Nutrición Hospitalaria

Nutr Hosp. 2015;32(5):1885-1893
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Consumption of cherries as a strategy to attenuate exercise-induced muscle damage and inflammation in humans

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Abstract

Background: **exercise-induced muscle damage (EIMD) is a multifactorial phenomenon that induces muscle function loss because of mechanical and immune stressor stimuli. This immunological stress is mostly caused by inflammation and increased oxidative status. Cherries are fruits that contain a phenolic compound known as anthocyanin, which serves as a pigment in natura. However, research suggests this pigment might provide a potent antioxidant and anti-inflammatory strategy when consumed by humans.**

Objectives: **the aim of this study was to critically review the literature on cherry consumption focusing on identifying protective strategies against EIMD conferred by it.**

Methods: **a research was performed in PubMed database. This review presents the results about cherry consumption and EIMD.**

Results: **the articles identified in this review support the notion that tart cherry consumption attenuates EIMD symptoms after intense exercise bouts. This attenuation seems to be related to the antioxidant and anti-inflammatory properties of anthocyanins and other phenolic compounds present in tart cherries.**

Conclusion: **daily consumption of tart cherries may attenuate inflammatory and oxidative responses to EIMD, leading to faster recovery after exercise bouts.**

(*Nutr Hosp*. 2015;32:1885-1893)

DOI:10.3305/nh.2015.32.5.9709

Keywords: *Cherries. Muscle damage. Flavonoids. Anthocyanins. Recovery.*

EL CONSUMO DE CEREZAS COMO ESTRATEGIA DE MITIGACIÓN DEL DAÑO MUSCULAR Y LA INFLAMACIÓN EN SERES HUMANOS

Resumen

Introducción: **el daño muscular es un fenómeno multifactorial que conduce a la pérdida de la función muscular como resultado de la tensión mecánica e inmune. Este estrés inmunológico es causado principalmente por la inflamación y el estado oxidativo aumentado. Las cerezas son frutas que contienen antocianinas con compuestos fenólicos conocidos, que sirven como pigmento en la naturaleza. Entre tanto, los estudios sugieren que este pigmento puede promover un potente efecto antioxidante y antiinflamatorio cuando se consume por los seres humanos.**

Objetivos: **el objetivo de este estudio fue realizar una revisión crítica de la literatura sobre el consumo de cerezas, con un enfoque en la identificación de las estrategias de protección contra el daño muscular.**

Métodos: **se realizó una encuesta en la base de datos PubMed. Esta revisión presenta los resultados para el consumo de cerezas y daño muscular.**

Resultados: **los artículos que se encuentran en esta revisión apoyan la idea de que el consumo de cerezas alivia los síntomas de daño muscular después de las sesiones de ejercicio. Esta atenuación parece estar relacionada con las propiedades antioxidante y antiinflamatoria de las antocianinas y otros compuestos fenólicos presentes en las cerezas.**

Conclusión: **el consumo diario de cerezas puede aliviar la respuesta inflamatoria y oxidativa de los entrenamientos y conseguir una recuperación más rápida de los marcadores de daño muscular.**

(*Nutr Hosp*. 2015;32:1885-1893)

DOI:10.3305/nh.2015.32.5.9709

Palabras-claves: *Cerezas. Daño muscular. Flavonoides. Antocianinas. Recuperación.*

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Recibido: 4-VIII-2015.
Aceptado: 19-VIII-2015.

Abbreviations

CH: Cherries.
CK: Creatine kinase.
COX: Cyclooxigenase.
CRP: C-reactive protein.
DOMS: Delayed-onset muscle soreness.
EIMD: Exercise-induced muscle damage.
IGF-1: Insulin-like growth factor-1.
IL-6: Interleukin-6.
NO: Nitric oxide.
PC: Protein carbonyls.
PLA: Placebo.
RANTES: Regulated on activation, normal T cell expressed and secreted.
ROS: Reactive oxygen species.
SOR - Soreness.
TAS: Total antioxidant status.
TBARS: Thiobarbituric acid reactive substances.
TNF-α: Tumor necrosis factor- α.

Introduction

Exercise-induced muscle damage (EIMD) refers to the disorganization of skeletal muscle induced by exercise[1], leading to strength loss, soreness (SOR), swelling and leakage of intracellular proteins [creatine kinase (CK) and myoglobin] to the blood stream[2]. This phenomenon frequently occurs after bouts of unaccustomed exercise comprising eccentric contractions[3]. However, recent evidence shows that the inflammatory response to the mechanical disruption of the muscular tissue plays an important role in aggravating initial damage[4-6]. This aggravation is referred to as the secondary damage response.

Many studies have investigated strategies to prevent and/or attenuate EIMD symptoms. For example, increasing muscle temperature[7], performing maximal isometric contractions[8] and augmenting flexibility levels[9] before damaging bouts were proven to decrease some EIMD symptoms. Therapeutic massage was also proven to slightly accelerate recovery following EIMD[10].

Many studies have investigated the effects of different supplementation types on EIMD prevention and recovery[11-13]. The ingestion of tart[14] cherries (CH) was proven to be a consistently effective supplementation strategy to attenuate EIMD[15]. The cause of this attenuation appears to be related to the antioxidant compound anthocyanin, which is abundant in dark-colored fruits and plants and, especially, CH[16] and, also, to other phenolic compounds, such as quercetin. CH consumption has been reported to blunt the inflammatory response, resulting in secondary damage after bouts of damaging exercise[17] and it has been suggested that the anthocyanins present in these cherries are one of the compounds responsible for this protection. Moreover, there are other compounds in cherries that are believed to play an important antioxidant and anti-inflammatory role.

Inflammation can trigger and worsen EIMD symptoms, such as soreness and strength loss. Inflammation can also cause extreme discomfort, which may compromise physical activity enthusiasts' and athletes' daily routines[2]. Therefore, investigation of the prevention and recovery-enhancement potential of these symptoms is needed. The aim of this review was to critically evaluate the current literature regarding the use of CH in the prevention of, and recovery from, EIMD.

Exercise-Induced Muscle Damage

EIMD is a multifactorial phenomenon characterized by skeletal muscle function loss due to exercise-related stress[2]. Although widely investigated over the last few decades, the exact mechanisms (and their respective contributions) which cause myocyte disruption during EIMD are still unclear. Two main factors induce EIMD, including mechanical (in a primary event) and inflammatory (in a secondary response) stress[6]. Both may occur when EIMD is elicited. However, the contribution of each to the damaging process remains to be determined. Therefore, for didactical purposes, the present study explained the two mechanisms separately, as illustrated in Figure I.

Primary Damage

A few decades ago, research focused on the soreness response to exercise and its underlying mechanisms. Francis[18] reviewed the existing data on delayed onset muscle soreness (DOMS), dividing it into four theories: accumulation of lactic acid in the exercised muscle; muscular spasms; disruption of contractile tissue; and connective tissue damage. All theories agreed that eccentric contractions caused the highest level of DOMS.

With the advent of new technologies, evidence has confirmed that eccentric contractions lead to more accentuated changes in DOMS and other EIMD symptoms than isometric and concentric contractions[19,20]. This exacerbated response is reported to occur due to a considerable part of the resistance against the external load during eccentric contractions being conferred by non-contractile structures of the sarcomere, such as titin, desmin, α-actinins and other ultrastructural components[21]. Morgan and Proske[22] explained the disruption of non-contractile structures using the popping sarcomere hypothesis. This hypothesis states that serial sarcomeres are not homogeneous and respond differently to external tension. As muscle length increases during contraction, the contractile proteins in longer (and weaker) sarcomeres lose their overlapping property and stop producing active tension. This diminished active tension is compensated by increa-

sed passive tension exerted by the aforementioned non-contractile structures. This elevated tension leads to Z-line streaming and a consequent disorganization of the myocyte[23]. The first mechanical damage can be evidenced by histological analyses, such as those performed by Lieber, Thornell and Friden[24].

It is worth mentioning that other non-contractile organelles, such as the sarcoplasmic reticulum, sarcolemma and T tubules, are also disrupted by mechanical stress[1]. Upon sarcolemma disruption, an influx of Ca^{2+} occurs in the cytosol of the myocyte, which compromises excitation-contraction coupling. These events, along with Z-line disorganization and contractile protein (myosin and actin) tearing, may lead to muscle function loss and signaling to a secondary damage response[5].

Secondary Damage

The secondary damaging response is believed to have its onset immediately after the primary mechanic event. Augmented Ca^{2+} concentration in the cytosol leads to myocyte membrane degradation through activation of enzymes like calpain and phospholipase A2[25,26]. This membrane degradation process is cyclical because calpain and phospholipase A2 activation leads to membrane degradation of adjacent non-damaged myocytes. This degradation augments permeability and, therefore, Ca^{2+} concentration. Additionally, the combination of eccentric contractions and aerobic exercise increases reactive oxygen species (ROS) production in the mitochondria during the respiratory chain, which aggravates damage via peroxidation of the myocyte membrane[27].

Myocyte membrane degradation is accompanied by the release of eicosanoids into the blood stream, triggering diapedesis (i.e., leukocyte migration to the damaged site). Neutrophils are the first leukocytes to reach the damaged tissue, peaking approximately 1 day after the damaging event[28]. These neutrophils produce ELR^+ CXC chemokines, attract other neutrophils and, most importantly, initiate removal of damaged or necrotic tissue through phagocytosis[29]. ROS and lysosomal proteases are produced during this process, causing secondary injury to previously damaged fibers and damaging adjacent, non-damaged, fibers via oxidative stress[30].

In addition to neutrophils, monocytes also migrate to the damaged site, differentiating into macrophages and presenting concentration peaks 3-7 days after the first damaging events[31]. Beyond aiding neutrophils in the phagocytosis process (24 to 48 hours after the damaging bout), macrophages also signal for tissue repair by secreting cytokines like interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), and leukemia

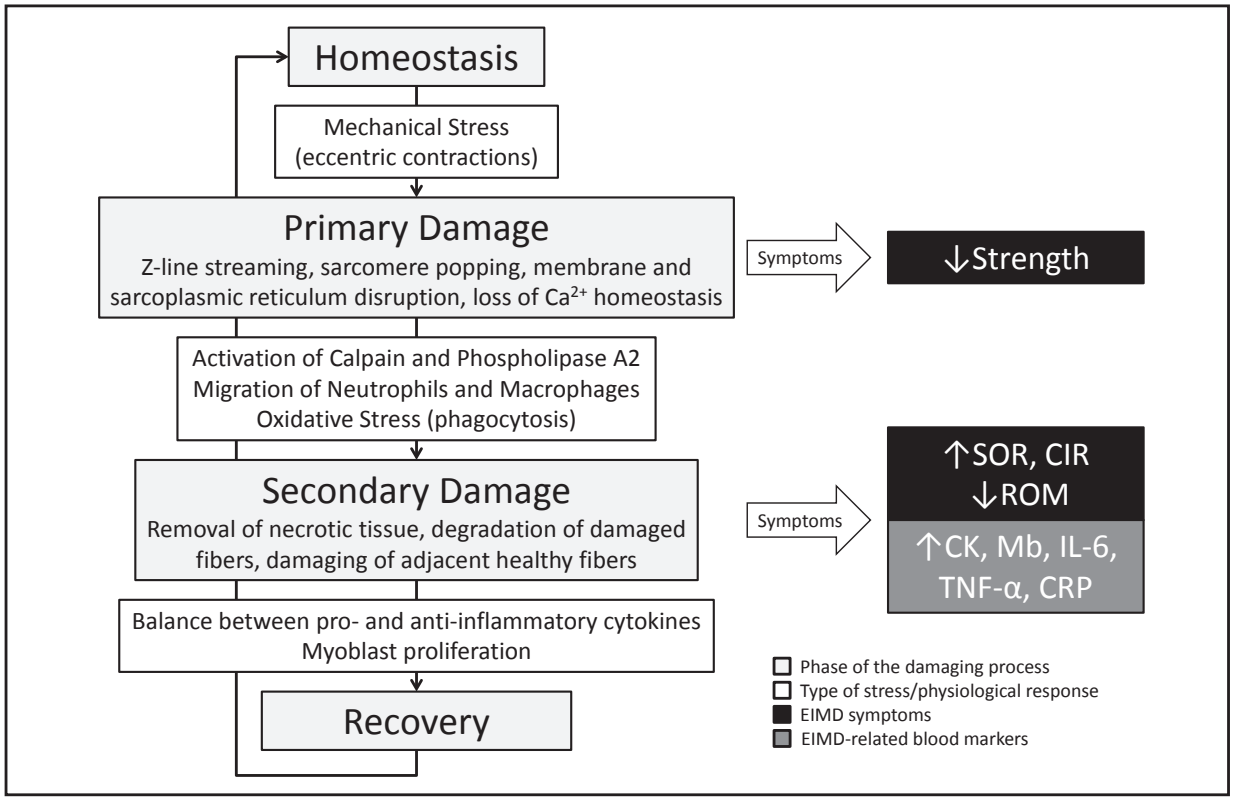

Fig. 1.—Representation of the damaging process dividing the phenomenon in two phases according to their mechanical and metabolic characteristics. SOR: muscle soreness; CIR: limb circumference; ROM: range of motion; CK: creatine kinase activity; Mb: myoglobin concentration in the blood stream; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; CRP: c-reactive protein.

inhibitory factor, which are reported to enhance myoblast proliferation and repair muscle tissue[32]. Therefore, while neutrophils' functions are to remove damaged tissue, macrophages are believed to be the most important factor in muscle repair following EIMD[33].

The magnitude of the inflammatory process is regulated by pro- (IL-1β, TNF-α, IL-6) and anti-inflammatory (IL-4, IL-5, IL-10, IL-13) cytokines[34]. The release of cytokines during the inflammatory process regulates the adaptive cellular response. Balance between pro- and anti-inflammatory cytokines may augment cellular protection against new stimuli. However, elevated EIMD magnitudes promote an intense inflammatory response, increasing pro-inflammatory cytokines like TNF-α[35]. This particular cytokine is synthetized by macrophages and other types of cells, including myocytes, and has roles in the immune system cellular metabolism, apoptosis and protein breakdown[36].

Santos, Bassit, Caperuto and Costa Rosa[37] reported that subjects' prostaglandin and TNF-α levels increased immediately after a 30-kilometer run. These levels remained elevated up to 24 hours following the exercise session, when compared to baseline values. Nieman et al.[38] also observed elevated levels of TNF-α and other cytokines (IL-1, IL-6, and IL-8) in trained athletes after three-hours of running at 70% of VO_2max.

Based on the current literature, it is possible to assume that the intensity of the first damaging event (i.e., mechanical stress) regulates the magnitude of the secondary response (i.e., inflammatory stress). However, a considerable part of the damage caused to the myocyte appears to be related to the inflammatory response and, in some cases, the oxidative status during the first event[6]. Therefore, it seems reasonable to investigate the control of the secondary response to EIMD and oxidative status during both events.

Cherries, Oxidative Stress, and Inflammation

Dietary supplement use has increased in recent decades. A wide range of products currently exist that can produce health- and performance-related benefits[11-13]. Phytochemicals are among these products believed to offer several benefits[39]. Anthocyanins are phytochemical compounds that have been extensively studied[15]. Found in high concentrations in all tissues of most dark-colored fruits and plants, these compounds are pigments that act as a natural sunscreen[16]. Along with their aglycon and cyaniding, anthocyanins (alongside other phenolic compounds) have been shown to produce potent antioxidant and anti-inflammatory actions when consumed by humans[40].

In an in vitro study, van Acker et al.[41] found that anthocyanins play an important role in the scavenging of nitric oxide (NO). NO is a free radical produced by macrophages during phagocytosis, which causes vasodilation and membrane damage, when in high concentrations. These effects are due to its precursor, peroxynitrite. Anthocyanins' NO scavenging activity has been shown to be 100 times more potent than that of glutathione, a natural antioxidant compound synthetized in the human body[41]. Wang et al.[42] reported that CH anthocyanins and their aglycon, cyanidin, produced an antioxidant action similar to commercially available supplements. Moreover, it was found that these compounds provide a more potent anti-inflammatory effect than aspirin due to the inhibition of cyclooxygenase (COX) activity[42]. Cyclooxygenase and lipoxygenase are responsible for the biosynthesis of prostaglandins and thromboxane, two important mediators of inflammation[43]. Accordingly, *in vitro* data from Seeram et al.[44] showed an inhibition of COX1 and COX2 induced by cyanidins from CH and berries. Wang and Mazza[45] also conducted an in vitro study investigating the effects of anthocyanins and other phenolic compounds on the production of TNF-α in artificially activated macrophages. Results showed a significant decrease in NO concentration (caused by NO scavenging) and, surprisingly, a dose-dependent increase in TNF-α production. This increase in TNF-α may contribute to inflammatory damage, which is contrary to what would be expected following consumption of anthocyanin rich products.

Jacob et al.[46] investigated the effects of consuming approximately 45 Bing cherries on plasma levels of urate, C-reactive protein (CRP), NO and TNF-α response. Results revealed that plasma urate, NO, and CRP levels significantly decreased after CH consumption. No changes in TNF-α levels were observed. A reduction in plasma urate concentration means that CH consumption might be a beneficial strategy to attenuate and prevent arthritic gout. Decreased NO and CRP levels after CH consumption indicate an antioxidant status, probably produced by anthocyanins present in CH. Although anthocyanins inhibit COX activity, the absence of TNF-α alterations indicate that this inflammation pathway might not be influenced by CH consumption. Using a similar research design, Bell et al.[47] investigated the effects of two dosages (30 and 60 ml) of Montmorency cherries on serum and urinary urate levels and antioxidant status. It was found that the 60 ml dosage was associated with significantly higher main anthocyanin (cyaniding-3-O-glucoside-rutinoside) bioavailability 1 hour after consumption. Interestingly, serum urate levels decreased and urinary urate levels increased, showing a urate eliminating effect induced by CH consumption. Bell et al.[47] found greater and faster changes in urate concentrations in both serum and urine due to Montmorency cherry consumption than Jacob et al.[46]. Even taking differences in consumption protocols and assessments into account, these finds seems to indicate that Montmorency cherries have a more potent antioxidant effect than Bing cherries.

Kelley et al.[48] investigated the effects of the consumption of 45 CH on inflammation markers in healthy

adults. Decreases in CRP, NO and regulated on activation, normal T cell expressed and secreted (RANTES), a chemokine that promotes diapedesis of circulating monocytes, were observed. No significant alterations in TNF-α and IL-6 were evident. Using an animal model, Saric et al.[40] found decreases in thiobarbituric acid reactive substances (TBARS), lipid peroxidation, and COX 2 activity following CH consumption. Increased activity of antioxidant enzymes, such as superoxide dismutase and gluthatione peroxidase, was also found. The authors suggest that the main antioxidant action produced by anthocyanins and their aglycones is the donation of electrons or hydrogen atoms from their hydroxyl portions to the circulating ROS.

The dissociated antioxidant and anti-inflammatory responses after CH consumption were not expected because CRP and NO are usually secreted by macrophages during phagocytosis, which is a process that occurs during inflammatory response. Additionally, inhibitions in COX activity and RANTES can be considered as markers of a blunted inflammatory response. Therefore, it is reasonable to consider that cherry consumption might also provide an anti-inflammatory effect, even though findings regarding IL-6 and TNF-α responses to CH consumption are inconsistent[17,47,48].

Cherries and Exercise-Induced Muscle Damage

CH's anti-inflammatory and antioxidant properties can be beneficial for patients with rheumatoid arthritis, atherosclerosis, and arthritic gout[46]. These properties are also beneficial for athletes and physical activity enthusiasts that avoid elevated EIMD magnitudes. Considering that the secondary response to EIMD contributes to damage via inflammation and oxidative stress[6], CH consumption might be considered a viable, low-cost, strategy to prevent this damage. Indeed, there is a growing body of evidence showing that CH consumption blunts the secondary response to EIMD (Table I).

Connolly et al.[49] conducted the first study investigating the effects of CH consumption on EIMD. Using a cross-over design, subjects ingested either tart CH juice or a placebo (PLA) (industrialized juice with no phytochemical properties) four days before, on the day, and four days after performing an exercise bout consisting of two sets of 20 maximal eccentric contractions of the elbow flexors. Results revealed that strength loss (4 N·m four days after the damaging bout for CH *vs*. 22 N·m for PLA at the same time point) and soreness (CH: 2.4 cm four days after the damaging *vs*. PLA: 3.2 cm at the same time point) were attenuated when subjects consumed CH. Although the authors did not assess any markers of inflammation or oxidative status, it was speculated that anthocyanins provided an anti-inflammatory and antioxidant effect, blunting the secondary damage event.

Similarly, Kuehl et al.[50] employed a randomized controlled trial design to investigate the effects of tart CH juice *vs*. PLA on soreness seven days before, and during, a relay race (in which each participant ran at least 20 km). The race was downhill, starting at altitude and finishing at sea level, which is known to induce significant EIMD[51]. The authors found reductions in soreness immediately post-race for the CH group. No inflammatory or oxidative stress markers were assessed. Similar to Connolly et al.[49], the authors speculated that CH juice's anti-inflammatory and antioxidant properties protected against soreness. Moreover, the authors believed that acute soreness was caused mostly by oxidative stress. This stress might have been reduced by the scavenging of ROS, induced by the phenolic compounds present in the CH juice. The studies of Connolly et al.[49] and Kuehl et al.[50] were important in the investigation of the effects of CH consumption on EIMD protection/recovery. However, although well controlled, their approaches to the problem were simplistic, considering the many alternative markers that can be assessed to investigate EIMD, such as inflammation.

Howatson et al.[17] conducted the first study ever to investigate the effects of CH consumption on EIMD based on inflammatory and oxidative stress markers. Using a randomized placebo trial, the authors recruited runners participating in the London marathon and assigned them to either a CH or PLA (fruit flavored concentrate with no phytochemical properties) group. All participants consumed their respective juices five days before, during, and two days after, the marathon. Markers of EIMD (strength, soreness, CK), inflammation (CRP, IL-6 and uric acid) and oxidative status [total antioxidant status (TAS), TBARS and protein carbonyls (PC)] were assessed before, immediately after, and two days after, the marathon. Strength was the only EIMD marker that presented a significant group-time interaction. Immediately after the marathon, both groups had similar losses in strength. However, the CH group subsequently presented a significantly faster recovery in strength when compared to the PLA group. The former returned to baseline 48 hours after the race while the latter did not fully recover until the end of the experiment. As for inflammation markers, the PLA group presented significantly higher CRP, IL-6 and uric acid peaks immediately after the marathon. Uric acid and CRP values were also significantly higher in the PLA group 24 h following the race. The TAS was significantly higher in the CH group immediately after the marathon. The PLA group presented significantly higher TBARS values 48 h after the marathon. Howatson et al.'s[17] results are similar to those of Connoly et al.[49] and Kuehl et al.[50]. However, Howatson et al.'s[17] study marked the first time a concrete relationship between CH consumption and EIMD protection could be partially demonstrated, as it was the first study to investigate inflammatory and oxidative status. One limitation of this study was the use of a zero calorie PLA.

Experimental data from Febbraio et al.[52] indicates that carbohydrate consumption alone can modulate acute IL-6 response. Therefore, the carbohydrates present in the CH beverage could have influenced the results because they were absent in the PLA. However, Bell et al.[14] evidenced an attenuation of IL-6 following CH concentrate consumption despite using an isocaloric PLA (i.e., containing the same amount of calories as the CH juice). Moreover, the results of Howatson et al.[17] differed from those of Kelley et al.[48], which found pro-inflammatory cytokine alterations after CH consumption. This difference might be justified by the absence of an exercise stimulus in the study of Kelley et al.[48]. The regulation of IL-6 conferred by CH consumption appears to only be significant in a pro-inflammatory status.

Bowtell et al.[53] also investigated associations between CH consumption, EIMD and oxidative response following a damaging bout. Their study consisted of a cross-over design in which subjects consumed either CH concentrate or a PLA (fruit concentrate without phytochemical properties) seven days before, during, and two days after performing an intensive resistance exercise protocol. The protocol consisted of 10 sets of 10 contractions of knee extensors at 80% of 1RM. The results supported Howatson et al.[17], showing similar strength losses immediately after the exercise bout for both conditions, but a faster recovery associated with CH consumption. Oxidative status, represented by PC, was higher in the PLA group during each assessed time point (i.e., 24 and 48 h after the exercise bout). These results corroborate those of Howatson et al.[17], showing an association between strength recovery and the antioxidant status conferred by CH consumption. The use of a cross-over design by Connolly et al.[49] and Bowtell et al.[53] may be a limitation, considering the manifestation of the repeated bout effect. There is, in fact, strong evidence pointing to contralateral protection conferred by damaging bouts[54,55].

Half of the aforementioned studies adopted damaging protocols that imposed mechanical stimuli through intense eccentric contractions[49,53]. The other half adopted protocols that induced EIMD through combined low-level mechanical, and high-level oxidative stress through long distance running[17,50]. CH consumption provided considerable protection against EIMD induced by both types of stimuli. However, considering the dissociation between stimulation strategies, Bell et al.[14] investigated the efficacy of CH concentrate consumption on protection from oxidative stress-induced damage to muscle cells in the absence of mechanical rupture. The researchers recruited trained cyclists and separated them into two groups (CH concentrate consumption *vs*. PLA). Both groups completed three separate trials of 66 sprint incorporated within nine sets on a cycle ergometer. Participants consumed their respective supplements four days before and on the days of the trials. Inflammation and oxidative markers were assessed at baseline, before, and after each trial. Performance during the trials was also monitored. A significant time effect was identified for CK, with no interaction between groups. The same result was found for trial performance. Significant time-group interactions were identified for IL-6, CRP and lipid peroxidation. Each of these markers was significantly higher in the PLA group after each trial. Additionally, lipid peroxidation was significantly lower compared with baseline values for the CH group, even after the exercise bouts. This finding showed that phytochemicals present in CH could confer a potent antioxidant defense, even in situations when oxidative stress should be extremely elevated (as occurred for the PLA group). These findings confirm that CH consumption significantly reduces inflammatory and oxidative status. However, this protection did not influence EIMD markers since the cycling activity did not impose significant mechanical stress to the sarcomeric apparatus. Therefore, it appears that CH consumption does not only accelerate recovery when EIMD manifests, but also protects against oxidative stress induced by strenuous, non-damaging, exercises.

Bell et al.[56] used a similar approach to investigate alterations in oxidative status, inflammation, and performance after a high-intensity stochastic cycling protocol. Sixteen well-trained cyclists were divided into two groups (CH concentrate consumption and PLA) and performed 9 sets of 66 cycling sprints. Performance (maximal voluntary isometric contractions of the knee extensors, cycling efficiency and peak power during 6-second sprints) was measured before, and 1-3 days after, the exercise bout. Inflammation markers (CRP, IL-1-β, IL-8, IL-6 and TNF-α), oxidative status (lipid hydroperoxides) and EIMD (CK and soreness) were assessed at baseline, immediately before, immediately after, and 1, 3, 5, 24, 48, and 72 hours after the stochastic cycling. A significant group effect was identified for maximal voluntary isometric force. Only the PLA group presented decrements for this marker. Only the PLA group experienced impaired cycling efficiency 24 hours after the exercise bout. A significant time effect was identified for peak power in the 6-second cycling test with no differences between groups. The same occurred for soreness, TNF-α, IL-8, lipid hydroperoxides, and CK. A significant group effect was found for IL-6 and CRP, with the CH group presenting lower levels of these inflammatory markers. The results from Bell et al.[56] confirm previous findings that Montmorency CH confers an anti-inflammatory effect after strenuous exercise. Most importantly, this study found no strength alterations in the CH group, differing from the PLA group. Additionally, the loss of cycling efficiency (which is known to be related to strength loss) was significantly greater for the PLA group 24 hours after the stochastic cycling. These results indicate that CH not only helps with recovery after strenuous exercise, but also may prevent performance decrements.

Table I
Summary of studies that investigated the effects of cherry consumption on inflammation, oxidative stress and exercise-induced muscle damage.

Study	*Population*	*Dosage Strategy*	*Exercise Bout*	*Muscle Damage*	*Oxidative Stress*	*Inflammation*
Connolly et al.49	14 male college students	355 ml twice a day: 3 days pre-, at, and 4 days post-EB	10 maximal eccentric contractions of the EF	↑ Strength recovery ↓ Soreness	N/A	N/A
Kuehl et al.50	54 healthy runners	355 ml twice a day: 7 days pre- and at the EB.	20 km downhill running	↓ Soreness	N/A	N/A
Howatson et al.17	20 experienced runners	236 ml twice a day: 5 days pre-, at, and 2 days post-EB	Marathon running	↑ Strength recovery	↑ TAS ↓ TBARS	↓ CRP; IL-6; uric acid
Bowtell et al.53	10 well-trained intermittent sports athletes	30 ml twice a day: 7 days pre-, at, and 2 days post-EB	10x10 contractions of the KE with 80%1RM	↑ Strength recovery	↓ PC	N/A
Bell et al.14	16 well-trained cyclists	30 ml twice a day: 4 days pre-, and at each EB	High-intensity stochastic cycling	→ CK	↓ lipid peroxidation	↓ IL-6; CRP
Bell et al.56	16 well-trained cyclists	30 ml twice a day: 4 days pre-, at, and 3 days post-EB	High-intensity stochastic cycling	↓ Strength loss → CK; soreness	→ LOOH	↓ IL-6, CRP → IL-8; TNF-α; IL-1-β

EB, exercise bout; EF, elbow flexors; KE, knee extensors; CK, creatine kinase; TAS, total antioxidant status; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; LOOH, lipid hydroperoxides; CRP, C-reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; IL-1-β, interleukin-1-β; 1RM, one maximum repetition.

Conclusion

Robust evidence shows that the damaging process continues through an inflammatory response after an initial mechanical disruption. Oxidative stress also plays an important role in this aggravation under two possible situations: when ROS are present during an initial mechanical disruption or metabolic challenging activity, and when leukocytes secrete ROS during the inflammatory response. Many studies showed that anthocyanins and their aglycones present in CH provide potent antioxidant effects by scavenging circulating ROS. Evidence also supports an inhibitory effect of inflammatory pathways signalized by the consumption of these phytochemicals.

All studies investigating the effects of CH consumption on EIMD have found that it conferred greater protection than PLA. All studies that evidenced an accelerated EIMD recovery used Montmorency tart CH (Prunus cerasus L.) juice as treatment. Results show that, although not efficient to protect from mechanical stress, CH consumption is an efficient strategy to accelerate recovery from EIMD-inducing strenuous exercise. Furthermore, this strategy promotes additional health benefits, such as the prevention against rheumatoid arthritis, arthritic gout and atherosclerosis.

More studies are needed to investigate the effects of CH consumption on other strenuous exercises and EIMD markers. Most studies investigating CH consumption have used the same quantity of CH and similar consumption intervals. Future studies should investigate optimal CH dosages and consumption periods before the damaging bouts (i.e., loading phase). Additionally, more studies are necessary to precisely discriminate what bioactive compounds contribute to Montmorency CH's anti-inflammatory and anti-oxidant properties. Finally, it is somewhat intriguing that all CH consumption studies have found significant positive effects on strenuous exercise recovery. This trend may be due to either a potent effect or research-related biases. Thus, the scientific community might feel encouraged to reproduce published data and conduct new studies to clarify if Montmorency CH's bioactive properties are as potent as they appear. Investigations on this effect are still scarce, with a potential publication bias favoring positive results.

Acknowledgements

The authors would like to thank the São Paulo Research Foundation (FAPESP) for their financial support.

References

1. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. *Am. J. Phys. Med. Rehabill.* 2002; 81(11): S52-69.
2. Brentano MA, Martins Kruel LF. A review on strength exercise-induced muscle damage: applications, adaptation mechanisms and limitations. *J. Sports Med. Phys. Fitness*. 2011; 51(1): 1-10.
3. Nosaka K, Newton M. Difference in the magnitude of muscle damage between maximal and submaximal eccentric loading. *J. Strength Cond. Res*. 2002; 16(2): 202-208.
4. Aoi W, Naito Y, Takanami Y, Kawai Y, Sakuma K, Ichikawa H, Yoshida N, Yoshikawa T. Oxidative stress and delayed-onset muscle damage after exercise. *Free Radic. Biol. Med*. 2004; 37(4): 480-487.
5. Hirose L, Nosaka K, Newton M, Laveder A, Kano M, Peake J, Suzuki K. Changes in inflammatory mediators following eccentric exercise of the elbow flexors. *Exerc. Immunol. Rev*. 2004; 10: 75-90.
6. Howatson G, Van Someren KA. The prevention and treatment of exercise-induced muscle damage. *Sports Med*. 2008; 38(6): 483-503.
7. Nosaka K, Sakamoto K, Newton M, Sacco P. Influence of pre-exercise muscle temperature on responses to eccentric exercise. *J. Athl. Train*. 2004; 39(2): 132-137.
8. Chen TC, Chen HL, Lin MJ, Chen CH, Pearce AJ, Nosaka K. Effect of two maximal isometric contractions on eccentric exercise-induced muscle damage of the elbow flexors. *Eur. J. Appl. Physiol*. 2013; 113(6): 1545-1554.
9. Chen CH, Nosaka K, Chen HL, Lin MJ, Tseng KW, Chen TC. Effects of flexibility training on eccentric exercise-induced muscle damage. *Med. Sci. Sports Exerc*. 2011; 43(3): 491-500.
10. Nelson N. Delayed onset muscle soreness: is massage effective? *J. Bodyw. Mov. Ther*. 2013; 17(4): 475-482.
11. Askari G, Hajishafiee M, Ghiasvand R, Hariri M, Darvishi L, Ghassemi S, Iraj B, Hovsepian V. Quercetin and vitamin C supplemtnation: effects on lipid profile and muscle damage in male athletes. *Int. J. Prev. Med*. 2013; 4(Suppl1): S58-S62.
12. Bassit RA, Pinheiro CH, Vitzel KF, Sproesser AJ, Silveira LR, Curi R. Effect of short-term creatine supplementation on markers of skeletal muscle damage after strenuous contractile activity. *Eur. J. Appl. Physiol*. 2010; 108(5): 945-955.
13. Nosaka K, Sacco P, Mawatari K. Effects of amino acid supplementation on muscle soreness and damage. *Int. J. Sport Nutr. Exerc. Metab*. 2006; 16(6): 620-635.
14. Bell PG, Walshe IH, Davison GW, Stevenson E, Howatson G. Montmorrency cherries reduce the oxidative stress and inflammatory responses to repeated days high-intensity stochastic cycling. *Nutrients*. 2014; 6(2): 829-843.
15. Bell PG, McHugh MP, Stevenson E, Howatson G. The role of cherries in exercise and health. *Scand. J. Med. Sci. Sports*. 2014; 24(3): 477-490.
16. Damar I, Ekşi A. Antioxidant capacity and anthocyanin profile of sour cherry (Prunus cerasus L.) juice. *Food Chem*. 2012; 135(4): 2910-2914.
17. Howatson G, McHugh MP, Hill JA, Brouner J, Jewell AP, Van Someren KA, Shave RE, Howatson SA. Influence of tart cherry juice on indices of recovery following marathon running. *Scand. J. Med. Sci. Sports*. 2010; 20(6): 843-852.
18. Francis K. Delayed muscle soreness: a review. *J. Orthop. Sports Phys. Ther*. 1983; 5(1): 10-13.
19. Clarkson PM, Byrnes WC, McCormick KM, Turcotte LP, White JS. Muscle soreness and serum creatine kinase activity following isometric, eccentric, and concentric exercise. *Int. J. Sports Med*. 1986; 7(3): 152-155.
20. Nosaka K, Newton M. Concentric or eccentric training effect on eccentric exercise-induced muscle damage. *Med. Sci. Sports Exerc*. 2002; 34(1): 63-69.
21. Lacourpaille L, Nordez A, Hug F, Couturier A, Dibie C, Guilhem G. Time-course effect of exercise-induced muscle damage on localized muscle mechanical properties assessed using elastography. *Acta Physiol*. 2014; 211(1): 135-146.
22. Morgan DL, Proske U. Popping sarcomere hypothesis explains stretch-induced muscle damage. *Clin. Exp. Pharmacol. Physiol*. 2004; 31(8): 541-545.
23. Lidstedt SL, LaStayo PC, Reich TE. When active muscles lengthen: properties and consequences of eccentric contractions. *New Physiol. Sci*. 2001: 256-261.
24. Lieber RL, Thornell LE, Friden J. Muscle cytoskeletal disruption occurs within the first 15 min of cyclic eccentric contraction. *J. Appl. Physiol*. 1996; 80(1): 278-284.
25. Gissel H. The role of Ca2+ in muscle cell damage. *Ann. N. Y. Acad. Sci*. 2005; 1066: 166-180.
26. Verbourg E, Murphy RM, Stephenson DG, Lamb GD. Disruption of excitation-contraction coupling and titin by endogenous Ca2+-activated proteases in toad muscle fibres. *J. Physiol*. 2005; 564(Pt.3): 775-790.
27. Mastaloudis A, Morrow JD, Hopkins DW, Devaraj S, Traber MG. Antioxidant supplementation prevents exercise-induced lipid peroxidation, but not inflammation, in ultramarathon runners. *Free. Radic. Biol. Med*. 2004; 15,36(10): 1329-1341.
28. Pizza FX, Koh TJ, McGregor SJ, Brooks SV. Muscle inflammatory cells after passive stretches, isometric contractions, and lengthening contractions in mice. *J. Appl. Physiol*. 2002; 92(5): 187-188.
29. Mastukawa A, Hogaboam CM, Lukacs NW, Kunkel SL. Chemokines and innate immunity. *Rev. Immunogenet*. 2000; 2(3): 339-358.
30. Pizza FX, Peterson JM, Bass JH, Koh TJ. Neutrophils contribute to muscle injury and impairs its resolution after lengthening contractions in mice. *J. Physiol*. 2005; 562(Pt 3): 899-913.
31. Koh TJ, Peterson JM, Pizza FX, Brooks SV. Passive stretches protect skeletal muscle of adult and old mice from lengthening contraction-induced injury. *A. Biol. Sci. Med. Sci*. 2003; 58(7): 592-597.
32. Hawke TJ, Garry DJ. Myogenic satellite cells: Physiology to molecular biology. *J. Appl. Physiol*. 2001; 91(2): 534-551.
33. Chazaud B, Brigitte M, Yacoub-Youssef H, Arnold L, Gherardi R, Sonnet C, Lafuste P, Chretien F. Dual and beneficial roles of macrophages during skeletal muscle regeneration. *Exerc. Sport Sci. Rev*. 2009; 37(1): 18-22.
34. Pedersen BK, Akerström TC, Nielsen AR, Fischer CP. Role of myokines in exrcise and metabolism. *J. Appl. Physiol*. 2007; 103(3): 1093-1098.
35. Pillon NJ, Bilan PJ, Fink LN, Klip A. Cross-talk between skeletal muscle and immune cells: muscle-derived mediators and metabolic implications. *Am. J. Physiol. Endocrinol. Metab*. 2013; 304(5): E453-E465.
36. Silveira EM, Rodrigues MF, Krause MS, Vianna DR, Almeida BS, Rossato JS, Oliveira LP, Curi R, Bittencourt PI. Acute exercise stimulates macrophage function: possible role of NF-kappaB pathways. *Cell. Biochem. Funct*. 2007; 25(1): 63-73.
37. Santos RV, Bassit RA, Caperuto EC, Costa Rosa LF. The effect of creatine supplementation upon inflammatory and muscle soreness markers after a 30k race. *Life Sci*. 2004; 75(16): 1917-1924.
38. Nieman DC, Dumke CI, Hensom DA, McAnulty SR, McAnulty LS, Lind RH, Morrow JD. Immune and oxidative changes during and following the Western States Endurance Run. *Int. J. Sports Med*. 2003; 24(7): 541-547.
39. Rebello CJ, Greenway FL, Finley JW. Whole grains and pulses: a comparison of the nutritional and health benefits. *J. Agric. Food Chem*. 2014; 62(29): 7029-7049.
40. Saric A, Sobocanec S, Balog T, Kusic B, Sverko V, Dragovic-Uzelac V, Levaj B, Cosic Z, Macak Safranko Z, Marotti T. Improved antioxidant and anti-inflammatory potential in mice consuming sour cherry juice (Prunus cerasus cv. Maraska). *Plant Foods Hum. Nutr*. 2009; 64(4): 231-237.
41. van Acker S, Tromp M, Haenen G, Vijgh W, Bast A. Flavonoids as scavengers of nitric oxide radical. *Biochem. Biophys. Res. Commun*. 1995; 214(3): 755-759.
42. Wang H, Nair MG, Strasburg GM, Chang YC., Booren AM, Gray JI, DeWitt DL. Antioxidant and anti-inflammatory activities of anthocyanins and their aglycon, cyanidin, from tart cherries. *J. Nat. Prod*. 1999; 62(2): 294-296.

43. Peake J, Nosaka K, Suzuki K. Characterization of inflammatory responses to eccentric exercise in humans. *Exerc. Immunol. Rev*. 2005; 11: 64-85.
44. Seeram NP, Momin RA, Nair MG, Bourquin D. Cyclooxygenase inhibitory and antioxidant cyanidin glycosides in cherries and berries. *Phytomedicine*. 2001; 8(5): 362-369.
45. Wang J, Mazza G. Effects of anthocyanins and other phenolic compounds on the production of tumor necrosis factor α in LPS/IFN-y-activated RAW 264-7 macrophages. *J. Agric. Food Chem*. 2002; 50: 4183-4189.
46. Jacob RA, Spinozzi GM, Simon VA, Kelley DS, Prior RL, Hess-Pierce B, Kader A. Consumption of cherries lowers plasma urate in healthy women. *J. Nutr*. 2003; 133(6): 1826-1829.
47. Bell PG, Gaze DC, Davison GW, George TW, Scotter MJ, Howatson G. Montmorrency tart cherry (Prunus cerasus L.) concentrate lowers uric acid, independent of plasma cyaniding-3-O-glucosiderutinoside. *J. Funct. Foods*. 2014; 11: 82-90.
48. Kelley DS, Rasooly R, Jacob RA, Kader AA, Mackey BE. Consumption of bing sweet cherries lowers circulating concentrations of inflammation markers in healthy men and women. *J. Nutr*. 2006; 136(4): 981-986.
49. Connolly DA, McHugh MP, Padilla-Zakour OI, Carlson L, Sayers SP. Efficacy of a tart cherry juice blend in preventing the symptoms of muscle damage. *Br. J. Sports Med*. 2006; 40(8): 679-683.
50. Kuehl KS, Perrier ET, Elliot DL, Chesnutt JC. Efficacy of tart cherry juice in reducing muscle pain during running: a randomized controlled trial. *J. Int. Soc. Sports Nutr*. 2010; 7: 1-6.
51. Assumpção CO, Lima LC, Oliveira FB, Greco CC, Denadai BS. Exercise-induced muscle damage and running economy in humans. *ScientificWorldJournal*. 2013; 2013: 1-7.
52. Febbraio MA, Steensberg A, Keller C, Starkie RL, Nielsen HB, Krustrup P, Ott P, Secher NH, Pedersen BK. Glucose ingestion attenuates interleukin-6 release from contracting skeletal muscle in humans. *J. Physiol*. 2003; 549(Pt 2): 607-612.
53. Bowtell JL, Summers DP, Dyer A, Fox P, Mileva KN. Montmorrency cherry juice reduces muscle damage caused by intensive strength exercise. *Med. Sci. Sports Exerc*. 2011; 43(8): 1544-1551.
54. Howatson G, van Someren KA. Evidence of a contralateral repeated bout effect after maximal eccentric contractions. *Eur. J. Appl. Physiol*. 2007; 101(2): 207-214.
55. Xin L, Hyldahl RD, Chipkin SR, Clarkson PM. A contralateral repeated bout effect attenuates induction of NF-kB DNA binding following eccentric exercise. *J. Appl. Physiol*. 2014; 116(11): 1473-1480.
56. Bell PG, Walshe IH, Davison GW, Stevenson EJ, Howatson G. Recovery facilitation with montmorrency cherries following high-intensity, metabolically challenging exercise. *Appl. Physiol. Nutr. Metab*. 2015; 40(4): 414-423.