

## **Blueberries and Metabolic Syndrome**

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### **Abstract**

Metabolic syndrome is a cluster of metabolic disorders that increase the risk of cardiovascular diseases, which includes type 2 diabetes, elevated blood pressure, and atherogenic dyslipidemia. Studies have shown that oxidative stress plays an important role in the etiology of cardiovascular diseases, as well as diabetes and its complications. Antioxidants provide protection from these chronic diseases. Antioxidants can be obtained from fruits, and blueberries have the highest antioxidant activity compared to other fruits. The health benefits of blueberries have been widely explored. The effects of blueberries on metabolic syndrome are reviewed.

**Key Words:** Blueberries; Metabolic syndrome; Antioxidants; Diabetes; Hypertension; Hyperlipidemia

### **Introduction**

Metabolic syndrome is a cluster of metabolic disorders that is associated with an increased risk of cardiovascular events (Daskalopoulou et al., 2006). Type 2 diabetes, hypertension and dyslipidemia are among the metabolic disorders included in the syndrome. In 2007, 76 million Americans were diagnosed with metabolic syndrome (American Heart Association, 2009). Because metabolic syndrome is tightly correlated with obesity, this number is more likely to increase due to the growing number of obese persons that is escalating to epidemic levels, which the Western society faces today. The U.S. National Cholesterol Education Program Adult Treatment Panel III has set diagnostic criteria for metabolic syndrome, defined as an individual having at least three of the five clinical parameters listed in Chart 1.

**Chart 1:** Parameters for the detection of the metabolic syndrome

- (Waist circumference  $\geq$  40 inches for men or 35 inches for women)
- (Triglycerides  $\geq$  150mg/dL)
- (HDL cholesterol  $\leq$  40mg/dL for men or  $\leq$  50mg/dL for women)
- (Blood pressure  $\geq$  130/85 mm Hg)
- (Fasting glucose  $\geq$  110 mg/dL)

In spite of efforts from academia and private companies, there is no magic pill that could collectively treat all the disorders encompassed under metabolic syndrome. Currently, the disorders are treated individually and the approaches are limited to drugs used for the treatment of obesity and type 2

diabetes (Flordellis et al., 2005). This approach has several disadvantages including non-specificity and cost. In one study, the effect of sibutramine, a weight loss drug, on some of the symptoms associated with the metabolic syndrome was evaluated (James et al., 2000). Sibutramine decreased the triglyceride and VLDL-cholesterol levels, and increased the HDL-cholesterol levels. These effects contributed positively in the treatment of lipid imbalance in patients with metabolic syndrome. However, sibutramine does not treat other cardiovascular risks such as hypertension. Hypertension, a condition defined as having blood pressure of 140/90 mm Hg or higher, is a major risk factor for stroke and myocardial infarction. Coronary heart disease and stroke make up the largest percentage of cardiovascular diseases and are leading causes of death in the US (Lloyd-Jones et al., 2009).

High costs of medications combined with complex diseases inadequately treated leave a place for the use of alternative therapies such as nutraceuticals and functional foods. Numerous epidemiological studies (e.g., Agudo et al., 2007; Benetou et al., 2008; Ellingsen et al., 2008) have provided results that emphasize the importance of fruits and vegetables as being part of the daily diet for better health, and for the prevention of degenerative diseases including cancer and neurological disorders (Ames et al., 1993). Most of the phytonutrients found in fruits and vegetables are antioxidants. Therefore, the protective effects of fruit- and vegetable-rich diets could be attributed to the antioxidant compounds. A large clinical study conducted for 7.5 years that included 5220 adults provided results in support of recommendations to consume antioxidant-rich foods to reduce the risk of metabolic syndrome (Czernichow et al., 2009). This study also found that antioxidant supplements were effective in reducing the risk of metabolic syndrome. Apart from their positive effects on metabolic disorders, dietary antioxidants also provide other health benefits such as prevention of

cancer (Ohigashi and Murakami, 2004; Khan et al., 2008). Antioxidants inhibit the initiation or propagation of oxidizing chain reactions that cause oxidative damage to lipids, proteins and nucleic acids (Yu, 1994). In addition to the well known antioxidants vitamins C and E, the flavonoids, which are ubiquitous in fruits and vegetables, have also been demonstrated to be effective antioxidants and to modulate various biological pathways (Benavente-Garcia et al., 2008; Soory, 2009). These polyphenols reduce oxidative stress by directly scavenging free radical species, chelating transition metals, quenching singlet oxygen, or inhibiting oxidative enzymes (Cos et al., 2000).

Among twenty-four fruits investigated, blueberries were found to have the highest total antioxidant capacity (TAC) in an oxygen radical absorbance capacity assay (13427 TAC/serving; Wu et al., 2004). In a cell-based assay, wild blueberries also showed the highest cellular antioxidant activity (Wolfe et al., 2008). Wild blueberries (*Vaccinium angustifolium*) are originally from North America and Canada. Maine is the largest producer in the world with blueberries being cultivated on over 60,000 acres (Yarborough, 2009). There are over 400 species of blueberries. Highbush blueberry, *Vaccinium corymbosum*, is the most commercialized species growing on over 100,000 acres in the US and Canada (Nesom, 2001). Highbush blueberry is cultivated predominantly in the northern states while in the southern states rabbiteye blueberry (*Vaccinium ashei*) is the species mostly produced. In Europe, bilberry (*Vaccinium myrtillus*) is the most common species.

In view of their strong antioxidant activity and in relation to recent reports that antioxidant-rich foods reduce the risk of metabolic syndrome, various studies on blueberries that could have applications for the treatment of the disorders encompassing metabolic syndrome are reviewed here.

## Blueberries and Type 2 Diabetes

The incidence of type 2 diabetes has reached epidemic levels in developed countries. It is estimated that by 2025, 380 million people will have diabetes (International Diabetes Federation, 2009). Among the disorders included in metabolic syndrome, diabetes is what concerns doctors the most. Some clinicians considered it a cardiovascular disease. Research has shown that patients with type 2 diabetes, but had no prior history of myocardial infarction, have similar risk of having a cardiac event as patients without type 2 diabetes but who are known to have an underlying coronary disease (Haffner, 1998). Insulin resistance plays an important role in the development of diabetes. Thus, therapeutic regimen includes insulin sensitizers such as thiazolidinediones and metformin, and insulin secretors such as sulfonylureas. Metformin, a widely prescribed drug for diabetes, is derived from the natural compound guanidine isolated from *Galega officinalis* (Bailey and Day, 2004). Metformin exemplifies the value of nature as a source of drugs for the treatment of diseases, and in this case, diabetes.

Blueberries have been used as traditional anti-diabetic medicine for many years (Jellin et al., 2005). In Canada, blueberry extracts are commercially available and used as a complementary treatment for diabetes (Martineau et al., 2006). Early indication of the use of blueberry leaf extract for the treatment of diabetes could be derived from a clinical study of Watson (1928), although it was concluded from this study that the extract exerted beneficial effects only in certain cases of diabetes, and had limited application in the treatment of diabetes. More recently, Martineau et al. (2006) performed an extensive study and explored the anti-diabetic potential of lowbush blueberry. In this work, the ethanolic extracts of the root, stem, leaf, and fruit were tested for anti-diabetic activity using various cell-based assays. This group found: 1) blueberry extracts had insulin like activity. Overnight incubation of C2C12 muscle cells with 12.5  $\mu$ L of root,

stem and leaf extracts increased glucose transport by 15-25%. In 3T3-L1 adipocyte cells, an increase of 75% was observed; 2) proliferation of  $\beta$ -cells was observed with the fruit extract only, which gave a 2.8 fold increase in  $^3$ H-thymidine incorporation by  $\beta$  TC-tet cells; 3) leaf extract showed a glitazone-like activity. Incubation of leaf extracts resulted in an increase in lipid accumulation in 3T3-L1 cells by 6.5 fold, similar to that of rosiglitazone (6.8 fold increase); 4) stem, leaf and fruit extracts conferred protection against glucose toxicity. The extract decreased apoptosis by 20-33% in PC12-AC cells.

In a 4-week clinical study, Abidov et al., (2006) investigated the effect of Blueberin, a phytomedicine containing 250 mg of leaf extracts of a blueberry-related species (*Vaccinium arctostaphylos* L.; synonym, Caucasian whortleberry), on fasting plasma glucose, levels of the enzymes alanine aminotransferases (ALT), aspartate aminotransferases (AST), glutamyltransferase (GGT), as well as serum levels of inflammatory C-Reactive proteins (CRP), in forty-two volunteer subjects diagnosed with Type 2 diabetes. Blueberin-treated group showed a reduction of fasting glucose, which correlated with reduction of serum CRP. The Blueberin group also had a significantly reduced plasma levels of ALT, AST and GGT, indicating that in addition to anti-diabetic effects, Blueberin also has anti-inflammatory properties. In another clinical trial (Nemes-Nagy et al., 2008) thirty type 1 diabetic children were treated with a dietary supplement containing blueberry and sea buckthorn concentrate for two months, and the effects on glycated hemoglobin, C peptide and two antioxidant enzymes (superoxide dismutase and glutathione peroxidase) were evaluated. Results obtained indicated that this dietary supplement had a beneficial effect in the treatment of type 1 diabetic children.

*Serratia vaccinii*, a new strain of bacteria isolated from blueberry fruits, when used in the fermentation of blueberry juice, resulted in an increase

in the phenolic content and antioxidant activity of the juice (Martin and Matar, 2005). In an *in vivo* study, biotransformed blueberry juice incorporated in the drinking water of KKA<sup>y</sup> mice (phenotypically obese with development of hyperleptinemia, insulin resistance, hyperinsulinemia, diabetes, dyslipidemia, and hypertension) protected the young mice from developing glucose intolerance and diabetes (Vuong et al., 2009). The biotransformed blueberry juice also caused a significant reduction in mice body weight gains. These results suggested the juice had antidiabetic and strong antiobesity potential. In one other study, blueberry powder incorporated in the high-fat diet of male C57BL/6J mice protected against inflammation of adipose tissue (DeFuria et al., 2009). Adipose tissue inflammation promotes insulin resistance and other obesity complications. Inflammatory genes (tumor necrosis factor- $\alpha$ , interleukin-6, monocyte chemoattractant protein 1, inducible nitric oxide synthase) were upregulated in the adipose tissues of mice fed with high-fat diet, while in mice fed diet fortified with blueberry powder gene upregulation was attenuated or nonexistent. Together with other results obtained on adipocyte physiology, the data from this study suggested dietary blueberry could provide metabolic benefits to combat obesity-associated pathology.

### **Blueberries and Hypertension**

According to the American Heart Association (2009), majority of people that suffered a heart attack, stroke, and congestive heart failure had blood pressure higher than 140/90mm Hg. One in three American adults has high blood pressure. Because hypertension can be asymptomatic, one third of those affected remain undiagnosed. Thus, the disease has been dubbed as the “silent killer.” Most of the cases are of essential (no medical cause) hypertension, the etiology of which is not known. However there are evidences that oxidative stress plays a role in human hypertension (Gao et al., 2001; Manning et al., 2003; Touyz et al., 2004).

The blood pressure lowering activity of polyphenols in spontaneously hypertensive stroke-prone rats (SHRSP) has been demonstrated (Negishi et al., 2004). Based on the known strong antioxidant properties of blueberries, presumably due to the phenolic compounds, Shaughnessy et al. (2009) evaluated the potential hypotensive effect of blueberries by feeding the fruits to SHRSP rats, and showed that the blueberry fed group had blood pressure 18% lower than the normal diet fed group. The highest systolic blood pressure reached by SHRSP rats fed with normal diet was  $216 \pm 11$  mm Hg while for the group fed with blueberry was  $178 \pm 15$  mm Hg.

In another work, blueberry leaves showed strong inhibition of angiotensin converting enzyme *in vitro* (Sakaida et al., 2007). When leaves were fed to spontaneously hypertensive rat the increase of blood pressure during the onset of essential hypertension was lower compared to the normal diet fed group.

### **Blueberry and Hyperlipidemia**

The correlation between cholesterol levels and risk of coronary heart diseases has been previously established. Hyperlipidemia is the major cause of atherosclerosis, which is one of the leading causes of cardiac deaths worldwide. Atherosclerosis is the accumulation of fat in the blood vessels resulting in narrowing of the lumen of artery. Free hydroxy radicals are the major cause of oxidative damage to low density lipoproteins (LDL) which are responsible for the development of atherosclerosis in hyperlipidemic patients (Parthasarathy, 1992).

Cignarella et al. (1996) reported the lipid lowering activity of blueberries for the first time. Blueberry leaf extracts administered orally to streptozotocin-diabetic rats decreased plasma triglycerides levels by 39%. The results were confirmed using different models of hyperlipidemia. Extracts of blueberry leaves also showed lipid lowering activity in Yoshida rats, a genetic model of hypertriglyceridemia. Supplementation of pig basal

diets (containing 70% of soya, oats and barley) with blueberries reduced blood lipid levels. At 2% of blueberries, total cholesterol was lowered by 11.7%, LDL by 15.1% and HDL by 8.3% (Kalt et al., 2008). The lipid lowering effect of blueberries was attenuated when plant based components was decreased from 70 to 20%, indicating that blueberry and dietary components might be interacting synergistically to lipid lowering effect. The hypolipidemic activity of blueberries was also demonstrated in another study using bile acids binding assay (Kahlon and Smith, 2006). The effect of blueberries on the lipid metabolism of OLETF (Otsuka Long-Evans Tokushima Fatty) rats, an animal model of type 2 diabetes with obesity, has also been investigated. Serum cholesterol and phospholipids levels were decreased, in a dose-dependent manner, in OLETF rats fed freeze-dried blueberry leaves. The hepatic levels of cholesterol and phospholipids were also lowered, but not significantly (Nagao et al., 2008). Biological assays analyzing the effects on the activity of enzymes involved in lipid metabolism suggested that the hypolipidemic activity of the leaves might be due to the inhibition of fatty acid synthase, a key enzyme in fatty acid synthesis, and to the activation of carnitine palmitoyl-transferase, an important enzyme involved in fatty acid beta-oxidation (Nagao et al., 2008). In a study using male Wistar rats the effects of daily intake of blueberries with those of spontaneous exercise were compared (Hamazu et al., 2005). Serum HDL-cholesterol level in rats fed with diet supplemented with blueberry paste every day was higher than those of the control rats, in one part of the study. Another part of the study rats were maintained in high-fat diet. The calcium/elastin level (an index of arterial calcification) was found to be lowest in rats that were supplied with blueberries daily. Blueberries and spontaneous exercise decreased the risk of arteriosclerosis differently.

Dietary supplementation with blueberries has also been shown to protect from ischemic brain damage (Wang et al., 2005). Adult male Sprague-Dawley rats

were fed with blueberry- (together with a group fed spinach-, and another group fed spirulina-) enriched diets for four weeks. Animals on blueberry (or spinach or spirulina) diets had a significant reduction in the volume of infarction in the cerebral cortex, and an increase in post-stroke locomotor activity compared to the control animals. Another study has also shown that blueberries protected the brain against damage from ischemia (Sweeney et al., 2002). Rats were fed a diet fortified with 14.3% lowbush blueberries, and stroke was simulated by ligation of the left common carotid artery (ischemia), followed by hypoxia. In rats on blueberry-supplemented diet, hypoxia-ischemia resulted in only  $17 \pm 2\%$  loss (while control rats lost  $40 \pm 2\%$ ) of neurons in the hippocampus of the left cerebral hemisphere, as compared to the right hemisphere. Neuroprotection was observed in the CA1 and CA2 regions, but not CA3 region, of the hippocampus. Results from this study suggested that ischemic stroke outcomes could be improved by inclusion of blueberries in the diet.

### **Blueberry Constituents and Metabolic Syndrome Disorders**

As earlier alluded to, the polyphenol content may be related to the lipid lowering activity of blueberries. Previous works have demonstrated *in vitro* and *in vivo* that polyphenols inhibited FAS activity (Li et al., 2002; Ikeda et al., 2005) and increased fatty acid beta-oxidation (Murase et al., 2002; 2005). Blueberries contain higher levels of polyphenols than most fruits and vegetables (Prior et al., 1998), which also provide strong antioxidant property of these fruits (Wang, 2000; Neto, 2007). The “phenolics” that are mostly referred to in much of the studies on blueberries are the anthocyanins. However, phenolic stilbene compounds, such as resveratrol and pterostilbene, have also been identified in blueberries (Rimando et al., 2004; Rimando and Barney, 2005). Resveratrol has long been associated with the “French Paradox,” and has been shown in various tests to protect the cardiovascular system by multidimensional

way (reviewed by Das and Das, 2007). Pterostilbene has likewise been shown to lower VLDL- and LDL-cholesterol, while increasing HDL-cholesterol, in hamsters fed high-fat diet fortified with pterostilbene (at a dose of 2.5 mg/kg body weight). Additionally, pterostilbene also lowered serum glucose levels. These activities were correlated with activation of the nuclear transcription factor PPAR $\alpha$  (Rimando et al., 2005).

The antidiabetic effect of anthocyanins in blueberries was evaluated *in vivo* using diabetic C57bl/6J mice (Grace et al., 2009). Phenolic rich and anthocyanin enriched fractions were administered, using a microemulsifying drug delivery system (Labrasol), at 500mg/Kg body weight. The phenolic fraction decreased blood glucose levels by 33% while the anthocyanin fraction exhibited better hypoglycemic activity (51% decrease in blood glucose levels), which suggested that the hypoglycemic activity was due to the anthocyanins. It must be noted that hypoglycemic activity was not significant when administered without Labrasol. Pure delphinidin-3-*O*-glucoside and pure malvidin-3-*O*-glucoside, at 300 mg/Kg body weight, both formulated with Labrasol, were then investigated. Malvidin-3-*O*-glucoside, but not delphinidin-3-*O*-glucoside, was found to be significantly hypoglycemic (Grace et al., 2009). Purified anthocyanins from blueberries incorporated in the drinking water were also shown to reduce obesity in C57BL/6J mice in an 8-week study (Prior et al., 2008). Interestingly, it was also found that the mice fed high-fat (45% calorie) diet (HF45) mixed with extracts from blueberries, body weight gains, body fat (percent of BW), and epididymal fat weights were significantly greater than those in the HF45-fed controls.

Besides phenolic compounds, blueberries also contain fibers (Avila da Silveira, 2007; Jeong et al., 2008). Research has shown that binding of dietary fibers to bile acids increased their fecal elimination, which was considered a possible mechanism by which fibers decreased cholesterol levels (Lund, 1989; Anderson and Siesel, 1990). Based on equal dry

matter, the bile acid binding of blueberries was higher than all the fruits tested. Considering equal total polysaccharides blueberry and plums presented the best binding (Kahlon and Smith, 2006).

### Summary

Several studies have shown that oxidative stress plays an important role in the etiology of cardiovascular diseases, as well as diabetes and its complications. Antioxidants provide protection from these disorders. Antioxidants can be obtained from fruits, and blueberries have been shown in studies to have the highest antioxidant activity compared to other fruits. We have reviewed the effects of blueberries on metabolic syndrome disorders such as diabetes, hypertension and hyperlipidemia. It is noteworthy that due to its high antioxidant property blueberries are also neuroprotective, and have been shown to prevent and reverse loss of cognitive performance in aged rats (Joseph et al., 1999, 2003, 2005).

In 2008, the North America estimated highbush blueberries production was over 400 million pounds (Villata, 2009). The production of blueberries has increased worldwide (mainly in South America, Europe, and China) due to increase in demand of the fruit, which was attributed to the various research works that provided evidence on the health benefits of blueberries. Gradually blueberries are being introduced to the diets of people in Asian countries such as India and Japan. Japan is one of the biggest consumers of the US exported blueberries. In 2008, 6.4 million pounds of blueberries were shipped to the country (Villata, 2009).

Current statistics show that diseases of the heart and cerebrovascular diseases are the top and third, respectively, top ten leading causes of deaths in the US, with *Diabetes mellitus* ranking sixth. A recent study projected that diabetes population was expected to rise from 8.2 to 14.6 million in 2034, and the associated spending was estimated to rise from \$45 to \$171 billion (Huang et al., 2009). It is at least comforting to know that disorders of the metabolic

syndrome could be combated by inclusion of fruits and vegetables in the diet. Blueberries have a great potential to be used as a complementary therapy to fight these chronic diseases.

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