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# Cherries and Health: A Review

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# Cherries and Health: A Review

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*Cherries, and in particular sweet cherries, are a nutritionally dense food rich in anthocyanins, quercetin, hydroxycinnamates, potassium, fiber, vitamin C, carotenoids, and melatonin. UV concentration, degree of ripeness, postharvest storage conditions, and processing, each can significantly alter the amounts of nutrients and bioactive components. These constituent nutrients and bioactive food components support the potential preventive health benefits of cherry intake in relation to cancer, cardiovascular disease, diabetes, inflammatory diseases, and Alzheimer's disease. Mechanistically, cherries exhibit relatively high antioxidant activity, low glycemic response, COX 1 and 2 enzyme inhibition, and other anti-carcinogenic effects in vitro and in animal experiments. Well-designed cherry feeding studies are needed to further substantiate any health benefits in humans.*

**Keywords** Sweet cherries, anthocyanin, antioxidant, cancer, diabetes, harvest

## INTRODUCTION

Cherry is a fruit belonging to the genus *Prunus* in the Rosaceae family, which contains over several hundred species distributed across northern temperate regions. The sweet cherry (*P. avium*) is native to Europe and western Asia with the most common cultivars grown in the U.S. being Bing, which produces large black firm fruits, while the tart cherry (*P. cerasus*) is produced from the Montmorency cultivar. The cherry fruit is considered a nutrient dense food with a relatively low caloric content and a significant amount of important nutrients and bioactive food components (BAFC). These range from vitamin C and fiber to select health-promoting BAFC including anthocyanins, quercetin, and carotenoids. Research has demonstrated several relevant biological activities that are enhanced or inhibited by constitutive components of sweet cherries suggesting that this fruit holds potential for the prevention of cancer, cardiovascular disease, diabetes, and other inflammatory diseases. These include reductions in oxidant stress, inflammation and/or tumor suppression, glucose control, and inhibition of uric acid production. This review provides information on the nutrients and BAFC in cherries and their potential role in disease risk reduction.

## PRODUCTION AND CONSUMPTION

Although the U.S. has historically been the largest exporter in the world cherry market, currently the world production of cherries is the highest in Turkey, followed by the U.S. and Iran (FAO, 2006). Annually more than 50,000 tons of sweet cherries and 10,000 tons of tart cherries are exported from the U.S. The total production area for all cherries produced in the U.S. is reportedly 31,677 ha (producing 253,286 tons in 2005), in which the production area for sweet cherry increased almost linearly over 10 years, while that of tart cherry decreased (USDA Census, 2002). The State of Washington records the highest production of sweet cherries in the U.S. (150,000 ton; USDA NASS, 2006).

The majority of sweet cherry production is for fresh consumption with the remaining 40% processed as brined, canned, frozen, dried or juiced. In contrast 97% of tart cherries are processed primarily for use in cooking and baking. Limited data are available to estimate sweet cherry intake in the U.S., although it is clear that the majority of sweet cherry consumption is fresh and that there are significant seasonal differences in intake.

### Factors Affecting the Nutrient Content or Bioavailability of Bioactive Food Components

#### Ripening and Environment

The anthocyanin content of cherries, a major form of antioxidants in cherries, increases exponentially as the fruit ripens.

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Serrano et al. (2005) reported changes in concentrations and activities of antioxidants of sweet cherry at 14 different stages of ripeness with total anthocyanins increasing exponentially from stage 8 to the maximum value at stage 14 (63.26 mg cyanidin equivalent activity per 100 g fresh sample). The total antioxidant activity (TAA) decreased from stage 1 to stage 8, and increased again from stage 8 to stage 14, coinciding with the total phenolic compound concentration and the accumulation of anthocyanins. TAA reached the maximum activity at stage 14 with average ascorbic acid equivalent activity of 50.03 mg per 100 g fresh sample. Thus, harvesting sweet cherries at stage 12 of ripening, when fruit reaches maximum size would support the development of the highest organoleptic, nutritional, and functional quality attributes.

Effects of the harvest year and the harvest time on anthocyanin concentrations also have been reported (Poll et al., 2003). Large differences in the concentration of soluble solids, acid, as well as anthocyanins have been demonstrated across repeat samples of "Stevnsbær" tart cherries harvested 7–10 times per year over a 3–year period. The highest levels of nutrients and bioactive food components were found in the year characterized by the highest temperature and greatest solar radiation exposure. The cyanidin-3-glucosid equivalent anthocyanin concentrations in the harvested cherry juice varied from as low as 500 mg/L to as high as 2300 mg/L. In fact, ultra violet light (UV-light) has reportedly increased anthocyanin concentrations of grapes (Kubota and Tsuchiya, 2001), apples (Arakawa et al., 1985), and sweet cherries (Arakawa, 1993). In cherries, a more significant increase of anthocyanin concentration was observed for postharvest cherries irradiated with UV-B (280–320 nm) than those with UV-A (320–400 nm) (Arakawa, 1993). Under a UV fluorescent lamp (1.3 W m$^{-2}$ irradiance), "Sato Nishiki" sweet cherries accumulated twice as much anthocyanin as those under a white fluorescent light (4.0 W m$^{-2}$) after 72 hours of irradiation. These data suggest that a small amount of UV light in the environment during cherry ripening has a significant effect on the resulting accumulation of anthocyanins.

### Processing

Bioactive compounds of fresh fruits and vegetables change according to pre-harvest conditions (including cultivation procedures, harvesting timings, and climate conditions), and postharvest conditions (including storage conditions and shipping conditions). Sweet cherries contain approximately 1500 mg total phenols per kg fresh weight, with the phenols comprised mainly of hydroxycinnamates, anthocyanins, flavin-3-ols (catechins), and flavonols (Gao and Mazza, 1995; Goncalves et al., 2004). Cherries are often stored at 2–5°C for several weeks during postharvest before reaching the consumers. Effects of storage temperature and duration on sweet cherry bioactive compounds (phenolics) were reported by Goncalves et al. (2004) demonstrating that the levels of phenolics and anthocyanins varied among cultivars and across storage conditions. Storage at 15°C increased the concentration of cynanidin-3-rutinoside (antho-

cyanin), while 2°C caused changes specific to cultivars. Extracts of fresh harvested cherries exhibited significantly higher antioxidant activities than the stored samples.

Comparisons in anthocyanins and polyphenolic compositions of fresh and processed cherries also have been reported (Chavanalikit and Wrolstad 2004). More than 75% of anthocyanins in frozen Bing cherries were lost after 6 months of storage at −23°C. Storage at −70°C caused less degradation in anthocyanins and total phenolics. Oxygen Radical Absorbance Capacity (ORAC) and Fluorescence Recovery After Photobleaching (FRAP) assays indicated a decrease in antioxidant activity after 3 or 6 months of storage at −23°C, but an increase after storage at −70°C. In studies of canned fruit, about half of the anthocyanins and polyphenolics were leached from the fruits into the syrup with little total loss per total can. Changes of anthocyanin concentrations after processing fresh fruits to jams are reported for four cultivars of tart cherries by Kim and Padilla-Zakour (2004). All cultivars showed a significant decrease in anthocyanin concentrations (21–24% of the original level of the fresh fruits) related to the canning process of heating under high acid and sugar concentrations. Of interest, the total phenolics and antioxidant capacity of the canned product were retained under these processing conditions.

## NUTRIENT AND BIOACTIVE FOOD COMPONENTS

Data regarding the nutrient and BAFC content of cherries and cherry products consumed in the U.S. (Table 1) and the nutritional composition of cherries in comparison to other *Prunus* genus fruits (Table 2) illustrate that sweet cherries are a comparatively good source of fiber, potassium, and in particular anthocyanins.

### Fiber

The sweet cherry contains an estimated 2.1 grams of dietary fiber per 100 grams. While this is not considered to be a significant source of fiber per serving, the fiber content does contribute to the health-promoting qualities of cherries in the diet. U.S. adults currently consume an average of 12 grams of fiber daily, less than half of the recommended daily intake of 14 g of fiber per 1000 kcals total energy intake (Institute of Medicine, 2002). High fiber diets have been associated with improved blood glucose control, reduced cholesterol levels, and possibly reduced energy intake and thus may have indirect effects on weight control through effects on satiety (Suter, 2005; Keenan et al., 2006).

### Potassium

Sweet cherries also are considered to be a good source of dietary potassium with approximately 260 mg potassium for

**Table 1** Nutrient, carotenoid, anthocyanin, and quercetin content of commonly consumed cherry products (per 100 grams or approx. 15 cherries)

| Nutrient/BAFC | Cherries, sweet | Cherries, tart | Cherries, sweet, canned | Cherries, sweet, frozen, sweetened | Maraschino |
|---|---|---|---|---|---|
| Energy (kcal)[a] | 63 | 50 | 46 | 89 | 165 |
| Protein (g)[a] | 1.06 | 1.0 | 0.8 | 1.15 | 0.22 |
| Fat (g)[a] | 0.2 | 0.3 | 0.13 | 0.13 | 0.21 |
| Carbohydrate (g)[a] | 16.0 | 12.2 | 11.8 | 22.4 | 42.0 |
| Fiber (g)[a] | 2.1 | 1.6 | 1.5 | 2.1 | 3.2 |
| Glycemic Index[b] | 22 | 22 | 22 | 22 | Not available |
| Vitamin C (mg)[a] | 7 | 10 | 2.2 | 1.0 | 0 |
| Vitamin A (IU)[a] | 64 | 1283 | 160 | 189 | 45 |
| Potassium (mg)[a] | 222 | 173 | 131 | 199 | 21 |
| $\beta$-carotene ($\mu$g)[a] | 38 | 770 | 96 | 113 | 27 |
| Lutein/Zeaxanthin ($\mu$g)[a] | 85 | 85 | 57 | 85 | 59 |
| Total anthocyanin (mg)[c] | 80.2 | Not available | Not available | Not available | Not available |
| Quercetin (mg)[c] | 2.64 | 2.92 | 3.2 | Not available | Not available |

[a] USDA ARS (2006).
[b] National Cancer Institute (2004).
[c] USDA ARS (2007).

every cup of fresh cherries consumed (USDA, 2006). In the past decade there has been increasing evidence of the importance of adequate potassium intake in reducing the risk for hypertension and stroke (He and MacGregor, 2003). Almost one-third of all American adults have high blood pressure levels (NIH, 2006), thus promoting diets high in potassium ( >4000 mg/day) as well as reduced in sodium and alcohol intake, is a reasonable and safe approach to promote improved blood pressure control.

Several mechanisms have been proposed and evaluated in relation to potassium intake and associated reduction in blood pressure and stroke risk. Of particular importance is the concurrent lowering of sodium intake with the integration of high potassium fruits into the diet as most fruits, including cherries, are free of sodium. The shift from a high sodium/low potassium diet to a low sodium/high potassium diet has been suggested to reduce hypertension through a promotion of natriuresis, a reduction of sympathetic nervous system activity, and an indirect

stimulation of angiotensin II and norepinephrine (Vaskonen, 2003).

A 2001 report in the American Journal of Hypertension suggested that Americans consume additional potassium-rich foods to achieve an intake of 4700 mg/day, well above the estimated usual intake of 1740 mg/day among participants enrolling in the Dietary Approaches to Stop Hypertension (DASH) intervention trial (Appel et al., 1997). The DASH trial was an eight week long clinical trial that included a diet high in fruits and vegetables, low-fat dairy products, and reduced saturated and total fat. This diet high in potassium rich foods led to a decrease in blood pressure in conjunction with decreased sodium levels (Sacks et al., 2001) although very high adherence, as judged by an index scoring system developed by Folsom et al. (2007), to the criteria of this diet may be essential for long-term protective effects. However, it is important to understand that an increase in dietary potassium intake alone, even in combination with sodium restriction, generally is not associated with a significant improvement in blood pressure control (Davis et al., 1994) but a combination of higher potassium, higher calcium, lower sodium intake, and weight control is efficacious in reducing blood pressure in people with hypertension (Wexler and Auckerman, 2006; Elmer et al., 2006). A recent meta-analysis of 121 publications from 1996–2004 suggests that these same dietary approaches that lower sodium and increase potassium result in lower blood pressure and are associated with a significant reduction in stroke risk (Ding and Mozaffarian, 2006).

**Table 2** Nutrient composition of fruits within the genus *Prunus* (values per 100 grams or approximately 15 cherries)[a]

| Nutrients | Sweet cherry | Tart cherry | Apricot | Plum | Peach |
|---|---|---|---|---|---|
| Energy (kcal) | 63 | 50 | 48 | 46 | 39 |
| Fiber (g) | 2.1 | 1.6 | 2.0 | 1.4 | 1.5 |
| Total sugars (g) | 12.82 | 8.49 | 9.24 | 9.92 | 8.39 |
| Sucrose (g) | 0.15 | 0.8 | 5.87 | 1.57 | 4.76 |
| Glucose (g) | 6.59 | 4.18 | 2.37 | 5.07 | 1.95 |
| Fructose (g) | 5.37 | 3.51 | 0.94 | 3.07 | 1.53 |
| Vitamin A (IU) | 64 | 1283 | 1926 | 345 | 326 |
| Vitamin C (mg) | 7 | 10 | 10 | 9.5 | 6.6 |
| Vitamin E (mg) | 0.07 | 0.07 | 0.89 | 0.26 | 0.73 |
| Potassium (mg) | 222 | 173 | 259 | 157 | 190 |
| $\beta$carotene ($\mu$g) | 38 | 770 | 1094 | 190 | 162 |
| Anthocyanins (mg) | 80.19[b] | Not available | Not available | 12.02[b] | 1.61[b] |

[a] USDA ARS (2006).
[b] USDA ARS (2007).

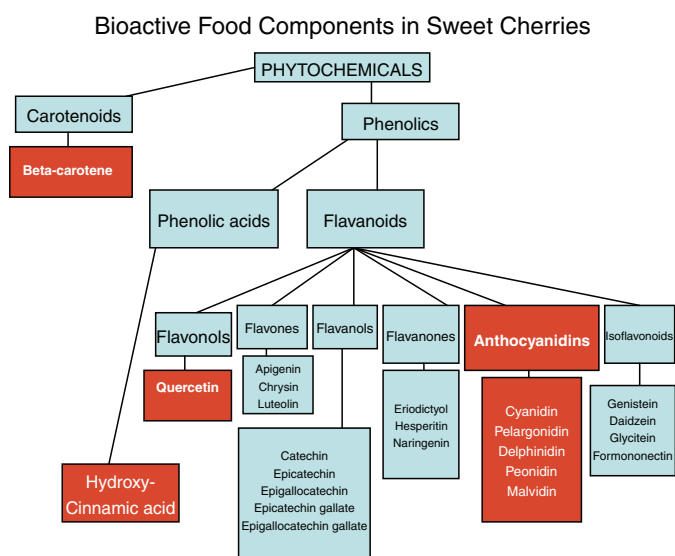### Bioactive Food Components

Figure 1 illustrates the chemical classifications of select BAFCs found in cherry fruit. Sweet cherries are a significant source of polyphenols in the human diet. Bing cherries contain an estimated 160–170 mg total polyphenols in a 100 gram serving. It is difficult to define an optimal dose for the intake of cherries in terms of health outcomes. Feeding trials have

Bioactive Food Components in Sweet Cherries



**Figure 1** Bioactive Food Components in Sweet Cherries (adapted from Liu, 2004).

provided polyphenols from various sources such as green tea, curcumin, or soy isoflavones and also have varied significantly in terms of total polyphenol exposure, ranging from 18.6 mg to 8 g daily. As a result, efficacy studies have resulted in inconsistent findings suggesting variable degrees of efficacy (Thomasset et al., 2006). Table 3 provides a summary of currently available data regarding the antioxidant capacity of select cherry cultivars. The total antioxidant activity associated with sweet cherry intake is thought to be largely influenced by the synergistic antioxidant effects of nutrients such as vitamin C and the BAFC present in sweet cherries such as anthocyanins and quercetin.

*Anthocyanins*

Both sweet cherries and tart cherries contain substantial amounts of anthocyanins and polyphenolics (Gao and Mazza,

1995), yet comparative data on sweet and tart cherry composition using similar analytical methodologies such as ORAC and FRAP are limited and variable (Chaovanalikit and Wrolstad, 2004). For example, Chaovanalikit and Wrolstad (2004) reported that Bing sweet cherries were highest in anthocyanins, whereas Montmorency tart cherries were highest in total phenolics and antioxidant activities. Further, the anthocyanins in Bing sweet cherries are found in the skins and flesh, while in Montmorency tart cherries anthocyanins are concentrated in the skins. Seeram et al. (2002) reported that sweet cherries had the highest antioxidant activity followed by blueberries. In this same report, sweet cherries were shown to have a greater anti-inflammatory activity than Montmorency tart cherries. In contrast, ORAC and FRAP analyses showed that the edible portion of Montmorency tart cherries showed a greater antioxidant activity than those in sweet cherries (Chaovanalikit and Wrolstad, 2004). Hence, due to the reported inconsistencies, the comparison of antioxidant activities between sweet cherries and tart cherries measurements are inconclusive and require further investigation. It is likely that the antioxidant capacity of the fruits may be relatively equivalent, while the specific nutrients(s) and/or BAFC contributing to the antioxidant capacity vary significantly across cherry cultivars.

Table 4 lists the specific anthocyanins found in sweet cherries as well as other commodity fruits. The anthocyanin content of cherries is compared to other plant foods for which evidence has suggested health-promoting effects related to anthocyanin and/or polyphenol content (Espín et al., 2007; Stevenson and Hurst, 2007; Thomasset et al., 2006). The primary distinction between sweet and tart cherries in terms of BAFC content is the greater concentration of anthocyanins in sweet cherries. It is noteworthy that sweet cherries are particularly rich in the anthocyanin cyanidin which constitutes over 90% of its total anthocyanin content. It has been previously demonstrated in animal studies that cyanidins exhibit biologically relevant antioxidant properties as well as the potential to ameliorate the age-related deficits in neuronal and behavioral functions (Amorini et al., 2001; Galli et al., 2002).

**Table 3** Comparison of total anthocyanins, total phenolics, and antioxidant properties of flesh, pits, and skins of different cherry cultivars adapted from (Chaovanalikit and Wrolstad, 2004).

| Cultivar | Portion | Anthocyanins (mg/100g fw[a])[b] | Total phenolics (mg/ g fw)[c] | ORAC ($\mu$mol TE[d]/g fw) | FRAP ($\mu$mol TE/g fw) |
|---|---|---|---|---|---|
| Bing (sweet) | Flesh | $26.0 \pm 0.7$ | $1.34 \pm 0.18$ | $9.07 \pm 0.35$ | $7.28 \pm 0.24$ |
| | Pits | $10.4 \pm 3.1$ | $0.92 \pm 0.09$ | $5.94 \pm 0.91$ | $5.04 \pm 0.96$ |
| | Skins | $60.6 \pm 2.5$ | $3.33 \pm 0.41$ | $28.26 \pm 1.10$ | $21.05 \pm 0.55$ |
| Rainier (sweet) | Flesh | $0.0 \pm 0.0$ | $0.65 \pm 0.05$ | $4.62 \pm 0.18$ | $2.27 \pm 0.22$ |
| | Pits | $0.1 \pm 0.0$ | $0.54 \pm 0.04$ | $3.38 \pm 0.26$ | $2.00 \pm 0.13$ |
| | Skins | $2.1 \pm 0.4$ | $1.42 \pm 0.05$ | $10.50 \pm 1.51$ | $5.92 \pm 0.39$ |
| Montmorency (tart) | Flesh | $0.0 \pm 0.09$ | $3.01 \pm 0.29$ | $15.00 \pm 1.00$ | $13.81 \pm 0.26$ |
| | Pits | $0.8 \pm 0.08$ | $1.57 \pm 0.02$ | $9.78 \pm 0.28$ | $8.48 \pm 0.85$ |
| | Skins | $36.5 \pm 1.6$ | $5.58 \pm 0.33$ | $51.02 \pm 1.97$ | $47.96 \pm 1.33$ |

[a] fresh weight.
[b] cyn-3-glu equivalent.
[c] gallic acid equivalent.
[d] Trolox equivalent.

**Table 4** Anthocyanins in sweet cherries and related plant foods.

| Plant Food (1 cup) | Anthocyanins | | | | | | |
|---|---|---|---|---|---|---|---|
| | Cyanidin (mg) | Deophinidin (mg) | Malvidin (mg) | Pelargonidin (mg) | Peonidin (mg) | Petunidin (mg) | Total (mg) |
| Cherries, Sweet | 75.2 | 0 | 0 | 0.5 | 4.5 | 0 | 80.2 |
| Cherries, Tart | 6.6 | Not available | Not available | Not available | Not available | Not available | Not available |
| Peaches | 1.6 | 0 | 0 | 0 | 0 | 0 | 1.6 |
| Plums | 12.0 | 0 | 0 | 0 | 0 | 0 | 12.0 |
| Blueberries, raw | 17.0 | 47.4 | 61.4 | 0 | 11.4 | 26.4 | 163.6 |
| Raspberries | 35.8 | 0.3 | 0.7 | 1.9 | 0 | 0 | 38.7 |
| Grapes, red | 1.5 | 3.7 | 34.7 | .02 | 2.9 | 2.1 | 44.9 |
| Red Wine | 0.4 | 1.0 | 7 | Not available | 0.8 | 0.9 | Not available |

USDA ARS (2007).

### *Quercetin*

Sweet cherries also contain quercetin, a phenolic BAFC belonging to a class of bioflavonoids that are widely distributed in a plant-based diet (Dunnick and Hailey, 1992). Quercetin is among the most potent of BAFC in terms of antioxidant activity (Boots et al., 2008). The ability of quercetin to act as a free radical scavenger suggests it could play a beneficial role in reducing reactive oxygen species (ROS) (i.e. hydrogen peroxide, superoxide anion) associated with chronic diseases such as cardiovascular disease and cancer (Johnson and Loo, 2000; Wilms et al., 2005). The unique catechol structure of quercetin, which possesses two hydroxyl groups at neighboring positions, allows for a greater level of radical scavenging activity as compared with most antioxidants (Murota and Terao, 2003). High doses of quercetin (10–100 uM) have been shown to diminish malondialdehyde concentration, a biomarker of lipid peroxidation (Alia et al., 2005 epub), and in vitro pre-treatment of human lymphocytes with quercetin (low concentrations 1–10 uM quercetin) has been demonstrated to be very effective in preventing DNA-induced oxidative damage in a concentration-dependent manner (Wilms et al., 2005).

In relation to cardiovascular disease risk reduction both oxidative stress and antiplatelet effects of quercetin have been evaluated. In rat in vivo studies, quercetin was shown to have vasorelaxant effects (Woodman and Chan, 2004) and a review of flavonoid effects on cyclooxygenase-2 supports strong inhibitory effects (O'Leary et al., 2004), but little follow up research has been completed. Human studies focused on quercetin feeding have shown mixed results on oxidative stress levels both supporting (Boyle, 2000; McAnlis et al., 1999; Lean et al., 1999) and not supporting (Beatty et al., 2000) a statistically protective effect. One supplementation trial conducted among 27 healthy adults showed no significant improvement in platelet aggregation or lipid levels after consuming 1 gram quercetin/day for 28 days (Conquer et al., 1998) despite this dose being well above the 69 mg/day demonstrated to be effective in the inhibition of platelet aggregation as demonstrated by Hubbard et al. (2006). Perhaps the recruitment of a healthy population in this study contributed to the non-significant effects. Further, dosage of quercetin used in in vitro studies which support anti-platelet effects are likely not plausible in human feeding studies due

to risk of prolonged bleeding time (Janssen et al., 1998). In a comprehensive review by Prior (2003), the bioavailability and antioxidant capacity of quercetin in vivo was reduced in relation to conjugation with glucuronide or sulfate and short half-life. Therefore, while significant antioxidant effects can occur and have been demonstrated in humans, further clinical trials need to be completed to determine an effective and safe physiologic dose.

It is important to note that the quercetin content alone in an average serving of cherries is insufficient to expect any significant effect on oxidant stress or inflammatory biomarkers, but in conjunction with other antioxidant and anti-inflammatory BAFCs, modulation of these biomarkers may be observed as previously discussed. Further, while sweet cherries are an available source of quercetin in the human diet, citrus fruits and onions, among other fruits and vegetables, are considerably higher in quercetin content. Well-controlled feeding studies are needed to more clearly assess the role of sweet cherries in modifying oxidant stress and inflammation.

### *Hydroxycinnamate*

The hydroxycinnamates are the primary phenolic class in sweet cherries, comprising approximately 40% of the total (Gonçalves et al., 2004). The hydroxycinnamates are increasingly receiving attention for their potential health promoting effects through their potent antioxidant action, ability to inhibit low-density protein (LDL) oxidation, and their chemopreventive properties (e.g. inhibitory effects on tumor promotion and the ability to block the formation of mutagenic compounds such as nitrosamines) as demonstrated by in vitro studies (Frankel et al., 1993; Nardini et al., 1995; Pieters et al., 1999). Yet, limited data exist regarding the health-promoting effects of hydroxycinnamates in in vivo studies. The extent of the hydroxycinnamates protective effect appears to be dependent upon, in part, its bioavailability. Hydroxycinnamates are present in plant-derived foods predominantly in esterified forms linked to polymers or other small molecules. These polymers must be cleaved by esterases and released as free acids in order to be absorbed efficiently via the small intestine (Andreasen et al., 2001). Analytical assays have been developed to quantify

hydroxycinnamate levels in human urine samples (Nielsen and Sandstrom, 2003; Bourne and Rice-Evans, 1998) and plasma (Cremin et al., 2001) suggesting that evaluating the relevance of these compounds in terms of health-promoting potential of cherry intake is possible.

## SELECT HEALTH BENEFITS

### Cancer

Sweet cherries have several cancer-preventive components including fiber, anthocyanins, vitamin C, and carotenoids. While cherries are a fair source of dietary fiber which has been associated with reduced risk for select cancers, this association remains inconclusive (Rock, 2007). Further, the dose of fiber in a single serving of sweet cherries (2.1 grams/15 cherries) is insufficient to modify risk in comparison to the recommended cancer-preventive dietary intake level of 30 or more grams daily (Butrum et al., 1988). Cherries also provide a reasonable source of lutein and beta-carotene in the diet, although below the levels associated with consumption of green leafy vegetables and orange-yellow vegetables such as carrots and sweet potatoes. Again, the presence of beta-carotene likely contributes to the total antioxidant effects of cherries, but not to any significant degree.

Of primary interest in terms of cancer risk reduction are the anthocyanins, particularly cyanidin, which are responsible for the red-purple color inherent in fresh sweet cherries. Anthocyanin concentration is one factor that differentiates the sweet cherry from the tart cherry in that while both contain anthocyanins, sweet cherry concentrations are more than 10-fold higher, particularly in relation to cyanidin content (USDA, ARCS 2007). Thus, while literature exists suggesting that the anthocyanin content of tart cherries is health promoting, in all likelihood this evidence would be even stronger for the sweet, dark red cherry varieties given the higher anthocyanin content.

Using a mouse model of colorectal cancer, a multiple regime feeding trial was conducted to assess the role of cherry BAFC in reducing cancer risk. Mice were fed one of the following: 1) a cherry diet, 2) anthocyanins, 3) cyanidin, 4) control diet or 5) control diet with added sulindac (an anti-inflammatory agent) to determine their effects on tumor development (Kang et al., 2003). Results suggested that mice assigned to any of the three test diets showed significantly fewer and smaller volume cecal tumors, but not colonic tumors, than control or sulindac supplemented mice, suggesting that the bioactivity of cyanidin may be responsible for the site specific inhibition of cecal tumors. Similar cancer-protective effects of cyanidin glucosides have been demonstrated in studies employing cancer cell lines (Chen et al., 2005) including apoptotic effects via G2/M growth cycle arrest.

Further, cyanidin has also been shown to act as a potent antioxidant in cell culture research. In a study by Acquaviva et al. (2003) cyanidin and cyanidin-3–O-beta-D-glucoside were shown to have a protective effect on DNA cleavage, a dose-dependent increase in free radical scavenging activity, and to significantly inhibit xanthine oxidase activity. A separate study also using cancer cell lines demonstrated cell cycle arrest and apoptosis of mutated cells exposed to cherry anthocyanins (Lazze et al., 2004; Shih et al., 2005). Further research suggests that the growth arrest characteristics of cyanidin are in part a result of the significant inhibitory effects of these cherry components on epidermal growth factor receptor (Meiers et al., 2001). Finally, cyanidin may also promote cellular differentiation and thus reduce the risk for malignant transformation (Serafino et al., 2004).

To date no human intervention trials assessing the role of cherries and/or cherry BAFC have been completed to assess the efficacy of a cherry-enriched diet on cancer risk reduction. Additionally, while available epidemiological data suggest fruits are protective against select cancers, no data are available specific to cherry intake and cancer risk. Based on the ever-expanding mechanistic research from cell culture and animal models, human cherry feeding trials should be pursued to test the efficacy of cherries and cherry BAFC in modulating intermediate biomarkers of cancer risk.

### Cardiovascular Disease

As with anti-cancer effects, much of the research suggesting cardio-protective effects of cherry constituents lies in well-designed cell culture studies. In one study endothelial cells were removed from bovine arteries and exposed to cyanidin-3-glycoside for several hours. This treatment was associated with a significant increase in nitric oxide (NO) output and thus could be associated with a significant reduction in local oxidant stress to the cardiac tissue (Xu et al., 2004), decreased vascular inflammation, and indirectly reduced foam cell formation, a precursor for the development of atherosclerotic plaque (Cannon, 1998). In a study using tart cherry seed extract, rat hearts were subjected to ischemic injury (which generally results in irregular and rapid heart beats and possibly heart attack) and exposed to cherry extract at variable doses. Extract at moderate doses was associated with reduced incidence of irregular and rapid heart rates as well significantly less cardiac damage as a result of heart attacks that did occur (Bak et al., 2006). As this model system to test cardio-protective effects seems promising, replications specific to sweet cherries are indicated as similar advantageous effects would be expected.

Expanding on this evidence, in 2002 Frank and colleagues investigated the role of the anthocyanin, cyanidin-3–O-glucoside, common to the cherry fruit, in reducing blood lipid levels in rats. While anthocyanin supplementation in the diet (in this study derived from blackcurrant and elderberry and not specifically sweet cherry) did not reduce serum cholesterol levels, it did modify vitamin E levels in vital organs, suggesting an increased, although indirect, antioxidant effect. In another animal study, investigators targeted the cholesterol transport pathways in assessing the role of anthocyanins in

reducing cardiovascular disease risk. The study isolated foam cells from mice and then exposed them to variable doses of cyanidin-3–O-$\beta$-glucoside. Results suggested that there was a dose-dependent removal of cholesterol from macrophages and their associated foam cells, illustrating a protective effect of this anthocyanin in reducing cardiovascular risk (Xia et al., 2005). This preliminary evidence suggests that the role of cherries and cherry BAFC in protection against cardiovascular disease is an area ripe for focused research. Given the expected tolerance and acceptance of cherries in human populations, human feeding trials assessing effects of cherry intake on heart health are an important next step toward advancing our understanding.

### *Diabetes*

Evidence suggesting a protective role of cherries and cherry components in the setting of clinical diabetes is relatively sparse. Yet, mechanistic studies in cancer and cardiovascular disease targeting common biological pathways for disease promotion, including both antioxidant and anti-inflammatory effects of cherries/cherry components point to diabetes as another potential disease target to assess the health-promoting effects of cherries. Oxidative stress is associated with many of the complications of diabetes (Halliwell, 1997; Cunningham, 1998) and antioxidants, such as the anthocyanins and quercetin found in cherries have the potential to potentially modulate those symptoms (McCune and Johns, 2003) and reduce the risk of the onset of diabetes (Salonen et al., 1995; Montonen et al., 2004).

Further, evidence suggests a role for anthocyanins in reducing insulin resistance and glucose intolerance. In a cell culture study, anthocyanins and anthocyanidins in cherry fruit combined with various glucose loads resulted in a significant enhancement in insulin production by the anthocyanin and anthocyanidin-enriched cells as compared to controls (Jayaprakasam et al., 2005). And while few, if any studies, have examined the use of cherries specifically in the control of blood sugar, studies have shown that anthocyanins are effective in improving insulin secretion in response to varying glucose loads (Ghosh and Konishi, 2007). This suggests that the BAFC found in cherry fruit are responsive to a glucose-rich environment in terms of enhanced insulin production and improved glucose levels. In a few studies using mouse models of hyperglycemia, similar glucose-lowering effects were demonstrated in relation to feeding of either cherry anthocyanins (Jayaprakasam et al., 2006) or 3-O-$\beta$-d-glucoside specifically (Tsuda et al., 2003). In both studies high fat diets were used to induce obesity and hyperglycemia and then supplemental feedings of cherry-specific BAFC were provided. Protective effects included reduced triglyceride synthesis as well as reduced glucose and leptin levels. Recent work by Seymour et al. (2007) found rat diets enriched with tart cherries significantly reduced levels of triglyceride, total cholesterol, insulin, and markers of oxidative stress.

Of late the role of glycemic index in diabetes control has gained renewed interest. Sweet cherries have an estimated glycemic index of 22, generally lower than most other fruits such as apricot (57), grapes (46), peach (42), blueberry (40), or plum (39) (Foster-Powell et al., 2002). The lower glycemic index makes sweet cherries a potentially more appropriate fruit-based snack food (as compared with many other fruits) for individuals with diabetes. The lower glycemic response shown in relation to cherry consumption may be the result of glucose-lowering effects of cherry BAFC in combination with the fiber content of cherries.

### *Inflammation*

An important new area for nutrition research is the role of naturally-occurring compounds in the food supply (primarily plant foods) to modify the inflammatory process in humans. It has been well recognized that low grade inflammation is a potential risk factor for a wide range of chronic illnesses including cancer, cardiovascular disease, obesity and arthritis (Margolis et al., 2007; Nicklas et al., 2004). To reduce inflammation many Americans with, or at risk, for chronic inflammatory related illnesses are advised to take low-dose aspirin or non-steroidal anti-inflammatory medications; however, these medication-based approaches are not without undesirable side-effects and thus more tolerable approaches such as dietary modification to enhance the anti-inflammatory response are warranted.

Cherries, and the constitutive BAFC, have been demonstrated to inhibit the cyclooxygenase (COX) enzymes responsible for inflammatory response. In a cell culture study assessing COX-1 and -2 enzyme activity the anthocyanin cyanidin, along with malvidin, were shown to have the greatest inhibitory effects (Seernam et al., 2003). The research also indicated that cyanidin had greater anti-inflammatory activity via COX enzyme inhibition than polyphenols found in green tea. The strong inhibitory potential of cyanidin is thought to be the result of the chemical structure which exhibits a hydroxyl group positioned in the B ring of the compound. These data provide evidence of anti-inflammatory effects of cherries that should be investigated further in human feeding studies examining the effect of cherry consumption on COX 1 and 2 activity and other inflammation-associated biomarkers.

One cell-culture study comparing the anti-inflammatory effects of cyanidin alone, anthocyanins from a wide variety of cherries and anti-inflammatory response to common anti-inflammatory medications (Seeram et al., 2001) showed that sweet cherries inhibited COX-1 enzyme activity by an average of 28% and COX-2 activity by 47%. This inhibitory response on inflammatory enzyme activity was approximately 60% of the Cox-1 inhibition demonstrated for the anti-inflammatory medications tested (ibuprofen and naproxen), and in fact, sweet cherries exhibited approximately 5% greater COX-2 inhibition than these medications. Similarly, data from the laboratory of Hou et al. (2005) also indicated a significant COX-2 inhibitory effect of anthocyanin constituents found in sweet

cherries and further demonstrated that these effects are related to down-stream inhibition of mitogen-activated protein kinase (MAPK).

The anti-inflammatory effects of cherries have also been investigated in animal models of arthritis, a primary inflammatory disease affecting over 43 million Americans (CDC, 2006). In a study conducted by He et al. (2006), using an induced arthritis model, male Sprague Dawley mice were fed 40, 20, or 10 mg/kg of total cherry anthocyanins daily in mouse chow for 28 days or standard un-enriched mouse chow. Anti-inflammatory response was assessed through the measurement of serum TNF$\alpha$ and prostaglandin E2 (PGE2) levels in paw tissue. Results suggested that, as expected, the induction of arthritis was successful as illustrated by elevated serum TNF$\alpha$ levels. Feeding at the highest dose of anthocyanins resulted in a significantly lower TNF$\alpha$ level as compared to standard feeding, but lower doses were not therapeutic in this regard. PGE2 levels in paw tissue samples showed a significant rise with induction of arthritis and a dose-responsive effect of anthocyanin feedings and while all doses reduced PGE2 levels as compared to standard feeding, this effect was greatest at the 40 mg/kg dose. This study provides preliminary evidence of the potential role of cherries in reducing the inflammatory response in those with inflammation-related chronic illness. It is important to consider that extrapolation of the doses used in this mouse study would suggest that a 70 kg man would need to eat 2800 mg anthocyanins daily for several weeks. This is the equivalent of 35 cups of sweet cherries daily, an amount unachievable in human feeding studies. While bioavailability differences are likely variable across species, the only valid way to assess dose-response would be via a well-designed cherry feeding study with standardized exposure in terms of anthocyanin content.

In a pilot study investigating the effects of sweet cherry consumption on inflammatory markers in humans, 18 healthy adults (age 45–61 years) were fed 280 grams or approximately 2.5 cups of sweet cherries daily for 4 weeks (Kelley et al., 2006). Inflammation was assessed by repeat measures of serum C-reactive protein (hsCRP) levels. hsCRP levels were reduced by 8 and 25%, respectively after 14 and 28 days of cherry feeding as compared to hsCRP levels prior to daily cherry consumption, indicating a significant drop only at the 28 day time point (P < 0.05). After cherry feeding was discontinued hsCRP levels rose in the study population by an average of 10% in 34 days, although this rise did not reach statistical significance. Interleukin 6 (IL-6) levels were not changed in relation to sweet cherry intake and this was corroborated by several ex vivo secretion levels of IL-6 and TNF$\alpha$. While of interest, these results need to be replicated. It would also be of value to evaluate the anti-inflammatory effects of sweet cherry feeding in study populations demonstrating baseline elevations in inflammatory status (obese, those with chronic inflammation-related illness) and to incorporate a broader range of inflammatory outcome markers.

In relation to the anti-inflammatory properties of sweet cherry components, cherries also have been investigated in relation to pain control. Evidence suggesting a role of dietary constituents in reducing pain is expanding (Tall et al., 2004). In a novel study testing the role of tart cherry anthocyanins in pain control in rats, Tall and colleagues (2004) showed that anthocyanins provided at a dose of 400 mg/kg resulted in a significant reduction in paw withdrawal from heat-induced pain stimuli and von Frey filament exposure, a neuropathic pain test.

Gout, a form of acute arthritis that causes severe pain and swelling in the joints as well as inflammation, affects over 4.3 million Americans, particularly obese males, and manifests as a consistent and significant elevation in plasma urate levels (Petraccia et al., 2008). It occurs when there are high levels of uric acid circulating in the blood which can then cause urate crystal deposition in the tissues of the joints. Thus, to assess the pain-reducing potential of cherries, a pilot study was conducted among ten healthy women (without gout), age 22–40 years who were fed a single 280 gram dose of de-pitted sweet cherries (Jacob et al., 2003). Blood samples to assess urate levels were collected before cherry feeding and 1.5, 3, and 5 hours postfeeding. Results demonstrated a significantly lower mean serum urate level 5 hours after cherry feeding, a protective effect not shown with grape, strawberry, or kiwi fruit feeding. This single-dose cherry feeding did not modify plasma CRP or nitric oxide as was suggested with longer term feeding (28 days) (Kelley et al., 2006).

### Additional Potential Health Benefits

Flavonoids and procyanidin compounds found in cherries have been shown to reduce oxidant stress and $\beta$-amyloid production and hence may indirectly reduce the risk for Alzheimer's disease (Yoshimura et al., 2003; Heo et al., 2004). Only recently has there been published evidence of the potential role of sweet cherry phenolic compounds in protecting neuronal cells involved in neurological function. In a cell culture study in which neuronal cells were exposed to a variety of sweet and tart cherry phenolic compounds, total phenolics, and predominantly anthocyanins, demonstrated a dose-dependent reduction in oxidant stress (Kim et al., 2005); effects on $\beta$-amyloid production were not assessed. However, this preliminary evidence should provide impetus for further investigation into the potential protective effects of sweet cherry bioactive compounds in reducing risk for or morbidity related to Alzheimer's disease.

Melatonin is a hormone produced by the pineal gland that in addition to antioxidant activity also plays a role in promoting healthy circadian rhythm and thus promoting healthy sleep patterns. Cherries are one plant food source of melatonin and melatonin levels have been estimated to be higher in tart cherries as compared to sweet cherries. In a study of melatonin content in Egyptian foods, melatonin levels in select grains ranged from 87 to 187 ng/100 grams food while concentrations in fruits such as pomegranates and strawberries were much lower, ranging from 13–29 ng/100 gram (Badria, 2002). Analytical work suggests that Montmorency cherries have an estimated melatonin content of 1.35 $\mu$g/100 gram serving while Balaton cherries

averaged 0.2 $\mu$g/100 gram serving, indicating that variety is an important determinant of the melatonin content of cherries (Burkhardt et al., 2001).

Melatonin supplementation appears to be efficacious in reducing jet lag (Herxheimer and Petrie, 2002; Suhner et al., 2001), although not consistently (Spitzer et al., 1999). One explanation for inconsistent results in published studies may be that efficacy appears to be dependent upon melatonin excretion levels during sleep in that a double-blind, placebo-controlled study of 576 adults showed melatonin significantly improved sleep among those with the lowest baseline melatonin excretion levels (Leger et al., 2004). Dosing levels used in clinical intervention trials for sleep or jet lag generally ranges between 2 and 5 mg/day. Thus, while sweet cherries hold potential to enhance sleep and reduce jet lag related to the available melatonin, it is not likely that usual intake levels required to replicate doses used in clinical trials can be attained or sustained via cherry intake alone. Although, it is feasible that in combination with other behavioral approaches to promote sleep or reduce jet lag, sweet cherry intake in usual amounts could prove to be useful.

## CONSIDERATIONS FOR FUTURE RESEARCH

### Dietary Measurement

Efforts to quantify cherry intake in the context of epidemiological research is warranted. While cherry intake has historically been seasonal in nature, with expanded access through importation from South America and Turkey, Americans can enjoy cherries almost year-round. More frequent intake and year-round access suggest that cherries should be considered for inclusion on food frequency questionnaire instruments commonly employed to assess diet-disease associations in large study populations. Expanded use of recall and food records in epidemiological research would also enhance our capacity to assess associations between cherry intake and disease outcomes.

### Biomarkers of Exposure

In addition to more accurately assessing reported dietary intake of cherries, biomarkers of cherry exposure are needed to assess potential health related effects of cherry intake, especially given the variability in nutrient and bioactive food component composition in relation to cherry cultivar, ripening, processing, etc. Identifying the most reliable and valid biomarkers of intake in humans will contribute significantly to advancing the testing of hypotheses in this area. Scientifically acceptable biomarkers need to be valid, correlate significantly with dietary intake, be reliable, and utilize biological samples which are easily collected from free-living people.

### Need for Human Feeding Studies

While the current state of the evidence suggests that eating sweet cherries holds potential for improving overall health, undoubtedly more research is essential to gain a better understanding of the role of cherry consumption in reducing chronic disease risk, particularly in relation to human studies and establishing dose-specific guidelines. The mechanistic evidence exists to suggest that specific bioactive food components in sweet cherries can modulate oxidant stress and inflammation. This evidence warrants further scientific investigation regarding the role of sweet cherries in health. Although isolation of key bioactive food components to establish a specific dose-response would be one approach, in all likelihood it is the synergy among bioactive food components found in sweet cherries such as ascorbic acid, carotenoids, and anthocyanins that results in the health-promoting effects realized from consuming the whole fruit. It is critical that the mechanistic research findings be further substantiated through the implementation of well-designed human cherry feeding studies using fruits produced, harvested, stored, and distributed under standardized conditions as both pre-harvest and post-harvest conditions can significantly affect the concentrations of bioactive food components.

## CONCLUSIONS

Cherries are important sources of nutrient and bioactive food components in the human diet. Epidemiological studies are needed to further assess the role of nutrients and BAFCs common to cherries and specific health outcomes. The health-promoting effects of cherries have been demonstrated in select basic and animal studies; however, human intervention trials remain sparse. Such feeding studies should include some assessment of dose-response under standardized cherry production methods in order to more fully understand the optimal dose of cherry intake necessary to promote modulation of disease-specific biomarkers.

## ACKNOWLEDGEMENTS

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