

Using an Eccentric Exercise–Testing Protocol to Assess the Beneficial Effects of Tart Cherry Juice in Fibromyalgia Patients

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Abstract

Background: Fibromyalgia is a common chronic pain disorder, and physical activity is often used to manage this illness. However, exercise can cause heightened discomfort following exertion (a fibroflare). Heightened symptoms and, perhaps, a manifestation of delayed-onset muscle soreness (DOMS) may contribute to the limited adherence to regular exercise observed among those with fibromyalgia. Previous studies show that tart cherry juice has antiinflammatory and antioxidant properties and reduces strength loss associated with DOMS among those without fibromyalgia.

Objective: To assess the safety and utility of an eccentric exercise–testing protocol and the efficacy of tart cherry juice on maintaining strength and reducing pain in fibromyalgia patients.

Methods: Fourteen female participants with fibromyalgia received 10 days of tart cherry juice or calorie/taste-matched placebo juice in a blinded, randomized, crossover design (1 arm/condition). An eccentric stimulus was used for elbow flexors, and participants returned daily for 4 days post-

treatment to assess strength, muscle tenderness, and overall pain via the visual analogue scale (VAS).

Results: Muscle threshold and maximal tolerable pain were constant for both conditions (juice and nonjuice). A trend was observed for better strength maintenance when tart cherry juice was ingested ($P=.06$). The change in VAS overall pain scores from baseline to follow-up day 1 showed a trend toward improvement with tart cherry juice ingestion ($P=.10$). A subset of participants (5 of 14) showed an improvement in VAS of more than 25 mm when ingesting tart cherry juice.

Conclusion: Ingestion of tart cherry juice demonstrated marginal benefits in maintaining muscle strength but did not affect local muscle tenderness after eccentric stress. A subset of participants who ingested tart cherry juice had a significant reduction in overall pain after the eccentric stimulus. Participants tolerated the testing protocol, indicating the potential utility of this paradigm in assessing effects of other agents in fibromyalgia patients.

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Fibromyalgia is a chronic disorder characterized by dysfunctional pain processing; in recent years, it has become the second most common rheumatologic diagnosis.¹ Traditional medications are of limited benefit,² and physical activity increasingly is used as therapy.^{1,3} However, that modality is limited because individuals often are unable to adhere to regular exercise.³

A recognized fibromyalgia component is heightened discomfort following exertion (fibroflares), with accelerated delayed-onset muscle soreness (DOMS) as a potential factor in

that type of exercise-associated pain. DOMS is an established consequence of intense exercise, especially if characterized by eccentric contractions in untrained muscles.⁴ The time course of DOMS reflects its pathogenesis.

Exercise-induced oxidative damage leads to an inflammatory response, resulting in secondary muscle soreness and strength loss 8 to 24 hours after exertion.^{5,6} DOMS may be accentuated among patients with fibromyalgia, perhaps because of recognized deficiencies in the growth hormone/insulin-like growth factor-1 axis that occur in fibromyalgia.⁷ Among individuals without fibromyalgia, growth hormone may have anabolic effects influencing muscle response to eccentric exercise.^{8,9}

Antioxidants and anti-inflammatory agents may attenuate DOMS,^{10,11} and tart cherries have both properties. Tart cherries contain flavonoids, that, among other actions, inhibit cyclooxygenase 1 and 2 and contain anthocyanins that have high antioxidant and anti-inflammatory activities.¹² Tart cherries reduced the strength loss associated with DOMS in individuals without fibromyalgia.¹³

Anecdotal reports indicate that tart cherries may benefit patients with fibromyalgia. We hypothesized that patients with fibromyalgia might benefit from the attenuation of DOMS when tart cherry juice is ingested; we used a blinded, randomized, crossover within-subject design to assess that potential. Although the paradigm of evoked DOMS has been

used for individuals without fibromyalgia, it has not been applied to patients with fibromyalgia.

Materials and Methods

Participant Recruitment, Consent, and Randomization

Women 21 to 65 years of age with a confirmed diagnosis of fibromyalgia¹⁴ were recruited for this study. Enrollment criteria included the following: (1) not pregnant or nursing, (2) receiving stable doses of medications, (3) no ongoing upper-body strength training or upper-extremity injuries, (4) no nutritional supplements, including the use of fruit/vegetable supplements, (5) stable typical Western dietary habits (eg, no raw vegetarian diets), and (6) no use of acupuncture, tender-point injection, or other investigational drug or devices in the preceding 90 days. The study was approved by the Institutional Review Board at Oregon Health & Science University, and each participant provided written informed consent before baseline assessment.

Women with fibromyalgia were randomly assigned to tart cherry juice or to the control beverage; the arm that would be assessed first was also randomly assigned. A randomized crossover design increased study power, as within-subject variability in muscle strength and DOMS is typically less than that found across participants. In addition, although DOMS is diminished after repeated bouts of exercise, that protective effect does not cross over to nonexercised muscles.¹⁵

At the first visit (day 1), participants were given 28 10.5-oz bottles of their initial beverage and instructed to consume 2 bottles each day (morning and evening). They were asked to return empty bottles to assess adherence. On day 10, individuals had baseline measures followed by the eccentric exercise stimulus. Participants returned the next 4 days (days 11-15) for follow-up testing. Those performing assessments used scripted protocols and were blinded as to the participants' study condition. On day 21, after a 1-week washout period, participants began taking the alternative beverage. On day 30, all participants underwent eccentric exercise with the contralateral arm and returned for the second serial testing on 4 consecutive days.

Cherry Juice and Control Beverage

The cherry juice blend was a Montmorency tart cherry concentrate, a natural flavoring, and purified water (CHERRish Corp; Bellevue, WA), which was processed following standard procedures and filled aseptically into 10.5-oz bottles. The phenolic and anthocyanic content of the beverage was assessed at Brunswick Laboratories (www.brunswicklabs.com), an independent contract laboratory providing analytical services specializing in antioxidants and oxidative stress. The tart cherry juice was measured by standardized methodology using the Oxygen Radical Absorption Capacity scale, which reflects water-soluble antioxidant content. Each bottle contained the equivalent of 50 to 60 cherries and provided at least 600 mg of phenolic compounds¹⁶ and 40 mg of anthocyanins.¹⁷

The tart cherry juice was mixed, bottled, and assessed in January 2007, and this study was performed from February through mid-April 2007. Because the product has a stable shelf life for 12 months at room temperature, no change in phenolic

content was expected over the study period.

The control beverage was a taste- and calorie-matched fruit punch drink mix (ingredients included citric acid, salt, calcium phosphate, red #40 and blue #1 dyes, and artificial flavor) (Fruitstorm Inc; Bellevue, Washington). Both were bottled in identical containers, and participants were blinded as to which was the study beverage.

Eccentric Stimulus, Muscle Testing, and Other Measures

Participants were assessed on a modified, seated, arm-curl (preacher) bench, with the upper arm resting on a padded support. Maximal isometric strength was tested at 90° of elbow flexion using an isokinetic dynamometer. The exercise regimen for DOMS induction was 2 sets of 10 eccentric elbow-flexor contractions at 75% of the maximal isometric strength using a single-arm dumbbell weight. Participants were instructed to apply maximal resistance using the elbow flexors and slowly lower the weight over 3 seconds. Before each subsequent repetition, spotters lifted the dumbbell into the starting position. Following the eccentric stimulus, participants returned for the next 4 days. On each occasion, strength, muscle tenderness, and overall discomfort were reassessed.

A pressure myometer was used to measure tenderness over the biceps muscle belly prior to the eccentric stimulus and at follow-up visits (Wagner Instruments; Greenwich, Connecticut; Model FDK10 and FDK20). Pressure was applied perpendicular to the skin surface and slowly increased. Participants were asked to indicate when they "first start to feel pain" (pain threshold) and when "it hurts so bad you want to stop" (pain tolerance).

At enrollment, participants completed a Fibromyalgia Impact Questionnaire, which measures physical impairment, symptom severity, and overall well-being. The maximum score is 100, and a value greater than 50 generally indicates moderate impairment.¹⁸ The most common outcome measure in fibromyalgia trials has been pain, often evaluated with a visual analog scale (VAS).¹⁹ To assess overall discomfort when taking the control beverage or the tart cherry juice, participants marked a 100-mm pain scale that used the following anchoring labels: 0 = no pain to 100 = most severe pain.

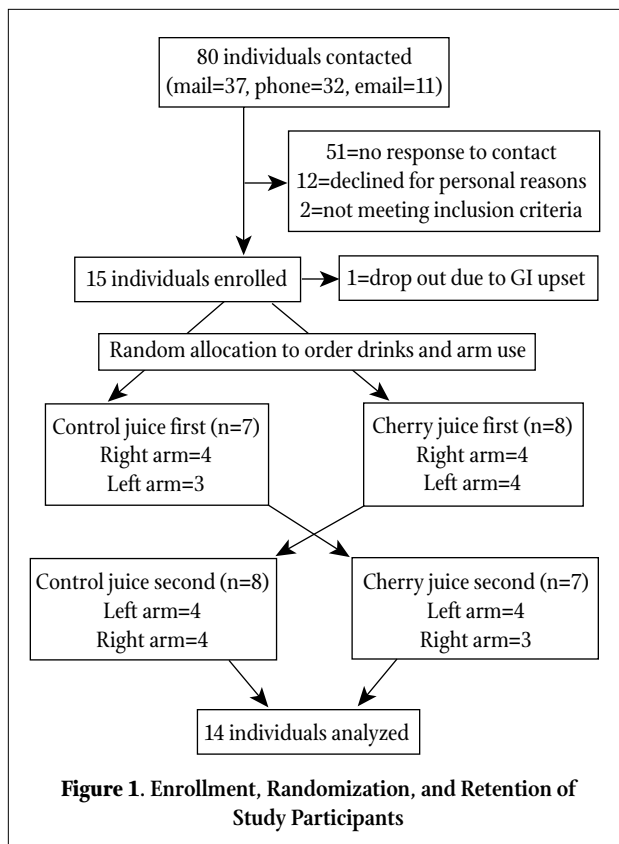
Because exercise can exacerbate fibromyalgia pain, we also calculated the difference in overall pain using the VAS on follow-up day 1 minus the baseline score before the eccentric stimulus. A positive score (follow-up day 1 minus baseline value) indicates an increase in pain, which might be the expected response to an eccentric stimulus in patients with fibromyalgia.

Statistics were calculated with SPSS 16.0 (IBM Company, Chicago). Changes in tenderness, strength, and overall pain between the tart cherry juice and placebo trials were assessed with repeated measures of analyses of variance or *t* tests for paired values. Continuous variables were compared using Pearson's correlation.

Results

Participant Characteristics

Participant recruitment, randomization, and retention are shown in Figure 1. During the study, no participants reported an



exacerbation of fibromyalgia symptoms or a serious adverse event. One participant withdrew because of gastrointestinal upset when drinking the tart cherry juice, and her data were removed from the analysis. Based on returned bottles, protocol

adherence was more than 90% with both beverages.

When queried at the study conclusion, all participants reported that they did not know for sure which beverage was the intervention beverage.

All enrollees were white women, and descriptive information is presented in the Table. Because it may have related to intervention effects, general classes of medications also are shown. The average age was 51.3 years, the average duration of fibromyalgia was 8.3 years, and participants took an average of 6.4 medications each.

The average score on the Fibromyalgia Impact Questionnaire was 65.4 out of 100. A wide range was observed for arm strength; however, within individuals, strength in the 2 arms was highly correlated ($r=0.86$, $P<.001$). Participants varied in their response to tart cherry juice, and those appearing to benefit based on the VAS overall pain score changes from baseline to follow-up day 1 are indicated by shaded rows in the Table.

Delayed-Onset Muscle Effects

Fibromyalgia participants' perception of pain from direct pressure to the elbow flexor muscles was relatively constant following the eccentric stimulus (Figure 2), with no statistically significant difference observed between the control beverage and the tart cherry juice. In general, the pain threshold was relatively constant; although the threshold was lower for the tart cherry juice, the difference from the control drink was not statistically significant. Similarly, the pain tolerance (the upper 2 curves in Figure 2) were not statistically significantly different when ingesting tart cherry juice and the control drink.

In all, both these levels were well below the typical pain threshold and tolerance for women without fibromyalgia

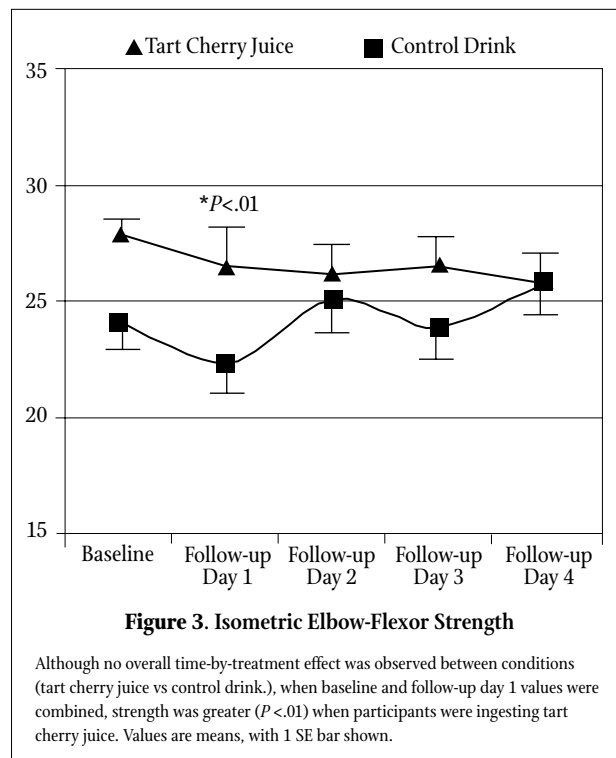
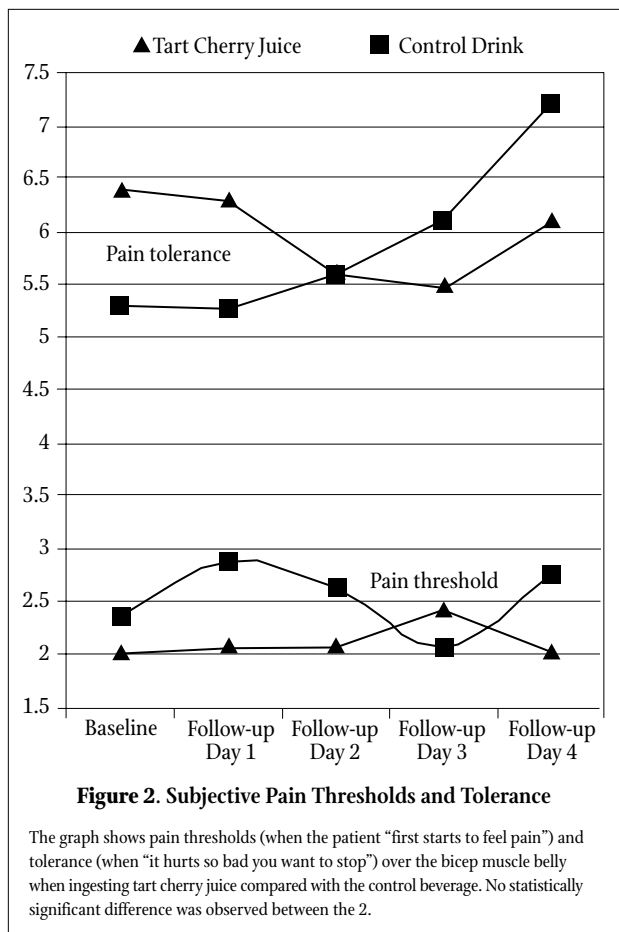
Table. Characteristics of Fibromyalgia Participants in the Eccentric Exercise–Testing Protocol to Assess the Beneficial Effects of Tart Cherry Juice*

Age (y)	Fibromyalgia Duration (y)	Fibromyalgia Impact Questionnaire Score □	Strength (lb)		Medications	
			Right Arm	Left Arm	No. Taken	Type
30	4	62	47.0	50.0 (J)	3	AD, O
44	5.5	72	49.5 (J)	36.5	11	NSAID, AD, G
46	13	65	20.5	28.0 (J)	3	
48	10	89	17.8	13.8 (J)	10	O
50	10	91	42.0 (J)	33.3	15	AD, ERT
51	10	39	24.0 (J)	18.3	6	AD, ERT
53	5	97	6.8	8.5 (J)	6	AD, O
54	1.5	47	23.8	23.0 (J)	6	NSAID, AD
54	11	51	23.3 (J)	24.8	0	
55	1	49	40.0	43.5 (J)	6	AD
55	3	73	29.3	14.5 (J)	5	AD, O, ERT
58	12	59	29.0 (J)	21.5	4	AD
58	26	46	30.0	25.0 (J)	6	NSAID, O
62	3.5	76	16.5 (J)	14.0	8	

Key: AD=antidepressants of any class; ERT= estrogen replacement therapy; G=gabapentin or pregabalin; J=arm tested when ingesting tart cherry juice; NSAID=nonsteroidal anti-inflammatory drug; O=opiate-type pain medication.

*Individuals in shaded rows showed benefits from cherry juice (Figure 4).

□ The maximum score is 100, and a value greater than 50 generally indicates moderate impairment.



ues, was statistically significant (-19.4 ± 12.7 control beverage vs 12.2 ± 15.3 tart cherry juice, $P < .001$). When the results for the 5 apparent responders were removed, the remaining 9 participants' VAS overall pain score still did not significantly differ for the control beverage vs the tart cherry juice.

under similar conditions: approximately 7 and 12 pounds/cm², respectively.

Although no overall time-by-treatment effect was observed for muscle strength between the control beverage and the tart cherry juice groups, when comparing follow-up day 1 (the time when strength loss was predicted to be highest), a trend was observed for significantly greater strength when ingesting tart cherry juice, as shown in Figure 3 (26.5 ± 11.2 vs 22.4 ± 11.2 [mean \pm SD], $P = .06$ assessed by paired t test).

Figure 4 presents the change in the VAS pain score (baseline value minus follow-up day 1) for the control beverage and tart cherry juice across participants. A negative score indicates that the participant's overall pain was higher after the eccentric stimulus. An up-sloping line indicates that the pain exacerbation by the eccentric stimuli was less when drinking the tart cherry juice.

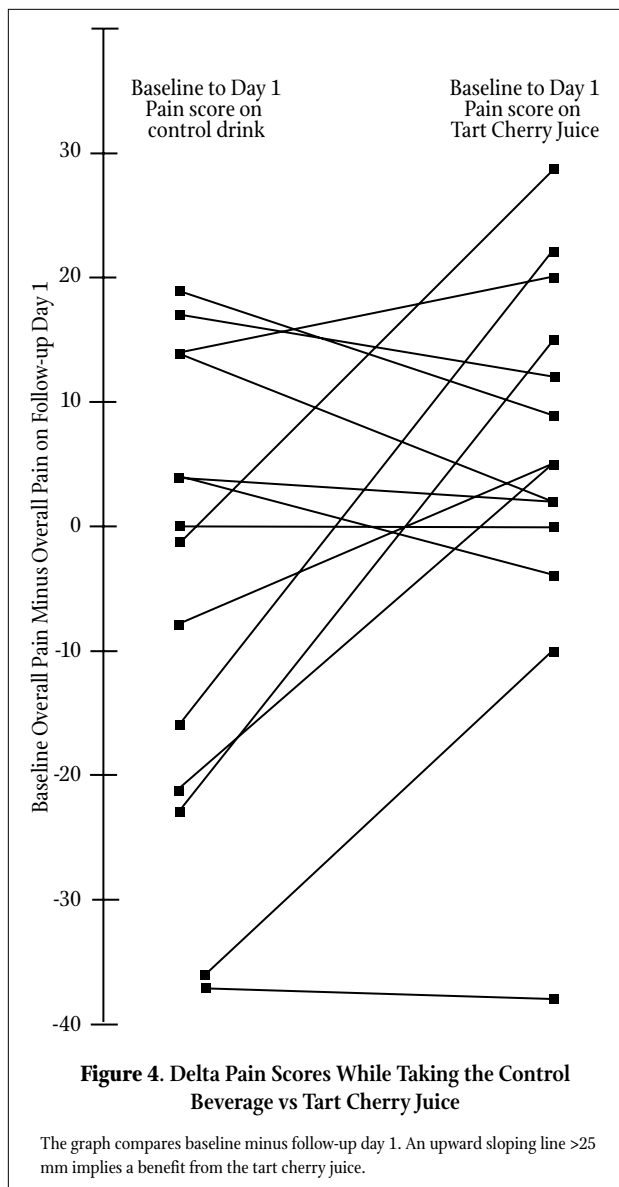
Baseline pain scores were not different for the 2 conditions, and the change in overall pain scores did not differ greatly for the 2 different drinks (-3.9 ± 19.3 for controls vs -4.9 ± 16.3 for the tart cherry juice, $P = .10$). Figure 4 reveals that, in general, 2 patterns were observed: Either scores were comparable for the 2 conditions or, as occurred among 5 participants, a benefit was observed (>25 mm difference between scores). In other settings using VAS, a difference of 20 mm has been considered a clinically significant change,²⁰ and these participants met that criterion. For those 5 individuals (shaded rows in the Table), the benefit of tart cherry juice, based on the overall pain score val-

Discussion

Cherry juice is promoted in lay publications as beneficial for those with fibromyalgia. The nutraceutical industry is experiencing exponential growth, and defining if and for whom these products provide benefit is an important task. Although DOMS assessment has been used to evaluate potential therapeutic agents for individuals without fibromyalgia,¹³ this was its initial use for patients with fibromyalgia. We found that tart cherry juice, equivalent to approximately 100 cherries a day, produced marginal benefits in women with well-documented fibromyalgia. Although response in local tenderness was unaltered based on overall VAS pain score changes, approximately one-third of the participants appeared to benefit from the tart cherry juice.

These findings demonstrate the potential utility of a within-subject crossover design and DOMS as a means to assess therapeutic agents for patients with fibromyalgia. Because the manifestations and time course of fibromyalgia are so variable, large numbers of participants may be required in efficacy studies.¹ Nevertheless, assessing DOMS using a blinded crossover design may be useful for others working with this challenging illness.

Our participants exhibited less DOMS and strength loss than is usually observed after an eccentric stimulus.^{13,21} Two factors may have contributed to that finding. We reduced the eccentric stimulus to induce DOMS to 75% of maximal strength, which may have attenuated its effects. This was done to avoid exacerbating the illness because of the potentially greater muscle microtrauma



among fibromyalgia patients due to altered growth hormone levels.⁷⁻⁹ Our observations suggest that the typical DOMS paradigm, using eccentric stress with 100% of maximal strength, could be used safely among individuals with fibromyalgia. A second factor may relate to fibromyalgia and a relative basement effect because our participants' baseline scores had little room for an increment in muscle soreness. Perhaps the pathophysiology of fibromyalgia or fear of exercise-induced symptom exacerbation constrained the pain response to eccentric stress.^{2,3,22}

Finding one subset of participants who benefited more than others is provocative. The response to most therapies for fibromyalgia is variable,² and our observation is consistent with previous studies of nutritional interventions—eg, when individuals with fibromyalgia ingested a raw vegetarian diet, approximately two-thirds reported improvement, with a reduction in pain.²³ However, unlike that investigation, our participants were blinded to which beverage was being ingested, which adds validity to the observed effects on the change in VAS overall pain scores.

Conclusion

Intense eccentric exercise to induce DOMS appears to be a safe assessment method for individuals with fibromyalgia. The paradigm may be a useful means to rapidly evaluate potential treatment effects. Using that design, tart cherry juice demonstrated marginal benefits in maintaining muscle strength, and, for a subset of participants, may have demonstrated a benefit in reducing the overall VAS pain score after eccentric exercise. Future studies may further use this within-group design to assess therapeutic modalities among those with fibromyalgia.

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