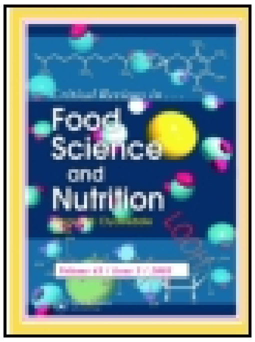

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Tart Cherries and health: Current knowledge and need for a better understanding of the fate of phytochemicals in the human gastrointestinal tract

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Abstract

Tart cherries are increasingly popular due to purported health benefits. This *Prunus cesarus* species is cultivated worldwide, and its market has increased significantly in the last two decades due to improvements in agricultural practices and food processing technology. Tart cherries are rich in polyphenols, with a very specific profile combining anthocyanins and flavonols (berries-like) and chlorogenic acid (coffee-like). Tart cherries have been suggested to exert several potentially beneficial health effects including: lowering blood pressure, modulating blood glucose, enhancing cognitive function, protecting against oxidative stress and reducing inflammation. Studies focusing on tart cherry consumption have demonstrated particular benefits in recovery from exercise-induced muscle damage and diabetes associated parameters. However, the bioconversion of tart cherry polyphenols by resident colonic microbiota has never been considered, considerably reducing the impact of in vitro studies that have relied on fruit polyphenol extracts. In vitro and in vivo gut microbiota and metabolome studies are necessary to reinforce health claims linked to tart cherries consumption.

Keywords

Tart cherries, Phytochemicals, Polyphenols, Gut microbiota, Metabolome

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1. Introduction

Tart cherries (*Prunus cerasus)* are among the ever-growing list of fruits branded as "super-foods". While the superfood concept tends to often rely on speculative assertions, the potential health benefits of tart cherries are relatively well documented. The significantly high phytochemical content in tart cherries (especially polyphenols) has most commonly been studied in the context of health, and there is solid evidence for high antioxidant properties at the very least (Blando et al. 2004,Ducharme et al. 2009,Levers et al. 2016,Matchynski et al. 2013,Wojdylo et al. 2014).

Functional food is a term broadly used to label foods that help to enhance some functions of the body as well as being nutritious (Hasler. 1996). It is important to note that "qualified health claims" are stringently regulated by FDA, and thus only few foods marketed as functional foods have strong scientific evidence of bringing health benefits. Therefore tart cherries, like other phytochemical-rich fruits, do not fulfill specific health claims (however, like most fruits and vegetables containing fibers and vitamins, they fulfill the general claims for reduced coronary heart disease and cancer risk). Still, there have been numerous reports of beneficial health impacts from consumption of phytochemical-rich fruits (Nile and Park. 2014). Tart cherries are particularly rich in polyphenolic compounds such as flavonoids: flavonols and anthocyanins; anthocyanins being responsible for the deep red color characteristic of the fruits (Damar and Eksi. 2012,Alrgei et al. 2016).

Several studies in recent years have suggested specific beneficial health properties from tart cherry consumption, notably a potential to alleviate muscle damage commonly associated with prolonged physical effort (Connolly et al. 2006,Kuehl et al. 2010,Kuehl. 2012). Tart cherries potential for prevention of chronic diseases such as cancer (Kang et al. 2003,Martin and Wooden. 2012) and cardiovascular abnormalities (Juhasz et al. 2013,Bak et al. 2006,Csiki et al. 2015), diabetes (Mahmoud et al. 2013) as well as inflammatory conditions (Ou et al. 2012,Saric et al. 2009) has also been reported. However, a significant portion of research has relied on *in vitro* or animal studies with isolated native polyphenolic extracts (in particular, antioxidant properties) (Kirakosyan et al. 2015,Kirakosyan et al. 2009,Mahmoud et al. 2014). Polyphenols, which are large and complex molecules, are known to be generally poorly absorbed in the small intestine. It has been shown that the colonic microbiota (the collection of microbes living in the large intestine) modifies and degrades polyphenols to smaller metabolites which become available to the host (Bohn. 2014,Bohn et al. 2015,Crozier et al. 2009). There is still only sparse knowledge on how fruit polyphenols modulate the gut microbiota, and into which metabolites they break down through colonic fermentation (Del Rio et al. 2013a). This represents a major limitation for previous in vitro studies using native polyphenols, since human cells/organs are most likely to be exposed to phenolic metabolites (Aura et al. 2013,Clifford et al. 2013,Larrosa et al. 2009a,Miene et al. 2011). Further, the strong individuality in human gut microbiota profiles (Turroni et al. 2017,Arumugam et al. 2011) and microbiome functions arguably leads to different metabolome profiles (Bolca et al. 2013,Tomas-Barberan et al. 2016).

The goal of this review is to present the current knowledge on tart cherries as a high value crop and describe the reported potential health benefits. The limited knowledge on gut microbiota modulation of tart cherries phytochemicals will also be presented.

2. Tart cherry economic importance

Cherry trees (genera *Prunus*) are represented by two subgenera, *Padus* (bird cherries) and *Cesarus*, however most berries of agricultural importance belong to the *Cesarus* subgenus. More specifically, the two main species grown worldwide are *Prunus avium* (sweet cherries) and *Prunus cesarus* (tart or sour cherries) (Brown-Skrobot et al. 1989). Cherries are considered high-value crop produced worldwide largely because of their purported health benefits (Bak et al. 2010,Bell et al. 2014a) rather than organoleptic properties. The current review will be focused on tart cherries.

Worldwide, tart cherries production has increased significantly in the last decades because of advances in agricultural practices, food technologies and raising global demand; from 2,154,000 to 3,057,000 metric tons. Europe leads the production with 65.8% of the total world production followed by Asia and America with 24.9% and 9.3% respectively (FAOSTAT, 2015). In 2013, the top five producer countries of tart cherry were Ukraine, Russian Federation, Poland, Turkey and the United States of America (USA). The USA produced 268,072 metric tons in 2013 and 2014 valued at more than $210 million. Michigan, Utah, and Washington are the three states with the highest production (USDA NASS, 2014). During the past decade, USA has been a leading exporter of this commodity and lately Chile has joined the export market, mainly to China, Russia and South Korea. Tart cherry production has increased due to recent improvement in agricultural practices, allowing producers to sell fruits at reasonable prices (Webster and Looney. 1995), before necessary processing into concentrate, juice, wine, brined, dried and powder, which have better palatability (Kirakosyan et al. 2009,Webster and Looney. 1995).

3. Pre and post-harvest and processing specificities

Tart cherry cultivars are the most tolerant plants to biotic and abiotic stress among their family (Rosaceae). However, during harvest tart cherries become susceptible to hot-dry weather, which reduces the harvest window and can be the cause of significant physico-chemical changes affecting color, polyphenol content and the detachment force, thus affecting the overall production (Aslantas et al. 2016). Appropriate harvest and postharvest handling are critical for higher quality of the commodity, however 55% of the total cost is spent when cherries are hand-harvested. In contrast mechanical harvesting was shown to lower the cost and enhance profits for the industry (Webster and Looney. 1995).

Tart cherry is a non-climacteric fruit, thus the variability of maturity throughout the tree influences quality and yields during harvest and processing. Industrial tart cherry processors rely on methods to determine optimum physio-chemical parameters of maturity including the fruit detachment force (FDF) and color parameters (Aslantas et al. 2016). The color characteristics, specifically the color intensity, have been reported to be an effective field indicator of maturity stage in cherry. Aslantas et al. (2016)

researched a standard procedure to determine the degree of maturity for harvest based on the fruit detachment force and fruit pomological and chemical characteristics. Tart cherries were classified into five stages of maturity per physical characteristics such as color and size by observation, where higher values meant higher level of maturity. The results indicated a strong relation between the physicochemical characteristics and the stage of maturation in the fruit; where the best three categories of maturity stages showed higher efficiency in poundage per tree, as well as improved homogeneity of color and reduced fruit detachment force. Ascorbic acid levels tend to decrease when maturity increases as degradation of organic acids occur, which is a desirable quality in the juice industry (Wojdylo et al. 2014,Karaaslan et al. 2016).

Around 95% of the tart cherry production is intended for industrial purposes; representing a great challenge for new processing technologies able to preserve bioactive compounds available for consumption. The production of juice accounts for about half of the tart cherry production destined to industry. Turkey, one of the largest producers, utilizes around forty percent of the tart cherries in production of juice or nectar because of the market demand and accessible handling for commercialization (Damar and Eksi. 2012). The rest of the production is distributed into frozen, purees, dried pitted tart cherry, powder from individually quick frozen (IQF), and concentrates. Every product undergoes different treatment technologies that have an impact on the content of bioactive compounds which varies according to the type of product. Table 1 presents an exhaustive list of the processing steps that tart cherries undergo to be converted to juice. In the production of juice, mash press extraction has been shown as the key step for optimal phenolic compounds recovery. To improve extraction three rinses are necessary to increase the recovery yield of bioactive compounds, reaching 83% of anthocyanin and 62% of procyanidins (oligomeric flavonoids) from the press cake (Toydemir et al. 2013b). The total extraction of these compounds is remarkably high in comparison to other fruits such as blueberries (Skrede et al. 2000); and two properties may explain this phenomenon. First, the molecular structure of the anthocyanin profile in tart cherry is dominated by water soluble chemical groups (tri-glycoside), which may increase the recovery of anthocyanins. Second, anthocyanins in the fruits are found mainly in the flesh facilitating disruption and enabling a higher yield of bioactive compounds in the end-product (Capanoglu et al. 2013,Toydemir et al. 2013a). Transformation of rich polyphenol plants tissues to processed products leads to changes in the phenolic profile with the formation of derived polyphenols (Crozier et al. 2009). The addition of sweeteners in cherry products has been shown to induce a slight decline in polyphenol concentration, especially the anthocyanins. Nevertheless, these products are more attractive to consumers and are still able to provide a high antioxidant activity and potential health benefits (Nowicka and Wojdylo. 2016).

Nutritional and health claims have substantially increased the demand of tart cherry in the industry and have generated interest of research in preservation and stability of the phytochemicals content and bioavailability in tart cherry after processing (Seeram et al. 2001a). During processed tart cherry products storage, physicochemical reactions take place where the antioxidant compounds are converted or degraded, and color may be altered. The concentration of polyphenolic compounds can also change due to

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enzymatic oxidation to quinones (Bonerz et al. 2007). Monomeric anthocyanins are the most affected by the storage steps that the products undergo. Furthermore, long term storage had been reported to affect the polyphenol profile and contents. Storage at 20°C for 6 months resulted in formation of polyphenol derivatives and significant decline (70–75%) of anthocyanin concentration (Bonerz et al. 2007). Also since this last step is key, packaging alternatives were tested to identify the most effective storage route for product quality (freeze-dried sour cherry) and polyphenols integrity. This study showed that most of polyphenols remain stable and in high concentration except anthocyanins which decreased by 62% after one year storage at lower temperatures (Zoric et al. 2016). These kind of food storage allow year-round tart cherry products availability, hence proper food processing practices to preserve the bioactive components is beneficial not only for the industry but for the consumers.

4. Tart cherry phytochemicals

Phytochemicals are secondary metabolites, non-nutritive molecules produced naturally by plants (Dillard and German. 2000) as a response to abiotic and biotic stress especially climate variation, mechanical damage, as well as a response to pathogen attack (Hirschi. 2009). Certain secondary metabolites are classified as phytochemicals if their chemical structure can provide potential health benefits over basic nutritional value (Dillard and German. 2000,Tsao. 2010). Phytochemical profiles are extremely variable across plant species (and even variety/cultivar); and environmental factors such as growth conditions, soil type and seasons result in further variability (Hirschi. 2009,Webster and Looney. 1995).

Cherries in general have been described as phytochemical rich fruits with potential health benefits, while reports on their phytochemical profiles have been somewhat conflicting (Kirakosyan et al. 2009,Kirakosyan et al. 2010,Ou et al. 2012). While there is convincing evidence that phytochemicals in general are safe to consume, one should remember that in vitro experiments that constitute a large fraction of our current knowledge are only partially representative of actual human metabolism and physiology (Nile and Park. 2014,Steinberg et al. 2003,Amin et al. 2015,Bak et al. 2006). Moreover, the interaction between phytochemicals may result in changes in physio-chemical characteristics such as solubility, stability and bioavailability of the active compounds in the products (Kirakosyan et al. 2010). Total polyphenol, monomeric anthocyanins, and ascorbic acid are well known to possess remarkable anti-oxidant properties (Moyer et al. 2002,Seeram et al. 2008,Del Rio et al. 2013b,Landete. 2012,Redondo et al. 2017). However, most of the antioxidant response was thought to come from the anthocyanins fraction but it actually derives mostly from phenolic acids (Damar and Eksi. 2012).

The phytochemicals in tart cherries are carotenoids and phenolics: phenolic acids and flavonoids (Damar and Eksi. 2012,Blando et al. 2004,Kirakosyan et al. 2009).

4.1. Phenolics

Phenolics are secondary metabolites produced by plants which have at least one aromatic ring with a single or several hydroxyl groups attached, ranging from simple low molecular weight up to complex large molecules such as tannins. Some phenolics are synthesized from carbohydrates following shikimate and phenyl propanoid pathways (Ferretti et al. 2010). The distribution and concentration of phenolics varies within each tree and within the fruit as shown in Table 2. Montmorency tart cherry cultivar have highest phenolic content in their skin, leading to higher antioxidant capacity (Chaovanalikit and Wrolstad. 2004). The synthesis and accumulation of phenolics in the skin is used as a natural harvest indicator, provides organoleptic characteristics to the fruit constituting a natural defensive mechanism.

The phenolic compounds in tart cherry contribute to their sensorial attributes like color and flavor (Ferretti et al. 2010) (Table3). There is also a great interest on the preventive functionality that phenolic compounds have shown in several animal and human models exposed to chronic and/or long term diseases such as, cancer or diabetes and associated features such as oxidative stress.

For a clearer understanding, phenolic compounds are classified into flavonoids and non-flavonoids (Bravo. 1998,Tsao. 2010).

4.2. Flavonoids

Flavonoids have attracted interest because of their influence as health promoter compounds. The widely-studied anthocyanins are well known for their antioxidant capacity (Casedas et al. 2016,Khoo et al. 2012,Wojdylo et al. 2014)(Khoo and others 2011; Wojdylo and others 2014b; Casedas and others 2016; Nowicka and others 2016). Other flavonoids include flavonols, flavones, flavanols, flavanones, and isoflavones. Flavonoids are recognized for their ability of scavenge hydroxyl and peroxyl radicals and also function in synergy with other antioxidants and other bio-compounds such as tocopherol and ascorbic acid.

4.3. Anthocyanins

Anthocyanins are synthetized mainly during ripening and are responsible for the color change from green to deep red (Karaaslan et al. 2016). Tart cherries have been shown to contain high levels of anthocyanins and phenolic acids which have an inverse relationship: during early stage the fruit is high in phenolic acids, while anthocyanins synthesis increases towards ripening (Karaaslan et al. 2016,Wojdylo et al. 2014,Blando et al. 2004,Damar and Eksi. 2012), resulting in the characteristic deep red color of tart cherries. Since color means such an important parameter for harvest and sensorial control, Kim et al (Kim et al. 2005) also evaluated the total content of anthocyanins in cherries using two approaches: a colorimetric assay and HPLC. While comparing both methods the anthocyanin levels from both were almost the same, meaning that the total count of anthocyanins colorimetric assays gave a similar result when compared with the sum of individual anthocyanins analyzed with HPLC.

Several factors strongly affect the anthocyanin content such as genetic background and environmental characteristics (Karaaslan et al. 2016) or if the tart cherries are analyzed as fresh fruit or as processed product (Kirakosyan et al. 2009). However, the major fraction corresponds to Cyanidin-3-glucosyl-rutinoside, accounting for approximately 70% of the total anthocyanin concentration (Blando et al. 2004,Chaovanalikit and Wrolstad. 2004,Daenen et al. 2007,Kang et al. 2003,Seeram et al. 2001a,Tall et al. 2004). Anthocyanins have been reported to be the major phenolic in tart cherries,in particular cyanidin and peonidin aglycones and anthocyanidins (Fang 2015) (Table 4).

Although, anthocyanins are the major compound in tart cherries, they are also the most unstable and handling in industrial levels is a challenge (Chaovanalikit and Wrolstad. 2004,Kirakosyan et al. 2009,Zoric et al. 2016). Vesna et al (2016) developed a cookie taking advantage of the positive interaction between proteins and phenolics, resulting in a satisfactory retention of anthocyanins (19-59%).

4.4. Flavonols

Flavonols are a subclass of flavonoids that are naturally produced by plants with important antioxidant potential (Kirakosyan et al. 2009). The reported flavonols content in cherry products vary significantly, this phenomenon can be due to several causes such as the kind of product itself, the conditions it was subjected during processing as well as to the environmental and agricultural conditions where the plant was grown (Toydemir et al. 2013b). In a study of interaction of isolated polyphenols from tart cherry fruits, it was found that kaempferol and quercetin were the primary contributors of the antioxidant (TEAC) properties (Kirakosyan et al. 2009), with Trolox equivalent antioxidant capacity (TEAC) values of 4.5 mM TEAC and 4.2 mM respectively. The flavonols reported from tart cherry products are kaempferol-3-rutinoside, quercetin-3-glucoside, quercetin-3-rutinoside, quercetin-3-(2-glucosyl-rutinoside) and isorhamnetin rutinoside (Table 5). They were found to be fairly stable in tart cherry juice stored six months at freezing temperature (-25°C) (Bonerz and others 2007a; Li and others 2008).

4.5. Phenolic acids

Phenolic acids are non-flavonoid polyphenolic compounds recognized for their strong antioxidant activity; and divided into two subclasses: hydroxyl-benzoic acids and hydroxyl-cinnamic acids. Recent studies reported that tart cherries are rich in chlorogenic and neochlorogenic acids (Table 6), which have only been described in similarly high quantities in coffee (Karaaslan and others 2016; Casedas and others 2016) and in lower abundances in apricots and blueberries (Cho et al. 2004,Dragovic-Uzelac et al. 2007).

4.6. Carotenoids and other phytochemicals

While carotenoids are assumed to be present in tart cherries, there have been no reports on detection and quantification specifically on tart cherries. Carotenoids, including α and β-carotens, lutein and neoxanthin have been detected in wild cherries; however total carotenoids levels did not exceed 12.6 mg/kg, whereas carotenoids-rich vegetables often contain hundreds of mg/kg of just one of these carotenoids (Mikulic-Petkovsek et al. 2016). Carotenoids have been reported to be present in sweet cherries (McCune et al. 2011), however original reports could not be tracked back. Carotenoids were also detected in very low levels (0.02 mg/g DW) in cherries (presumably sweet) in comparison with carrots and bell peppers in a study conducted in New Zealand (Leong and Oey. 2012).

The potentially antioxidant melatonin (N-acetyl-5-methoxytryptamine) had been reported in high levels in tart cherries (Burkhardt et al. 2001), however more recent reports indicated that melatonin was in low concentration in Montmorency and Balaton tart cherries and completely absent in processed tart cherry products (Kirakosyan et al. 2009). Finally, tart cherries contain relatively low (3-9 mg/100 g) amounts of ascorbic acid (Vitamin C) (Papp et al. 2010), confirming that tart cherries antioxidant potential mainly derive from phenolic compounds.

5. Impact on nutrition and health

There are several studies suggesting health promoting benefits could be associated to tart cherries consumption including effects on chronic diseases such as cancer, diabetes and cardiac complications (Bajerska et al. 2016,Czompa et al. 2014,Bobe et al. 2006,Martin and Wooden. 2012,Saleh et al. 2017). These studies have generally focused on the content and functionality of phytochemicals of tart cherries and connected specifically with the antioxidant activity.

5.1. Nutrition

Tart cherry fruits have somewhat unremarkable nutritional composition (Table 7), with low fiber and vitamin C content, but represent a good source of minerals and vitamin A. In addition, the necessary food processing tends to even lower the contents of valuable nutrients. One advantage is that unsweetened tart cherries products have low sugars and calories.

5.2. Tart cherries impact on exercise

The antioxidant effect phytochemicals in powdered tart cherry has been suggested to improve muscle function recovery and reduce inflammation, oxidative stress and pain

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associated with intensive exercise (Bell et al. 2014a). Consumption of tart cherry juice blend have been shown to reduce significantly muscle damage symptoms caused by intensive strength exercise or running in humans (Connolly et al. 2006,Kuehl et al. 2010,Howatson et al. 2010,Bowtell et al. 2011) and horses (Ducharme et al. 2009).Tart cherries supplementation intake was shown to improve the average of race pace, as well as modulating the balance in oxidative stress, decreasing inflammation markers and improving muscle recovery (Levers et al. 2015,Levers et al. 2016). Another study investigated the potential effect of tart cherry concentrate on muscle recovery after prolonged and intermittent exercise such as soccer Tart cherry supplementation resulted in faster recovery and lower muscle soreness suggesting modulation of oxidative stress and inflammation post-exercise (Bell et al. 2016). Similar results were reported in water-polo players consuming tart cherry products (McCormick et al. 2016) as well as other type of high intensity exercise (Bell et al. 2015) including cycling (Bell et al. 2014b). Another concern about extended exercise recovery has to do with airway inflammation (respiratory mucosal inflammation) directly linked with induced pulmonary stress. Tart cherry juices seemed to have a modulatory effect as well as reducing inflammatory markers in the respiratory tract of healthy athletes, leading to faster recovery (Dimitriou et al. 2015).

5.3. Antioxidant and anti-inflammatory potential

Tart cherries have been shown to modulate inflammatory and oxidative stress expression in HAPI cells (rat microglial cells) such as nitric oxide, inducible nitric oxide synthase and cyclooxygenase-2 in dose and time dependent manner (Shukitt-Hale et al. 2016a). The inflammatory activity in the hippocampus of older rats, measured through COX-2 expression, decreased significantly after six weeks of tart cherry supplementation (Thangthaeng et al. 2016). Similar anti-inflammatory potential were observed in mice consuming tart cherry juice (Saric et al. 2009). A double-blind, placebo-controlled, crossover dietary intervention demonstrated that consumption of tart cherry juice improved the ability of older men and women to resist oxidative damage and stress (Traustadottir et al. 2009). Another study demonstrated that various tart cherry products possessed remarkable antioxidant (ORAC properties), but that concentrates in particular have higher anti-inflammatory properties as measured by COX-1 inhibition in vitro (Ou et al. 2012).

Tart cherry have also been used as supplementation for treatment of rheumatoid arthritis, in this case tart cherry seeds were used to investigate its promoting health activity over inflammatory disorder. Blood leukocytes from rheumatic arthritis patients were used and subjected to lipopolysaccharide and seeds extract for 24 hours and was reported a decreased expression of heme oxygenase-1 (inflammatory marker) that control oxidative stress and therefore intervene on inflammation expression (Mahmoud et al. 2014,Mahmoud et al. 2013).

5.4. Potential impact of metabolic diseases

5.4.1. Diabetes and Obesity

Phenolic compounds have shown promising results associated with neutralization of development and progression of diabetes and its complications (Lachin. 2014).

Although further in vivo studies are needed, this may represent an alternative to current treatments.

Two enzymes are in charge to hydrolyze carbohydrates: pancreatic alpha-amylase and intestinal alpha-glucosidase needed to break down to monosaccharides. Therefore, one postulated manner to control hyperglycemia and type 2 diabetes is to interfere the role of these enzymes. Nowicka et al (2016) showed effective inhibition of those enzymes in in vitro assays through consumption of smoothies made of tart cherry and other fruits rich in phytochemicals. Comparable in vitro results were found with tart cherries anthocyanins having inhibitory activity towards alpha-amylase (Homoki et al. 2016).

A recent study was carried out to evaluate the hypoglycemic effect of tart cherry extracts in acute and sub-chronic injections to mice, both leading to dose-dependent restorative effects. The acute injection resulted in a decrease of blood glucose level and the sub-chronic scenario an even stronger amelioration of glucose levels as well as effects on weight loss and oxidative stress and significant pancreatic cell regeneration (Saleh et al. 2017). Another health problem associated with diabetes is obesity and the harmful impact of adiposity over metabolism. Here again the consumptions of tart cherry extracts also resulted in lower blood glucose in obese mice fed with polyphenol-rich cherry extract after food deprivation. The extract consumption also reduced lipid accumulation, adiposity accumulation in the liver tissue and remediate the uncontrolled accumulation of fat cultured cells (Snyder et al. 2016).

The potential to use by-products such as pomace of juice production has been considered due to the elevated content of phytochemicals. A human randomized crossover trial (one test meal followed by glycemic response measurements) was performed using tart cherry pomace as ingredient of muffins replacing part of the flour (20 or 30%). The results in terms of controlling glucose levels were similar to other studies mentioned before but the enriched muffins were also effective managing hunger and food intake. Those food products could be a suitable alternative for a healthy breakfast or snack in additions to its sensorial acceptance (Bajerska et al. 2016).

Certain phytochemicals are also associated with antihyperlipidemic effect. An investigation in rats showed reduction of lipid accumulation in liver tissue, which appeared to be linked with phenolic acids in tart cherry such as chlorogenic acid and more specifically its metabolites rather than anthocyanins. Such metabolites may have a connection with enzymes of hypocholesterolemic functions (Papp et al. 2015). In a similar way another study was done with a cell culture model which explained a dose-dependent influence decreasing lipid accumulation when the cells are expose to 100 µmol/L of quercetin (Snyder et al. 2016). More studies will be needed to conclude on the potential antihyperlipidemic and antiadiposity properties of tart cherries.

5.4.2. Cardiovascular disease

Cardiovascular dysfunction is a leading cause of death among chronic diseases in industrialized countries. Polyphenol-rich fruits have seen increased interest for potential cardiovascular health protective effects (Habauzit and Morand. 2012,Habauzit

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et al. 2015). Tart cherries kernel extracts were shown to alleviate ischemia reperfusion-induced damage in isolated rat (Bak et al. 2006) and rabbit (Juhasz et al. 2013) hearts. Only marginal impact was observed when humans where given similar extracts in a limited double-blind study (Csiki et al. 2015).

An acute, placebo-controlled, double-blinded, cross-over, randomized intervention was performed in a group of middle age volunteers with early hypertension. Volunteers consumed tart cherry concentrates (60mL equivalent to 180 cherries). The concentrate consumption was effective in reducing their systolic blood pressure but not microvascular reactivity nor arterial stiffness. This effect maybe associated to the phenolic acids content and could be extended to other rich phytochemical fruits which can serve as systolic blood pressure modulators (Keane et al. 2016b). Another study reported no detectable effect on the same cardiovascular disease biomarkers, however the study focused on healthy subjects consuming only 30 mL of the same concentrate (Lynn et al. 2014).

5.5. Other potential health benefits

Tart cherries consumption was shown to improve the working memory in aged rats having an influence on reducing inflammation linked with aging and therefore promoting delay on neurodegenerative diseases (Thangthaeng et al. 2016). Furthermore, tart cherry anthocyanins were reported to accumulate in brain cells of rats after three weeks in a dose-dependent manner as well (Kirakosyan et al. 2015). Casedas et al (2016) reported that tart cherry juice may have protective effect against neurological diseases, with antidepressant and anxiolytic properties, possibly due to the ability to inhibit monoamine oxidase A and tyrosinase. In addition, another study showed improved memory and cognition in older adults affected with dementia through consumption of (sweet) cherry juice (Kent et al. 2017)

Tart cherries, in fact all cherries; have been increasingly suggested as beneficial to reduce the risk of gout attacks, a specific inflammatory arthritis condition. However, FDA has warned several cherry producers about claims based on unsubstantiated data, and an epidemiological dietary study provided limited evidence for potential gout protective effect (Zhang et al. 2012) and a later internet based survey suggested that any correlation seen may be due to the fact that patients with milder symptoms are more likely to consume cherries or other plant-based supplements and no treatment, effectively skewing the data (Singh et al. 2015). However, a human study showed that tart cherry concentrate consumption resulted in significant decrease of plasma uric acid, which is purported as the main driver of gout attacks (Bell et al. 2014c).

6. Fate of cherry polyphenols in the digestive system

It has been assumed for a long time that the impact of polyphenols on health could be identified by exposing human cell lines to more or less purified fractions from fruits (or other plant material) (Haddad et al. 2013,Hanbali et al. 2013,Mahmoud et al. 2014,Mahmoud et al. 2013,Martin and Wooden. 2012,Shukitt-Hale et al. 2016b). However, it is also well known that most polyphenols cannot be absorbed by cells or reach the blood circulation due to their high molecular size (Moco et al. 2012a,Marin et al. 2015). In the mammalian digestive system, large non-digestible dietary molecules are subject to fermentation, modifications and degradation by the resident microbes (designed under the terms microbiome or microbiota) (Sheflin et al. 2017). The human colonic microbiome has therefore become the subject of intense research (Flint et al. 2012,Holmes et al. 2011), in particular in relation to health and diseases (Candela et al. 2014,Carbonero et al. 2012b,Carbonero et al. 2012a,O'Keefe et al. 2015,Everard and Cani. 2013,Sartor. 2008,Kostic et al. 2014) It is now well known that diet composition strongly influences the gut microbiome taxonomic composition and metabolic functions (Flint. 2012,Sheflin et al. 2017). A corollary research field is metabolomics; the study of the metabolites deriving from gut microbe activities (Wishart et al. 2016,Moco et al. 2012b). The human metabolome is known to include thousands of small molecules detected in stool, urine and blood; which are far more bioavailable than parent molecules. As far as we know, there has been no attempt to decipher the impact of tart cherries consumption on the human gut microbiome and metabolome. Therefore, in this section, we will describe the potential effects based on published data on relevant pure polyphenols or fruits/plants with similar polyphenolic profiles.

6.1. Polyphenols and polyphenol-rich food impact on the gut microbiota

Several reviews on the impact of dietary polyphenols on the gut microbiota are available (Duda-Chodak et al. 2015,Tomas-Barberan et al. 2016,Sheflin et al. 2017). The two genera that are reported the most often as being stimulated by polyphenols are *Bifidobacterium* and *Lactobacillus*, both known for their probiotic properties (Larrosa et al. 2009b,Chen et al. 2016,Li et al. 2015,Espley et al. 2014,Faria et al. 2014a,Mills et al. 2015). In addition, it has been shown that those genera are the primary converters of quercetin (Zhang et al. 2014), and chlorogenic acid (Ludwig et al. 2013), while their role in bioconversion of other polyphenols remains elusive. Quercetin has been shown to be degraded by *Escherichia coli* and *Bacteroides fragilis (Zhang et al. 2014)*. Isoflavones are converted by *Aldercreutzia* spp. and *Slackia* spp (Guadamuro et al. 2017). Elagitannins were found to increase the numbers of *Akkermansia* in vivo (Li et al. 2015).

Tea, coffee, cocoa, berries mango and pomegranate, all rich in polyphenols were all found to stimulate *Lactobacillus* and *Bifidobacterium* (Jaquet et al. 2009,Bialonska et al. 2010,Ojo et al. 2016,Jakobsdottir et al. 2013,Truchado et al. 2012,Puupponen-Pimiä et al. 2013,van Duynhoven et al. 2013). The main exception is lingonberries, which have been shown to increase *Faecalibacterium*, *Bacteroides* and *Clostridium* levels (Heyman-Linden et al. 2016,Matziouridou et al. 2016).

To the best of our knowledge, there have been no in vitro, animal or human dietary intervention studies on the impact of tart cherries (and sweet cherries) consumption on the gut microbiome. Based on cherries polyphenolic profiles, stimulation of *Lactobacillus*, *Bifidobacterium* and/or *Bacteroides* can be hypothesized, but the bioavailability of specific polyphenols in various tart cherry products probably influence their impact on gut microbiota. It can be hypothesized that other phytochemicals would have limited impact because of very low concentration; and the near-absence of fibers suggests that tart cherries would provide low amounts of polysaccharides for microbial fermentation.

6.2. Microbial derived metabolites from dietary polyphenols

Isoflavones have been studied extensively because microbial biotransformation leads to the very beneficial equol metabolite (Setchell and Clerici. 2010,Setchell et al. 2002). However, it was also shown that equol production is not universally distributed (Frankenfeld et al. 2014,Reverri et al. 2016) leading to the concept of metabotypes. While the potential health benefits of resveratrol have been put under scrutiny, it is known that equol producing bacteria are able to convert trans-resveratrol to dihydroresveratrol (Bode et al. 2013). There is extensive evidence that elagitannins are converted to urolithins (Espin et al. 2013,Selma et al. 2014,Puupponen-Pimia et al. 2013,Gimenez-Bastida et al. 2012) and proanthocyanidins to phloroglucinol and benzoic acid derivatives: gallic, syringic and coumaric acids (Faria et al. 2014b,Hanske et al. 2013).

Metabolomics studies have been conducted on different food types. Tea catechins were found to be converted to conjugated catechins, valerolactones, valeric acids and other phenolic acids(Grun et al. 2008,Gross et al. 2010). Berries and pomegranate were shown to enrich metabolomes in urolithins, phloroglucinol and benzoic acid derivatives (Truchado et al. 2012,Jakobsdottir et al. 2013). Studies on citrus fruits, which are rich in esperetin, naringenin, and ferulic acid, showed microbial production of different hydroxyphenyl propionic acids(Pereira-Caro et al. 2015).

Chlorogenic acid from coffee was shown to be converted to dihydrocaffeic acid, dihydroferulic acid, and 3-(3'-hydroxyphenyl) propionic acid in rats (Gonthier et al. 2003) and in humans (Ludwig et al. 2013). The anthocyanin cyanidin-3-glucoside was shown to be converted mainly to phenolic, hippuric, phenylacetic, and phenylpropenoic acids in humans through isotope pulse-chase studies (Czank et al. 2013). These metabolites were shown to modulate vascular reactivity (Edwards et al. 2015) and reducing the expression of inflammatory mediators (Amin et al. 2015) in vitro. Protocatechuic acid in particular has been reported as the main metabolite of gut microbiota fermentation of cyaniding glucosides and has been shown to exert several potential health benefits (Amin et al. 2015,Hornedo-Ortega et al. 2016,Olivas-Aguirre et al. 2016,Wang et al. 2016,Woodward et al. 2011,Seeram et al. 2001b). It is expected that similar metabolites are produced through gut microbiota fermentation of tart cherries, though it is possible that the unique polyphenol profile results in different metabolic pathways and metabolomics profiles.

7. Conclusions and perspectives

This review provides an update on the current investigation in regard to the promising phytochemicals content in tart or sour cherries. Improvements in agricultural practices and processing combined with health claims have resulted increased worldwide production. Health claims are mainly associated with high polyphenol concentration, as well as specific profile. However, it is necessary to determine the fate of those polyphenols in the human gastrointestinal tract. Based on studies on other polyphenol-rich fruits, it is expected that tart cherries consumption has potential to significantly modulate the gut microbiota composition and metabolic activities, leading to the release of specific phenolic metabolites. The potential health benefits of modulated gut microbiota and phenolic metabolites presumably differs from health properties described by in vitro studies of native polyphenols extracts from tart cherries.

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Table 1.Description of tart cherry juice processing steps

Processing step	Treatment & conditions	Aim	Weight data
Fresh fruit	Washing and selection	Removal of unwanted material	3.5% reduction in wet-weight
Fresh fruit and stalk	Separation of stalks	Stalk removal	2% and 4% reduction in wet- and dry-weight bases
Mash heat	Mash heating; 80°C for 90s	Enzyme inactivation	No change
Mash press	Pressing; 110bar-horizontal press	Obtaining the juicy part	73% juice yield
Mash press cake extract	Mash press extraction-(repeated 3 times)	Increasing the yield of juice	Juice yield increased to 85%
Press cake with seeds	Press cake resulting after mash press	Removal of insoluble fruit parts	15% reduction wet-weight; 29% dry-weight
Pasteurized juice	Pasteurization of pressed juice; 95°C for 90s	Microbial inactivation	No change
Enzyme treated juice	Enzymation; 50°C for 2h	Degradation of pectic substances and starch	pectolytic enzyme and amylolytic enzyme
Clarified juice	Clarification; 50°C for1h	Precipitating haze precursors	780 g gelatin/t juice1.2 kg bentonitef/t juice
Filtered juice and filtration residue	Ultrafiltration	Obtaining the clear juice by removing precipitates	6% and 7% reduction in wet- and dry-weight -
Concentrated juice	Evaporation to 65˚Brix (Bx); 65-80°C	Volume reduction for storage	12.5˚Bx evaporated to 65˚Bx
Non paper-filtered and paper-filtered	Paper filtration	Elimination of *Alycyclobacillus* bacteria	Negligible
Nectar	Addition of sucrose and citric acid	Production of nectar	56% sucrose on dry-weight basis with:
Pasteurized nectar	Pasteurization of final nectar; 95°C for 45s	Microbial inactivation	

Table 2.

Cultivar	Portion	Anthocyanins (mg cy-3-glu/100gfw)	Total phenolics (mg GAE/g fw)	ORAC (µmoles TE/g fw)	FRAP (µmolesTE/g fw)
Montmorency	Flesh	0 ± 0.1	3.± 0.3	15 ± 1	13.8 ± 0.3
	Pits	0.8 ± 0.1	1.6 ± 0.02	9.8 ± 0.3	8.5 ± 0.9
	Skins	36.5 ± 1.6	5.6 ± 0.3	51 ± 2	48 ± 1.3

Table 3. Phytochemical profiles and antioxidant properties in different tart cherries food products

Product	Total anthocyanin	Phenolic acids	Total phenolic	Antioxidant capacity	Reference
Puree (mg/100g)	21.5-25.1	9.3-23.3	147.2-200		(Nowicka and Wojdylo. 2016)
Fruit (Italian cultivars) (mg/100g)	27.8-80.4			2000-2600 µmol TE/100g fw	(Blando et al. 2004)
Fruit (Turkish cultivars) (mg/100g)	21-285				(Damar and Eksi. 2012)
Fruit (Turkish cultivars) (mg/100g)	45		275.4	19 mmol TE/Kg	(Karaaslan et al. 2016)
Dried (µg/g)	62-564[a]		3522-7813[b]	3.3.5 mmol/L	(Kirakosyan et al. 2009)
frozen(µg/g)	533-1741[a]		6742-12665[b]	4.4-4.5 mmol/L	
Concentrate (µg/g)	213-722[a]		2541-4013[b]	3.5 mmol/L	
IQF powder(µg/g)	482-1063[a]		7752-10323[b]	9.8-9.9 mmol/L	
Lyophilized juice (mg/Kg)	0.19		9.84		(Casedas et al. 2016)

[a]dry weight of cyanidin -3-glucoside equivalent;

[b]dry weight of gallic acid equivalent

Table 4. Anthocyanins concentrations across varieties and product presentation

Product	Cyanidin-3-sophoroside	Cyanidin-3-glucosylrutinoside	Cyanidin-3-glucoside	Cyanidin-3-rutinoside	Reference
Fruit (Italian cultivars) (mg/100g)	0.7-2.3	17.3-71.9	0.5-0.9	9.3-25.3	(Blando et al. 2004)
Fruit (Turkish cultivars) (mg/100g)	0.48	28.1	1.2	9.2	(Karaaslan et al. 2016)
Juice (German and Hungarian cultivars) (mg/L)	39-185	361-515		125-213	(Bonerz et al. 2007)
Juice (Turkish cultivars) (mg/L)	2.6-21.5	140.3-320.9	2-9.9	35.4-85.5	(Damar and Eksi. 2012)
Dry (µg/g)	1.9-15.7	11.1-203.6	0.7-7.6	6.9-95.8	(Kirakosyan et al. 2009)
Lyophilized juice(µg/g)		0.08			(Casedas et al. 2016)

Table 5. Flavonols profile and concentration in tart cherry products.

Flavonol/Unit	Dry	Frozen	Concentrate	IQF powder	Juice	
	µg/g	µg/g	µg/g	µg/g	mg/L	References
Isorhamnetin rutinoside	35.8-383.1	250.2-328.9	163.7-288.1	62.9-176.6	14-33	(Kirakosyan et al. 2009)
kaempferol	12.9-42.9	3.8-13.1	5.2-11.9	16.8-85.9		
Quercetin	1.9-8.8	5.9-8.5	2.1-6.7	556.2-292.6		
Melatonin	nd	2.9-12.3	nd	1.7-7.5		
Quercetin-3-(2-glucosylrutinoside					11-31	(Bonerz et al. 2007)
Quercetin-3-rutinoside					18-59	
Quercetin-3-glucoside					3-8	
Kaemferol-3-rutinoside					4-13	

Table 6. Phenolic acids profile in tart cherry.

Sample	Neochlorogenic acid	Chlorogenic acid	Caffeic acid	Author
Fruit (mg/Kg)	584.7	-	33.3	(Karaaslan et al. 2016)
Lyophilized juice (mg/Kg)	1.6	0.6		(Casedas et al. 2016)

Table 7. Nutrient composition of Tart cherry compared to Sweet cherry (values in 100 grams: Adapted from USDA ARS 2017).

		Sweet cherry	Tart Cherry
Nutrient	Unit	Value/100 g	Value/100 g
Energy	kcal	63	50
Protein	g	1.06	1
Fiber, total dietary	g	2.1	1.6
Sugars, total	g	12.8	8.5
Minerals	mg	267.4	216.4
Vitamin C, total ascorbic acid	mg	7	10
Thiamin	mg	0.03	0.03
Vitamin A, IU	IU	64	128
Vitamin E (alpha-tocopherol)	mg	0.07	0.07
Vitamin K (phylloquinone)	µg	2.1	2.1

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