



# Acute Ingestion of Montmorency Tart Cherry Reduces Serum Uric Acid but Has no Impact on High Sensitivity C-Reactive Protein or Oxidative Capacity

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## Abstract

Tart cherries are particularly high in anthocyanins and are believed to have many health benefits, including reducing inflammation and oxidative stress. However, comparison between dosages and formulations are lacking. Forty-eight participants were randomly allocated to one of six experimental treatment groups where they ingested tart cherry or placebo in either juice (240 ml *per* bottle) or powdered capsule form (480 mg *per* capsule) once or twice daily for 48 h and markers of inflammation (uric acid (UA), high-sensitivity C-reactive protein (hsCRP)) and oxidative capacity (plasma oxygen radical absorbance capacity (ORAC)) were measured. There was a group x time interaction for UA ( $p = 0.02$ ), which declined up to 24 h post ingestion for a single capsule dose, up to 8 h for a two capsule dose, and up to 2 h for a single juice dose. There was an increase in UA from 8 h until 48 h post ingestion in a single juice dose. Overall, there was an average 8% decrease in UA. There was no significant change over time in hsCRP ( $p = 0.64$ ) or ORAC ( $p = 0.42$ ) or between groups in hsCRP ( $p = 0.47$ ) or ORAC ( $p = 0.21$ ). Our data indicates tart cherry ingestion can transiently decrease UA and not maintained with continued supplementation. Additionally, there were differences in formulations and doses indicating a single powdered capsule is most effective for lowering UA suggesting capsules may be used by those who do not enjoy the taste of tart cherry juice. This study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov), NCT04497077, 7/29/2020, retrospectively registered.

**Keywords** Montmorency tart cherry · Uric · Gout · Inflammation

## Introduction

A considerable amount of interest has recently focused on the use of nutraceutical supplements for health, particularly those containing polyphenols such as anthocyanins and flavonols, in part because they are potent antioxidants and possess strong anti-inflammatory properties [1, 2]. Many dark colored foods, such as berries are high in anthocyanins; indeed the Montmorency (tart) cherry (*Prunus cerasus*) appears to have some of the highest anthocyanin content of any food [3, 4]. Thus, tart cherries have been used in exercise-related capacity,

reducing pain and inflammation while aiding recovery [5–8]. They may also have clinical applications, as there is evidence of reduced signs and symptoms of inflammation in arthritis [9] and gout [10]. However, the dose-response is not well known, nor has comparison between formulations been made. Tart cherry products come in a variety of forms, the most common is either concentrate or fresh juice that is pure or blended with other fruits. Additionally, tart cherries can be consumed frozen or dried (whole fruit or in powder form).

Many of the investigations focusing on exercise have utilized loading protocols of 7–14 days; however, the use of these foods in the clinical world have utilized ingestion periods of up to 6 months. While it may be reasoned that the longer the substance is ingested, the more anthocyanins would accumulate systemically, this has not been demonstrated [11]. On the contrary, anthocyanin absorption appears to be saturated with larger doses [12]. Therefore, it is unknown if a loading protocol is necessary or if acute dosing is sufficient. In a review of bioavailability studies, Manach et al. [13] found that absorption of anthocyanin from berries, berry extracts and

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concentrate occurs rapidly and inefficiently with peak plasma concentration between 0.75–4 h (mean 1.5 h) and maximal urinary concentration occurring 2.5–3 h after ingestion. Similarly, Keane et al. [14] found concentration of anthocyanin metabolites peaked in plasma 1 h after ingestion, returning to near baseline within 8 h, agreeing with previous work [11]. Interestingly, the vast majority of studies utilize a twice-daily ingestion protocol and unfortunately data on whether this is necessary or beneficial is limited and equivocal. For example, Bell et al. [11] found significantly greater plasma anthocyanin content 1 h post ingestion in 60 vs. 30 mL of tart cherry concentrate, whereas Keane et al. [14] found no differences in peak or max concentration, nor area under the curve for 8 h between a 30 or 60 mL dose.

Although the use of tart cherry concentrate dominates the literature, the use of powdered cherry supplements has increase recently [15, 16]. One might consider the use of powdered tart cherries, particularly in clinical populations, because it is lower in sugar than the juice or concentrate versions, contains the skins of the cherry where many of the anthocyanins are found, and each capsule contains more cherry product. There has only been one comparison of the two formulations *in vivo*, which demonstrated lowered insulin with powdered tart cherry vs. concentrate and placebo [15]. However, the authors of this work did not investigate changes in inflammatory markers, which are clinically relevant. Therefore, the purpose of this study was to investigate changes in inflammatory markers and oxidative capacity between acute ingestion of tart cherry supplements in juice or powdered form. We hypothesized that powdered tart cherry would increase oxidative capacity and decrease UA and inflammation as measured by hsCRP to a greater extent than tart cherry juice and placebo.

## Materials and Methods

Following approval by the Marywood University Institutional Review Board (protocol 801,765), participants were recruited

who were non-smokers, free of arthritis or an inflammatory condition, uncontrolled cardiovascular disease, high blood pressure, diabetes, fibromyalgia, or irritable bowel syndrome. Participants could not be regular consumers of cherries or other anti-inflammatory supplements (curcumin, greens, etc.), and not currently taking anti-inflammatory medications or corticosteroids in the last two months.

## Procedures

This study used a double-blind parallel design (Supplemental Fig. 1 and 2). Participants were randomly assigned using a random number generator and spreadsheet to one of six groups where they ingested either one tart cherry capsule, two tart cherry capsules, one bottle of tart cherry juice, two bottles of tart cherry juice, one placebo capsule, or one bottle of placebo juice (see Table 1 for demographics). Tart cherry capsules (CherryPURE®, Shoreline Fruit, LLC, Traverse City, MI) contained 480 mg of freeze-dried tart cherries, while the placebo capsules contained equal amounts of color matched maltodextrin. The tart cherry juice (Cheribundi, Geneva, NY) and placebo (black cherry Kool-Aid) was provided in 240 ml bottles. Participants were instructed to keep the juice refrigerated and to shake well before consumption. Participants arrived at the lab at 8 am after an overnight fast of at least 10 h and had their height (Seca 213, Seca North America, California), weight, and body composition (InBody 230, InBody USA, California) assessed before providing a blood sample. They ingested their study treatment and remained in the lab for a further blood sample at 1 and 2 h post baseline draw. During this time, they were provided with a small breakfast of a Nutri-Grain® bar, a cheese stick, and a bottle of water. They were asked to return to the lab in 8 h (approximately 5 pm) and provided another blood sample. If they were in a twice daily group, they ingested their next supplement at this time. Participants then arrived at the lab 24 h post baseline (approximately 8 am) for a blood draw and consumed their supplement. If they were in the twice daily

**Table 1** Anthropometric parameters of participants

	Juice		Capsule		Placebo	
	Once daily	Twice daily	Once daily	Twice daily	Juice	Capsule
Males, Females	5, 3	3, 5	5, 3	2, 6	3, 5	3, 5
Age (years)	20.63±1.77	23.88±6.27	23.75±5.73	20.75±1.91	23.63±7.33	24.13±5.08
Height (cm)	174.91± 8.15	170.70± 6.20	174.40± 8.39	170.21± 17.38	171.82± 7.73	172.38± 11.12
Weight (kg)	78.14± 11.49	67.17±6.07	93.10± 12.03	70.08±20.41	74.24± 20.39	80.63±18.10
Body fat (% BIA)	18.76±7.16	20.85±7.71	30.26±9.89	26.75±7.21	24.04±8.03	25.26±12.72

ingestion group, they were sent with their next supplement to be ingested 8 h after this appointment. Finally, 48 h after baseline draw participants arrived after an overnight fast for their last blood sample. During the study, participants maintained diet and activity records for the 5 days before, 3 days during testing and for 5 days post (a total of 13 days). Participants were asked to follow a low-polyphenolic diet and were provided with a list of the top 100 polyphenol containing foods to avoid consuming. Venous blood samples were collected from an antecubital vein into EDTA and serum tubes immediately before supplementation and 1, 2, 8, 24, and 48 h post ingestion of the supplement. Serum tubes were stored at room temperature for 30 min then centrifuged with EDTA tubes for 15 min (2,500 x g) and 4 °C after which supernatants were collected and stored at -80 °C for later analysis. Uric acid (UA) and high sensitivity C-reactive protein (hsCRP) were analyzed via by Geisinger Proven Diagnostics, Danville, PA, USA while plasma oxygen radical absorbance capacity was measured in-house via assay (ORAC, Zen-Bio Inc.). Reference range for hsCRP was 0–3 and 3.4–7.0 mg dL<sup>-1</sup> for UA. Inter-assay coefficient of variation for ORAC was 2.1% and for intra-assay coefficient of variation was 5.5%.

## Statistical Analysis

*A priori* power analysis with an effect size of 0.40 for hsCRP activity [17], 0.70 for UA [6, 17], an  $\alpha$  level of 0.05 and  $\beta$  level of 0.20 (80% power) indicated a need for eight participants *per* group. Statistical analysis was completed using Statistical Package for the Social Sciences (SPSS 23.0, Chicago, IL, USA). Exploratory data analysis was performed to check the normality of the data using quantile-quantile plots. Linear mixed models were used to examine the differences in hsCRP, UA, ORAC, and dietary intake between groups. Different covariance structures were systematically fit to the data, and the one that minimized the Hurvich and

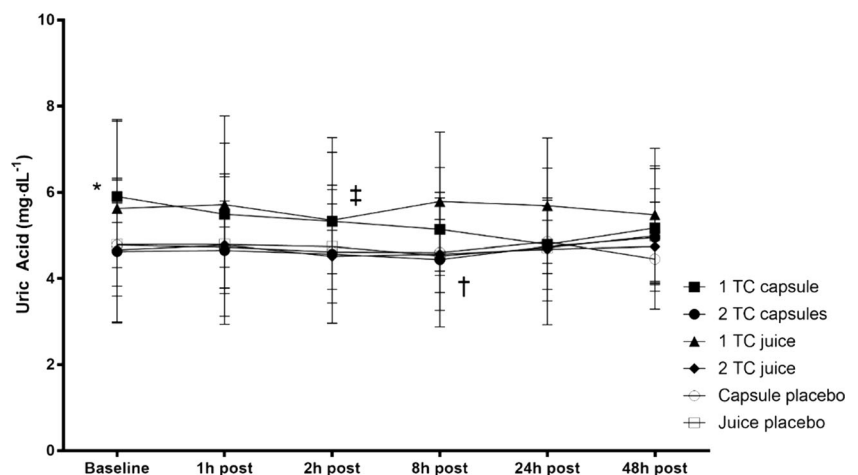
Tsai's criterion was chosen for the final model. Where a significant F ratio was observed, *post hoc* comparisons with LSD-adjusted *p* values were used to identify which pairs of means were significantly different. Two-tailed statistical significance was accepted as  $p < 0.05$ . Data are represented as mean  $\pm$  SD.

## Results and Discussion

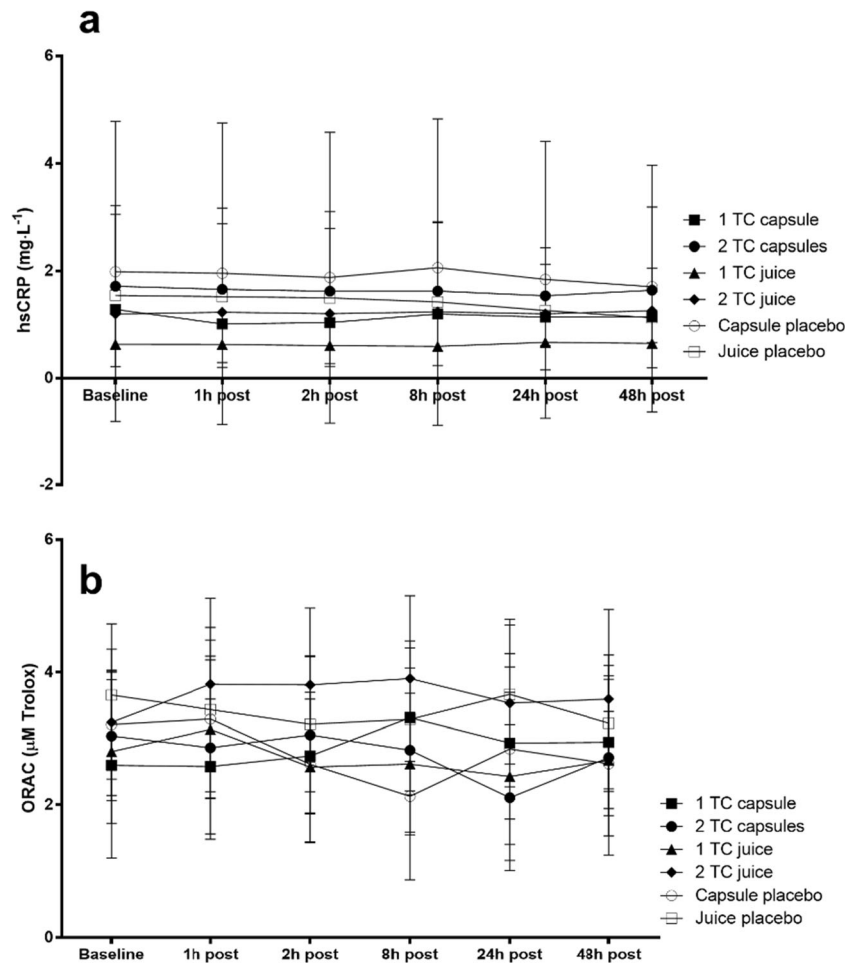
There was a main effect for time ( $F = 2.23$ ,  $p = 0.05$ ,  $\eta_p^2 = 0.70$ ) and a group x time interaction ( $F = 1.79$ ,  $p = 0.02$ ,  $\eta_p^2 = 0.52$ ) for UA. Specifically, UA steadily declined up to 8 h post ingestion (mean: 8%, 95% CI: 7.3–8.9%) with the exception of one bottle of juice, which was significantly elevated at 8 h post ingestion (Fig. 1). There was no significant main effect for time ( $F = 0.68$ ,  $p = 0.64$ ,  $\eta_p^2 = 0.14$ ) or groups ( $F = 0.94$ ,  $p = 0.47$ ,  $\eta_p^2 = 0.04$ ) and no interaction ( $F = 0.38$ ,  $p = 0.99$ ,  $\eta_p^2 = 0.17$ ) for hsCRP Fig 2. Similarly, there was no time ( $F = 1.01$ ,  $p = 0.42$ ,  $\eta_p^2 = 0.10$ ), group ( $F = 1.51$ ,  $p = 0.21$ ,  $\eta_p^2 = 0.19$ ), or interaction ( $F = 1.44$ ,  $p = 0.10$ ,  $\eta_p^2 = 0.20$ ) effects for ORAC (Fig. 2). There were no significant differences between groups or changes over time during the study for dietary intake, with the exception that the juice placebo group ate more vegetable servings than the twice daily capsule group and sugar intake was greater 5 days pre vs. 5 days during supplementation in the twice daily juice group ( $p = 0.04$ ) and was greater 5 days post vs. 5 days pre for the capsule placebo group ( $p = 0.02$ ; Supplemental Table). There were no correlations between any of the dietary intake measures and CRP, UA or ORAC.

The purpose of this study was to evaluate acute ingestion of tart cherry supplements, in either juice or powdered form on inflammation (hsCRP, UA) and oxidative capacity (ORAC) in healthy subjects. We found that UA was the only variable affected where it steadily declined until 8 h post ingestion and then returned to baseline levels 24 and 48 h post ingestion.

**Fig. 1** Uric acid levels following supplementation. \*Single tart cherry (TC) capsule, UA was lower at 1 h ( $p = 0.05$ ), 2 h ( $p = 0.02$ ), 8 h ( $p = 0.01$ ) and 24 h ( $p < 0.01$ ) compared to baseline. †Two TC capsules, UA was lower at 8 h vs. 24 h ( $p = 0.04$ ). ‡single bottle of juice, UA increased from 8 h to 24 h ( $p < 0.01$ ) and 48 h ( $p = 0.04$ )



**Fig. 2** **a** High-sensitivity C-reactive protein (hsCRP) and **b** oxygen radical absorbance capacity (ORAC) levels following tart cherry supplementation. There were no significant changes in hsCRP or ORAC over time or between formulations



hsCRP and ORAC were not significantly affected by any of the supplementation protocols or formulations.

One of the primary research targets for tart cherries is UA reduction capacity, particularly for gouty arthritis, where UA crystallizes in the joints (hyperuricemia) and results in pain and stiffness in the affected areas. The prevalence of gout in the US is approximately 3.9% [18] and individuals with gout also have high incidence of metabolic syndrome [19], likely because both conditions have underlying oxidative stress and inflammation [20]. Interestingly, gut microbiome dysbiosis has been found in gout sufferers, similar to those with type II diabetes, which may explain the increased oxidative stress and inflammation [21]. Recent meta-analytic data indicates a positive correlation between tart cherry consumption and a decrease in UA concentrations [22], however the authors note there is a lack of available literature and a significant amount of variation between study methodologies. However, of all the variables investigated with tart cherry ingestion, UA appears to be one that is unequivocal; the vast majority of studies indicate tart cherry ingestion does indeed reduce serum UA both acutely [11] and long term [17]. Our data corroborates these findings, that acute tart cherry ingestion reduces UA, at least up to 24 h post ingestion, depending on the formulation

and dose. Specifically, a single powdered capsule supplement led to the greatest decrease 24 h post ingestion, while the lowest UA from two capsules was 8 h post ingestion vs. 24 and 48 h. Interestingly, there was a rise in UA levels at 24 and 48 h compared to 2 h with a single dose of tart cherry juice. These findings are in line with those of Bell et al. [11] who reported that UA levels increased between the second dose for the day and the following morning, indicating tart cherry juice may have a limited effect on UA. This might indicate that a twice *per* day approach is more appropriate, although our data does not support this. These authors also found no difference between a single and double dose (30 vs. 60 ml) of tart cherry concentrate, similar to our study, where we do not see a significant difference between single and double doses or juice or powdered supplements. Our data also indicates that powdered tart cherry supplements provide similar levels of efficacy to tart cherry juice and therefore may be used by those who do not enjoy the taste of tart cherry juices.

Unfortunately, the effect of tart cherry supplements on inflammation and oxidative stress is more equivocal in the literature. hsCRP is an acute phase protein that is utilized as a marker of short term inflammation, however evidence suggests it plays a greater role in the inflammatory process than

previously thought [23] making it a potential target for anti-inflammatory treatment. Tart cherry has been investigated extensively for aiding recovery from exercise. While the work from one group indicates tart cherry ingestion improves inflammation following marathon running [8] and cycling [5, 6] and another group found improvements with powdered tart cherry [16], most other studies do not find any significant changes in inflammatory markers with juice [24–29] or powdered cherry supplements [30]. Clinical-focused research is similarly equivocal. In osteoarthritis patients, hsCRP decreased over six weeks with tart cherry supplementation, but rose when participants consumed the placebo [9]. Similarly, Martin and Coles [17] found a non-significant 19% decrease in hsCRP from four weeks of supplementation. It is important to note that the individuals in these studies had either diagnosed inflammatory conditions or elevated inflammatory markers before the study, increasing the likelihood of a difference in hsCRP. In healthy individuals, no significant changes have been found following six weeks of supplementation [31]. There appears to be only one investigation of acute tart cherry juice ingestion on hsCRP [11]. These authors found hsCRP decreased over an 8 h period following ingestion of a 30 and 60 ml dose of tart cherry concentrate followed by an increase 24 h later and a subsequent decrease with a third dose of juice. These changes track closely with changes in UA. In the current study, we did not find any significant changes in hsCRP over the course of a similar time frame to the study of Bell and colleagues [11]. We had a number of participants with values out of normal range for the tests at baseline or during the course of the intervention, indicating some level of inflammation, whether it be clinical or not.

Antioxidant capacity, measured via ORAC in this study, was unchanged by acute tart cherry ingestion, findings that match some in the literature [30, 31], while others have found a decrease in oxidative stress following tart cherry supplementation pre- and post-exercise [6, 8, 32]. However, comparisons between the current study and others investigating change in oxidative stress are tenuous because of differences in measurements (*i.e.*, antioxidant capacity vs. oxidative damage by-products). It has been proposed that increases in antioxidant capacity, specifically ORAC, from polyphenol-containing foods results from increased levels of UA [33], however that does not explain why ORAC tended to increase in this study, as UA decreased.

Our study provides further evidence for the efficacy of tart cherry to acutely reduce levels of UA, supporting its therapeutic use for gout. In addition, our study adds to the body of literature of null findings for the efficacy of tart cherries for reducing inflammation or improving antioxidant status. Further work is needed to elucidate the relationship between tart cherry supplements and inflammatory and oxidative stress markers. Finally, our study provides evidence of the efficacy of powdered tart cherry supplements and provides evidence

that a single dose is as effective as a double dose. This can provide cost savings and an alternative to drink the juice, which some find unpalatable. The current study has some limitations. First, we used a commercially available tart cherry juice not from concentrate that also contained apple juice, which has not been analyzed for phenolic content or ORAC. Therefore, it is unknown if our equivocal changes in hsCRP and ORAC are due to the product formulation. It is also plausible that null findings in inflammatory markers result from the use of healthy participants, making it harder to find a difference, which may have been resolved by utilizing a larger sample or individuals with inflammation.

## Conclusions

Our study provides further evidence for the efficacy of tart cherry to acutely reduce levels of UA up to 8 h post ingestion. Additionally, a single dose of either tart cherry juice or powdered tart cherry supplements decrease UA; therefore, tart cherry capsules are an effective alternative to juice for those who find the juice unpalatable. Tart cherry supplements did not impact hsCRP or ORAC, therefore further research is required to determine the impact of these supplements on markers of inflammation and oxidative capacity in healthy participants. Perhaps a broader evaluation of inflammation including multiple markers of early and late-phase inflammation would help characterize the role tart cherry plays in inflammation. Additionally, longer-term supplementation periods of different doses (single vs. double daily) and formulations (juice vs. powdered tart cherry) should be investigated particularly because there is large variation in the published literature.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11130-021-00879-7>.

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**Code Availability** Not applicable.

**Authors' Contributions** All authors contributed equally to the design, collection and analysis of data, and drafting of the manuscript.

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**Data Availability** Data is available upon request.

## Declarations

**Ethics Approval** Ethical approval was provided by the Marywood University Institutional Review Board (protocol 801,765).

**Consent to Participate** Participants provided written informed consent to participate.

**Consent for Publication** All authors approve this manuscript for publication.

**Conflicts of Interest/Competing Interests** The authors declare no conflicts of interest or competing interest.

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