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File: ■ Tart Cherry (*Prunus cerasus*, Rosaceae) ■ Phytochemistry

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RE: Review of Tart Cherry Phytochemistry Reports High Content of Beneficial Compounds and Promising Bioactivities

Mayta-Apaza AC, Marasini D, Carbonero F. Tart cherries and health: current knowledge and need for a better understanding of the fate of phytochemicals in the human gastrointestinal tract. *Crit Rev Food Sci Nutr*. September 28, 2017; [epub ahead of print]. doi: 10.1080/10408398.2017.1384918.

Tart cherry (*Prunus cerasus*, Rosaceae) fruits, polyphenol rich, are cultivated worldwide with growing popularity. Tart cherries have an unusual polyphenol profile, combining anthocyanins and flavonols, as found in berry (e.g., *Vaccinium* spp., Ericaceae; *Rubus* spp. and *Fragaria* spp., Rosaceae; and *Sambucus* spp., Viburnaceae) fruits, with chlorogenic acid, which is plentiful in coffee (*Coffea* spp., Rubiaceae). Potential health benefits include reducing blood pressure (BP), modulating blood glucose, enhancing cognition, protecting against oxidative stress, and reducing inflammation. While tart cherries have not been qualified under US requirements for specific health claims, tart cherries meet the requirements of the general claim that consumption of nutritious fruits and vegetables reduces risks of cardiovascular (CV) disease and cancer. Studies report benefits in recovery from exercise-related stress and some parameters of diabetes mellitus type 2 (DM2). However, in vitro and in vivo studies of polyphenol extracts from tart cherries neglect the crucial role of human gut microbiota in reducing these molecules into absorbable, bioavailable form. In addition, wide individual variability in gut microbiota profiles likely produces different metabolites. Sparse evidence about these variables limits the usefulness of tart cherries for potential health benefits.

Without revealing their search strategy but with an extensive reference list, the authors discuss tart cherries' crop value, potential health benefits, and reported effects of their constituents on the microbiome. As with other crops widely cultivated from antiquity, there are many common names for tart cherries (sour cherry, pie cherry, etc.) and the other most-cultivated type, sweet cherry (bird cherry; *P. avium*), and some differences in nomenclature and classification depending upon source. These authors state that both tart and sweet cherry are members of the subgenus "*Cesarus* [*sic**]," and that all species not classed in subg. *Cerasus* are in subg. *Padus* ("bird cherries"); however, modern classifications of *Prunus* recognize at least three subgenera, necessarily including subg. *Prunus*.[1]

Tart cherry production rose over 1,000,000 metric tons "in the last decades." Almost two-thirds of production is in Europe, but the United States is the fifth-biggest producer; Chile

also is an exporter. Tart cherry is non-climacteric; that is, does not ripen after harvest. Variable maturity affects yield and quality. Processors have developed field indicators for ripeness that include fruit detachment force (FDF) and color parameters, especially intensity. Harvest at the best levels of maturity provides more pounds per tree, better color homogeneity, and reduced FDF compared to immature fruit, as well as decreased ascorbic acid (vitamin C) accompanying degradation of organic acids, a desirable quality in juice processing.

About 95% of the tart cherry harvest is commercially processed, with juice accounting for about half that amount. The rest are frozen, pureed, pitted and dried, powdered and quick-frozen, or concentrated. Processing affects chemical content. For tart cherry juice, mass press extraction preserves up to 83% anthocyanins and 62% procyanidins, "remarkably high" when compared to fruits such as blueberry (*Vaccinium* spp.). Tart cherry's anthocyanins are mostly water-soluble triglycerides and found mainly in fruit pulp, enabling higher yield. Adding sweeteners (unspecified) to tart cherry juice slightly reduces anthocyanin content. During storage, antioxidant compounds may degrade and color may change. Levels of polyphenols also change due to enzymatic oxidation, with monomeric anthocyanins most affected. Storage for six months at 68°F (20°C) led to formation of polyphenol derivatives and up to 75% decline in anthocyanin content. Innovations in processing, packaging, and storage are needed to better preserve tart cherry's bioactive compounds.

The authors define phytochemicals as secondary metabolites and as "non-nutritive molecules produced … by plants as a response to … stress. … " that "can provide potential health benefits over basic nutritional value. … " and "in general are safe to consume … ." However, this is confusing as the term "phytochemicals" is commonly used to refer to all plant constituents. The authors say that "reports on [tart cherries'] phytochemical profiles have been somewhat conflicting"; one must add that the information they present also is not well organized.

Phenolics, secondary metabolites with at least one aromatic ring and one or more hydroxyls attached, occur as simple low-molecular-weight molecules or large, complex ones like tannins. Some are synthesized from carbohydrates, with distribution and concentration of compounds varying within each tree and the fruit itself. The Montmorency cultivar has the greatest phenolic content in fruit skin and the highest antioxidant capacity. Flavonoids, hydroxyl and peroxyl radical scavengers, function synergistically with other antioxidants like ascorbic acid and tocopherol (vitamin E). Anthocyanins are the most prominent flavonoids in tart cherry. Others include flavonols, flavones, flavanols, flavanones, and isoflavones. With ripening, anthocyanin content increases, giving mature fruits their deep red color, and phenolic acid content falls. Color is a key harvest indicator. Colorimetric analysis and high-performance liquid chromatography register about the same levels of anthocyanins, supporting colorimetric field analysis. Genetic and environmental factors and processing affect anthocyanin content. The major fraction (about 70%) is cyanidin-3-glucosyl-rutinoside. Tart cherry anthocyanins include cyanidin and peonidin aglycones and anthocyanidins. Preserving these unstable compounds, a major challenge, has been addressed in one case with a cookie, using interactions between phenolics and protein to retain 19-59% of anthocyanins, which the authors consider "satisfactory." Flavonols in tart cherry include the antioxidants kaempferol, quercetin, and isorhamnetin rutinoside. Levels vary widely according to the original product and processing but are reported to be fairly stable in juice for six months at −13°F (−25°C). Non-flavonoid phenolics (phenolic acids) also are strong antioxidants. Tart cherries' chlorogenic and neochlorogenic acids are found in

similar quantities only in coffee; lesser amounts are found in blueberries and apricots (*P. armeniaca*).

Carotenoids in tart cherry have not been specifically investigated but are "assumed to be present." They have been reported for sweet cherry. Wild cherry (*P. serotina*, also in the subg. *Cerasus*) contains α- and β-carotene, lutein, and neoxanthin, but at modest levels. Another antioxidant, melatonin, was reported in tart cherries in 2001, but a 2009 report found low levels in Montmorency and Balaton cultivars and none in processed products. Tart cherries have little ascorbic acid (3-9 mg/100 g), again pointing to phenolics as the fruits' main antioxidant compounds.

While tart cherries' nutritional profile is "unremarkable," with low vitamin C and fiber, they offer unspecified minerals and vitamin A, with few calories if no sugar is added. Powdered tart cherry is used to improve muscle function, inflammation, oxidative stress, and pain from intense exercise. A tart cherry juice blend improved pace and inflammation markers in human runners and race horses. Cherry products are also reported to benefit soccer players, water polo players, and cyclists. Tart cherry juice modulates airway inflammation from induced pulmonary stress, reducing inflammatory markers in healthy athletes' respiratory tracts. Tart cherries reduce markers of inflammation and oxidative stress in rat microglial HAPI cells, including inducible nitric oxide synthase and cyclooxygenase-2, in a dose- and time-dependent manner. In a double-blinded, placebo-controlled, crossover study, tart cherry juice improved the ability of older subjects to resist oxidative damage and stress. In vitro, concentrates have especially high anti-inflammatory effects. Tart cherry seeds were investigated for effects on leukocytes from patients with rheumatoid arthritis, lowering heme oxygenase-1 expression. Cherries are traditionally used for gout, a chronic inflammatory condition. The US Food and Drug Administration has warned some producers against unproven claims. An internet-based study suggested that people with mild gout were more likely to try cherry products and therefore more likely to gain relief. However, an epidemiological study provided some support for a gout-protective effect, and a human study found significant decreases in plasma uric acid, excessive levels of which lead to gout attacks, with tart cherry concentrate use.

Phenolic compounds show potential against the development and progression of DM2 and its complications. Pancreatic α-amylase, one of two enzymes that hydrolyze carbohydrates into sugars, was inhibited in vitro by smoothies made with tart cherries and other polyphenol-rich fruits. In vivo, acute and subchronic injections of tart cherry extracts lowered blood glucose and exerted benefits in weight loss, reduced oxidative stress, and resulted in significant pancreatic cell regeneration. Obesity, strongly associated with DM2 and CV dysregulation, may be modulated with tart cherry consumption; in obese mice, a polyphenol-rich extract reduced blood glucose, reduced lipid accumulation and adiposity in liver tissue, and remediated uncontrolled accumulation of fat cells. A human randomized crossover trial replaced 20-30% of flour (from wheat [*Triticum aestivum*, Poaceae]) in muffins with tart cherry pomace. Glucose control was seen, as in other studies, with added benefits in hunger management and lower food intake. Metabolites of chlorogenic acid may be linked with reduced lipid accumulation. Quercetin also is reported to reduce lipid accumulation in liver cells in a dose-dependent manner. Besides reducing obesity, tart cherry offers other potential CV health benefits. Extracts from seeds alleviated ischemia-reperfusion-induced damage in rat and rabbit hearts in vitro. In a limited double-blind human study, similar extracts had little impact. In an acute, placebo-controlled, double-blind, randomized crossover trial, middle-aged patients with early hypertension who drank tart cherry concentrates had

lower systolic BP, but there was no effect on microvascular reactivity or arterial stiffness. Another study found no effect on the same CV disease markers but used healthy subjects who took half as much of the test substance as in the trial mentioned.

Tart cherries improved working memory in vivo, reducing age-related inflammation and slowing neurodegenerative disease. Tart cherry anthocyanins accumulated in rat brain cells after three weeks of supplementation, in a dose-dependent manner. Tart cherry juice may protect against neurodegeneration and exert antidepressant and anxiolytic effects in part because it inhibits monoamine oxidase A and tyrosinase. One study reported better memory and cognition in older adults with dementia who drank sweet cherry juice.

Metabolomics is the study of metabolites (collectively, the metabolome) produced by cells and tissues. In this review, the authors discussed metabolomics in the context of metabolites produced by gut microbiota (the microbiome). Increased knowledge of the metabolome and microbiome is needed to understand the fate of phenolic compounds within, and effects upon, the small intestine and its microscopic inhabitants. There has been no attempt to assess cherries' impact on these complex relationships. The authors summarize data on relevant pure polyphenols or fruits and plants with similar polyphenol content. Two genera of gut bacteria are reported to increase with polyphenol consumption, *Bifidobacterium* and *Lactobacillus* spp., both known as probiotics and the primary converters of quercetin and chlorogenic acid. They are stimulated by many other high-polyphenol foods.† The near absence of fiber in tart cherries offers few polysaccharides for fermentation. Microbial transformation of isoflavones has been well studied, as it produces the desirable metabolite equol. Equol production is not universal, however, leading to awareness of metabotypes. Equol-producing bacteria can also convert *trans*-resveratrol into dihydroresveratrol. Ellagitannins become urolithins; proanthocyanidins are converted to phloroglucinol and benzoic acid derivatives, including gallic, syringic, and coumaric acids. "Berries" (unspecified) and pomegranate (*Punica granatum*, Lythraceae) increase content of urolithins, phloroglucinol, and benzoic acid derivatives in the metabolome. Chlorogenic acid from coffee converts to dihydrocaffeic, dihydroferulic, and 3-(3'-hydroxyphenyl) propionic acids in rats and humans. In humans, the anthocyanin cyanidin-3-glucoside converts mostly to phenolic, hippuric, phenylacetic, and phenylpropenoic acids, known to modulate vascular reactivity and reduce inflammatory mediators. Protocatechuic acid, the main metabolite of cyanidin glucosides, has many potential health benefits. Tart cherries' unique polyphenol profile may produce metabolites from other pathways and gut biota.

—Mariann Garner-Wizard

* A spelling error repeated several times throughout this manuscript.

† An exception is lingonberry (*V. vitis-idaea*), shown to stimulate undesirable *Faecalibacterium*, *Bacteroides*, and *Clostridium* spp.

Reference

[1]Shi S, Li J, Sun J, Yu J, Zhou S. Phylogeny and classification of *Prunus* sensu lato (Rosaceae). *J Integr Plant Biol*. 2013;55(11):1069-1079.

Referenced article can be accessed at https://www.researchgate.net/publication/320095224_Tart_Cherries_and_health_Current_knowledge_and_need_for_a_better_understanding_of_the_fate_of_phytochemicals_in_the_human_gastrointestinal_tract.