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Review

The role of cherries in exercise and health

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Recently, cherries and cherry products have received growing attention within the literature with regard to their application in both exercise and clinical paradigms. Reported to be high in anti-inflammatory and anti-oxidative capacity, cherries and their constituents are proposed to provide a similar but natural alternative akin to over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics. Within exercise paradigms, concern has been raised with regard to the use of products, which inhibit such inflammatory or oxidative actions, because of the possibility of the blunting of physiological training adaptations. Despite this, numerous scenarios exist both within exercise and clinical populations where a goal of optimal recovery time is more important than physiological adaptation. This review critically evaluates and discusses the use of cherries as a supplementation strategy to enhance recovery of muscle function, inhibit exercise-induced inflammation, oxidative stress, and pain primarily; furthermore, the potential application of cherries to clinical populations is discussed.

Research into supplementation with "functional foods" in health and exercise science has gained momentum in recent years. Beetroot juice (Bailey et al., 2009, 2010; Ferreira & Behnke, 2010; Vanhatalo et al., 2010; Lansley et al., 2011a,b), purple sweet potatoes (Chang et al., 2007, 2010), blueberries (Sanchez-Moreno et al., 2008; McAnulty et al., 2011), pomegranate juice (Trombold et al., 2010, 2011), green tea (Eichenberger et al., 2010; Jowko et al., 2011), lychee extract (Nishizawa et al., 2011; Kang et al., 2012), and cherries (Connolly et al., 2006; Ducharme et al., 2009; Howatson et al., 2010, 2011a, b; Kuehl et al., 2010; Bowtell et al., 2011) have received varying degrees of attention in relation to their purported applications. The last of these, cherries, have provided several avenues for research because of the high levels of bioactive compounds present within them and have been compared favorably with other functional foods. More specifically, both sweet and tart cherries contribute to dietary fiber intake and contain high levels of antioxidants such as melatonin, carotenoids, hydroxycinnamates, and several flavonoid groups including anthocyanins, as well as the flavonol quercetin (McCune et al., 2011). Bioavailability of these potent phytochemicals has been shown to differ depending upon food source and dose (Manach et al., 2005). Reports suggest that quercetin metabolites have a slow elimination rate, with half-lives ranging from 11 to 28 h reported, and as a result, plasma accumulation may be possible with multiple doses (Manach et al., 2005). Conversely, anthocyanins are rapidly absorbed with poor efficiency and are quickly eliminated (Manach et al., 2005). Although it has been suggested that anthocyanins may be efficiently absorbed into the gastrointestinal tract tissue efficiently, with the subsequent transport into the circulation being the point at which overall dose efficiency decreases (Wallace, 2011). Additionally, the food matrix and gut microflora may also play a significant role in the metabolism, absorption, and subsequent bioavailability of anthocyanins (Manach et al., 2005; Wallace, 2011). A detailed review has recently been provided by McCune et al. (2011) outlining specific nutritional properties of cherries.

Such antioxidants have been demonstrated to be: (a) proficient in the reduction of cell damaging oxidative stress (Wang et al., 1997, 1998, 1999; Boyle et al., 2000; Bitsch et al., 2004; de Boer et al., 2005; Traustadottir et al., 2009); (b) high in anti-inflammatory capacity (Howatson et al., 2010; Kelley et al., 2006; Seeram et al., 2001); and (c) inhibit uric acid production (Jacob et al., 2003), which, although is a powerful antioxidant, is also implicated in the development of gouty arthritis (Schlesinger & Schlesinger, 2012; Zhang et al., 2012; Kelley et al., 2013). Resultantly, cherries have been implicated in their use as a natural nutritional supplement

for the treatment of chronic inflammatory and hematological diseases, cancer, cardiovascular disease, and diabetes. To date, only a single clinical trial (Schumacher et al., 2011) has been conducted to support such implications; however, several anecdotal reports dating back as early as 1950 have promoted cherry supplementation in the treatment of chronic inflammatory disease (Blau, 1950; Jacob et al., 2003; Schlesinger & Schlesinger, 2012; Kelley et al., 2013).

While cherry supplementation has received attention for its application in clinical populations (Jacob et al., 2003; Kang et al., 2003; Kim et al., 2005; Kelley et al., 2006; Traustadottir et al., 2009; Pigeon et al., 2010; Howatson et al., 2011a, b), a growing body of research has investigated its use within the exercise domain. The ability to recover quickly and efficiently after exercise is important to athletes, and as a result, several interventions have been investigated within the literature. Reports have suggested that both tart Montmorency and sweet cherries reduce inflammation (Kelley et al., 2006; Howatson et al., 2010). Meanwhile, oxidative stress, muscle soreness, and improved recovery of muscle function have been demonstrated using the tart Montmorency cherry cultivar, each of which are desirable to the exercising/recovering athlete (Connolly et al., 2006; Ducharme et al., 2009; Traustadottir et al., 2009; Howatson et al., 2010; Kuehl et al., 2010; Bowtell et al., 2011). Concerns have been raised with regard to inhibiting inflammation and oxidative stress because of the possible blunting of adaptive responses after antioxidant supplementation (Gomez-Cabrera et al., 2005, 2006, 2008a). The cited studies used vitamin C or allopurinol supplementation to blunt oxidative stress using human (Gomez-Cabrera et al., 2006) and/or animal cohorts (Gomez-Cabrera et al., 2005, 2008b); however, there is a lack of evidence demonstrating attenuated adaptation using cherry or any other functional food products. In support of this notion, Yfanti et al. (2010) demonstrated that 12 weeks of vitamin C and E supplementation had no negative effects upon adaptations to endurance training. Additionally, polyphenols have also been suggested to enhance adaptation in animal models, where resveratrol-fed rats showed an ~21% improvement in endurance performance (Dolinsky et al., 2012). A recent review with regard to antioxidant supplementation and adaptation has suggested that despite a number of studies demonstrating attenuated oxidative stress, implications upon exercise-induced muscle damage and performance have not been consistently demonstrated (Peternelj & Coombes, 2011). Lastly, there are several scenarios where optimal recovery is more important than physiological adaptation, e.g., tournament scenarios, where the ability to perform on a daily basis may be required. The focus of this review is to evaluate research evidence of cherries and their derivatives within exercise paradigms and its potential applications in clinical populations.

Muscle function

Disruption of the structures in exercising muscle leads to a cascade of events resulting in impaired muscular function (Proske & Morgan, 2001). Eccentric muscle actions, particularly prominent in downhill running (Eston et al., 1996), plyometrics (Byrne & Eston, 2002a, b), and multiple repeat sprint-based exercise (Thompson et al., 1999; Twist & Eston, 2005; Howatson & Milak, 2009) are accepted as the source of mechanical stress that causes primary muscle damage (Proske & Morgan, 2001; Howatson & van Someren, 2007; Howatson et al., 2007; Cockburn et al., 2008) and the subsequent secondary inflammatory cascade and impaired muscle function (Howatson & van Someren, 2008). Connolly et al. (2006) was the first to investigate the application of cherry juice supplementation in a damaging exercise model. The supplementation consisted of freshly prepared tart Montmorency cherry juice mixed with apple juice in a proprietary ratio, with each serving containing ~50–60 tart cherries. In a single blind crossover design, participants completed 9 days of supplementation spanning 4 days pre-exercise on the day of exercise and 4 days post-exercise, consuming two 237-ml servings per day (am/pm). In the 96 h following eccentrically biased contractions of the elbow flexors, maximal isometric strength loss was attenuated with the tart Montmorency cherry juice blend vs placebo (4% vs 22%); consequently, recovery was accelerated with the tart Montmorency cherry juice blend. Furthermore, recent research supported these findings using a similar study design with a damaging bout of knee extensor exercise; Bowtell et al. (2011) reported faster recovery of isokinetic knee extensor force when supplementing with a tart Montmorency cherry juice concentrate vs isoenergetic placebo. Creatine kinase (CK) showed a trend to be raised in the placebo trial when compared to cherries, although this did not reach statistical significance. Similarly, Ducharme et al. (2009) found trends of increased post-exercise muscle damage indices in horses. In the days following an exhaustive exercise test, horses supplemented with tart Montmorency cherry juice blend showed lower values of CK in comparison to a placebo ($P = 0.054$), although only six horses were used in this crossover design. A secondary muscle damage biomarker (aspartate aminotransferase, AST) showed treatment effects, whereby the tart Montmorency cherry juice supplementation resulted in less AST activity during both exercise and recovery periods.

Despite the three previously mentioned studies providing positive results in relation to attenuated muscle damage, caution should be used when interpreting these data. Each study utilized a crossover design where the protocol was repeated in the second trial. Crossover studies using eccentric exercise are subject to repeated bout effect, whereby a protective effect is shown on subsequent bouts of damaging exercise following just a

single bout of damaging exercise (Newham et al., 1987; Nosaka et al., 1991; McHugh et al., 1999; McHugh, 2003; Howatson et al., 2007), thereby confounding results in subsequent trials. The Connolly et al. (2006) and Bowtell et al. (2011) studies have attempted to resolve the issue associated with the repeated bout effect through the use of the contralateral limb. However, recent work has indicated that a contralateral repeated bout effect may be present (Howatson & van Someren, 2007; Starbuck & Eston, 2011) in which the adaptive effect is carried over to the non-exercising limb, albeit to a lesser extent. Despite this, the use of randomized or counterbalanced treatment order in these studies could conceivably wash out any potential contralateral repeated bout effects. As a result, the findings of these studies suggest efficacy in the use of tart Montmorency cherry juice for reducing muscle damage symptoms.

Like the aforementioned research, improvements in isometric strength recovery have been found following marathon running after consumption of tart Montmorency cherry juice supplementation vs placebo (Howatson et al., 2010). Using a placebo-controlled, independent groups design, other muscle damage indices, delayed onset of muscle soreness (DOMS), CK, and lactate dehydrodgenase (LDH) were not different between conditions. However, although there are acknowledged limitations in determining the magnitude of damage from CK measures, similar to the aforementioned studies, a trend toward lower CK values was apparent in the tart Montmorency cherry juice group. For example, peak CK values at 24 h post-exercise showed a 21% lower value for tart Montmorency cherry juice vs placebo (2227 IU/L vs 2814 IU/L). High levels of inter-individual variability of CK have been reported, with the causes of the variability being explained by inherent high and low responders, muscle fiber composition, and size and training status (Brancaccio et al., 2007). Subsequently, it is unsurprising that significant differences in CK between groups or conditions within the cherry supplementation literature have not been found, with high data scedasticity and only a small number of studies conducted in the field.

It is unlikely that that cherry juice exerts its protective effect through directly impacting upon the primary mechanical stress caused during exercise. Mechanical damage caused through eccentric muscle actions are thought to cause so-called sarcomere "popping" (Morgan, 1990) due to excessive strain and sarcomere inhomogeneities (Julian & Morgan, 1979). As a result, the function of affected sarcomeres is compromised and a cascade of events takes place, leading to secondary damage. Additionally, post-exercise maximum voluntary contraction is generally the same, suggesting that primary damage alone is not responsible for performance decrement. This is demonstrated by Howatson et al. (2010) and Bowtell et al. (2011), following marathon running and eccentric knee extensor exercise,

respectively, who showed strength loss was not different between cherry juice and placebo treatments in the immediate post-exercise period. However, subsequent recovery of strength was more rapid with the cherry juice treatments (Howatson et al., 2010; Bowtell et al., 2011). These results point to protection against the secondary damage response. The bioactive food components of cherry juice do not provide any rationale for the prevention of the initial primary damage, and more relevance should be placed upon secondary damage in the form of oxidative stress and inflammation. Circulating reactive oxygen/nitrogen species (RONS), resulting from exercise, theoretically may cause oxidative damage to muscle cell membranes (Girotti, 1985) providing a vehicle for the leakage of intracellular proteins and membrane-bound proteins to be attacked by RONS (Powers & Jackson, 2008). Although there is a lack of conclusive evidence for any direct interaction of antioxidants with cell membranes, reducing the magnitude of oxidative stress and inflammation through antioxidant supplementation may attenuate the proteolytic and lipolytic response, lowering the subsequent secondary inflammatory cascade. However, it has been postulated that fat-soluble antioxidants may stabilize muscle membranes via their action with membrane phospholipids (Van Der Meulen et al., 1997). Vitamin E has been suggested to protect against membrane damage following a reduced serum CK response to exercise in rats (Van Der Meulen et al., 1997; McGinley et al., 2009), although conversely, it has been speculated that lipid peroxidation does not contribute to muscle membrane damage (Warren et al., 1992).

Oxidative stress

Increasing the bioavailability of antioxidants through cherry ingestion could be desirable in preventing oxidative damage from RONS, commonly referred to as free radicals. RONS are produced endogenously as a result of biological metabolism and may also be brought into the body through exogenous sources such as smoking (Valavanidis et al., 2009). Exercise increases the endogenous production of RONS above resting levels, altering the cellular pro-oxidative : antioxidative ratio (Gomez-Cabrera et al., 2006) or redox balance. Disruptions in redox balance can result in altered cell signaling (Powers & Jackson, 2008; Powers et al., 2010), degradation of cellular performance (Powers & Jackson, 2008; Powers et al., 2010; McAnulty et al., 2011), and as a result, cause a decrement in physical performance (Vollaard et al., 2005; Hillman et al., 2012). Consequently, when RONS outweigh the antioxidative capacity of an organism, free radical species attack lipids, proteins, and DNA, challenging the functionality and structural integrity of these materials (Wang et al., 1999). Additionally, RONS have been implicated in the fatigue of muscle because of decreased myofibrillar

calcium sensitivity (Lamb & Westerblad, 2011) and may impact upon muscle glucose uptake (Bashan et al., 2009; Merry et al., 2009). It has been postulated, however, that a moderate increase in oxidative stress (i.e., an increase in pro-oxidative : antioxidative ratio) is beneficial to the exercising muscle, although excessive levels might reduce muscle function (Reid et al., 1993; Andrade et al., 1998; Reid, 2001). Reid et al. (1993) demonstrated increased muscular twitch force in rat diaphragm muscle through increasing oxidative stress, while increased antioxidant infusion significantly decreased twitch characteristics. Further work by Andrade et al. (1998) supports this, with findings showing increased force of mouse muscle fibers following brief exposure to oxidative stress. In the same report, it was found that prolonged exposure to a pro-oxidative environment resulted in progressive decline in force output (Andrade et al., 1998). Despite research suggesting that cellular damage from oxidative stress only occurs when exercise is exhaustive (Gomez-Cabrera et al., 2006), others have demonstrated increased biomarkers indicative of damage, following high-intensity (Powers & Jackson, 2008; Bowtell et al., 2011) or prolonged duration exercise (Powers & Jackson, 2008; Howatson et al., 2010); hence, attenuating such damage with antioxidant supplementation has received attention in the literature (Gomez-Cabrera et al., 2006; Powers & Jackson, 2008).

Ducharme et al. (2009) was the first to investigate the effects of cherry juice supplementation upon indices of oxidative stress, following damaging exercise in thoroughbred horses. The exhaustive treadmill exercise increased plasma thiobarbituric acid reactive species (TBARS), a measure of lipid peroxidation. While there were significant elevations in TBARS indicating oxidative stress, there were no differences between tart Montmorency cherry juice and placebo conditions. TBARS have been criticized as a measure of lipid peroxidation because it lacks specificity in human studies (Urso & Clarkson, 2003), as the assay also reacts with both saturated and unsaturated non-functional aldehydes, carbohydrates, and prostaglandins (Alessio, 2000).

The first human study to examine the influence of cherry juice on oxidative stress and inflammatory variables after exercise-induced damage was carried out by Howatson et al. (2010). Oxidative stress was induced via both mechanical and metabolic pathways through the completion of a marathon. Participants who were supplemented twice per day for 120 h prior to and 48 h post-marathon with tart Montmorency cherry juice showed significantly lower levels of TBARS than their placebo-fed counterparts at 48 h post-marathon (21.4 µmol/L vs 30.2 µmol/L). Interestingly, plasma total antioxidative status (TAS), a measure encompassing all biological components with antioxidant activity (Randox, 2013), of the placebo group fell below baseline measures at 48 h, suggesting that the maintained TAS (and, hence, redox balance) of the cherry juice group

may have contributed to staving off any associated oxidative stress. Protein carbonyls (PC), a marker of protein oxidation, showed no significant elevation above pre-exercise levels in either group following the marathon run. Oxidative stress was also measured by Bowtell et al. (2011) following tart Montmorency cherry juice supplementation; although, in contrast to Howatson et al. (2010), the exercise protocol used in this study placed a relatively low metabolic cost (eccentric exercise) on participants. Following eccentrically biased knee extensions, participants given tart Montmorency cherry juice showed a trend ($P = 0.079$) of lower levels of PC 24-h post-exercise (Bowtell et al., 2011). Although this finding provides limited support for the antioxidative actions of tart Montmorency cherry juice, the use of PC as a measure of oxidative stress in *in vivo* human studies has been criticized as unreliable, non-specific, and, whether it represents a good marker of protein oxidation in exercise paradigms, is somewhat controversial (Urso & Clarkson, 2003). Carbonyl groups are formed when RONS attack protein side chains (Dalle-Donne et al., 2003) and amino acids (Urso & Clarkson, 2003); however, the formation of such groups is not restricted to protein structures. Carbonyl groups may also be formed with protein through secondary reactions with aldehydes produced during lipid peroxidation (Dalle-Donne et al., 2003), making it difficult to discriminate between the sources of oxidative damage through the measure of protein carbonyls alone.

Interestingly, tart Montmorency cherry juice supplementation for 14 days has been applied in a non-exercising ischemia/reperfusion (I/R) model that was used to initiate acute oxidative stress (Traustadottir et al., 2009). Following I/R, oxidative stress (plasma F_2-isoprostanes) was attenuated in the tart Montmorency cherry juice condition compared to a placebo. F_2-isoprostanes are considered the "gold standard" measure (Michel et al., 2008) of lipid peroxidation when analyzed by liquid chromatography mass spectrometry. No differences between baseline measures of F_2-isprostanes were found after the 14-day loading phase of tart Montmorency cherry juice or placebo, suggesting that cherries had no impact upon basal F_2-isoprostane levels. Additional measures showed lowered basal levels urinary 8-oxo-2′-deoxyguanosine and 8-oxo-guanine (markers of DNA and RNA oxidation, respectively) after tart Montmorency cherry juice consumption. Three suggestions were proposed to explain how the phytonutrients in tart Montmorency cherry juice may exert their protective effects: (a) direct free radical scavenging; (b) formation of cyaniding–DNA complexes resistive to oxidative damage; and (c) the activation of protective xenobiotic responses (Traustadottir et al., 2009). The direct neutralization of free radicals by cherry anthocyanins is possible; however, the absorption of anthocyanins from other foods has been shown to be poor (Bitsch et al., 2004; Charron et al., 2007; Charron et al., 2009), with

fast clearance (Felgines et al., 2003; Kurilich et al., 2005; Traustadottir et al., 2009). However, the dose-response of tart Montmorency cherry anthocyanins has yet to be elucidated, so this explanation remains a possibility. The formation of cyanidin-DNA complexes resistive to oxidative damage is a second theory (Traustadottir et al., 2009), although this mechanism does not account for any changes in lipid peroxidation or protein oxidation, meaning a further mechanism may be possible. Third, the activation of xenobiotic responses, up-regulating the expression of endogenous antioxidants, may be responsible for the protective effects (Shih et al., 2007; Traustadottir et al., 2009). Finally, a synergistic effect of all three theories remains a possibility.

The mechanism by which cherries exert their protective effect against oxidative stress is unclear and requires further investigation. However, it is apparent that the role of cherries in attenuating oxidative stress does not appear to be selective to the type of oxidative stress caused by the exercise mode (mechanical or metabolic challenges), although the methods used to assess these indices in the aforementioned studies have limitations. Conceivably, the pathway for mechanical and metabolic oxidative stress may be different; however, this has yet to be established as no exercise study using a purely metabolically challenging protocol has been conducted.

Inflammation

The use of an antioxidant supplementation strategy to limit inflammation after exercise may be a desirable outcome in order to maintain muscular function and attenuate pain. However, the pro-inflammatory response to exercise and its implication on resulting protein synthesis and subsequent adaptation remains a point of conjecture (Trappe et al., 2002; Krentz et al., 2008). In the acute phase, it has been proposed that protein fractional synthesis rate (FSR) may be attenuated through the down-regulation of the inflammatory cascade associated with stressful exercise (Trappe et al., 2002), although it has been demonstrated in elderly participants that non-steroidal anti-inflammatory drugs (NSAID) administration does not affect muscle protein synthesis rate following low-grade inflammation (Petersen et al., 2011). Chronically, Krentz et al. (2008) demonstrated that muscle hypertrophy was not inhibited through NSAID ingestion over a 6-week training study, whereas a review by Schoenfeld (2012) stated that long-term NSAID use may be detrimental to hypertrophy.

Alternatively, pro-inflammatory cytokines have been proposed as inhibitors of protein synthesis (Caiozzo et al., 1996; Frost et al., 1997) and, as such, may play a negative role in recovery from damaging bouts of exercise. Nemet et al. (2002) demonstrated attenuated plasma levels of insulin-like growth factor-1 (IGF-1) in adolescents following a single intense exercise session. Additionally, increases in inflammatory cytokines interleukin-6 (IL-6), tumor necrosis alpha (TNF-α), and interleukin-1-beta (IL-1β) were found. These findings suggest a reduced anabolic environment in the presence of inflammatory cytokines in the early stage of training (Nemet et al., 2002). Conversely, however, it has been postulated that increases in systemic inflammation and oxidative stress are necessary for gaining the beneficial physiological adaptations to training or exercise (Trappe et al., 2002; Soltow et al., 2006; Gomez-Cabrera et al., 2006, 2008a, b; Powers et al., 2011). Soltow et al. (2006) demonstrated reduced hypertrophy of 50% in overload trained rats with 14 days of NSAID administration. Nevertheless, there are numerous sporting paradigms where adaptation is not important and the critical element is to facilitate recovery and, hence, the ability to compete in subsequent competition and training.

An *in vitro* study identified cherry anthocyanins as being inhibitors of cyclooxygenase-1 and -2 (COX-1, COX-2) activity (Seeram et al., 2001). Inhibition of COX-2 is believed to be mainly responsible for anti-inflammatory actions (Masferrer et al., 1994) and has been shown to dampen the inflammatory response within skeletal muscle (Bondesen et al., 2004). Sweet cherry, Balaton tart cherry, and Montmorency tart cherry anthocyanins were shown to reduce COX-2 activity by 47.4%, 38.3%, and 36.6%, respectively, which was similar to the actions of the NSAIDs ibuprofen and naproxen that showed reductions in COX-2 activity of 39.8% and 41.3%, respectively (Bondesen et al., 2004). Subsequently, research has focused on the effects of cherries and their anthocyanins on inflammation *in vivo*.

Several studies have investigated the impact of cherry supplementation on inflammatory responses to exercise. In Ducharme et al.'s (2009) study on horses, serum amyloid A (SAA), an indicator of inflammation, showed no differences between tart Montmorency cherry juice and placebo-supplemented groups. However, overall SAA was only marginally elevated by the exercise intervention, so SAA may not be a good marker of equine exercise-induced inflammation. In horses, SAA is typically used as a marker of inflammation secondary to infection (Pepys et al., 1989). Moreover, markers of muscle damage showed great variation among horses, making it increasingly unlikely that significant differences would be found within the secondary inflammatory response. Further to this, horses were not supplemented throughout the recovery period where the secondary inflammatory and oxidative stress variables are likely to be greatest. Additionally, the repeated bout effect (McHugh et al., 1999; McHugh, 2003; Howatson et al., 2007; Howatson & van Someren, 2007) may have influenced the results due to the crossover design of the protocol.

Using human participants, Howatson et al. (2010) demonstrated attenuation in inflammatory variables following marathon running using tart Montmorency
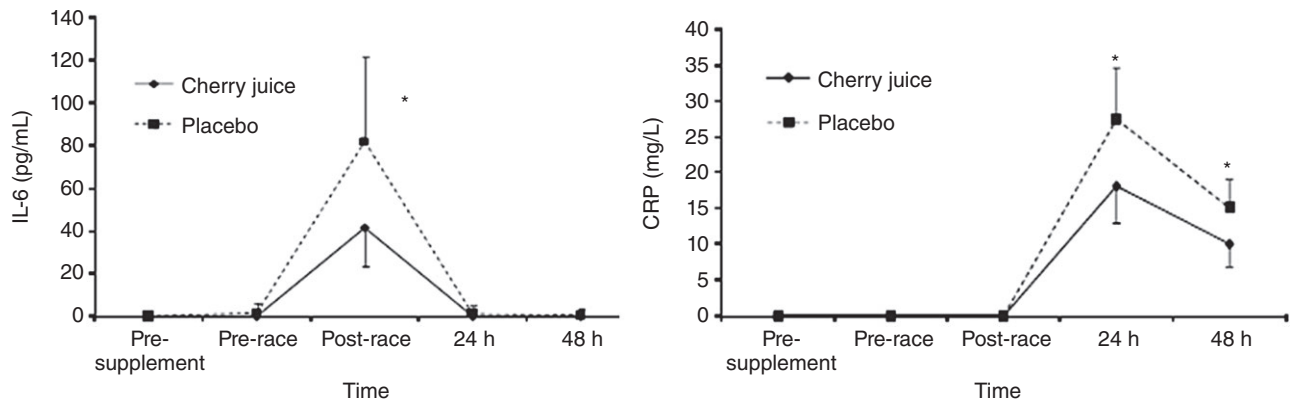
Fig. 1. Serum interleukin (IL)-6 and C-reactive protein (CRP) concentrations for tart Montmorency cherry juice and placebo groups following marathon running (taken from Howatson et al., 2010).

cherry juice supplementation. IL-6 and C-reactive protein (CRP) were both significantly reduced with tart Montmorency cherry juice vs placebo consumption. Serum IL-6 showed immediately post-race values of 41.8 pg/mL vs 82.1 pg/mL, and CRP was reported to be lower at 24 and 48 h in tart Montmorency cherry juice-fed participants (see Fig. 1).

Bowtell et al. (2011) were unable to detect any effects of tart Montmorency cherry juice concentrate on high sensitivity CRP (hsCRP) following eccentrically biased knee extensions. The protocol did not significantly elevate hsCRP from baseline, although the authors did report a tendency for hsCRP to be higher in the placebo group in the hours following the exercise protocol. Kelley et al. (2006) showed decreases in circulating plasma levels of hsCRP using healthy participants supplementing their diets with Bing sweet cherries. Reductions of 8% and 25% were found for CRP following 14 and 28 days of supplementation (280 g/day), respectively. Further evidence for the anti-inflammatory actions of cherries was provided by Jacob et al. (2003), who showed trends of decreased circulating CRP in healthy women following two servings (280 g each) of Bing sweet cherries. These early results provide a good evidence base for further research into the anti-inflammatory actions of cherries and their constituent anthocyanins.

Pain

In the hours and days following intense physical activity, muscular pain is regularly reported in exercise tasks that are heavily eccentric biased. Following these types of exercise task, muscular pain has been shown to increase in the following 24–96 h, with peak muscle soreness (DOMS) usually occurring at 24–48 h (Semark et al., 1999; Marginson et al., 2005; Twist & Eston, 2005; Twist et al., 2008; Davies et al., 2009). The origin of what causes pain is not established; however, it is conceivable that it is related to inflammation of the surrounding area (Howatson & van Someren, 2008). Cherry

anthocyanins were first shown to inhibit pain by Tall et al. (2004). Using anthocyanins extracted from Balaton tart cherries, inflammation-induced pain, as measured by thermal hyperalgesia, mechanical hyperalgesia, and paw edema was significantly suppressed in rats when compared to a control saline solution. Results showed that the administration of Balaton tart cherry anthocyanins provided similar pain inhibiting effects as indomethacin (NSAID). These findings in an animal model provided a template for the future work conducted in human populations.

Several aforementioned studies reported pain scores following supplementation with cherry juice. Connolly et al. (2006) reported that the development of pain in the elbow flexors was significantly attenuated in a tart Montmorency cherry juice supplemented trial vs a placebo, assessed using a visual analog scale (VAS) with scores averaged over 96 h. Additionally, peak pain scores occurred at 24 h in the cherry juice trial as opposed to 48 h in the placebo trial. In contrast to VAS results, pressure pain threshold (PPT) was not found to be different between cherry juice and placebo groups. The PPT results from Bowtell et al.'s (2011) study showed a trend towards lowered pain following tart Montmorency cherry juice supplementation vs a placebo, although the results did not reach significance 48 h after exercise.

Further research conducted by Kuehl et al. (2010) provided support for the analgesic effects of tart Montmorency cherry juice. Participants completed a distance running event (average distance completed 26.3 km) and those supplemented with tart Montmorency cherry juice blend provided significantly lower pain (VAS) following the race, although it should be noted that the time between completing the run and pain assessment was not standard across participants due to the relay-based nature of the race. No further measurements of pain were taken by the authors, which may have provided further evidence for pain relief, given that the onset of post-exercise inflammation and subsequent peak of pain would be unlikely to have manifested until 24–48 h post-exercise.

Conversely, Howatson et al. (2010) reported no difference in pain scores between tart Montmorency cherry juice and placebo groups up to 48-h post-marathon running. The inconsistent results between these studies immediately after exercise seem surprising given the similarity in exercise task and participant demographic. Given the results of these aforementioned studies, it appears there may be a beneficial effect of cherry juice and cherry anthocyanins on post-exercise pain. However, results are not consistent in the literature currently available, leaving scope for further research to investigate both analgesic effects of cherries and the possible mechanistic cause of any effects.

Dosage strategies

The majority of research into cherry supplementation has provided positive findings; however, there appears to be little rationale provided for the dosing strategies employed in the literature. In human exercise studies, dosing strategies range from 7 days pre-exercise through to 4 days post-exercise inclusive; and in animal studies up to 14 days of pre-exercise dosing has been used (Ducharme et al., 2009). Non-exercising studies have used longer loading phases, implementing up to 28 days (Kelley et al., 2006) of cherry or cherry analog consumption (Table 1). Although efficacy has been demonstrated using a range of dosing strategies, it would seem prudent to identify an optimal strategy in order to confidently prescribe supplementation.

The pharmacokinetic nature of cherry anthocyanins has yet to be elucidated; however, dose–response studies of other functional food anthocyanins have shown low bioavailability (Bitsch et al., 2004; Manach et al., 2005; Charron et al., 2009), as shown by limited absorbance efficiency recovery of <0.05% (Charron et al., 2009) and rapid excretion (Kurilich et al., 2005; Hollands et al., 2008). Timings of systemic anthocyanin concentration appear to be consistent across these studies, with peaks in plasma concentrations being reported at 1.5–2 h post dose despite differences in dose volume and anthocyanin magnitude. Additionally, the clearance of systemic anthocyanins appears to be fast, with returns to baseline values typically occurring by 8-h post-dose. Charron et al. (2009) suggested the dose volume range (76–380 µmol) of anthocyanins provided in their study may be reasonable, given previous work showed anthocyanin absorption mechanisms to be saturated at higher amounts (Kurilich et al., 2005). It must be noted, however, that findings from these papers might not be generalizable to all plant or food stuffs containing anthocyanins as bioavailability and metabolism may be affected by the plant matrix (Charron et al., 2009). It is unclear whether there is biological storage of anthocyanins, although it has been suggested that due to the discovery of anthocyanin metabolites in 24-h urine samples (Felgines et al., 2003), there may be potential

for some minor tissue accumulation (Kay et al., 2004). A further complication with regard to anthocyanins bioavailability is the influence of microbiota during transport in the large intestine. Flavonoids have been suggested to be degraded to low-molecular-weight aromatic compounds through the actions of colonic microbiota (Serra et al., 2012). Such effects could make assessment of anthocyanins bioavailability troublesome as such compounds may exhibit variance with regard to metabolism and systemic bioavailability.

The bioavailability of cherry anthocyanins may impact upon dosing strategy for optimizing recovery from exercise. If the high RONS scavenging ability of anthocyanins (Wang et al., 1999; Seeram et al., 2001; Ducharme et al., 2009) is responsible for the protective effects of cherries, it would be reasonable to suggest that a dosing strategy resulting in optimal systemic anthocyanin concentration at the point of peak oxidative stress would be appropriate. However, if cherry anthocyanins have pharmacokinetic properties similar to other foods, it would mean supplementing ~2 h prior to exercise, possibly interfering with dietary routines and raising the potential for gastrointestinal distress during exercise. At the very least, a period of supplementation-exercise habituation would be recommended prior to embarking on such a dosage strategy. Despite this, Howatson et al. (2010) reported significant increases in total antioxidant status (TAS) following 5 days (2 times per day) of pre-exercise supplementation, in conjunction with decreased inflammation, oxidative stress, and faster recovery of isometric strength, suggesting this dosing strategy is appropriate prior to exercise. However, this measure does not discriminate between antioxidants, so the systemic level of anthocyanins may not have been optimal. Additionally, dosing continued for 2 days post exercise, making it difficult to differentiate between the effects of the cherry supplement pre- and post-exercise.

As previously discussed, the ability of anthocyanins to form cyanidin–DNA complexes resistive to oxidative damage and/or the activation of xenobiotic responses has been proposed as mechanism for the protective effects of cherries (Kong et al., 2003; Sarma & Sharma, 1999; Traustadottir et al., 2009). The time-course for the formation of cyanidin-DNA complexes has not been reported in human studies; however, an *in vitro* study has shown that 1 min following the mixing of anthocyanins (cyanidin) with calf thymus DNA (ctDNA), oxidative stress was diminished (Sarma & Sharma, 1999) when compared with anthocyanins or ctDNA alone. Similarly, the activation of xenobiotic responses has not been assessed through human *in vivo* study, although Shih et al. (2007) showed that treating rat liver cells with anthocyanins for 24 h increased the cells' expression of endogenous antioxidants.

The mechanism by which cherries exert their protective effects is still unclear, and as a result, it is difficult to definitively prescribe a dosage strategy. Regarding

Table 1. Summary of human and animal studies investigating the effects of supplementation with cherry or cherry products

Authors	Participant cohort	Exercise	Supplement type	Supplementation strategy	Change in antioxidant status	Muscle damage/ function/pain	Inflammation	Oxidative stress
Tall et al. (2004)	32 male rats	N/A	Tart cherry anthocyanins (400 mg/kg)	3 days pre	Not reported	Pain (thermal hyperalgesia)† ↓	N/A	N/A
Connolly et al. (2006)	14 male students	2 × 20 maximum eccentric elbow flexions	Tart cherry juice blended with apple juice (12 fl oz, 2/day)	4 days pre, 4 days post	Not reported	Iso strength recovery‡ ↑ Pain* ↓	N/A	N/A
Kelley et al. (2006)	18 healthy volunteers (16 female, 2 male)	N/A	Bing sweet cherries (280 g/day)	28 days	Not reported	N/A	↓CRP*	N/A
Ducharme et al. (2009)	6 horses	Stepwise incremental treadmill test until horses unable to maintain speed	Tart cherry juice blend (1.42 L/day)	14 days pre	Not reported	AST* ↓	N/A	N/A
Traustadottir et al. (2009)	12 volunteers (6 male, 6 female)	Pre-supplement and post supplement Ischemia/Reperfusion (3 × 10 min ischemia using blood pressure cuff inflated to 200 mm Hg, with 2 min reperfusion of upper arm)	Tart cherry juice blend (240 mL, 2/day)	14 days pre	Not reported	N/A	N/A	F2-isoprostane response to I/R ↓
Howatson et al. (2010)	20 recreational marathon runners (13 male, 7 female)	Marathon	Tart cherry juice blend (8 fl oz, 2/day)	5 days pre, 2 days post	TAS↑†	Iso strength recovery* ↑	IL-6‡ ↓CRP† ↓Uric acid* ↓	TBARS* ↓
Kuehl et al. (2010)	54 healthy runners (36 male, 18 female)	Running (mean 26.3 ± 2.5 km over 2 days)	Tart cherry juice mixed with apple juice in propriatary ratio (355 mL)	7 days pre	Not reported	VAS pain‡ ↓	N/A	N/A
Bowtell et al. (2011)	10 well-trained males	10 × 10 single-leg-knee extensions at 80% 1 RM, with elongated eccentric phase	Tart cherry juice (30 mL, 2/day)	7 days pre, 2 days post	No difference	MVC recovery* ↑	N/A	PC* ↓

*P < 0.05.
†P < 0.01.
‡P < 0.001.

AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin 6; I/R, ischemia-reperfusion; MVC, maximum voluntary contraction; N/A, not applicable; PC, protein carbonyl; TBARS, thiobarbituric acid reactive species; VAS, visual analog scale.

dosage volume, bioavailability studies suggest anthocyanin volume per supplement should not exceed 380 µmol (322.7 mg) due to diminishing efficiency in absorbance (Charron et al., 2007; Charron et al., 2009). In relation to the frequency and timing of dosage, it appears likely that supplementation should begin at some point prior to exercise; although in exercise studies, it is unclear as to whether pre or post exercise dosing alone would provide any differences in results. Furthermore, it has not been established as to whether multiple doses are necessary to gain the same beneficial effects. Additionally, the above speculation requires cherry anthocyanins to act as per other functional food anthocyanins, which has yet to be confirmed. Clearly, further work is warranted to identify an optimal dosing strategy to gain the beneficial effects of cherries. Despite this, cherry supplementation has showed a degree of efficacy in all exercise and recovery paradigms regardless of loading phase or post-exercise

dosing. It remains to be elucidated whether such prolonged phases are necessary to gain the beneficial effects associated.

Clinical application

The anti-inflammatory and antioxidative capacity of cherries has led to focus on supplementation for a number of pathologies. Inflammation and oxidative stress is associated with numerous pathologies such as cancer, cardiovascular disease, diabetes (McCune et al., 2011), arthritis (Wang et al., 1999), and acceleration of the aging process (Golden et al., 2002; Vollaard et al., 2005; McAnulty et al., 2011). Cherries compare favorably with other functional foods in terms of anthocyanin (Table 2) and antioxidative capacity (Fig. 2), and as a result, increasing exogenous antioxidant availability through cherry consumption has become of interest to researchers investigating methods of reducing inflammation and oxidative stress in clinical populations.

Tart Montmorency cherry juice has been suggested as a benefit for those suffering from chronic inflammatory diseases such as osteoarthritis (Schumacher et al., 2011). Recent data from Schumacher et al. (2011) demonstrated significant reductions of the inflammatory marker CRP in patients diagnosed with osteoarthritis given twice daily servings of tart cherries. In association with this, participants reported lower scores of pain and WOMAC (Western Ontario and McMaster Universities Arthritis Index). Whole Bing sweet cherries have been shown to lower systemic plasma urate concentration (Jacob et al.,

Table 2. Anthocyanin concentration of various fruit juices [adapted from Clifford (2000)]

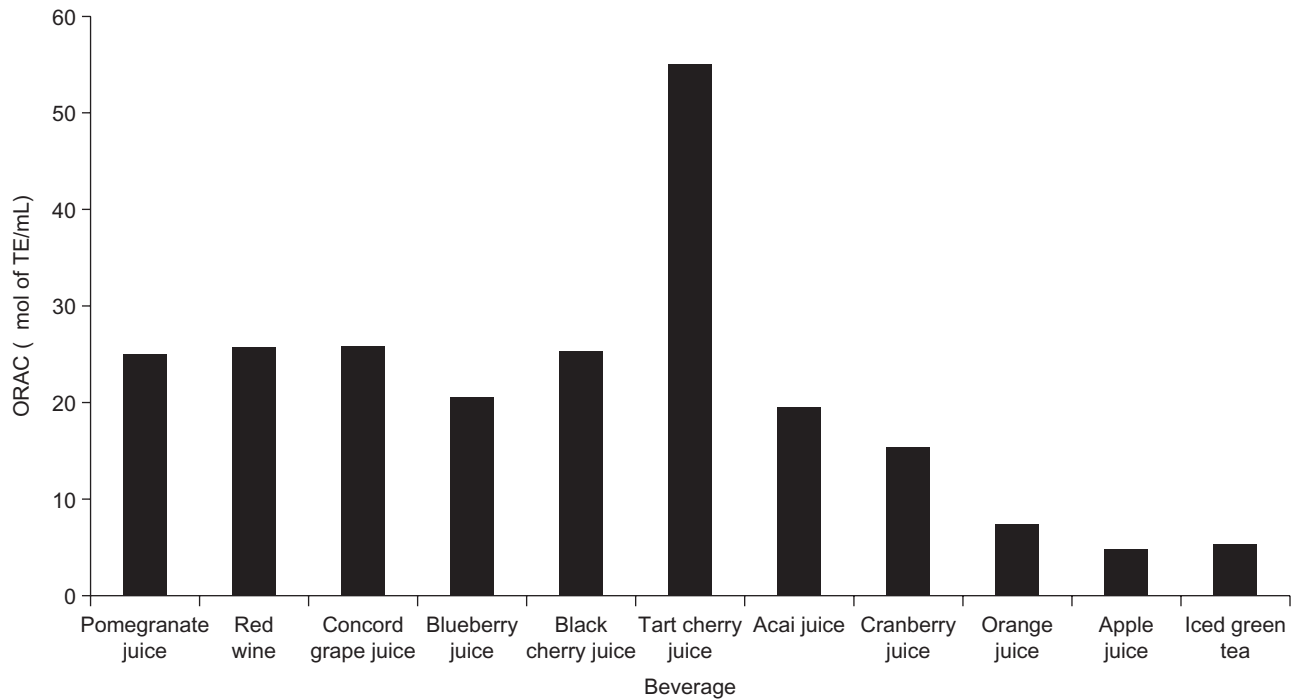| Food	Anthocyanin content (mg/L)
Montmorency tart cherry juice	9117 (Biosciences 2010)
Blackberry	1150
Blueberry	825–4200
Grape (Red)	300–7500
Sweet cherry	20–4500
Strawberry	150–350
Cranberry	600–2000

Fig. 2. Comparison of antioxidant status of fruit juice beverages as assessed through oxygen radical absorbance capacity [ORAC; values sourced from Seeram et al. (2008) and Howatson et al. (2010)].

2003), suggesting the incidence of gout may be reduced. Gout occurs as the result of crystallization of uric acid in joints, causing tenderness, swelling, and pain in the associated areas. In this study, asymptomatic participants consumed a single dose of 280 g of whole Bing sweet cherries. Results showed significantly lower measures of plasma urate 5-h post-dose following Bing sweet cherry consumption, although the observed mean decrease of 14.5% maintained values in the normal range expected within humans (Jacob et al., 2003). Additionally, trends of lowered CRP were found; however, they did not reach statistical significance. Supporting this, Kelley et al. (2006) showed that following multiple dosages (280 g/day for 28 days) of Bing sweet cherries lowered circulating levels of CRP. These early findings provide a foundation for further research into gout using symptomatic participants. It is conceivable to expect that using a concentrated tart Montmorency cherry juice supplement may be of greater benefit due to the higher concentration of anthocyanins present.

Recent work has shown further positive results for cherry supplementation in the management of sleep (Pigeon et al., 2010; Howatson et al., 2011a). Chronic sleep disruption has been associated with the stimulation of inflammatory responses (Irwin et al., 2008) and may increase the risk of several chronic disorders such as atherosclerosis, diabetes mellitus, Crohn's disease, and rheumatoid arthritis (Walsh et al., 2011). More recently, Cohen et al. (2009) found that adults reporting sleep of less than 7 h per night were approximately three times more likely to develop symptoms of upper respiratory tract infections. Furthermore, despite the knowledge of disturbed sleep impairing both physical (Mougin et al., 1991) and mental performance (Alhola & Polo-Kantola, 2007), sleep is often overlooked in its contribution to recovery and recuperation (Halson, 2008). Additionally, studies have found reductions in endurance exercise performance following one night of sleep deprivation (Oliver et al., 2009), and associations between over-reached soccer players and sleep quality have also been established (Brink et al., 2012). With regard to cherries, in addition to their high anti-inflammatory and antioxidative capacity, tart Montmorency cherries contain high quantities of melatonin (Burkhardt et al., 2001), a compound associated heavily with regulation of the sleep–wake cycle (Hughes et al., 1998). Howatson et al. (2011a) showed significant increases in total sleep time, sleep efficiency and time in bed in tart Montmorency cherry juice fed asymptomatic participants. These results support the findings of Pigeon et al. (2010) who, following anecdotal reports of improved sleep during an unrelated tart Montmorency cherry juice study (Connolly et al., 2006), conducted a pilot study supplementing insomniacs with a tart Montmorency cherry juice blend. The authors reported improvements in insomnia severity with tart Montmorency cherry juice compared to a placebo group,

although the effect sizes were reported as "modest." The application of improved sleep spans a range of scenarios, including shift workers, insomniacs, time-zone travelers, and those suffering from disturbed sleep. These initial studies provide foundation for further work to be conducted investigating the use of cherries as a sleep regulator.

Perspectives

Cherries and their constituents have received growing attention for application in sport and exercise and other potential clinical populations; the beneficial effects appear promising and are supported with a growing body of evidence regarding its efficacy. The food science, animal, and human literature currently available clearly demonstrates the anti-inflammatory and antioxidative effects of cherries. The research suggests that there are benefits of cherry consumption in enhancing recovery from exercise and sleep regulation and lends itself well to further investigation into numerous clinical scenarios. Currently, the mechanisms of action are somewhat speculative with regard to recovery from exercise, and as a result, confident prescription of the optimal supplementation strategy is troublesome, although efficacy for a loading phase has been established. Despite this, no negative effects of supplementation with cherries have been reported. As a result, the use of any of the dosing strategies in the reviewed papers may be deemed appropriate, although there is conjecture regarding the manipulation of the stress responses to exercise (inflammation and oxidative stress), with a suggestion that adaptation may be blunted as a result of down-regulating the stress response (Gomez-Cabrera et al., 2005, 2006, 2008b). However, it should be noted that such negative adaptive effects have not been reported in cherry studies or any other functional foods and perhaps warrant further investigation. It should also be noted that the specific compounds responsible for any beneficial effects of cherry juice may not be limited to anthocyanins and their metabolites. As discussed, quercetin has also been implicated in antioxidative actions and should therefore not be forgotten in the future study of cherries. In summary, cherries appear to provide an efficacious option for assisting with recovery from damaging bouts of exercise. Possibly of greater importance is the potential for application within clinical pathologies. In particular, chronic inflammatory conditions where the option of natural remedies may be more desirable than the use of pharmacological interventions such as NSAIDs, although research is required prior to prescription of such a strategy.

Key words: recovery, muscle function, antioxidants, inflammation, oxidative stress, Montmorency tart cherries.

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