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ORIGINAL ARTICLE

# The efficacy of a tart cherry drink for the treatment of patellofemoral pain in recreationally active individuals: a placebo randomized control trial

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## Abstract

**Purpose** This study aimed to explore the efficacy of U.S. Montmorency tart cherry in treating recreationally active individuals with patellofemoral pain.

**Methods** Twenty-four recreationally active participants with patellofemoral pain were randomly separated into either placebo (males $N=8$, females $N=4$, age = 43.30 ± 7.86 yrs, mass = 72.10 ± 17.89 kg, stature = 171.16 ± 10.17, BMI = 24.31 ± 3.75 kg/m$^2$, symptom duration = 30.18 ± 10.90) or Montmorency tart cherry (males $N=9$, females $N=3$, age = 41.75 ± 7.52 yrs, mass = 76.96 ± 16.64 kg, stature = 173.05 ± 7.63, BMI = 25.53 ± 4.03 kg/m$^2$, symptom duration = 29.73 ± 11.88) groups. Both groups ingested 60 mL of either Montmorency tart cherry concentrate or taste matched placebo daily for 6 weeks. Measures of self-reported pain (KOOS-PF), psychological wellbeing (COOP WONCA), and sleep quality (PSQI) alongside blood biomarkers (C-reactive protein, uric acid, TNF alpha, creatinine, and total antioxidant capacity) and knee biomechanics were quantified at baseline and 6 weeks. Differences between groups were examined using linear mixed-effects models.

**Results** There was 1 withdrawal in the cherry and 0 in the placebo group and no adverse events were noted in either condition. The placebo condition exhibited significant improvements (baseline = 67.90 ± 16.18 & 6 weeks = 78.04 ± 14.83) in KOOS-PF scores compared to the tart cherry group (baseline = 67.28 ± 12.55& 6 weeks = 67.55 ± 20.61). No other statistically significant observations were observed.

**Conclusion** Tart cherry supplementation as specifically ingested in the current investigation does not appear to be effective in mediating improvements in patellofemoral pain symptoms in recreationally active individuals.

**Keywords** Montmorency tart cherry · Patellofemoral pain · Supplement · Biomechanics · Randomized control trial

## Introduction

Patellofemoral pain is a common chronic knee pathology that typically manifests as retropatellar or diffuse peripatellar pain and inflammation, aggravated by activities that frequently load the joint [1]. This pathology has an extremely high overall prevalence of 15–45% in the general population [2, 3], and the long-term prognosis for those who present with patellofemoral pain is poor, with between 71 and 91% of patients experiencing symptoms up to 20 years following diagnosis [4]. Females are 2–3 times more likely to suffer from patellofemoral pain in comparison to males [5], and those who experience patellofemoral symptoms habitually present with radiographic evidence of osteoarthritis at this joint in later life [6]. Pain symptoms force many to reduce or even end their participation in physical activity [7], and

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thus, many individuals with patellofemoral pain also develop associated psychological disorders [8].

As pain and inflammation are the main symptoms of patellofemoral pain syndrome, pain-mediating medications are often utilized [9]. According to the FDA, the aforementioned medications accounted for over 70 million prescriptions sold annually in the USA alone; making them the most utilized pharmaceutical modalities in the world [10]. There are, however, adverse cardiovascular and gastrointestinal side effects associated with traditional ingestible pain medications [11], and alternative treatments are increasingly being sought. Indeed, most researchers advocate conservative treatment for patellofemoral pain, and a range of different therapeutic and orthopaedic mechanisms have been explored, including exercise therapy, taping, bracing, insoles, soft-tissue manipulation, and acupuncture [12]. However, recent Cochrane reviews indicate that there is still insufficient clarity about the effectiveness of current conservative treatment modalities [13–15], likely owing to the heterogeneous nature of patellofemoral pain presentation and aetiology [16].

In recent years, phytochemicals with anti-inflammatory activity have received attention as a beneficial and safer alternative to ingestible pain-mediating medications [17]. Epidemiological studies have shown that a high intake of plant foods is associated with a lower risk of chronic degenerative diseases [18]. Nutritional analyses of plants have identified a wide range of phenolic phytochemicals that have various biological activities in humans [19]. Specific examples of these phenolic compounds are the flavonoids and anthocyanins, which have potent antioxidant and anti-inflammatory properties [19, 20]. Antioxidant effects relate to free radical scavenging activity and anti-inflammatory effects can be attributed to inhibition of cyclooxygenase [19, 20]. Recently, there has been considerable interest in the role of phytochemicals to reduce musculoskeletal inflammation and pain [21].

Montmorency tart cherries are considered one of the richest sources of phenolic compounds, including the cyclooxygenase inhibitory flavonoids and anthocyanins, with high levels of antioxidant and anti-inflammatory activity demonstrated [22]. Importantly, studies concerning the antioxidant levels in U.S. grown Montmorency tart cherry extracts including juice demonstrate that processing and storage have minimal impact on antioxidant capacity [23]. This makes Montmorency tart cherries a useful source of antioxidants, and consumption on a regular basis may impact on oxidative damage and inflammatory processes [24]. As a source of these biologically active phytochemicals, tart cherry consumption may be of benefit to patients with chronic pain and other inflammatory diseases [24]. Dietary interventions for patellofemoral pain have not received any attention in clinical literature, despite there being a growing body of evidence, indicating that cherries have significant anti-inflammatory, antioxidant, and pain-mediating effects in musculoskeletal conditions [25–27].

A recent randomized placebo-controlled trial exploring the effects of Montmorency tart cherry supplementation on inflammatory biomarkers in patients with osteoarthritis showed a statistically significant decrease in high-sensitivity C-reactive protein [25]. Further randomized studies examining the efficacy of a tart cherry juice in patients with symptomatic knee osteoarthritis have shown significant reductions in self-reported pain symptoms and also in markers of inflammation (high-sensitivity C-reactive protein) and cartilage degeneration (glycoprotein 39) in the cherry juice treatment groups [26, 27]. These analyses have emphasized that U.S. grown Montmorency tart cherry juice may provide beneficial anti-inflammatory and cartilage shielding activity helping osteoarthritis patients manage their disease with less adverse effects than traditional non-steroidal anti-inflammatory medications.

Therefore, although there is a growing body of evidence, indicating that cherries have significant anti-inflammatory and pain-mediating effects, nutritional interventions for patellofemoral pain have not received any attention in clinical literature. Much like osteoarthritis, pain, and inflammation are the main symptoms of patellofemoral pain, and patellofemoral pain is recognized as a precursor to subsequent osteoarthritis at this joint 6. As tart cherry supplementation is renowned for its ability to mediate both perceived pain and inflammatory biomarkers [25–27], it can be speculated that an intervention using cherry juice may be effective in recreational athletes with patellofemoral pain. Given the debilitating nature of patellofemoral pain, the associated healthcare costs, and its negative influence on psychological wellbeing, a controlled investigation examining the efficacy of Montmorency tart cherry juice supplementation in those with patellofemoral pain would be of practical as well as clinical significance.

Therefore, the primary purpose of this investigation was to explore the efficacy of U.S. Montmorency tart cherry in treating recreationally active individuals with patellofemoral pain using a placebo randomized controlled trial. A randomized control investigation of this nature may provide important new information concerning the non-surgical and non-pharmaceutical treatment of patellofemoral pain.

## Methods

### Participants

An a priori power analysis was undertaken, driven by the change in WOMAC scores provided by Schumacher et al. [26] in the cherry condition, who also examined the effects

of Montmorency tart cherry juice on pain symptoms and the principles outlined by Gogtay [28]. As the key outcome variable in the investigation is pain measured using the KOOS-PF which features an identical scoring scale to that of the WOMAC (i.e., from 0 to 100), this was deemed acceptable. This showed that a total sample size of 24 was necessary to provide 80% power to detect a change of 6.9, accounting for a loss to follow-up rate of 10%.

The present study was conducted at the University of Central Lancashire in the United Kingdom. Both males and females of diverse race and ethnicities who lived in Preston and the surrounding areas were recruited. Recruiting materials were placed in the local community, including gymnasium and sports facilities, sports therapy clinics, public bulletin boards, as well as via social media. Participants were recruited during November 2018–January 2020. The study was approved by the institutional review board (STEMH 960), and all participants provided informed consent in written form before taking part in compliance with the Declaration of Helsinki. The trial was registered prospectively via clinicaltrials.gov (*NCT03743519*).

## Inclusion criteria

Inclusion criteria were the capacity to give informed consent, age over 18 years, recreationally active as described by Sinclair et al. [29], suffering from mild to moderate patellofemoral pain as described by Crossley et al. [30], with no evidence of any other condition; (a) anterior knee pain resulting from two or more of the following; sustained sitting, climbing stairs, squatting, running, kneeling, and hopping or jumping; (b) initiation of pain symptoms not caused by a specific painful incident; and (c) manifestation of pain with palpation of the patellar facets.

## Exclusion criteria

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

## Study design

This investigation represents a 6-week double-blind randomized placebo-controlled trial (Fig. 1). Participants were randomized by a computer program (Random Allocation Software) to either the Montmorency tart cherry or placebo groups and both lead investigators and participants were blinded to trial arm assignments until the data were analysed. Participants were also instructed to maintain their habitual sport/exercise regime and also record the number of minutes spent exercising/ playing sport during the 6 weeks prior to the intervention and also during the intervention itself.

## Procedure

### Cherry juice supplementation

Participants consumed 60 mL daily of Montmorency tart cherry concentrate or a placebo equivalent for a total of 6 weeks 26. The cherry concentrate (King Orchards Montmorency Tart Cherry Juice Concentrate, Lot number 19079) was produced from Montmorency tart cherries grown in North Michigan USA. The concentrate itself was diluted with water, such that each 30 mL serving was made up into a 130 mL beverage. Both the cherry and placebo were consumed in two equal doses each day: 130 mL in the morning and 130 mL in the evening. According to the manufacturer and previous literature concerning the same product, a 30 mL dose of cherry concentrate (Energy: 80 kcal, carbohydrates: 19 g of which sugars: 15 g, protein: 1.10 g, fibre: 1 g) is equivalent to approximately 90 whole Montmorency tart cherries containing approximately 9.117 mg/mL of anthocyanins and 6.63 total phenolics/ mL (expressed as gallic acid equivalents) [31, 32].

### Placebo

Preparation of the placebo involved mixing 100% unflavoured maltodextrin carbs (MyProtein, UK, Lot number W126147907) into drinking water using a magnetic stirrer (Stuart Scientific, UK) and stir bar (Fisher Scientific, USA). 666 g of maltodextrin was added to water to create a litre of placebo concentrate, working out as 20 g of maltodextrin per 30 ml serving; closely matching the Montmorency tart cherry concentrate. Even amounts of red and black food colouring (1 ml) were added to match the colour of the Montmorency tart cherry concentrate, cherry flavdrops (1 ml) (MyProtein, UK, Lot number L69285) were then added to match the flavour. The placebo concentrate was also diluted with water, such that each 30 mL serving was made up into a 130 mL beverage. A 30 ml dose of placebo concentrate (80 kcal, carbohydrates 20 g of which sugars: 0 g, protein: 0 g, and Fibre 0 g) contained 0 mg/ml of anthocyanins.

After the 6-week intervention, all participants were asked to return any un-used supplementation to the laboratory to determine the actual amount of supplement/ placebo that was consumed (mL) and the % compliance in both groups. Furthermore, to explore the total quantity of supplementary ingested anthocyanins (mg/day), total phenolics (gallic acid equivalents/day), experimental average daily energy intake

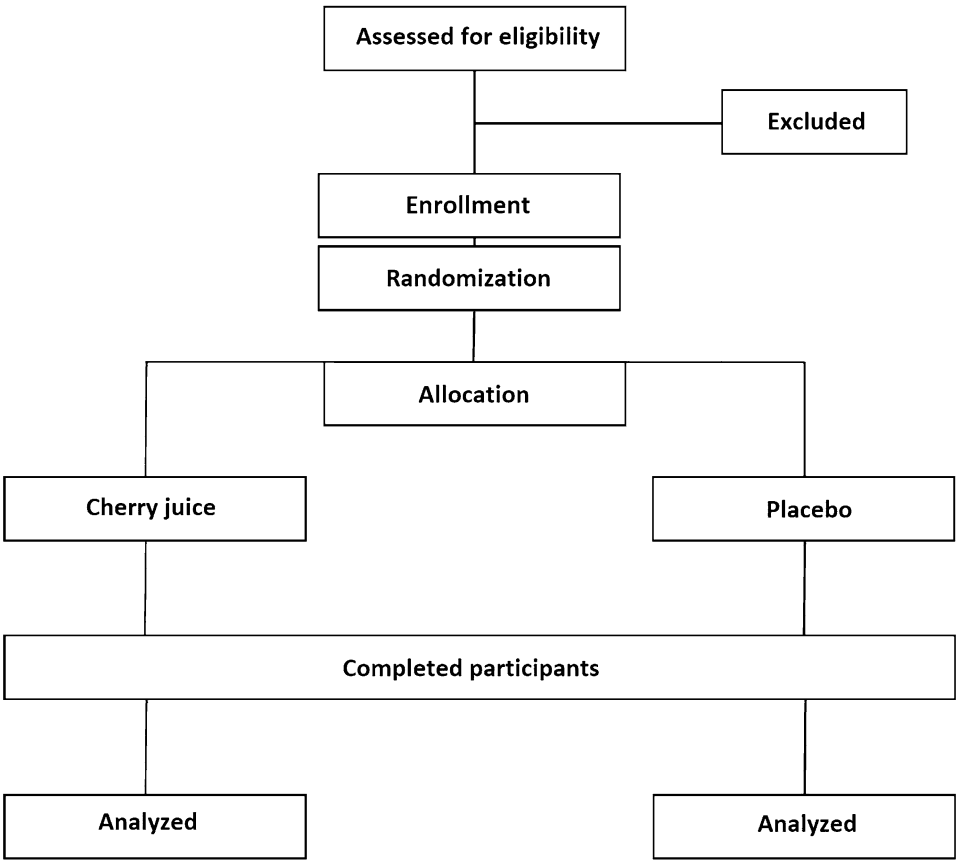


**Fig. 1** Consort diagram showing the study design

(kcal/day), and supplementary average daily sugars (g/day), the amount of supplementation that was consumed was multiplied by the anthocyanin, phenolic, energy, and sugar contents established by the manufacturer. Furthermore, to examine blinding efficacy, each participant was asked which trial arm that they felt that they had been allocated to at the conclusion of their second data collection session. In both groups, loss to follow up was monitored as were any adverse events.

### Questionnaires

All questionnaires were presented in paper format. As pain is the main symptom of patellofemoral pain, the primary outcome measurement is self-reported pain, which was examined using the KOOS-PF [33]. This scale is scored from 0 to 100, with 100 representing no disability and 0 representing maximum disability. This was recorded at baseline, and after the 6-week treatment period in both trial arms, and has a defined minimal clinically important difference (MCID) of 16.2 points [33]. In addition, as patellofemoral pain has been shown to negatively affect mood-states, psychological wellbeing was also assessed at baseline and post-treatment using the COOP WONCA chart [34]. Furthermore, as sleep quality is also associated with pain symptoms [35] and Montmorency tart cherry supplementation has been shown to enhance sleep quality [36], this was also examined via the Pittsburgh Sleep Quality Index (PSQI) [37]. Furthermore, to ensure that there were no differences in dietary patterns between groups and that participants did not alter their nutritional approach in a manner that could have influenced the experimental outcomes, 4-day diet diaries were completed for the days prior to the baseline assessment and the days prior to the follow-up examination at the end of the 6-week treatment period [38].

### Blood plasma collection

Whole blood samples (12 mL) were collected from the antecubital vein directly into blood collection tubes coated with Ethylenediaminetetraacetic acid (EDTA). Blood collection was undertaken with participants in a 4 h postprandial and euhydrated status between the hours of 11am-2 pm, having avoided strenuous exercise for 12 h prior to collection. Immediately following collection, the tubes were then centrifuged at 2000 rpm for 10 min at 4 °C using an Eppendorf 5702R centrifuge (Eppendorf, Germany). Cell-free plasma was then removed and stored at -20 °C until analysis.

### Knee biomechanics

Previous analyses have shown that those suffering from patellofemoral pain exhibit reduced knee joint range of motion as a compensatory strategy to decrease knee loading and reduce pain during sports movements [39, 40]. This is an undesirable mechanism in active individuals, as it negatively affects the ability to perform functional sports movements effectively, making reductions in pain particularly important in this population from the standpoint of biomechanical function. Therefore, participants' knee kinetics and three-dimensional kinematics were measured at baseline and after the 6-week intervention, during three functional athletic tasks [29]. Data collection was undertaken within an 18 m in length biomechanics laboratory. Participants were required to complete five repetitions of three sports specific movements'; jog, cut, and single leg hop. Kinematic information from the lower extremity joints was obtained using an eight-camera motion capture system (Qualisys Medical AB, Goteburg, Sweden) using a capture frequency of 250 Hz. Dynamic calibration of the system was performed before each data collection session. Calibrations producing residuals < 0.85 mm and points above 4000 in all cameras were considered acceptable. To measure kinetic information, an embedded piezoelectric force platform (Kistler National Instruments, Switzerland Model 9281CA) operating at 1000 Hz was utilized. The force platform was positioned in the middle of the laboratory, and the kinetic and kinematic information was synchronously obtained and interfaced using Qualisys track manager.

To quantify joint kinematics in all three planes of rotation, the calibrated anatomical systems technique was utilized [41]. To define the anatomical frames of the thorax, pelvis, thighs, shanks, and feet, 19 mm retroreflective markers were placed at the C7, T12, and xiphoid process landmarks and also positioned bilaterally onto the acromion process, iliac crest, anterior superior iliac spine (ASIS), posterior super iliac spine (PSIS), medial and lateral malleoli, medial and lateral femoral epicondyles, greater trochanter, calcaneus, first metatarsal, and fifth metatarsal. Carbon-fibre tracking clusters comprising of four non-linear retroreflective markers were positioned onto the thigh and shank segments. In addition to these, the foot segments were tracked via the calcaneus, first metatarsal, and fifth metatarsal, the pelvic segment was tracked using the PSIS and ASIS markers and the thorax segment was tracked using the T12, C7, and xiphoid markers. The hip joint centre was determined using a regression equation that uses the positions of the ASIS markers [42]. The centres of the ankle and knee joints were delineated as the mid-point between the malleoli and femoral epicondyle markers [43, 44]. Each tracking cluster comprised four retroreflective markers mounted onto a thin sheath of lightweight carbon fibre. Static calibration trials were obtained allowing for the anatomical markers to be referenced in relation to the tracking markers/clusters. The Z (transverse) axis was oriented vertically from the distal segment end to the proximal segment end. The Y (coronal) axis was oriented in the segment from posterior to anterior. Finally, the X (sagittal) axis orientation was determined using the right-hand rule and was oriented from medial to lateral. Data were collected during run, cut, and hop movements according to below:

#### Run

Participants started at one end of the laboratory and ran at a self-selected velocity and struck the force platform with their injured limb. As the force plate is positioned in the middle of the laboratory, the total distance to the force platform was 9 m. The stance phase of running was defined as the duration over > 20 N of vertical force was applied to the force platform [45]. The running velocity was recorded and then maintained for the retest after 6 weeks.

#### Cut

Participants completed 45° sideways cut movements using a self-selected approach velocity, striking the force platform with their injured limb. To ensure that the desired cut angle was adopted, in accordance with previous analyses, cut angles were measured from the centre of the force plate and the corresponding line of movement was delineated using masking tape, so that it was clearly evident to participants [46]. Participants started at once end of the laboratory, so the total distance to the force platform was 9 m. The stance phase of the cut movement was similarly defined as the duration over > 20 N of vertical force was applied to the force platform [44]. The approach velocity was recorded and then maintained for the retest after 6 weeks.

#### Hop

Participants began standing by on their injured limb; they were then requested to hop forward maximally, landing on the force platform with same leg without losing balance. The arms were held across the chest to remove arm-swing contribution. The hop movement was defined as the duration from foot contact (defined as > 20 N of vertical force applied to the force platform) to maximum knee flexion [46]. In accordance with previous analyses, the hop distance was recorded in the initial data collection session and maintained for the second testing session 6 weeks later. The mean and standard deviation hop distance across all participants was $0.53 \pm 0.27$ m.

Previous analyses have shown that those suffering from patellofemoral symptoms exhibit diminished knee joint

proprioception [47, 48], with pain and inflammation contributing to proprioceptive deficiency [49]. This is problematic in active individuals; particularly as reduced proprioception causes diminished performance across a range of movements [50]. Therefore, taking into account the proposed pain-mediating and anti-inflammatory properties of tart cherries, improvements in proprioception mediated as a function of the intervention would be particularly important in this population. Therefore, in addition to the biomechanical movement information, the effects of the tart cherry supplementation on knee joint proprioception were also examined using a weight-bearing joint position sense test. This was conducted, in accordance with the procedure of Sinclair, et al. [51], whereby participants were assessed on their ability to reproduce a target knee flexion angle of 30˚ whilst in single leg stance of their affected limb. To accomplish this, participants were asked to slowly squat to a knee flexion angle of 30 ˚, which was verified using a handheld goniometer by the same researcher throughout data collection. Participants then held this position for 15 s during which time the knee criterion angle was captured using the motion analysis system. Following this, participants were asked to return to a standing position and wait for 15 s, and they were required to repeat the above process without guidance via the goniometer. Again, this position was held for a period of 15 s and the replication trial was also collected using the motion analysis system. This above process conducted on three occasions and between each trial participants walked for 20 ft to eliminate any proprioceptive memory of the previous trial. The absolute difference in degrees calculated between the criterion and replication trials was averaged over the three trials to provide an angular error value in, which was extracted for statistical analysis. The above process was undertaken at baseline and 6 weeks.

## Processing

### Questionnaires

The KOOS-PF, COOP WONCA, and PQSI were quantified in accordance with their recommended scoring systems. The results of the 4-day diet diaries were inputted into WinDiets (RGU, Aberdeen UK) and the following micronutrient composition variables were extracted and expressed as absolute average daily intake values; total energy intake (kcal/day), total fat (g/day), saturated fat (g/day), polyunsaturated fat (g/day), monounsaturated fat (g/day), protein (g/day), total carbohydrate (g/day), and carbohydrate (sugars) (g/day). Furthermore, the predominant antioxidant vitamins, vitamin C (mg/day), vitamin E (mg/day), and total carotenoids (µg/day), were also extracted.

### Blood analyses

Blood plasma samples were analysed for multiple inflammatory biomarkers using competitive enzyme-linked immunosorbent assay (ELISA) techniques. The kits included uric acid (Cayman Chemical, USA, catalogue number CAY700320-96 wells, Lot number 0579042, manufacturer's intra- and inter-assay coefficients were 4.1% and 4.3%, respectively), human creatinine (BioMatik, USA, catalogue number EKF59083, Lot number H4306F038, manufacturer's intra- and inter-assay coefficients were < 10% and 12%, respectively), human TNF-alpha (Invitrogen, USA, catalogue number KHC3011, Lot number 243058–001, manufacturer's intra- and inter-assay coefficients were 4.4% and 7.5%, respectively), total antioxidant capacity (Abcam, UK, catalogue number ab65329, Lot number GR3328705-1, manufacturer's intra- and inter-assay coefficients were 4.4% and 7.5%, respectively), and high-sensitivity C-reactive protein (Invitrogen, USA, catalogue number KHA003, Lot number 226513–005). All controls, standards, and plasma samples were pipetted into 96-well microlitre plates coated with the respective antibody; all measurements were performed in duplicate to account for intra-assay variation. Each microplate was analysed in a plate reader (Perkin Elmer, USA), following standard ELISA protocols against a known standard curve with ranges of optical absorbance or fluorescence set at the specified ranges outlined by the manufacturer. The results are expressed as µmol/L (uric acid), nmol/mL (human creatinine), pg/mL (human TNF-alpha), mM (total antioxidant capacity), and mg/L (high-sensitivity C-reactive protein).

### Knee biomechanics

Dynamic trials were digitized using Qualisys Track Manager (Qualisys Medical AB, Goteburg, Sweden) to identify anatomical and tracking markers then exported as C3D files to Visual 3D (C-Motion, Germantown, MD, USA). All data were linearly normalized to 100% of the stance or landing phase. Ground reaction force data and marker trajectories were smoothed with cut-off frequencies of 50 Hz at 12 Hz, respectively, using a low-pass Butterworth 4th-order zero-lag filter. Knee joint kinematics were quantified using an XYZ cardan sequence of rotations (where X is flexion–extension; Y is ab-adduction; Z is internal–external rotation). Discrete three-dimensional knee joint kinematic measures that were extracted for statistical analysis were the range of motion (ROM), representing the angular displacement from footstrike to peak angle.

Following this, data during the stance phase were exported from Visual 3D into OpenSim 3.3 software (Simtk.org). A validated musculoskeletal model was used to process the biomechanical data which was scaled to account for

the anthropometrics of each participant. This model, which featured 12 segments, 19 degrees of freedom, and 92 musculotendon actuators [52], was used to estimate knee joint forces. As muscle forces are the main determinant of joint compressive forces [53], muscle kinetics were quantified using the static optimization procedure within OpenSim in accordance with Steele et al. [54]. Compressive patellofemoral, medial tibiofemoral, and lateral tibiofemoral forces were calculated via the joint reaction analyses function within OpenSim using the muscle forces generated from the static optimization process as inputs. Furthermore, patellofemoral stress was quantified by dividing the patellofemoral force by the contact area. Patellofemoral contact areas were obtained by fitting a polynomial curve to the sex-specific data of Besier et al. [55], who estimated patellofemoral contact areas as a function of the knee flexion angle using MRI. From the above processes, the peak patellofemoral stress (KPa/BW), lateral tibiofemoral force (BW), and medial tibiofemoral force (BW) were extracted following normalization, which was undertaken by dividing the net values by each participants bodyweight.

### Statistical analyses

Descriptive statistics of means and standard deviations were obtained for each outcome measure. Comparisons between groups for continuous participant characteristics at baseline, all of the experimental variables at baseline, the amount of supplement consumed, % compliance, supplemental anthocyanins, supplemental phenolics, supplemental energy intake, supplemental sugars, and weekly exercise during the intervention were undertaken using linear mixed-effects models, with group modelled as a fixed factor and random intercepts by participants [56]. To determine the effects of the intervention on questionnaire, blood biomarkers, knee proprioception, knee biomechanics, and dietary variables between the two groups, linear mixed-effects models were adopted, with group again modelled as a fixed factor and random intercepts by participants, adjusting for baseline values [56, 57]. Blinding efficacy was also examined using a one-way chi-squared goodness of fit test. Finally, $2 \times 2$ Pearson chi-square tests of independence were also used to test for differences in binary outcomes, i.e., lost to follow-up (yes/ no) and adverse outcomes (yes/no) during the intervention in each group and similarly to contrast categorical baseline outcomes between groups, i.e., sex (male/female) and ethnicity (Caucasian/Asian) between groups [56]. All analyses were conducted using SPSS v27 (IBM, SPSS, Armonk, NY: IBM Corp), and statistical significance for all analyses was accepted as the $P \leq 0.05$ level.

## Results

### Baseline characteristics

There were no significant differences between groups at baseline for participant characteristics age, body mass, stature, BMI, symptom duration, sex, or ethnicity (Table 1). Similarly, there were also no significant differences between groups at baseline for any of the experimentally measured variables ($P = 0.125$–$0.938$) (Supplemental table).

### Loss to follow up, compliance, ingested anthocyanins, exercise duration, and adverse events

Total trial completion numbers in each group were cherry ($n = 14$) and placeboaa ($n = 15$), and a number of adverse effects were cherry ($n = 0$) and placebo ($n = 0$). The chi-squared tests were non-significant ($X2\ (1) = 1.04$, $P = 0.301$ & $X2\ (1) = 0.00$, $P = 1.00$), indicating that there were no statistically significant differences between groups in either loss to follow up or adverse events (Fig. 2). There were no differences in actual amount of supplement/ placesbo that was consumed, % compliance or experimental average daily energy intake between groups (Table 2). However,

**Table 1** Baseline characteristics (mean & SD) for both placebo and experimental groups

| | Placebo | | Cherry | | *P* value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (yrs) | 43.30 | 7.86 | 41.75 | 7.52 | 0.626 |
| Mass (kg) | 72.10 | 17.89 | 76.96 | 16.64 | 0.612 |
| Stature (cm) | 171.16 | 10.17 | 173.05 | 7.63 | 0.628 |
| BMI ($kg/m^2$) | 24.31 | 3.75 | 25.53 | 4.03 | 0.764 |
| Symptom duration (months) | 30.18 | 10.90 | 29.73 | 11.88 | 0.903 |
| Weekly exercise duration (mins) | 450.60 | 449.60 | 497.80 | 199.95 | 0.782 |
| Sex (male/ female) | 8/ 4 | 9/ 3 | *0.653* | | |
| Ethnicity | Caucasian = 12 | Caucasian = 11/ Asian = 1 | *0.307* | | |

Italic text = categorical variables examined using Chi-squared tests

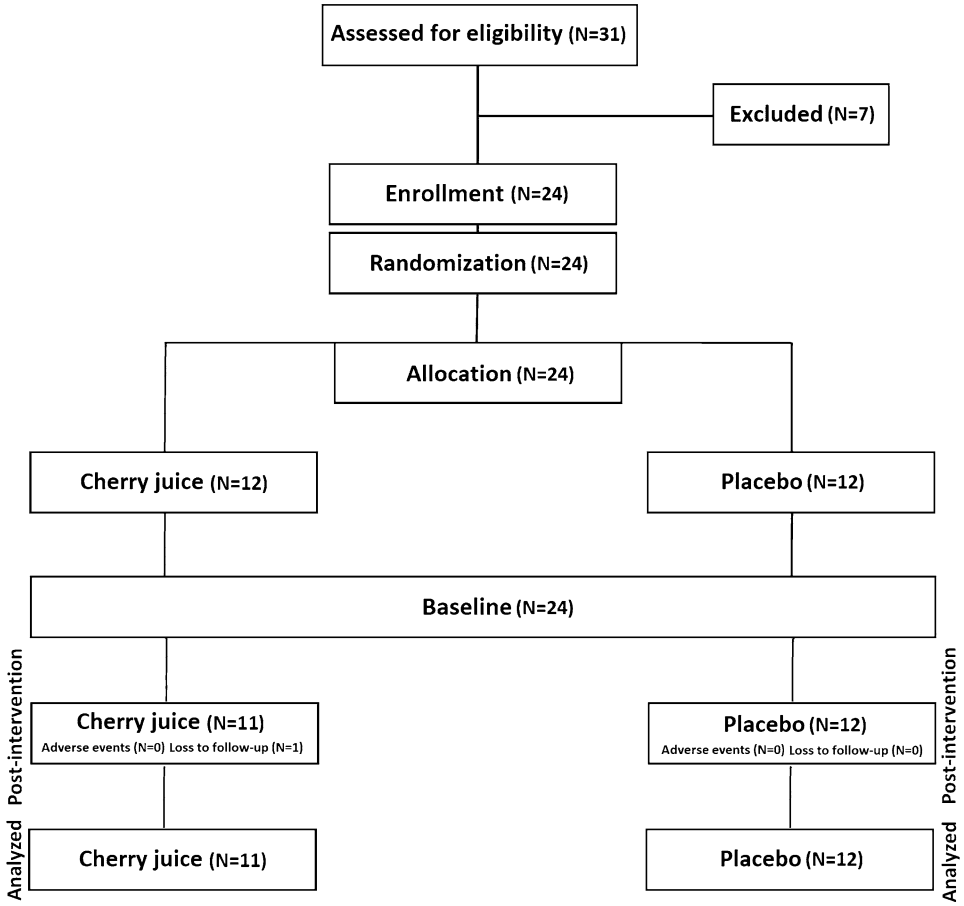


**Fig. 2** Consort diagram showing of participant flow throughout the study

**Table 2** Supplementary compliance and consumption (mean & SD) for both placebo and experimental groups throughout the intervention

| | Placebo | | Cherry | | *P* value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Amount of supplement consumed (mL) | 2293.89 | 213.42 | 2307.08 | 189.03 | 0.901 |
| Compliance (%) | 91.03 | 7.52 | 91.55 | 6.67 | 0.901 |
| Supplemental anthocyanins (mg/day) | 0 | 0 | 500.80 | 36.44 | < 0.001 |
| Supplemental energy intake (kcal/day) | 145.64 | 18.44 | 146.48 | 10.66 | 0.897 |
| Supplemental phenolics (gallic acid equivalents/day) | 0 | 0 | 363.99 | 26.48 | < 0.001 |
| Supplemental sugars (g/day) | 0 | 0 | 27.47 | 2.00 | < 0.001 |
| Weekly exercise duration (min) | 488.08 | 404.39 | 446.36 | 270.12 | 0.887 |

Bold text = significant difference between groups

supplementary ingested anthocyanins, supplemental phenolics, and supplementary average daily sugars were significantly greater in the cherry group (Table 2). Finally, there were no significant differences in weekly exercise duration during the intervention period between groups (Table 2).

## Blinding efficacy

Of the participants that completed the trial N = 13 correctly identified their designated trial arm, the chi-squared test was non-significant ($X2$ (1) = 0.391, P = 0.532), indicating that an effective blinding strategy was adopted.

## Questionnaires

The analyses showed that after adjustment for baseline, the placebo group exhibited significantly greater improvements in KOOS-PF scores at 6 weeks compared to the cherry group. There were, however, no significant differences for either the COOP WONCA or PSQI scores (Table 3).

**Table 3** Questionnaire outcomes (mean ± SD) from both placebo and experimental groups

| | Placebo | | | | Mean difference | Cherry | | | | Mean difference | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 weeks | | | Baseline | | 6 weeks | | | |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | *SD* | | |
| KOOS-PF | 67.90 | 16.18 | 78.04 | 14.83 | 10.14 | 67.28 | 12.55 | 67.55 | 20.61 | 0.27 | *0.027* |
| COOP WONCA | 1.70 | 0.36 | 2.18 | 0.35 | 0.48 | 1.93 | 0.52 | 2.11 | 0.64 | 0.18 | 0.696 |
| PSQI | 5.63 | 2.83 | 6.13 | 2.85 | 0.50 | 6.22 | 2.95 | 6.44 | 2.46 | 0.22 | 0.529 |

Bold text = significant difference between groups as a function of the intervention

### Blood analyses

There were no significant differences for C-reactive protein, uric acid, TNF alpha, creatinine, and total antioxidant capacity (Table 4).

### Diet diaries

There were no significant differences in dietary intakes (Table 5).

### Proprioception

There were no significant differences for proprioception (Table 6).

## Knee biomechanics

### Run

There were no significant differences in knee biomechanics for running (Table 6).

### Cut

There were no significant differences in knee biomechanics for cutting (Table 6).

### Hop

There were no significant differences in knee biomechanics for the hop movement (Table 6).

# Discussion

The primary purpose of this novel investigation was to examine using a placebo randomized control investigation, the ability of a tart cherry juice drink to provide pain relief in recreationally active individuals with patellofemoral pain. This represents the first randomized controlled trial to examine the effects of tart cherry supplementation in patellofemoral pain, and an investigation of this nature may provide important new information concerning the management of this condition.

Importantly, in relation to the primary outcome, the current investigation showed that there were no statistical improvements in pain scores as measured via the KOOS-PF in the cherry group. However, it was shown in the placebo group, that pain scores at 6 weeks were significantly improved compared to baseline, although it should be noted that the mean improvement was below the MCID threshold [33]. This observation does not concur with those of previous controlled trials in knee osteoarthritis, where significant improvements in pain symptoms were observed in the cherry group [26, 27]. Whilst statistically significant improvements in the placebo group are not uncommon in control trials of musculoskeletal disorders [26], the lack of improvement in the experimental group was not expected. This observation indicates that tart cherry supplementation as specifically ingested in the current investigation is not effective in mediating improvements in pain symptoms in recreationally active individuals with patellofemoral pain.

In addition, this investigation revealed that there were no differences in either COOP WONCA or PSQI scores in either of the two experimental groups as function of the 6-week intervention. In relation to sleep quality, this observation opposes the general consensus within the literature as even in non-sleep disturbed individuals, tart cherry supplementation has been shown to enhance sleep quality [58]. With respect to the COOP WONCA indices, as patellofemoral pain and psychological wellbeing are known to be associated 34, it was expected that there would be no change in the cherry group. Though, with the statistical improvement in symptoms in the placebo participants, it would be anticipated that there would be a corresponding change in psychological wellbeing in this group. However, changes in psychological wellbeing may take longer to manifest than alterations in pain symptoms [59], and similarly, it could also be speculated that because the improvement in pain symptoms did not exceed the MCID, this was not sufficient to mediate similar improvements in psychological wellbeing.

**Table 4** Blood biomarker outcomes (mean & SD) for both placebo and experimental groups

| | Placebo | | | | Mean difference | Cherry | | | | Mean difference | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 weeks | | | Baseline | | 6 weeks | | | |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | | |
| C-reactive protein (mg/L) | 0.70 | 0.27 | 0.57 | 0.33 | 0.13 | 0.53 | 0.20 | 0.49 | 0.19 | 0.04 | 0.714 |
| Uric acid (μmol/L) | 25.98 | 9.57 | 28.67 | 12.38 | 2.69 | 27.69 | 9.30 | 26.04 | 4.66 | 1.65 | 0.385 |
| TNF Alpha (pg/mL) | 20.58 | 11.75 | 17.93 | 7.81 | 2.65 | 18.55 | 12.84 | 18.89 | 14.96 | 0.34 | 0.217 |
| Creatinine (nmol/mL) | 306.81 | 98.94 | 268.06 | 103.74 | 38.75 | 302.40 | 152.65 | 282.93 | 99.67 | 19.47 | 0.845 |
| Total antioxidant capacity (mM) | 13.56 | 4.15 | 13.52 | 5.47 | 0.04 | 18.41 | 14.21 | 16.50 | 9.47 | 1.91 | 0.339 |

**Table 5** Dietary outcomes (mean & SD) for both placebo and experimental groups

| | Placebo | | | | Mean difference | Cherry | | | | Mean difference | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 weeks | | | Baseline | | 6 weeks | | | |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | | |
| Total daily kcal | 1826.00 | 437.08 | 1700.75 | 436.39 | 125.25 | 2053.78 | 455.79 | 2100.56 | 341.22 | 46.78 | 0.071 |
| Total daily fat (g) | 64.73 | 10.29 | 59.28 | 20.13 | 5.45 | 77.79 | 27.58 | 80.29 | 27.17 | 2.5 | 0.203 |
| Saturated daily fat (g) | 22.91 | 4.07 | 20.13 | 8.53 | 2.78 | 27.09 | 10.37 | 27.31 | 8.03 | 0.22 | 0.155 |
| Polyunsaturated daily fat (g) | 7.78 | 2.55 | 7.63 | 3.49 | 0.15 | 11.09 | 6.10 | 13.43 | 6.87 | 2.34 | 0.125 |
| Monounsaturated daily fat (g) | 17.50 | 3.77 | 16.01 | 6.33 | 1.49 | 22.19 | 7.66 | 24.40 | 9.54 | 2.21 | 0.156 |
| Daily protein (g) | 93.78 | 29.79 | 84.49 | 29.91 | 9.29 | 97.37 | 31.97 | 86.38 | 20.37 | 10.99 | 0.981 |
| Daily carbohydrate (g) | 216.45 | 82.31 | 212.49 | 63.87 | 3.96 | 262.98 | 68.57 | 255.13 | 44.46 | 7.85 | 0.326 |
| Daily sugars (g) | 72.91 | 17.20 | 71.36 | 31.49 | 1.55 | 91.66 | 16.87 | 88.23 | 30.78 | 3.43 | 0.882 |
| Daily vitamin C (mg) | 103.89 | 56.93 | 68.60 | 39.88 | 35.29 | 108.69 | 79.58 | 59.69 | 38.95 | 49 | 0.441 |
| Daily vitamin E (mg) | 7.54 | 3.99 | 5.75 | 3.31 | 1.79 | 6.66 | 3.77 | 8.73 | 6.47 | 2.07 | 0.063 |
| Daily total carotenoids (μg) | 2595.88 | 1647.76 | 1099.13 | 986.23 | 1496.75 | 2198.00 | 1757.78 | 1153.44 | 974.93 | 1044.56 | 0.512 |

**Table 6** Biomechanical outcomes (mean ± SD) from both placebo and experimental groups

| | Placebo | | | | Mean difference | Cherry | | | | Mean difference | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 weeks | | | Baseline | | 6 weeks | | | |
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | | |
| Proprioception (°) | 4.24 | 3.83 | 4.46 | 2.69 | 0.22 | 4.31 | 3.86 | 4.03 | 3.54 | 0.28 | 0.767 |
| *Run* | | | | | | | | | | | |
| Sagittal plane ROM (°) | 24.35 | 3.61 | 25.60 | 5.02 | 1.25 | 23.08 | 6.10 | 23.94 | 5.83 | 0.86 | 0.681 |
| Coronal plane ROM (°) | 3.03 | 2.48 | 1.80 | 2.00 | 1.23 | 3.21 | 2.12 | 2.23 | 2.01 | 0.98 | 0.626 |
| Transverse plane ROM (°) | 13.12 | 3.58 | 11.89 | 4.79 | 1.23 | 14.14 | 4.93 | 12.95 | 3.60 | 1.19 | 0.738 |
| Peak patellofemoral stress (KPa/BW) | 7.53 | 1.77 | 7.98 | 1.39 | 0.45 | 6.81 | 1.68 | 7.67 | 2.49 | 0.86 | 0.790 |
| Peak medial tibiofemoral force (BW) | 6.64 | 1.20 | 6.48 | 1.08 | 0.16 | 6.97 | 1.58 | 7.18 | 1.68 | 0.21 | 0.153 |
| Peak lateral tibiofemoral force (BW) | 4.29 | 0.98 | 4.30 | 0.90 | 0.01 | 3.75 | 0.79 | 3.97 | 0.97 | 0.22 | 0.587 |
| *Cut* | | | | | | | | | | | |
| Sagittal plane ROM (°) | 30.13 | 3.65 | 31.50 | 4.52 | 1.37 | 27.76 | 6.52 | 28.94 | 6.02 | 1.18 | 0.640 |
| Coronal plane ROM (°) | 4.34 | 2.86 | 4.05 | 3.37 | 0.29 | 5.24 | 3.26 | 3.59 | 2.31 | 1.65 | 0.500 |
| Transverse plane ROM (°) | 11.73 | 6.00 | 12.51 | 5.35 | 0.78 | 13.65 | 5.63 | 12.16 | 4.06 | 1.49 | 0.397 |
| Peak patellofemoral stress (KPa/BW) | 11.15 | 3.31 | 11.43 | 2.95 | 0.28 | 10.11 | 3.55 | 10.10 | 3.46 | 0.01 | 0.660 |
| Peak medial tibiofemoral force (BW) | 7.64 | 1.94 | 7.56 | 1.69 | 0.08 | 7.82 | 1.79 | 7.85 | 1.83 | 0.03 | 0.694 |
| Peak lateral tibiofemoral force (BW) | 4.96 | 1.15 | 4.82 | 0.95 | 0.14 | 4.44 | 1.10 | 4.30 | 1.12 | 0.14 | 0.716 |
| *Hop* | | | | | | | | | | | |
| Sagittal plane ROM (°) | 34.96 | 6.28 | 33.10 | 5.54 | 1.86 | 32.66 | 10.18 | 31.91 | 10.02 | 0.75 | 0.415 |
| Coronal plane ROM (°) | 2.60 | 3.76 | 1.68 | 2.49 | 0.92 | 2.32 | 2.31 | 0.96 | 1.59 | 1.36 | 0.352 |
| Transverse plane ROM (°) | 5.04 | 2.99 | 5.52 | 3.90 | 0.48 | 7.42 | 5.68 | 7.29 | 5.70 | 0.13 | 0.823 |
| Peak patellofemoral stress (KPa/BW) | 9.40 | 3.41 | 9.47 | 3.42 | 0.07 | 8.56 | 3.23 | 7.88 | 3.35 | 0.68 | 0.209 |
| Peak medial tibiofemoral force (BW) | 6.31 | 1.11 | 6.36 | 1.38 | 0.05 | 8.99 | 1.78 | 9.63 | 1.83 | 0.64 | 0.180 |
| Peak lateral tibiofemoral force (BW) | 4.08 | 1.04 | 4.21 | 1.10 | 0.13 | 7.30 | 1.75 | 7.04 | 1.87 | 0.26 | 0.244 |

The current investigation also showed that there were no significant changes for any of the blood biomarkers in either of the two experimental groups as function of the 6-week intervention. This observation opposes previous analyses concerning the effects of cherry supplementation in musculoskeletal disorders where significant reductions in high-sensitivity C-reactive protein were observed [25, 26]. However, it should also be noted that in agreement with the current investigation, Schumacher et al. [26] also found no effect of cherry juice on either uric acid or creatinine levels. The C-reactive protein values at baseline in this study are lower than those reported by both Kuehl et al. [25] and Schumacher et al., [26]. Although patellofemoral osteoarthritis is considered a common sequela of pain at this joint 6, the patients examined in previous trials had existing knee osteoarthritis, so it is likely that their inflammation levels were greater than in the current study [60]. This may provide insight into the lack of improvement in high-sensitivity C-reactive protein in the current investigation, as the sensitivity to change of biological measures is known to be baseline dependent. Nonetheless, the current investigation shows that tart cherry supplementation as ingested in the current study had no effect on blood biomarkers in recreationally active individuals with patellofemoral pain.

In addition, the current investigation showed that there were no changes in proprioception, knee biomechanics, or key dietary parameters between the two groups; indicating that they were not responsible for the observed alterations in self-reported pain symptoms. As the investigations of Kuehl et al. [25] and Schumacher et al. [26] were primarily concerned with physiological outcomes, this the first investigation to examine biomechanical responses to cherry supplementation in participants suffering from any musculoskeletal disorder. However, taking into account the improvements in self-reported symptoms observed in the placebo group, it could be speculated that there would also be corresponding alterations in knee biomechanics mediated by this attenuation in pain [61]. Much like alterations in psychological wellbeing, however, improvements in knee mechanics are likely to take longer to manifest than changes in self-reported pain [62]. Regardless, in relation to the effects of the experimental group, this investigation confirms that U.S. grown Montmorency tart cherry supplementation has no effect on proprioception or biomechanical function at the knee joint.

Overall, the current investigation exhibited an effective level of blinding efficacy, a very low number of adverse incidences, a high retention rate, and very good compliance levels. Therefore, it can therefore be concluded that Montmorency tart cherry concentrate is a safe and tolerable supplement modality. However, taking into account the lack of significant improvements allied with the statistically greater mean daily sugar and associated kilocalorie intake, the findings from the current investigation do not support the utilization of Montmorency tart cherry in recreational athletes with patellofemoral pain. A limitation to the current and indeed previous analyses exploring the effects of tart cherry is that the extent of anthocyanin absorption from the supplementation was not examined. As such, although the amount of consumed supplement was monitored, the bioavailability of anthocyanins from the ingestion of tart cherries was unknown. Uhley et al. [63] have shown that anthocyanin metabolites can be identified in human blood and urine using liquid chromatography–mass spectrometry analyses. Therefore, future trials investigating the effects of tart cherry supplementation should seek to examine the extent of anthocyanin absorption. Furthermore, although participants were requested to maintain their habitual sport and exercise regimen, and exercise duration was monitored prior to and during the intervention itself, that exercise modality and intensity were not monitored may serve as a limitation to this trial. Therefore, subsequent randomized interventions exploring the effects of tart cherry supplementation on musculoskeletal symptoms should seek to more accurately quantify physical activity throughout the intervention period. Finally, although knee joint kinetics and kinematics were examined during functional athletic movements alongside proprioception indices, pain symptoms during each movement were not explored. As such pain symptoms during physical activity were only examined in recall fashion as part of the KOOS-PF rather than directly during the activities themselves. Further exploration of self-reported pain during different movements using visual analogue pain scales should therefore form part of future interventions examining different treatment modalities in recreational athletes with patellofemoral pain.

## Conclusion

The current investigation adds to the current clinical literature by examining using a placebo randomized control investigation, the ability of a tart cherry juice drink to provide pain relief in recreationally active individuals with patellofemoral pain. The findings show that the placebo group exhibited significant improvements in pain symptoms compared to the cherry group. Therefore, it can be concluded that tart cherry supplementation as ingested in the current investigation does not appear to be effective in mediating improvements in patellofemoral pain symptoms in recreationally active individuals.

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## Declarations

**Conflict of interest** The authors declare they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** All participants provided written informed consent.



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