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Brief report

Randomized double-blind crossover study of the efficacy of a tart cherry juice blend in treatment of osteoarthritis (OA) of the knee

H.R. Schumacher †‡, S. Pullman-Mooar †‡, S.R. Gupta †, J.E. Dinnella †, R. Kim †§, M.P. McHugh ||*

† *University of Pennsylvania School of Medicine, USA*
‡ *Philadelphia VA Medical Center, USA*
§ *Children's Hospital of Philadelphia, USA*
|| *Nicholas Institute of Sports Medicine and Athletic Trauma, Lenox Hill Hospital, USA*

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SUMMARY

Objective: To assess the efficacy of tart cherry juice in treating pain and other features of knee osteoarthritis (OA).
Methods: 58 non-diabetic patients with Kellgren grade 2–3 OA were randomized to begin treatment with cherry juice or placebo. Two 8 oz bottles of tart cherry juice or placebo were consumed daily for 6 weeks with a 1 week washout period before switching treatments (crossover design). Western Ontario McMaster Osteoarthritis Index (WOMAC) scores and walking times were recorded prior to and after each treatment period. Additionally, plasma urate, creatinine and high sensitivity C-reactive protein (hsCRP) were recorded at baseline, after the first treatment period and after the second treatment period. Acetaminophen was allowed as a rescue drug and self reported after each treatment period. Treatment effect was examined with repeated measures analysis of variance (ANOVA) using an intention-to-treat (ITT) analysis.
Results: There were five withdrawals during the cherry juice treatment (four adverse events (AEs)) and seven withdrawals during the placebo treatment (three AEs). WOMAC scores decreased significantly ($P < 0.01$) after the cherry juice treatment but not after the placebo treatment ($P = 0.46$); differences between treatments were not significant ($P = 0.16$). hsCRP declined during the cherry juice treatment vs placebo ($P < 0.01$). The decline in hsCRP was associated with WOMAC improvement ($P < 0.01$). Walking time, acetaminophen use, plasma urate and creatinine were unaffected by treatments.
Conclusions: Tart cherry juice provided symptom relief for patients with mild to moderate knee OA, but this effect was not significantly greater than placebo. Tart cherry juice lowered hsCRP levels and this effect was associated with improved WOMAC scores.

Introduction

Nonoperative treatments for patients with mild to moderate knee osteoarthritis (OA) include nonsteroidal anti-inflammatory medications, intra-articular injections (corticosteroids, hyaluronic acid) or non-pharmacological treatments such as physical therapy, exercise, lifestyle alterations, and nutritional supplementation[1]. While nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used nonoperative treatment for mild to moderate knee OA, alternative treatments are increasingly sought due to the cardiovascular and gastrointestinal side effects of NSAIDs[1]. Dietary supplements such as glucosamine, chondroitin sulfate, and methylsulfonylmethane have been examined in the treatment of knee OA but with equivocal efficacy[2–5].

Dietary interventions for knee OA have focused on weight loss[6] since body mass index (BMI) is a risk factor for disease progression. Less attention has been given to the role of natural food products in the treatment of knee OA. Consumption of cherries or cherry juice has traditional reputation for alleviating pain in arthritis and gout[7]. While supporting clinical trials are lacking, a growing body of literature indicates that cherries can have significant anti-inflammatory, antioxidant and pain-mediating effects. Studies have identified a range of phenolic compounds in cherries that have

* Address correspondence and reprint requests to: M.P. McHugh, Nicholas Institute of Sports Medicine and Athletic Trauma, Lenox Hill Hospital, 100 E 77 ST, NY 10075, USA. Tel: 1-2124342714.
E-mail addresses: schumacr@mail.med.upenn.edu (H.R. Schumacher), sally.pullman-mooar@va.gov (S. Pullman-Mooar), Smita.Gupta@uphs.upenn.edu (S.R. Gupta), jdinnell@mail.med.upenn.edu (J.E. Dinnella), rosakim330@gmail.com (R. Kim), mchugh@nismat.org (M.P. McHugh).

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antioxidant and anti-inflammatory actions[8–11], with effects demonstrated in animal models of cancer[12], and arthritis[13] along with pain mediating effects[14]. Consumption of tart cherry juice has been shown to reduce pain[15,16], muscle damage[15,17], inflammation[17] and oxidative stress[17] after strenuous exercise. Additionally, antioxidant and anti-inflammatory effects from eating cherries or drinking cherry juice have been demonstrated in healthy humans in non-exercise models[18–20]. Kelley *et al.*[19] reported a 25% reduction in high sensitivity C-reactive protein (hsCRP) when healthy adults ate 280 g of sweet cherries daily for 28 days.

OA progression is associated with inflammation and oxidative stress[21,22]. Elevated baseline hsCRP in patients with knee OA was associated with greater subsequent cartilage loss and a poorer symptomatic response to treatment[22]. Similarly, patients with knee OA had increased oxidative stress and decreased total antioxidant capacity[21]. Prolidase activity, a marker of collagen resynthesis, was inversely correlated with markers of oxidative stress and positively correlated with antioxidant capacity.

Since consumption of cherries or cherry juice decreased CRP[17,19], and oxidative stress[17,20] and increased total antioxidant capacity[17], it was hypothesized that such effects might provide symptom relief in patients with knee OA. The primary purpose of this study was to test the ability of a tart cherry juice blend to provide symptom relief in knee OA. It was hypothesized that consumption of cherry juice would show a measurable difference on the Western Ontario McMaster Osteoarthritis Index (WOMAC) scale evaluating pain, stiffness and function, the amount of non-prescription pain medication taken, the score on a timed walking test[23], and in hsCRP as a measure of low grade inflammation in OA[24]. Because of previous reports suggesting benefit from cherry consumption on gout pain[7] and serum uric acid (UA)[18], this was also examined.

Methods

Participants

Subjects were identified during June 2007–June 2010 by physicians in the Rheumatology or Primary Care Clinics at the Department of Veterans Affairs Medical Center in Philadelphia, PA based on presence of clinical OA and evaluated, and treated in the Rheumatology Clinic. The study was approved by the institutional review board, with all patients providing written informed consent before participating and the study was performed in compliance with the Helsinki declaration.

Inclusion criteria were capacity to give informed consent, age over 18 years, and mild to moderate OA of the knee that met clinical ACR criteria[25] (knee pain plus at least three of the following six): age >50 years, stiffness <30 min, crepitus, bony tenderness, bony enlargement, and no palpable warmth. Kellgren grade had to be 2–3 on a standing knee X-ray within the previous 24 months, and a VAS pain score of 4–9 at the screening visit.

Exclusion criteria were rheumatoid arthritis or other systemic inflammatory condition, chronic pain syndrome (fibromyalgia), corticosteroid medication in last 2 months (intra-articular or oral), intra-articular injections of hyaluronic acid in the last 9 months, pregnancy, diabetes, inability to discontinue prescription medication for arthritis, unstable medical conditions that would likely prevent the subject from completing the study, or food allergies – cherries, apples.

Trial agents

This study used a cherry juice blend that is regulated by the food and drug agency (FDA) as a food, not a drug. The blend and placebo were prepared by Cherrypharm Inc., Geneva, NY. The cherry juice was prepared by mixing freshly prepared tart cherry juice with commercially available apple juice (>90% cherry juice). Frozen tart cultivar Montmorency cherries were used to prepare the cherry juice following standard procedures. The blended juice was pasteurized by heating to 85°C, hot packed into 8 oz. polyethylene (PET) bottles with a 3 min hold time to achieve commercial sterility, and then force cooled in a water tunnel. One 8 oz bottle of the juice provided at least 450 mg phenolic compounds, expressed as gallic acid equivalents by the method of Singleton and Rossi[26] and at least 30 mg anthocyanins, calculated as cyanidin-3-glucoside equivalents by the pH differential method described by Giusti *et al.*[27]. Each bottle contained the equivalent of 50 cherries.

The placebo was matched for color, sweetness and cherry flavor. It was prepared by mixing unsweetened black cherry Kool-aid soft drink mix (Kraft North America, Ryebrook, New York, USA; ingredients listed: citric acid, salt, calcium phosphate, red 40, artificial flavor, ascorbic acid, blue 1) with water in the proportion recommended by the manufacturer (about 2 g/l). There was no true cherry in the placebo. Sugar was added to match the concentration of soluble solids in the cherry juice blend to a final concentration of 13°Brix (total percentage soluble solids by weight). One degree of Brix equals 1 g of sucrose in 100 g of solution. A clouding agent (which was listed on the ingredient statement as flavor) was added to increase the turbidity of the Kool-aid in order to look similar to juice. The flavored beverage was then pasteurized and bottled following the same procedure used for the juice. Both the placebo and juice blend contained 31 g of sugar per serving.

Subjects were randomized by a computer program developed by the research pharmacy. Investigators and subjects were blinded to group assignments.

In this crossover design subjects began taking cherry juice or placebo at visit two (visit one screening/baseline visit) after a washout period of at least 1 week from any prescription pain medications. After 6 weeks of using either cherry juice or placebo they began taking the alternative treatment at visit four, after a washout period of not less than 1 week between the treatment/placebo legs of the study.

Acetaminophen was allowed as a rescue medication (500 mg tablets) and subjects recorded their intake in a diary and took no acetaminophen for 12 h before each visit. NSAIDs or other analgesics were not allowed.

Subjects were shipped a 6-week supply of juice or placebo in 8 ounce bottles at visit two and visit four, and instructed to drink one bottle each in the morning and evening. All bottles were shipped back at visit three and visit five. These were counted to determine compliance. Rationale for the dosage is based on previous studies on muscle damage and oxidative stress[15,17,20].

Outcome measures

WOMAC (VA 3.1) score was the primary outcome measure including pain, stiffness and function subscale (scales from 0 to 100 for each subscale). Secondary outcome measures were plasma hsCRP, UA and creatinine, time to walk 10 m[23] and acetaminophen use. WOMAC scores and timed walking tests were recorded at baseline, after the first 6-week treatment, after the washout period (prior to the second treatment) and after the second treatment. Blood samples were drawn at baseline, after the first treatment and after the second treatment. Analyses were performed by random access immunoassay analyzer using standard enzyme based creatinine and UA tests, and infrared particle immunoassay for hsCRP.

Safety monitoring

All adverse events (AEs) were recorded as mild, moderate or severe and the perceived relationship to the treatment noted. The

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severity of toxicities was assessed using the National Cancer Institute's (NCI's) Common Toxicity Criterion for AEs version 3 (CTCAEv3)[28]. Where a CTCAE criterion did not exist we used the following grade: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening or disabling, and 5 = fatal. The relationship of AEs to the cherry juice blend was assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study supplement?" Answer Yes or No.

Statistics

For statistical analyses of WOMAC scores within subjects factors (repeated measures) were Treatment (cherry juice vs placebo) and Time (pre treatment vs post treatment), and the between subjects factor was Treatment Order (cherry juice or placebo in first period). Total WOMAC scores, and each subscale were analyzed with Treatment × Time × Treatment Order mixed-model analysis of variance (ANOVA). If a significant three-way interaction occurred the Treatment × Time effects were reported for each treatment period separately (patients starting with cherry juice then proceeding to placebo vs patients starting with placebo then proceeding to cherry juice). Effect of Time (pre treatment vs post treatment) within each treatment period (cherry juice or placebo) was assessed using paired *t*-tests with Bonferroni corrections for planned pairwise comparisons (*P* value multiplied by two). WOMAC scores were analyzed with an intention to treat approach (ITT). If a patient dropped out during the initial treatment period and a post treatment WOMAC was not obtained ($n = 7$) the pre treatment WOMAC was entered as the post treatment score. Since these patients did not receive a treatment in the second treatment period no attempt was made to impute missing data. For patients dropping out during the second treatment period ($n = 3$) pre treatment WOMAC scores were entered as the post treatment score.

Based on the responsiveness of the WOMAC score to acetaminophen, celecoxib and placebo in subjects with knee and hip OA[29], and the excellent test–retest reliability of the WOMAC score[30], it was estimated that a 5.5 point difference in the change in WOMAC scores between cherry juice and placebo could be detected at $P < 0.05$ with 80% power using a sample of 50 subjects. Allowing for a 20% dropout rate (which is higher than expected) the detectable effect size was estimated to be 6.5 points. In a previous study the difference in the change in WOMAC score was 6–8 points between placebo and celecoxib, 2–3 points between placebo and acetaminophen, and 3–5 points between celecoxib and acetaminophen[29].

As a secondary analysis patients were classified as having a positive treatment response if the WOMAC pain or function scores improved by at least 50% and at least 20 points, or if both scores improved by at least 20% and by at least 10 points. Treatment differences were assessed with Fisher exact tests. Effects of gender, race and BMI on treatment effects were also assessed using mixed-model ANOVA.

Since blood samples were only taken on three occasions (baseline, post first treatment, and post second treatment) these variables were analyzed using Time by Treatment Order (cherry juice first vs placebo first) mixed-model ANOVA. Effect of change in hsCRP on WOMAC scores in each treatment group was assessed by independent *t*-tests comparing WOMAC scores between patients greater than and less than the median change for the respective treatment.

Compliance was compared between placebo and cherry juice treatments using Chi-Square analysis or Fisher's exact test, where appropriate, to compare dropout rates and paired *t*-tests to compare consumption of juice and placebo bottles based on the number of empty bottles returned after each treatment period.

Table I
Baseline characteristics of the patients

Age (year)	56.7 ± 11.3
Gender	44 men, 14 women
Race	39 African American, 19 White
BMI	31.8 ± 6.2
BMI classification	7 normal, 17 overweight, 34 obese
Baseline WOMAC	48.2 ± 19.9
NSAID Use (prior to enrollment)	10 yes, 48 no

Results

Compliance

Fifty-nine patients were enrolled with 27 randomized to begin with the cherry juice treatment and 32 to begin with the placebo treatment. One patient scheduled to begin with the placebo treatment withdrew before the study began, as he was not prepared to withdraw from medication for OA. Thus data on 58 patients are reported (44 men, 14 women; 57 ± 11 yo; 98.5 ± 19.0 kg; 177 ± 8 cm; Table I). Forty-six patients completed both treatments (Fig. 1). Of the 12 patients who did not complete both treatments seven dropped out during the first treatment period (three cherry juice, four placebo), two dropped out between the first and second treatments (both after cherry juice treatment) and three dropped out during the second treatment (all placebo). For ITT analysis 49 patients were included in the Treatment by Time analysis. For analyses of the main effect of time 53 patients were included for the cherry juice treatment and 53 were included for the placebo treatment.

Compliance with allocated treatment was similar for the two treatments with respect to the number of empty bottles returned after each treatment (92 ± 16% cherry juice vs 89 ± 17% placebo; $P = 0.27$).

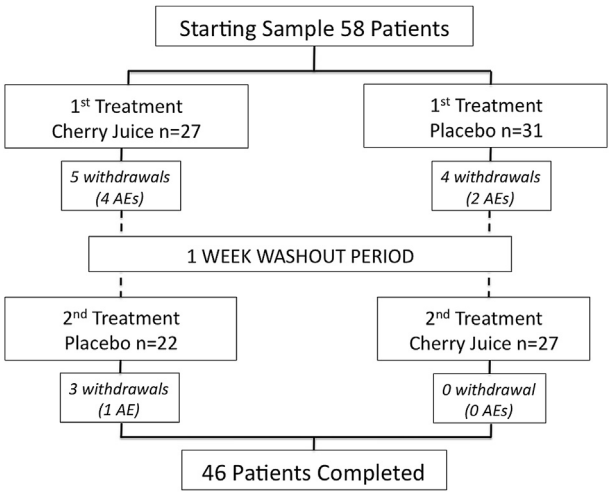

Fig. 1. Breakdown of randomization of treatments showing treatment order, number of patients completing each period of the study, withdrawals and AEs. One patient who sustained a back injury in the first treatment period (cherry juice) was not included in analysis of WOMAC scores because the back injury necessitated taking NSAIDs. Any improvement in WOMAC score was confounded by the potential benefit of the NSAID regardless of any effect of cherry juice.

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WOMAC scores

Total WOMAC scores improved significantly during the cherry juice treatment ($P = 0.002$) and did not change during the placebo treatment ($P = 0.46$). The change in WOMAC scores was not significantly different between treatments ($P = 0.16$, Table II). Treatment order (cherry juice or placebo first) did not affect changes in total WOMAC scores, or pain and function scores, but did affect stiffness scores (Table II). During the cherry juice treatment there were significant improvements in pain ($P = 0.042$), and function ($P < 0.001$) with no change during the placebo treatment ($P = 0.99$, $P = 0.81$, respectively; Table II). For patients beginning with the cherry juice treatment improvements in stiffness scores were greater during the cherry juice treatment vs the placebo ($P = 0.048$) but this was not the case for patients beginning with the placebo treatment ($P = 0.29$). A sensitivity (per protocol) analysis including the 46 patients who completed both treatments similar results as the ITT analysis (Table II).

Table II
WOMAC results

		Cherry juice $n = 53$	Placebo $n = 53$	Difference $n = 49$	P value difference
WOMAC score	Pre treatment	46.1 ± 23.2	45.8 ± 23.5	1.7 ± 17.1	$P = 0.98$
	Post treatment	39.2 ± 25.1	43.0 ± 27.0	−2.7 ± 17.6	$P = 0.58$
	Difference	6.9 ± 13.7	2.8 ± 16.9	4.4 ± 23.6	$P = 0.16$*
	95% CI difference	3.1–10.7	−1.8 to 7.5	−2.4 to 11.2	
	P value ITT	$P = 0.002$	$P = 0.46$	$P = 0.16$*	
	P value per protocol	$P = 0.002$	$P = 0.52$	$P = 0.15$*	
Pain score	Pre treatment	42.1 ± 22.9	41.5 ± 24.4	0.9 ± 18.0	$P = 0.99$
	Post treatment	36.3 ± 27	40.0 ± 26.6	−3.6 ± 20.5	$P = 0.46$
	Difference	5.8 ± 17.7	1.5 ± 17.4	4.5 ± 27.3	$P = 0.24$*
	95% CI difference	0.9–10.7	−2.9 to 6.8	−3.7 to 11.7	
	P value ITT	$P = 0.042$	$P = 0.99$	$P = 0.24$*	
	P value per protocol	$P = 0.07$	$P = 0.99$	$P = 0.21$*	
Stiffness score	Cherry juice in first treatment period				
		$n = 26$	$n = 22$	$n = 22$	
	Pre Treatment	51.1 ± 29.3	39.5 ± 34.3	13.4 ± 27.8	$P = 0.07$
	Post Treatment	39.1 ± 30.1	42.4 ± 32.8	−3.6 ± 16.3	$P = 0.64$
	Difference	12.0 ± 26.3	−2.9 ± 20.0	16.9 ± 37.9	$P = 0.048$*
	95% CI Difference	1.4–22.6	−11.7 to 6.0	0.1–33.7	
	P Value ITT	$P = 0.06$	$P = 0.99$	$P = 0.048$*	
	P Value per protocol	$P = 0.08$	$P = 0.99$	$P = 0.06$*	
	Cherry juice in second treatment period				
		$n = 27$	$n = 31$	$n = 27$	
	Pre treatment	48.3 ± 25.8	55.1 ± 19.8	−6.1 ± 21.2	$P = 0.30$
	Post treatment	44.0 ± 28.5	47.0 ± 26.8	−1.5 ± 19.7	$P = 0.99$
	Difference	4.3 ± 19.1	8.1 ± 18.8	−4.6 ± 22.1	$P = 0.29$*
	95% CI difference	−3.3 to 11.8	1.2–15.0	−13.3 to 2.2	
	P value ITT	$P = 0.52$	$P = 0.046$	$P = 0.29$*	
	P value per protocol	$P = 0.52$	$P = 0.06$	$P = 0.29$*	
Function Score	Pre treatment	46.9 ± 23.7	46.7 ± 24.0	1.8 ± 17.9	$P = 0.96$
	Post treatment	39.1 ± 25.9	44.7 ± 27.2	−4.4 ± 18.9	$P = 0.22$
	Difference	7.8 ± 13.7	2.0 ± 17.2	6.2 ± 24.9	$P = 0.13$*
	95% CI difference	4.0–11.6	−1.9 to 7.9	−2.0 to 12.3	
	P value ITT	$P = 0.0002$	$P = 0.81$	$P = 0.13$*	
	P value per protocol	$P = 0.0002$	$P = 0.48$	$P = 0.16$*	

Mean ± SD; *Significance of Time by Treatment interaction; other P values adjusted for planned pairwise comparisons (P values multiplied by 2). Stiffness scores differentiated by treatment order because of significant three-way interaction (Time × Treatment × Treatment Order $P = 0.017$ for ITT analysis and $P = 0.016$ for per protocol analysis). The three-way interaction was not significant for total WOMAC scores ($P = 0.2$), Pain scores ($P = 0.14$) and Function scores ($P = 0.27$).

A positive treatment response occurred in 21 of 53 patients during the cherry juice treatment vs 11 of 53 patients during the placebo treatment ($P = 0.06$).

WOMAC scores prior to the second treatment period (43.8 ± 25.7) were not different from baseline scores (48.2 ± 19.9; $P = 0.06$) or different from scores at the end of the first treatment period (42.8 ± 24.7; $P = 0.33$). For patients who started with the cherry juice treatment WOMAC scores prior to the placebo treatment (41.4 ± 30.5) tended to be lower than baseline values (48.0 ± 24.8; $P = 0.065$) and not different from values at the end of the cherry juice treatment (39.3 ± 26.9; $P = 0.47$). For patients who started with the placebo treatment WOMAC scores prior to the cherry juice treatment (44.3 ± 23.2) were not different from baseline values (46.6 ± 15.0; $P = 0.49$) or values at the end of the placebo treatment (41.0 ± 24.6; $P = 0.15$).

Treatment effects on WOMAC scores were unaffected by race ($P = 0.5$) and BMI ($P = 0.62$), with a trend for an effect of gender ($P = 0.09$); WOMAC improvement during the cherry juice treatment was not different between genders (0.99) but during the placebo treatment WOMAC scores improved somewhat in men ($n = 40$) and declined somewhat in women ($n = 13$; gender effect $P = 0.09$).

Other outcome measures

Acetaminophen use was not different between treatments in the 41 patients who provided records of use in both treatment periods. During the cherry juice treatment average use of acetaminophen was 85 ± 77 tablets compared with 83 ± 74 tablets during the placebo treatment ($P = 0.83$). Timed walking performance was documented for 46 patients prior to and after both treatments. Walking performance was unaffected by treatment (Cherry juice treatment Pre 11.0 ± 3.7 s, Post 10.6 ± 2.8 s; Placebo treatment Pre 11.3 ± 4.7 s, Post 11.2 ± 4.2 s; Time effect $P = 0.13$, Time by Treatment $P = 0.43$).

Serum markers

Serum samples were obtained from all 58 patients at baseline, from 52 patients after the initial treatment period and from 44 patients after the second treatment period. Urate and creatinine levels were unaffected by the treatments (Time by Treatment Order: UA $P = 0.5$, creatinine $P = 0.84$; Table III). At baseline 13 of 58 patients had hyperuricemia (>6.8 mg/dl). This did not affect changes in UA during placebo vs cherry juice treatment (Time × Treatment Order × Hyperuricemia $P = 0.78$).

Serum hsCRP levels were significantly affected by the treatment (Time by Treatment Order $P = 0.006$, Table III). For patients who began with the cherry juice treatment hsCRP declined from baseline to the end of the treatment and then increased from end of the

Table III
Serum markers at baseline, after the first treatment period and after the second treatment period. Mean ± SD

		Pre first treatment	Post first treatment	Post second treatment
hsCRP (mg/L)	Cherry juice first	2.38 ± 1.83	1.98 ± 1.73	3.49 ± 4.00
	Placebo first	2.99 ± 2.39	4.21 ± 2.98	3.17 ± 2.55
UA (mg/dl)	Cherry juice first	6.08 ± 1.51	5.85 ± 1.13	6.02 ± 1.25
	Placebo first	6.10 ± 1.41	6.31 ± 1.99	6.32 ± 2.05
Creatinine (mg/dl)	Cherry juice first	1.01 ± 0.218	1.02 ± 0.202	1.03 ± 0.202
	Placebo first	1.14 ± 0.422	1.12 ± 0.424	1.13 ± 0.368

Time × Treatment Order: hsCRP $P = 0.006$; UA $P = 0.50$; Creatinine $P = 0.84$. Decreased hsCRP during cherry juice treatment ($P = 0.043$); increased hsCRP during placebo treatment ($P = 0.004$).

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cherry juice treatment to the end of the placebo treatment. The opposite was true for patients who began with the placebo treatment; hsCRP levels increased from baseline to the end of the placebo treatment and then declined from the end of the placebo treatment to the end of the cherry juice treatment (Table III). Overall hsCRP decreased by 23% during the cherry juice treatment ($P = 0.043$) and increased by 51% during the placebo treatment ($P = 0.004$).

Patients in whom hsCRP decreased more than the median value during the cherry juice treatment (>10% decrease, $n = 23$) showed significantly greater improvements in total WOMAC scores ($P = 0.01$, Fig. 2) than patients whose hsCRP did not decrease more than the median value (≤10% decrease, $n = 21$) (Fig. 2).

Ten of 58 pts were on NSAIDs at the time of the first blood draw. Baseline hsCRP levels were 3.1 ± 3.0 mg/L for 10 NSAID users and 3.2 ± 3.1 mg/L for the 45 non-users and the three NSAID users who had withdrawn a week prior ($P = 0.91$). NSAID use did not affect changes in hsCRP over time between the cherry juice and placebo treatments (Time × Treatment Order × NSAID use $P = 0.17$). Changes in WOMAC scores were not different between patients with above vs below median increases in hsCRP during the placebo treatment ($P = 0.75$).

Effectiveness of blinding

At the end of the cherry juice treatment 57% of patients thought that they had been on the cherry juice. At the end of the placebo treatment 63% of patients thought that they had been on the placebo. Thus adequate blinding was achieved. Changes in WOMAC scores between treatments were unaffected by whether the patients correctly determined if they were on placebo or cherry juice (Time × Treatment × correct vs incorrect determination $P = 0.26$).

Safety

Of the 12 patients who did not successfully complete both treatments, seven experienced AEs (four during the cherry juice treatment, three during the placebo treatment). The AEs during the cherry juice treatment were (1) a skin reaction due to possible allergy to cherries (withdrew during first treatment period), (2) gastrointestinal symptoms (withdrew after completing cherry juice treatment but was not compliant with taking juice; this was first treatment period), (3) low back injury during exertion which necessitated taking an NSAID (withdrew after cherry juice treatment (first treatment) and WOMAC data not included since NSAID use confounded symptom change) and (4) elevated blood glucose at the end of the cherry juice treatment and withdrawn from study before placebo treatment. The AEs during the placebo treatment were (1) patient withdrew due to increased symptoms and sought treatment for suspected meniscal tear (placebo was the second treatment), (2) elevated blood glucose and blurry vision (placebo was first treatment and patient withdrew from study), (3) increased symptoms necessitating withdrawal after placebo treatment (first treatment).

Of the remaining five patients who did not complete both periods of the study one withdrew during the cherry juice treatment (first treatment) because she did not like the taste of the juice and four were lost to follow-up (three during the placebo treatment and one during the cherry juice treatment; three of these four patients were lost to follow-up during first treatment period).

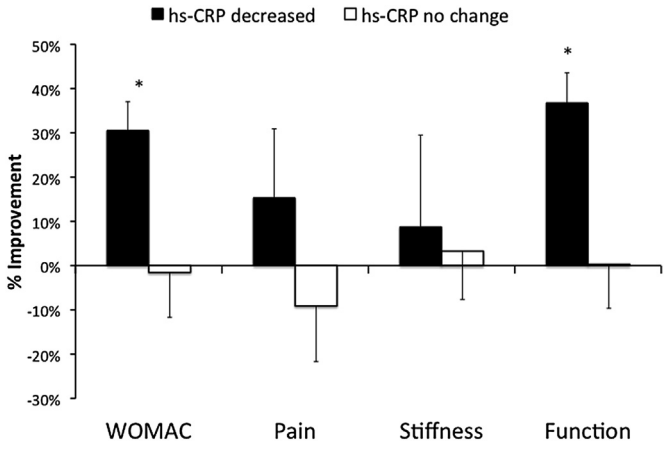

Fig. 2. Effect of decrease in hsCRP during cherry juice treatment on improvement in WOMAC scores. Black bars are patients that had >10% decrease in hsCRP. White bars are patients with ≤10% decrease in hsCRP. *Greater improvement in patients with decreased hsCRP vs patients with no change in hsCRP tested by independent *t*-test (WOMAC $P = 0.01$; Function $P = 0.004$; Pain $P = 0.23$; Stiffness $P = 0.82$). Mean ± standard error (SE) for % improvement in WOMAC scores displayed.

Discussion

These data provided the first objective evidence that the cherry juice as studied here can have beneficial effects for patients with OA. WOMAC scores improved during the cherry juice treatment with no significant improvement during the placebo treatment. However, the improvement during the cherry juice treatment (15%) was not significantly different from the change during the placebo treatment (6%), thus, clear efficacy was not demonstrated. The cherry juice treatment resulted in a reduction in hsCRP (23%) that contrasted with a 51% increase in hsCRP during the placebo treatment. The reduction in hsCRP during the cherry juice treatment was associated with improvements in WOMAC scores (Fig. 2) indicating that symptom improvement may have been due to an anti-inflammatory effect of the cherry juice. However, it is unclear why the elevation in hsCRP with the placebo treatment was not associated with an increase in symptoms as measured by WOMAC scores. The cherry juice effect is consistent with studies on healthy individuals showing anti-inflammatory effects of cherries[17,19] and may prove beneficial in other clinical conditions.

The increase in hsCRP during the placebo treatment may be attributable to the sucrose content of the drink (31 g per 8 fl oz bottle). Aerberli *et al.*[31] showed that consumption of sugar–sweetened beverages elevated hsCRP. Consumption of beverages containing 80 g sucrose per day, for 3 weeks, resulted in a 105% increase in hsCRP. In the present study patients consumed 62 g sucrose per day for 6 weeks during the placebo treatment and hsCRP increased by 51%. Aeberli *et al.*[31] studied healthy young men with normal baseline hsCRP values (0.21 mg/L) while patients with OA in the present study had elevated baseline hsCRP (3.2 mg/L). Of note, the sucrose content of the cherry juice was the same as the placebo. Presumably the cherries counteracted the negative effect of sucrose. Cherry juice with a lower sucrose level may prove even more beneficial in reducing hsCRP.

The baseline hsCRP values in the present study (3.2 ± 3.1 mg/L) are comparable to values reported for a larger sample of patients ($n = 755$) with knee or hip OA (3.4 ± 4.7 mg/L)[24]. Importantly, systemic hsCRP levels were associated with increased synovial inflammation in the affected joints[24]. Future research is needed to determine if synovial inflammation is reduced in parallel with reduced hsCRP levels in patients with knee OA consuming cherry juice.

Since an effect of cherries on gout flares and UA levels has been suggested[7,32,33] it is of interest that we found no effect on UA. Baseline UA values were within normal limits and did not change with 6-week consumption of tart cherry juice. Fructose-rich

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beverages have been reported to actually increase UA in some trials[34,35]. More studies will be needed to determine if cherry juice suppresses inflammation in patients with gout and if it thus can decrease flares.

There are limitations to this study. As a small short study it should be considered as hypothesis generating and additional trials are merited. Patients with diabetes were not studied and are not ideal candidates for this treatment because of the sugar content in the juice.

The WOMAC scores were more variable than expected in terms of absolute values and responsiveness to treatment when compared to the studies on which the sample size estimates were based[29,30]. The study was powered to detect a difference in WOMAC improvement between treatments of 5.5. A difference of 4.4 was detected. Thus given the higher than expected variability and the smaller response difference the power to detect a treatment effect greater than placebo was less than expected.

The potential for multiplicity of influences contributing to the variability in treatment outcomes is an inherent problem in studies on OA. In the present study the use of a crossover design and including treatment order as a factor in the ANOVA served to minimize multiplicity of influences on WOMAC scores. Additionally, effects of BMI and race were insignificant. A trend for an effect of gender ($P = 0.09$) was not expounded on since there were only 13 women in the study.

Typically the WOMAC pain subscale is the most responsive subscale to treatment, but that was not the case here. The function subscale showed a larger improvement. The effect of reduced hsCRP on WOMAC scores during the cherry juice treatment was apparent for the function and stiffness subscales, but not for the pain subscale. It is unclear why the pain subscale was less responsive in this study.

The lack of a significant placebo effect is inconsistent with most randomized clinical trials in OA. This may be due to patient expectations in a trial testing a food vs a drug. For example, studies examining the benefits of food supplements have also shown no significant placebo effect on WOMAC scores[36–38].

Conclusion

In conclusion, WOMAC scores improved significantly when patients were taking tart cherry juice but this effect was not significantly better than placebo. Additionally, patients had significantly decreased hsCRP when taking cherry juice compared to placebo. The decline in hsCRP when taking cherry juice was associated with improved WOMAC scores. Both cherry juice and placebo were generally well tolerated.

Conflict of interest

Dr McHugh has served as a consultant to CherryPharm Inc. and owns equity in CherryPharm Inc.

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