

Ellagitannin Consumption Improves Strength Recovery 2–3 d after Eccentric Exercise

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ABSTRACT

TROMBOLD, J. R., J. N. BARNES, L. CRITCHLEY, and E. F. COYLE. Ellagitannin Consumption Improves Strength Recovery 2–3 d after Eccentric Exercise. *Med. Sci. Sports Exerc.*, Vol. 42, No. 3, pp. 493–498, 2010. **Purpose:** Dietary supplementation with polyphenols, particularly ellagitannins, may attenuate the muscular damage experienced after eccentric exercise, producing delayed-onset muscle soreness. The purpose of this study was to determine whether ellagitannin supplementation from Wonderful variety pomegranate extract (POMx) improved recovery of skeletal muscle strength after eccentric exercise. **Methods:** Recreationally active males were randomized into a crossover design with either pomegranate extract (POMx) or placebo (PLA), each given during a period of 9 d. To produce delayed-onset muscle soreness, subjects performed two sets of 20 maximal eccentric elbow flexion exercises with one arm. Maximal isometric elbow flexion strength and muscle soreness as well as serum measures of creatine kinase, myoglobin, interleukin 6, and C-reactive protein were made at baseline and 2, 24, 48, 72, and 96 h after exercise. **Results:** With both treatments, strength was similarly reduced 2 h after exercise (i.e., 72% of baseline), and recovery of strength was incomplete after 96 h (i.e., 91% of baseline). However, strength was significantly higher in POMx compared with that in PLA at 48 h ($85.4\% \pm 2.5\%$ and $78.3\% \pm 2.6\%$, $P = 0.01$) and 72 h ($88.9\% \pm 2.0\%$ and $84.0\% \pm 2.0\%$, $P = 0.009$) after exercise. Serum markers of inflammation and muscle damage did not provide insight regarding possible mechanisms. **Conclusions:** Supplementation with ellagitannins from pomegranate extract significantly improves recovery of isometric strength 2–3 d after a damaging eccentric exercise. **Key Words:** POLYPHENOLS, ISOMETRIC STRENGTH, DELAYED-ONSET MUSCLE SORENESS, INFLAMMATION

Polyphenols derived primarily from fruits have been observed to improve function of people placed under stress because of cellular insult from colon cancer (1), rheumatoid arthritis (29), and cardiovascular disease (2,3,14,16,20). Eccentric exercise in people produces delayed-onset muscle soreness (DOMS) and provides a good model for evaluating the functional significance of polyphenol supplementation for enhancing some aspects of *in vivo* tissue recovery. The acute muscle damage from eccentric exercise can cause local inflammation (22,27), oxidative stress (33), and release of Ca²⁺-activated proteases (4,6,21). These processes are generally similar to pathological types of cellular damage. Several days are required to recover from DOMS, and thus, careful measures

of strength can be used to describe the time course of recovery of function.

Recently, polyphenol supplementation from tart cherries has been reported to accelerate recovery of strength after performing eccentric exercise (12). To our knowledge, no other study using humans has identified a treatment that is effective at improving recovery of muscle strength with DOMS. The mechanisms mediating the biological benefits of polyphenol supplementation from fruit are not clear but may be linked to the attenuation of oxidative stress and inflammation (1,18,20). Supplementation with vitamin E or C has no influence on soreness or strength (5,11) and NSAID supplementation reduces soreness but does not improve strength (15). Ingestion of various mixtures of tocopherols, docosahexaenoate, selenium, or flavanoids (i.e., quercetin and hesperetin) has been observed to reduce oxidative stress (17) or inflammation (26) after eccentric exercise, yet strength was not measured. It seems that no study in humans has shown that a nutritional supplement improves recovery of muscle function by reducing inflammation or oxidative stress.

The purpose of this study was to determine in humans if polyphenol supplementation from ellagitannins in pomegranate extract improves recovery of muscle strength and soreness and attenuates markers of inflammation and

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cellular stress during the 4-d recovery period after performing an eccentric exercise.

METHODS

Subjects. Sixteen healthy, nonsmoking, and recreationally active males (24.2 ± 1.4 yr, 73.2 ± 1.7 kg, 177.5 ± 1.2 cm) were recruited. Subjects were disqualified if they had participated in resistance exercise training of any kind in the previous 3 months, were currently participating in a formalized endurance training program, or had previous history of upper body injury. Throughout the duration of the study, subjects were instructed to maintain their normal level of physical activity and were asked to discontinue consumption of vitamin/mineral supplements and over-the-counter pain medicine 1 month before the start and throughout the duration of the study. Other criteria for participation exclusion were recent weight change of >5 kg, history of hypertension, use of anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, lipid-lowering medications, or selective serotonin reuptake inhibitors. This study was conducted under a protocol approved by the University of Texas at Austin's Institutional Review Board, and each subject provided written informed consent.

Design. This study was a double-blind, randomized, placebo (PLA)-controlled crossover experiment with two testing periods, each lasting 9 d. A 14-d washout period separated the two testing periods. During each of the 9-d testing periods, the bout of eccentric exercise used to elicit DOMS was performed on the fifth day, with measures of recovery made during the subsequent 4 d. Subjects were randomly assigned to perform the first testing period with either pomegranate extract (POMx) or PLA treatment. Furthermore, for each testing period, the eccentric exercise was performed with only one arm, and the ordering of dominant or nondominant arm was randomized. Before the start of the study, subjects reported to the laboratory on three occasions for familiarization testing of maximal isometric strength during elbow flexion.

Baseline measures of soreness and isometric strength were collected 5 d before and immediately before eccentric exercise. Recovery measures were made 2, 24, 48, 72, and 96 h after exercise. Subjects reported to the laboratory at the same time of day during each treatment and were instructed to avoid caffeine ingestion before each visit.

Supplementation. Supplements of POMx or PLA (500 mL) were taken twice daily at 12-h intervals during each 9-d testing period. On the fifth day of supplementation, eccentric exercise was performed, and subjects consumed an additional bottle of POMx or PLA immediately after eccentric exercise. POMx and PLA drinks were provided by POM Wonderful (Los Angeles, CA) using Wonderful variety pomegranates grown in California. Products were shipped frozen and stored at 4°C . Each 480-mL bottle of POMx beverage contained 650 mg of pomegranate polyphenols (as measured by gallic acid equivalent) consisting of 95.5% ellagitannins, 3.5% ellagic acid, and 1% antho-

cyanins. Both POMx and PLA contained 4 g of carbohydrate (maltodextrin and sucralose) with additional coloring and flavoring used to blind the treatments. Subjects were reminded verbally and through e-mail communication to consume the experimental supplements at the required times.

Eccentric exercise. A Biodex isokinetic dynamometer (Cybex International, Medway, MA) was used to perform the eccentric exercise protocol. On the morning of fifth day of each testing period, subjects performed the eccentric exercise bout 15 min after the preexercise measurements of strength, soreness, and blood collection. Subjects performed two sets of 20 maximal eccentric elbow flexion repetitions starting with the elbow at 50° of full flexion and ending at 170° . The axis of rotation was aligned with the lateral epicondyle of the humerus. Repetitions were performed once every 15 s, with each repetition lasting 3 s at a velocity of $0.7 \text{ rad}\cdot\text{s}^{-1}$. During the 3-s contraction, subjects were verbally encouraged to maximally resist the motion of the lever arm. After completing the first set, subjects rested 4 min before performing the second set. Total work performed in joules (J) was recorded.

Isometric strength test. At the beginning of the study before supplementation, three familiarization sessions to practice the isometric strength tests were required to ensure that each subject was comfortable and able to generate maximal isometric force for each arm at both 150° and 135° of complete elbow extension.

Isometric elbow flexion strength tests were performed using a modified preacher curl bench. Force was recorded using a load cell (LC101-500; Omega Engineering, Stamford, CT) secured to the ground using a galvanized steel cable and a strap secured to the wrist of the subject. The subject performed four trials, two at both 150° and 135° of complete elbow extension, with a 180-s rest in between each trial. Strength was reported as the average of the peak value at angles of 150° and 135° of elbow flexion because results were similar at both angles. Strength was measured before exercise (BASELINE) and at 2, 24, 48, 72, and 96 h after eccentric exercise for both trials, using only the arm that performed the exercise.

Soreness. Soreness of the elbow flexor muscles was determined by having the subject subjectively rate the degree of soreness using a visual analog scale of 0 to 10, with 0 described as "no soreness" and 10 described as "unbearable soreness." This rating was obtained before the measurement of strength while performing unloaded elbow flexion of the tested arm. Soreness was normalized to 100% of the maximal level perceived during either trial.

Blood collection. Blood was collected from an antecubital vein from the contralateral arm that was being tested at BASELINE and at 2, 24, 48, 72, and 96 h for both trials, before the soreness and strength tests ($n = 15$). Blood was distributed into commercially produced vacuum-sealed serum collection tubes (Vacutainer, Franklin Lakes, NJ) that were kept at room temperature for 15 min to allow for coagulation, then centrifuged at $3000g$ for 15 min at 4°C and then

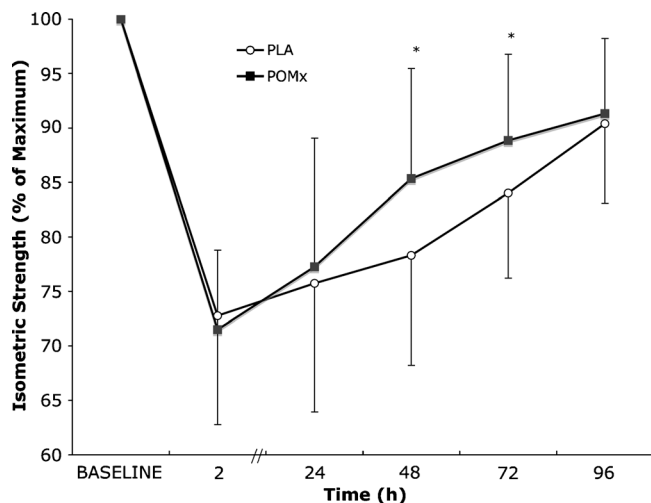


FIGURE 1—Isometric strength during elbow flexion expressed as a percent of initial baseline levels ($n = 16$). Treatments were POMx (filled squares) or a sweetened and colored PLA (open circles). *POMx significantly greater than PLA ($P < 0.05$). Values are reported as mean \pm SD.

allocated into microcentrifuge collection tubes. All samples were stored immediately after allocation at -80°C . Serum was analyzed for creatine kinase (CK) using the spectrophotometric UV kinetic method (Teco Diagnostics, Anaheim, CA). Serum was analyzed for myoglobin (Mb), interleukin 6 (IL-6), and C-reactive protein (CRP) using commercially available ELISA kits (Oxis International, Foster City, CA; R&D Systems, Minneapolis, MN; Endogen, Woburn, MA).

Statistical analysis. Two-way repeated-measures ANOVA and least significant difference (LSD) was used for treatment \times time, time, and treatment analyses. If the Mauchly test of sphericity was violated, the Greenhouse–Geisser correction was used. If treatment or treatment \times time interactions were found to be significant, paired t -tests were used for the analysis of time interaction in each treatment and to compare treatments at specific time intervals. Confidence interval (CI) was assessed for strength recovery from 2 to 48 and 72 h after exercise (95% CI). All statistical analyses were performed for strength, soreness, CK, Mb, IL-6, and CRP unless otherwise stated. Significance was assessed at the α level of $P < 0.05$. Values are reported as mean \pm SD.

RESULTS

Isometric Elbow Flexion Strength

There was no difference in eccentric work performed in POMx and PLA treatments (3358 ± 385 and 3393 ± 367 J, respectively, $P = 0.49$). Two hours after eccentric exercise, isometric strength was significantly ($P < 0.001$) reduced to $71.5\% \pm 7.3\%$ and $72.8\% \pm 10.0\%$ of BASELINE in POMx and PLA, respectively, with no difference between treatments (Fig. 1). At 24 h, strength was also not different in POMx versus PLA ($77.3\% \pm 11.8\%$ vs $75.7\% \pm 11.3\%$).

At 48 h, strength was significantly improved from 2 h in both POMx and PLA ($P = 0.001$ and $P = 0.003$, respectively). However, the recovery of strength during the 24- to 48-h period was more rapid in POMx, and thus, strength was significantly higher in POMx versus PLA at 48 h ($85.4\% \pm 10.1\%$ vs $78.3\% \pm 10.1\%$, $P = 0.01$). This difference persisted, and at 72 h, POMx was still significantly higher than PLA ($88.9\% \pm 7.9\%$ vs $84.0\% \pm 7.8\%$, $P = 0.009$). At 96 h, strength in POMx and PLA was $91.3\% \pm 6.9\%$ and $90.4\% \pm 7.3\%$ of BASELINE and significantly less than BASELINE in both treatments ($P < 0.001$), indicating incomplete recovery in both treatments. The decline in strength from BASELINE to 48 h was significantly less in POMx ($14.6\% \pm 10.4\%$) compared with PLA ($21.7\% \pm 10.1\%$, $P = 0.023$). Comparison of the rate of recovery from 2 to 48 h (PLA = 5.5% , 95% CI = 2.38% – 8.68% ; POMx = 13.9% , 95% CI = 7.84% – 19.9%) and from 2 to 72 h (PLA = 11.3% , 95% CI = 7.98% – 14.52% ; POMx = 17.4% , 95% CI = 12.13% – 22.59%) indicates improved recovery of isometric strength in POMx. An ordering effect was observed between trials 1 and 2, with trial 2 greater than trial 1 at 2 h ($P = 0.01$), 72 h ($P = 0.019$), and 96 h ($P = 0.006$). No differences in strength were observed between the use of dominant or nondominant limbs when compared independent of treatment or ordering.

Soreness

Two hours after eccentric exercise, perceived muscle soreness was significantly less in POMx versus PLA ($P = 0.035$; Fig. 2). Thereafter, soreness was highest during the 24- to 48-h period of recovery in both trials. However, during the 24- to 96-h period of recovery, our measures did not detect a significant difference in perceived muscle soreness with POMx compared with PLA.

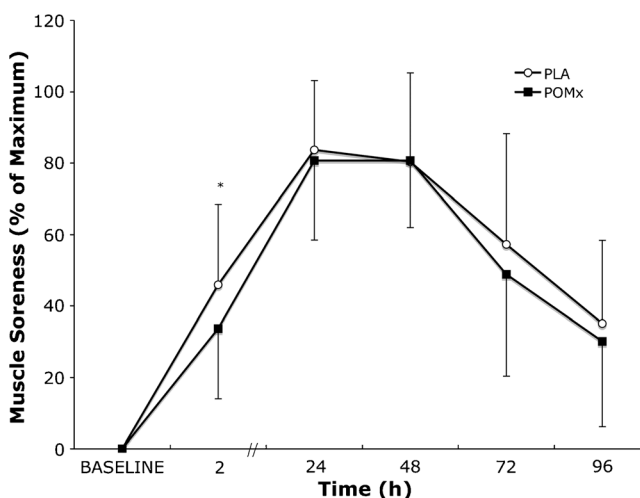


FIGURE 2—Muscle soreness reported as a percent of the maximum soreness from each subject in either trial ($n = 16$). Treatments were POMx (filled squares) or a sweetened and colored PLA (open circles). *PLA significantly greater than POMx ($P < 0.05$). Values are reported as mean \pm SD.

Serum Markers of Muscle Damage

Creatine kinase (CK) was higher at all time points (main effect of time) than at BASELINE. In the POMx treatment, CK was significantly greater at 2 h ($P = 0.034$), 24 h ($P = 0.024$), and 72 h ($P = 0.026$) than at BASELINE. In the PLA group, CK was significantly greater at 24 h ($P = 0.006$), 72 h ($P = 0.030$), and 96 h ($P = 0.036$) than at BASELINE. There were no significant differences between treatments (Fig. 3).

Mb was higher at all time points (main effect of time) than at BASELINE. There were no significant changes in serum Mb during POMx treatment. During the PLA treatment, Mb was significantly increased at 72 h ($P = 0.006$) compared with BASELINE. There were no significant differences between groups (Fig. 4).

Inflammation

IL-6. There were no significant changes during the testing period in either treatment. Mean \pm SE serum IL-6 concentrations in the PLA treatment were 1.33 ± 1.43 , 2.12 ± 2.99 , 1.25 ± 0.89 , 0.93 ± 0.79 , 1.16 ± 0.88 , and 1.27 ± 0.65 $\text{pg}\cdot\text{mL}^{-1}$ at BASELINE and at 2, 24, 48, 72, and 96 h after exercise, respectively. In the POMx treatment, mean \pm SD serum IL-6 concentrations were 1.08 ± 0.55 , 1.39 ± 0.97 , 1.23 ± 0.86 , 1.19 ± 0.75 , 1.10 ± 0.52 , and 1.61 ± 0.49 $\text{pg}\cdot\text{mL}^{-1}$ at BASELINE and at 2, 24, 48, 72, and 96 h after exercise, respectively.

CRP. There were no significant alterations over time or differences between treatments. In the PLA treatment, mean \pm SE serum CRP concentrations were 1.59 ± 2.10 , 1.66 ± 1.87 , 1.78 ± 2.4 , 1.32 ± 1.8 , 0.91 ± 0.97 , and 0.90 ± 0.66 $\text{ng}\cdot\text{mL}^{-1}$ at BASELINE and at 2, 24, 48, 72, and 96 h after exercise, respectively. In the POMx treatment, mean \pm SD serum CRP concentrations were 0.90 ± 0.83 , 1.97 ± 0.97 ,

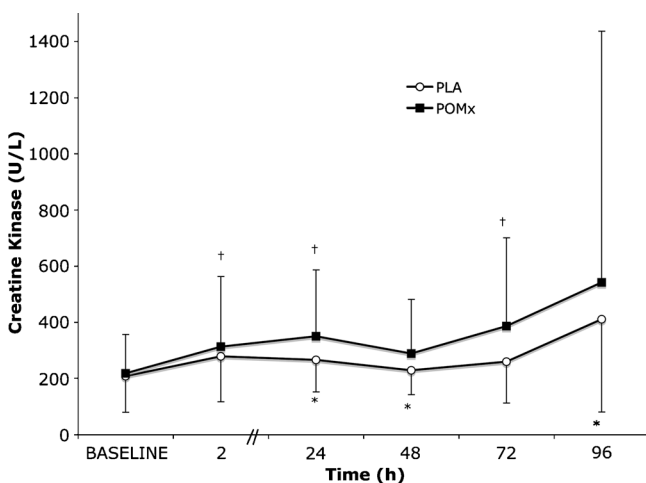


FIGURE 3—Serum CK reported in units per liter ($\text{U}\cdot\text{L}^{-1}$; $n = 15$). Treatments were POMx (filled squares) or a sweetened and colored PLA (open circles). *PLA significantly greater than BASELINE ($P < 0.05$). †POMx significantly greater than BASELINE ($P < 0.05$). Values are reported as mean \pm SD.

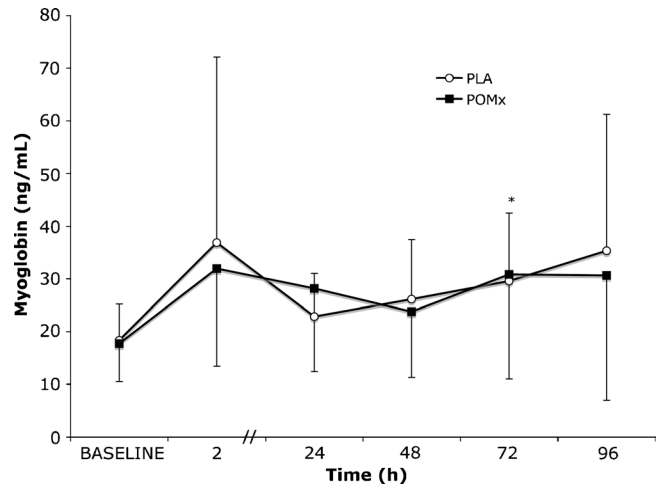


FIGURE 4—Serum Mb concentration in nanograms per milliliter ($\text{ng}\cdot\text{mL}^{-1}$; $n = 15$). Treatments were POMx (filled squares) or a sweetened and colored PLA (open circles). *PLA significantly greater than BASELINE ($P < 0.05$). Values are reported as mean \pm SD.

1.14 ± 0.86 , 0.95 ± 0.75 , 0.80 ± 0.52 , and 0.72 ± 0.49 $\text{ng}\cdot\text{mL}^{-1}$ at BASELINE and at 2, 24, 48, 72, and 96 h after exercise, respectively.

DISCUSSION

The primary finding of this study was that dietary supplementation with POMx compared with PLA improves the recovery of isometric strength during the 48- to 72-h period after eccentric exercise (Fig. 1). This finding confirms previous observations using tart cherry juice containing 600 mg of phenolic compounds (11). In this study, improved acute strength recovery with POMx supplementation occurred without a measurable attenuation of muscle soreness compared with PLA. However, muscle soreness was significantly reduced in the POMx treatment compared with PLA treatment at 2 h after exercise.

Nutritional interventions to reduce the soreness and weakness of DOMS have yielded mixed results. In humans, supplementation of either vitamin E or C seems ineffective at influencing DOMS (5,11). NSAID supplementation attenuates soreness but does not accelerate recovery of strength (15). Ingestion of mixtures of tocopherols, docosahexaenoate, and flavanoids (quercetin and hesperetin) has been reported to attenuate systemic markers of inflammation (CRP and IL-6) (26). Furthermore, ingestion of a combination of ascorbic acid, α -tocopherol, and selenium reduced oxidative stress after eccentric exercise (17). However, muscle strength was not measured in either study (16,24). Connolly et al. (12) reported that supplementation with polyphenols from tart cherry juice accelerated strength recovery, but muscle damage, inflammation, or oxidative stress was not measured. Therefore, to our knowledge, no single study in humans has yet shown that ingestion of nutritional supplements accelerates recovery of muscle function while simultaneously reducing inflammation or muscle damage. The present study

found improved strength recovery 2–3 d after exercise when ellagitannins from pomegranate extract were ingested for 4 d before eccentric exercise and throughout the 4-d recovery period; however, it failed to detect a benefit regarding inflammation or muscle damage.

Polyphenols represent one of the largest groups of phytochemicals primarily found in fruits, vegetables, and certain plant-derived products. The efficacy of POMx is attributed to its high content of polyphenols primarily in the form of ellagitannins. These have been found to possess high biological activity during pathological inflammation and/or oxidative stress (18,29). Consumption of pomegranate juice and pomegranate extract has been shown to have cardioprotective effects (2,3,31) as well as benefits with cancer (1), atherosclerosis (16,20), and rheumatoid arthritis (29). The present observation that POMx accelerated recovery after 24 h, with strength being significantly higher at 48 and 72 h, is consistent with the general time course for posteccentric development of local and systemic inflammation and oxidative stress. Previous work in animal models has shown reduction in postexercise inflammation (7) or oxidative stress (33) to attenuate myofiber damage and *in situ* muscle force during electrical stimulation, respectively.

The exercise protocol used in the present study significantly increased serum measures of the muscle CK, thus indicating that typical damage to myocytes did occur. Serum Mb also increased in general, yet there was much variability in this response with the only significant increase observed at 72 h in the PLA treatment. From these data, it is unclear if muscle damage occurred; however, recent evidence suggests that reduction in isometric strength is a more valid and reliable indicator of exercise-induced muscle damage compared with traditional blood markers (32). In this study, CK and Mb were increased compared with that in BASELINE (main effect of time), indicating an exercise effect but to a lesser extent than previously reported (10,28). However, measurements of inflammation in this study, using serum markers of IL-6 and CRP, were unable to detect a postexercise increase from BASELINE in either treatment. Previous research in sedentary individuals performing eccentric exercise has observed postexercise increases in systemic IL-6 and CRP (26) and local inflammation (22). In the present study, it is not clear if the amount of muscle mass experiencing damage and DOMS was too small, if these serum markers are not reflective of inflammation under these experimental conditions, or if inflammation did not occur.

The eccentric exercise proved effective at reducing strength equally in PLA and POMx when measured after 2 h of recovery. Furthermore, perceived muscle soreness was highest during the 24- to 48-h period (Fig. 2). These observations are consistent with the previously described phenomenon of DOMS (9,22,24,28). The subjective measure of perceived muscle soreness, although sufficient for describing the general time course, may not be sensitive enough for detecting subtle benefits of supplementation, if benefits do exist. However, it is interesting that the increase in perceived muscle

soreness 2 h after eccentric exercise was attenuated in POMx compared with that in PLA. The equal reductions in strength 2 h after eccentric exercise and the similar elevation in CK suggest similar levels of damage or acute fatigue with the two treatments, but apparently, POMx lowered the level of perceived muscle soreness in response to this damage.

Given this study's primary focus on muscle function as assessed through isometric strength, a pretest familiarization period was used to control for acute improvements because of learning or disinhibition (13). The absence of familiarization may lead to less than maximal strength measurement at baseline resulting in artificially high strength recovery during the experiment. This possibility was minimized in the present study. We observed incomplete strength recovery to approximately 91% of baseline values after 4 d, in agreement with previous studies (23,25,28,30). Typically, full recovery requires 7–14 d (8,11,30). In a recent study using polyphenol supplementation from tart cherry juice (12), strength after 4 d of recovery was reported to be 108% of the preexercise value. It is unknown if a pretest familiarization occurred because such procedures were not described in their study design. It seems unlikely that strength would improve 8% above baseline after a single eccentric exercise bout.

In this study, there was an ordering effect when assessed independent of the treatment provided. A recent study suggests that unilateral eccentric exercise offers protection from a subsequent bout performed with the contralateral limb (19). However, because of the randomized study design (nine subjects started with PLA first compared with six starting with POMx), it is difficult to determine a true ordering effect. In addition, when ordering effects are assessed dependent of the treatment, trial 1 PLA was not significantly greater than trial 2 PLA and trial 1 POMx was not significantly greater than trial 2 POMx. This indicates that the observed ordering effect, independent of the treatment, is likely a result of the treatment not an ordering effect *per se*.

The finding that POMx resulted in a significant improvement in strength of untrained muscles 48–72 h after intense eccentric exercise has potential practical relevance to people whose performance depends on optimal strength. These subjects were physically active, with some participating in recreational sports, yet none performed weight lifting-type training. Therefore, people called on to work intensely using muscles that have not been exercised intensely or exposed to eccentric contraction in the past 6 wk may benefit from supplementation with POMx if they are required to work again in 2–3 d. Examples include emergency workers, policemen, firefighters, soldiers, and construction workers. In addition, individuals participating in rigorous sports or recreational activities lasting 2–3 d (i.e., weekend sporting competition) might benefit from POMx supplementation if a 6%–9% improvement in maximal strength affects the outcome. In conclusion, this study demonstrates that twice-daily pomegranate ellagitannin supplementation during a 9-d period improves strength recovery 48–72 h after a damaging bout of eccentric exercise.

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The authors' responsibilities were as follows: J.R.T., J.N.B., and E.F.C. developed the concept for the study; J.R.T., J.N.B.,

and L.C. collected the data; J.R.T. performed the statistical analysis and drafted the manuscript; and E.F.C. provided critical revisions and contributed to intellectual content. There were no conflicts of interest this study. The results of this study do not constitute endorsement by the American College of Sports Medicine.

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