Papandreou MA, Tsachaki M, Efthimiopoulos S, Klimis-Zacas D, Margarity M, Lamari FN.Cell-line specific protection by berry polyphenols against hydrogen peroxide challenge and lack of effect on metabolism of amyloid precursor protein. Phytother Res. 2012 Jul;26(7):956-63.
34. Zhu Y, Bickford PC, Sanberg P, Giunta B, Tan J. Blueberry Opposes β -Amyloid Peptide-Induced Microglial Activation Via Inhibition of p44/42 Mitogen-Activation Protein Kinase. Rejuvenation Res. 2008; 11(5):891-901.
35. Liu Y, Wang D, Zhang D, Lv Y, Wei Y, Wu W, Zhou F, Tang M, Mao T, Li M, Ji B. Inhibitory effect of blueberry polyphenolic compounds on oleic acid-induced hepatic steatosis in vitro. J Agric Food Chem. 2011 Nov 23;59(22):12254-63.
36. Ben Lagha A, Dudonné S, Desjardins Y, Grenier D. Wild Blueberry (Vaccinium angustifolium Ait.) Polyphenols Target Fusobacterium nucleatum and the Host Inflammatory Response: Potential Innovative Molecules for Treating Periodontal Diseases. J Agric Food Chem. 2015 Aug 12;63(31):6999-7008.

37. Roy S , Khanna S, Alessio HM, Vider J, Bagchi D, Bagchi M, Sen CK. Anti-angiogenic property of edible berries. Free Radic Res. 2002 Sep;36(9):1023-31.
38. Seeram NP, Adams LS, Zhang Y, Lee R, Sand D, Scheuller HS, Heber D.Blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts inhibit growth and stimulate apoptosis of human cancer cells in vitro. J Agric Food Chem. 2006 Dec 13;54(25):9329-39.
39. Faria A, Pestana D, Teixeira D, de Freitas V, Mateus N, Calhau C. Blueberry anthocyanins and pyruvic acid adducts: anticancer properties in breast cancer cell lines. Phytother Res. 2010 Dec;24(12):1862-9.
40. Aiyer HS, Srinivasan C, Gupta RC. Dietary berries and ellagic acid diminish estrogen-mediated mammary tumorigenesis in ACI rats. Nutr Cancer. 2008;60(2):227-34.
41. Bomser J, Madhavi DL, Singletary K, Smith MA. In vitro anticancer activity of fruit extracts from Vaccinium species. Planta Med. 1996 Jun;62(3):212-6.
42. Adams LS, Kanaya N, Phung S, Liu Z, Chen S. Whole blueberry powder modulates the growth and metastasis of MDA-MB-231 triple negative breast tumors in nude mice. J Nutr. 2011 Oct;141(10):1805-12.
43. Adams LS, Phung S, Yee N, Seeram NP, Li L, Chen S. Blueberry Phytochemicals Inhibit Growth and Metastatic Potential of MDA-MB-231 Breast Cancer Cells Through Modulation of the Phosphatidylinositol 3-Kinase Pathway. Cancer Res. 2010 May 1;70(9): 3594–3605.
44. Ofek I, Goldhar J, Zafriri D, Lis H, Adar R, Sharon N. Anti-Escherichia coli adhesion activity of cranberyy and blueberry juices. N Engl J Med. 1991;324(24):1599
45. Howell AB, Vorsa N, Marderosian AD, Foo LY. Inhibition of the Adherence of P-Fimbriated Escherichia coli to Uroepithelial-Cell Surfaces by Proanthocyanidin Extracts from Cranberries. N Engl J Med. 1998; 339(15):1085-86.
46. Kalt W, McDonald JE, Fillmore SA, Tremblay F. Blueberry effects on dark vision and recovery after photobleaching: placebo-controlled crossover studies. J Agric Food Chem. 2014 Nov 19;62(46):11180-9.
47. Chen CF, Li YD, Xu Z. [Chemical principles and bioactivities of blueberry]. [Article in Chinese] Yao Xue Xue Bao. 2010 Apr;45(4):422-9.
48. Dutot M, Rambaux L, Warnet JM, Rat P. [Oxidative stress modulation using polyphenol-rich blueberries: application on a human retinal cell model]. [Article in French] J Fr Ophtalmol. 2008 Dec;31(10):975-80.
49. Bornsek SM , Ziberna L, Polak T, Vanzo A, Ulrih NP, Abram V, Tramer F, Passamonti S. Bilberry and blueberry anthocyanins act as powerful intracellular antioxidants in mammalian cells. Food Chem. 2012 Oct 15;1 34(4):1878-84.

50. Youdim KA, Shukitt-Hale B, MacKinnon S, Kalt W, Joseph JA. Polyphenolics enhance red blood cell resistance to oxidative stress: in vitro and in vivo. Biochim Biophys Acta. 2000 Sep 1;1523(1):117-22.
51. Han GL, Li CM, Mazza G, Yang XG. [Effect of anthocyanin rich fruit extract on PGE2 produced by endothelial cells]. [Article in Chinese] Wei Sheng Yan Jiu. 2005 Sep;34(5):581-4.
52. Huang WY, Liu YM, Wang J, Wang XN, Li CY. Anti-inflammatory effect of the blueberry anthocyanins malvidin-3-glucoside and malvidin-3-galactoside in endothelial cells. Molecules. 2014 Aug 21;19(8):12827-41.
53. Louis XL, Thandapilly SJ, Kalt W, Vinqvist-Tymchuk M, Aloud BM, Raj P, Yu L, Le H, Netticadan T. Blueberry polyphenols prevent cardiomyocyte death by preventing calpain activation and oxidative stress. Food Funct. 2014 Aug;5(8):1785-94.
54. Shukitt-Hale B.Blueberries and Neuronal Aging. Gerontology 2012;58:518–523
55. Joseph JA, Denisova N, Fisher D, Shukitt-Hale B, Bickford P, Prior R, Cao G. Membrane and receptor modifications of oxidative stress vulnerability in aging. Nutritional considerations. Ann N Y Acad Sci. 1998 Nov 20;854:268-76.
56. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci. 1999 Sep 15;19(18):8114-21.
57. Bickford PC, Gould T, Briederick L, Chadman K, Pollock A, Young D, Shukitt-Hale B, Joseph J. Antioxidant-rich diets improve cerebellar physiology and motor learning in aged rats. Brain Res. 2000 Jun 2;866(1-2):211-7.
58. Zhu Y, Bickford PC, Sanberg P, Giunta B, Tan J. Blueberry opposes beta-amyloid peptide-induced microglial activation via inhibition of p44/42 mitogen-activation protein kinase. Rejuvenation Res. 2008 Oct;11(5):891-901.
59. Aiyer HS, Kichambare S, Gupta RC. Prevention of oxidative DNA damage by bioactive berry components. Nutr Cancer. 2008;60 Suppl 1:36-42.
60. Faria A, Pestana D, Teixeira D, de Freitas V, Mateus N, Calhau C. Blueberry anthocyanins and pyruvic acid adducts: anticancer properties in breast cancer cell lines. Phytother Res. 2010 Dec;24(12):1862-9.
61. Aiyer HS, Srinivasan C, Gupta RC. Dietary berries and ellagic acid diminish estrogen-mediated mammary tumorigenesis in ACI rats. Nutr Cancer. 2008;60(2):227-34.
62. Adams LS, Phung S, Yee N, Seeram NP, Li L, Chen S. Blueberry phytochemicals inhibit growth and metastatic potential of MDA-MB-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway. Cancer Res. 2010 May 1;70(9):3594-605.

63. Adams LS, Kanaya N, Phung S, Liu Z, Chen S. Whole blueberry powder modulates the growth and metastasis of MDA-MB-231 triple negative breast tumors in nude mice. J Nutr. 2011 Oct;141(10):1805-12.
64. Blacker BC, Snyder SM, Eggett DL, Parker TL.Consumption of blueberries with a high-carbohydrate, low-fat breakfast decreases postprandial serum markers of oxidation. Br J Nutr. 2013 May;109(9):1670-7.
65. McAnulty SR, McAnulty LS, Morrow JD, Khardouni D, Shooter L, Monk J, Gross S, Brown V. Effect of daily fruit ingestion on angiotensin converting enzyme activity, blood pressure, and oxidative stress in chronic smokers. Free Radic Res. 2005 Nov;39(11):1241-8.
66. McAnulty LS, Nieman DC, Dumke CL, Shooter LA, Henson DA, Utter AC, Milne G, McAnulty SR. Effect of blueberry ingestion on natural killer cell counts, oxidative stress, and inflammation prior to and after 2.5 h of running. Appl Physiol Nutr Metab. 2011 Dec;36(6):976-84.
67. Giongo L, Bozza E, Caciagli P, Valente E, Pasquazzo MT, Pedrolli C, Iorio EL, Costa A. Short-term blueberry intake enhances biological antioxidant potential and modulates inflammation markers in overweight and obese children. J Berry Res. 2011;1(3):147-158.
68. Kornman K, Rogus J, Roh-Schmidt H, Krempin D, Davies AJ, Grann K, Randolph RK. Interleukin-1 genotype-selective inhibition of inflammatory mediators by a botanical: a nutrigenetics proof of concept. Nutrition. 2007 Nov-Dec;23(11-12):844-52.
69. Del Bo' C, Porrini M, Fracassetti D, Campolo J, Klimis-Zacas D, Riso P. A single serving of blueberry (V. corymbosum) modulates peripheral arterial dysfunction induced by acute cigarette smoking in young volunteers: a randomized-controlled trial. Food Funct. 2014 Dec;5(12):3107-16.
70. Stull AJ, Cash KC, Champagne CM, Gupta AK, Boston R, Beyl RA, Johnson WD, Cefalu WT. Blueberries improve endothelial function, but not blood pressure, in adults with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial. Nutrients. 2015 May 27;7(6):4107-23.
71. Johnson SA, Figueroa A, Navaei N, Wong A, Kalfon R, Ormsbee LT, Feresin RG, Elam ML, Hooshmand S, Payton ME, Arjmandi BH. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and stage 1-hypertension: a randomized, double-blind, placebo-controlled clinical trial. J Acad Nutr Diet. 2015 Mar;115(3):369-77.
72. Rodriguez-Mateos A , Rendeiro C, Bergillos-Meca T, Tabatabaee S, George TW, Heiss C, Spencer JP. Intake and time dependence of blueberry lavonoid-induced improvements in vascular function: a randomized, controlled, double-blind, crossover intervention study with mechanistic insights into biological activity. Am J Clin Nutr. 2013 Nov;98(5):1179-91.
73. Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, Aston CE, Lyons TJ. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. J Nutr. 2010 Sep;140(9):1582-7.

74. McAnulty LS, Collier SR, Landram MJ, Whittaker DS, Isaacs SE, Klemka JM, Cheek SL, Arms JC, McAnulty SR. Six weeks daily ingestion of whole blueberry powder increases natural killer cell counts and reduces arterial stiffness in sedentary males and females. Nutr Res. 2014 Jul;34(7):577-84.
75. Krikorian R, Shidler MD, Nash TA, Kalt W, Vinqvist-Tymchuk MR, Shukitt-Hale B, Joseph JA. Blueberry supplementation improves memory in older adults. J Agric Food Chem. 2010 Apr 14;58(7):3996-4000.
76. Reque PM, Steffens RS, Jablonski A, Flores SH, Rios AdO, de Jong EV. Cold storage of blueberry (Vaccinium spp.) fruits and juice: Anthocyanin stability and antioxidant activity.
77. J Food Comp Anal. 2014;33:111–116.
78. Baynes JW. The Maillard Hypothesis on Aging: Time to Focus on DNA. Ann NY Acad Sci. 2002;959:360-367.
79. Del Bó C, Riso P, Campolo J, Møller P, Loft S, Klimis-Zacas D, Brambilla A, Rizzolo A, Porrini M. A single portion of blueberry (Vaccinium corymbosum L) improves protection against DNA damage but not vascular function in healthy male volunteers. Nutr Res. 2013 Mar;33(3):220-7.
80. Riso P, Klimis-Zacas D, Del Bo' C, Martini D, Campolo J, Vendrame S, Møller P, Loft S, De Maria R, Porrini M. Effect of a wild blueberry (Vaccinium angustifolium) drink intervention on markers of oxidative stress, inflammation and endothelial function in humans with cardiovascular risk factors. Eur J Nutr. 2013 Apr;52(3):949-61.
81. Stull AJ, Cash KC, Johnson WD, Champagne CM, Cefalu WT. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. J Nutr. 2010 Oct;140(10):1764-8.
82. Kalt W, McDonald JE, Fillmore SA, Tremblay F. Blueberry effects on dark vision and recovery after photobleaching: placebo-controlled crossover studies. J Agric Food Chem. 2014 Nov 19;62(46):11180-9.
83. Blueberry monograph. Heath Canada. Natural Health Products Ingredients Database. Date Modified: 2015-06-23. Retrieved September 4, 2015 from http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=blueberry.bleuet&lang=eng
84. Blueberry monograph. Natural Medicines Comprehensive Database. Last reviewed on 03/10/2014 and last updated on 02/14/2015.
85. Wang SY, Lin HS. Antioxidant activity in fruits and leaves of blackberry, raspberry, and strawberry varies with cultivar and developmental stage. J Agric Food Chem 2000;48:140-6.
86. Hanley MJ, Masse G, Harmatz JS, Cancalon PF, Dolnikowski GG, Court MH, Greenblatt DJ. Effect of blueberry juice on clearance of buspironeand flurbiprofen in human volunteers. Br J Clin Pharmacol. 2013 Apr;75(4):1041-52.

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