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The beneficial effect of tart cherry on plasma levels of inflammatory mediators (not recovery after exercise): A systematic review and meta-analysis on randomized clinical trials

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ABSTRACT

Background: Chronic inflammation has been classified as one of the most important threats to health. Scientists suggested that tart cherry (TC) can reduce plasma levels of inflammatory mediators. Therefore, the aim of this study was to summarize the effect of TC on circulating C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) among adult participants in non-exercise randomized clinical trials (RCTs).
Methods and materials: The eligible English-language RCTs were found by searching databases including PubMed, Web of Science, Cochrane Library, Scopus, and clinical Trials.gov up to May 2022, with no time limit. We used the mean change from baseline and its standard deviation for both intervention and comparison groups to calculate the effect size. The random-effects model proposed by DerSimonian and Laird was used to estimate the overall summary effect and the heterogeneity. We used PRISMA 2020 guidelines to report this study.
Results: Ten RCTs were included in this study. The results demonstrated that TC had a significant decreasing effect on plasma CRP level compared with the comparison group (weighted mean differences (WMD) = −0.55 mg/L; 95% confidence interval (CI): − 1.03, − 0.06; p = 0.029), but had no significant effect on plasma IL-6 compared with comparison group (WMD = 0.08 pg/mL; 95% CI: −0.02, 0.17; p = 0.10). The effect of TC consumption on plasma TNF-α level was evaluated in only three studies that showed no significant effects (p>0.05).
Conclusion: Our results confirmed a significant decreasing effect of TC on CRP. Regarding IL-6 and TNF-α, our study did not present any significant effect of TC.

1. Introduction

Chronic inflammatory diseases have been classified as the most important health threat and are responsible for 3 out of 5 deaths worldwide.[1,2] Chronic inflammation is also a risk factor for some chronic diseases such as insulin resistance, diabetes, stroke, heart disorders, chronic respiratory diseases, and cancers.[1–5]

Scientific evidence has shown that fruits and vegetables contain non-nutritive bioactive compounds or phytochemicals, which have anti-inflammatory and antioxidant activity effects and even health benefits.[6] One of the main groups of phytochemicals is polyphenols which are linked to the health benefits of diets rich in fruits and vegetables.[7–9] Previous studies have shown that polyphenols can reduce the expression of pro-inflammatory cytokines in muscles,[10,11] adipose,[10,12] and hepatic[13,14] tissues. They are also associated with decreased risk of cardiovascular diseases (CVDs),[15] some cancers,[16] and neurodegenerative diseases.[17] Anthocyanins are one of the most important flavonoid subgroups belonging to the polyphenols family.[18] There is some evidence that anthocyanins play an important role in the protective effect of diets rich in flavonoids[19–21].

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In vitro studies show that anthocyanins are even superior to α-tocopherol and the commercially available antioxidants agents such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole[22] in the reduction of lipid peroxidation.[23] They inhibited the production of reactive oxygen species (hydrogen peroxide) and at the same time, upregulate the expression of endogenous antioxidants, glutathione peroxidase, glutathione reductase, and glutathione S-transferase.[24]

Tart cherry (TC) (Prunus cerasus) is one of the rich sources of dietary anthocyanins.[22] It is indicated that the anti-inflammatory properties of anthocyanins from TCs are similar to non-steroidal anti-inflammatory drugs (NSAIDs), such as Ibuprofen and Naproxen.[25] Numerous studies have shown the beneficial effects of TCs in exercise recovery. In these studies, consumption of TC juice has reduced inflammation,[26] oxidative stress,[26] pain,[27,28] and muscle damage[26,27] after persistent exercise. But, there are also scientific documents on antioxidant and anti-inflammatory effects of TCs in non-exercise human studies, although with some controversies.

The antioxidant and anti-inflammatory effects of TC in exercise recovery have been evaluated in previous studies.[29–31] Han et al. also performed a meta-analysis to evaluate the anti-inflammatory effects of TC in randomized clinical trials (RCTs), but they reviewed all studies regarding the anti-inflammatory effect of TC on recovery after exercise and non-exercise studies together[32]; furthermore, several relevant RCTs have been published in 2020 and 2021. Hence, this study performed a systematic review and meta-analysis on the effect of TC on plasma inflammatory markers only in non-exercise RCTs.

2. Material and methods

2.1. Search strategy

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISMA).[33] The protocol was registered with PROSPERO (No. CRD42021262809).

The eligible English-language RCTs were found by searching several databases including PubMed, Web of Science, Cochrane Library, Scopus, and clinicalTrials.gov up to May 2022 with no time limit. To find the eligible RCTs which assessed the effect of TC on inflammatory mediators (not recovery after exercise) in the above-mentioned databases, a search strategy was done using Medical Subject Heading (MeSH) terms and non-MeSH terms. The following MeSH and non-MeSH terms were used for searching: C-reactive protein, tumor necrosis factor-alpha, interleukin-6, Prunus avium,clinical trial, "Protein-C Reactive", "CRP", "Tumor Necrosis Factor", "Tumor Necrosis Factorα", "TNFα", "TNF-α", "Cachectin", "Interleukin6", "IL6", "IL-6", Inflammat* , "Prunus avium", "Prunus cerasus", "Sour Cherry", "Cherries, Sour", "Cherry, Sour", "Sour Cherries", "Tart cherry", Cherry*, "Clinical Trials", , "RCT". The search strategy was designed by using Boolean operators, Asterisks, Quotation marks, and Parentheses. Later, all searched papers were imported into reference manager software (EndNote X7). In order to find the relevant RCTs, the titles and abstracts of all papers were assessed independently by two reviewers (MH and BA). Furthermore, reference lists of the included trials were checked for confirming the comprehensiveness of searches.

2.2. Study eligibility criteria

Inclusion criteria were outlined according to the PICOS (Patient/Population, Intervention, Comparison, Outcome, Study types) framework. We included the crossover or parallel RCTs conducted on adults aged ≥ 18 years old. The trials were included in this study that had assessed the effects of TC on plasma levels of C-reactive protein (CRP) or tumor necrosis factor-alpha (TNF-α) or interleukin-6 (IL-6). Studies screening, quality assessment, selection, and data extraction were assessed independently by two reviewers (MH and BA). In a discussion session, the challenges of the study in each step were identified and solved.

The selected RCTs were read in full text on the basis of inclusion criteria. Studies with the following criteria were excluded from our study: 1) the articles in which other nutrient supplements was taken besides TC; 2) the articles included no comparison group; 3) the studies in which the anti-inflammatory effect of TC after exercise was assessed; 4) the articles reported taking TC for less than one week; 5) the RCTs that provided no information on CRP, TNF-α or IL-6 levels at either baseline or after taking TC, and 6) the studies did not report sufficient information to calculate either baseline or after intervention values of CRP or TNF-α or IL-6.

2.3. Data extraction

The following information was independently extracted from the included trial by two reviewers (MH and AGh): information on articles including first author's last name, publication year, country of origin, features of RCTs designs such as crossover or parallel, single blinding, double-blinding or open, intervention duration, sample size in each group, a daily dose of TC, participants' characteristics including health status, age, sex, and body mass index (BMI), as well as baseline and after intervention plasma concentration of CRP, TNF-α or IL-6. The data for CRP, TNF-α, and IL-6 were converted to the same unit (mg/L, pg/mL, and pg/mL; respectively). Studies with more than one-time point for follow-up were considered separate studies for each follow-up time point. Moreover, the studies with two independent data groups were treated as two trials. In case of any unclear information, an e-mail was sent to the corresponding author.

2.4. Quality assessment

The quality of each RCT was assessed using Cochrane Collaboration's tool[34] based on the following items: I) conducting random sequences; II) implementing allocation concealment; III) implementing participants and personnel blinding; IV) conducting outcome assessment blinding; V) reporting incomplete outcome; and VI) selective reporting. Two independent reviewers (MH, AGh) judged each entry in terms of "high risk", "low risk", or "unclear risk". Articles that had at least three and two criteria with a low risk of bias were scored as "good quality" and "fair quality" respectively. The articles were judged to be "weak quality" when they had less than two criteria with a low risk of bias.

2.5. Data synthesis and statistical analysis

We considered the treatment effects as weighted mean difference (WMD) and referred to Cochrane Handbook for its corresponding standard deviation (SDs) in plasma concentrations of inflammatory mediators (CRP, IL-6, and TNF-α).[35] Mean estimation was performed applying Hozo's method[36] if the authors reported the median or range instead of the mean. In addition, SDs were calculated by multiplying standard errors by the square root of the sample size in RCTs which reported standard errors. The random-effects model proposed by DerSimonian and Laird was used to estimate the overall summary effect and the heterogeneity.[37] If heterogeneity was observed, the I-squared statistic and Cochran's Q test were used to assess the significant heterogeneity where I-squared was $> 50\%$ and the p-value for the Cochran's Q test was ≤ 0.10[38].

To investigate the potential sources of heterogeneity for CRP, we ran subgroup analyses. The subgroup analyses were done by study design (crossover vs. parallel), intervention duration (<42 days vs ≥42 days), the baseline plasma concentration of CRP (<2.3 mg/l vs ≥2.3 mg/l), health status (healthy vs. at-risk/disease), sample size (<40 persons vs ≥40 persons), geographical region (Americas vs. Europe vs. Asia), sex (male vs. female vs. both sex), participants' age (<51 years old vs ≥51 years old), participants' BMI (<28.5 vs ≥28.5), quality assessment (good

vs. fair vs. weak), publication year (<2019 vs ≥2019). Subgroup analysis for intervention duration, baseline plasma concentration of CRP, sample size, participants' age, and participants' BMI was done based on their median. Sensitivity analysis was performed to explore the specific effect of each study on the overall estimation. Publication bias was evaluated by Egger's weighted regression, Begg's rank correlation, and visual inspection of Begg's funnel plot.[39,40]

3. Results

3.1. Study selection

Five databases were systematically searched and 641 articles were retrieved. 161 articles were duplicated and then removed. Therefore, 480 titles and abstracts were screened in order to find the relevant RCTs. 461 papers including reviews, cross-sectional studies, congress abstracts, non-human studies, study protocols, unrelated studies, studies on the effect of cherry and those studies that assessed TC effect on recovery after exercise were excluded from our analysis. Nineteen articles were read in full text and nine studies were excluded due to the following reasons: they had no comparison group (n = 2), used other interventions besides TC (n = 1), consumed TC less than one week (n = 1), and measured the plasma concentration of other inflammatory mediators (n = 5). Finally, ten clinical trials were selected for this systematic reviews[41–50] (Fig. 1). Since serum concentration of inflammatory mediators were not reported in one article,[50] meta-analysis was conducted on nine studies.[41–49]

3.2. Study characteristics

The effect of TC on plasma CRP, IL-6, and TNF-α was assessed in 10,[41–50] 4,[41,44,46,48] and 3[43,48,50] studies, respectively. Among the included studies, the freeze-dried powder, the juice, and the concentrated form of TC were consumed in 2,[41,50] 5[42,43,48–50] and 4[44–47] studies as interventions, respectively.

Concerning the study design, four and six RCTs had crossover design[41,42,48,49] and parallel design,[43–47,50] respectively. The duration of treatment was 2–12 weeks. Dealing with the subjects' health status, 2 studies were performed on healthy old men and women,[43,44] 4 studies on middle-aged adults,[45–47,50] 3 studies on overweight and obese participants,[41,42,48] and 1 study [49]on patients with osteoarthritis.

In one study TC was used in both forms of freeze-dried powder and juice; therefore, we considered this study as two separated studies in Table 1.[50] The effect of TC on plasma CRP was assessed at two time points in one article (the first and second treatment period in a crossover design),[49] thus the article was reviewed as two separate articles with two separate effect sizes for CRP. Moreover, another study was excluded from our meta-analysis because it illustrated the effect of TC on plasma CRP in a figure with no values and the authors didn't respond to our sent emails for more data.[48] Finally, 8 studies[41–47,49] with 9 datasets and 332 subjects assessed the effect of TC on plasma CRP and 4 studies[41,44,46,48] with 4 datasets and 66 subjects assessed the effect of TC on plasma IL-6 were remained to be included in this meta-analysis. The effect of TC on plasma TNF-α was not meta-analyzed as there were only 3 studies in this field[43,48,50] and one of them did not report serum concentration of TNF-α after intervention.[50] The study characteristics are detailed in Table 1.

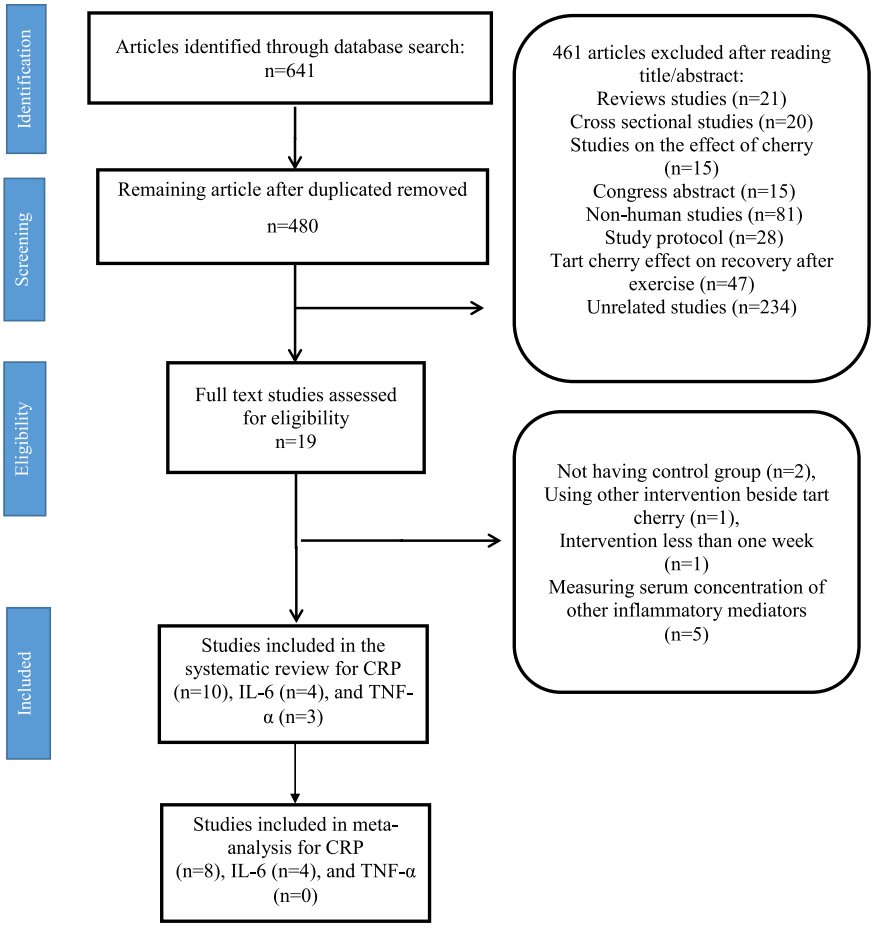

Fig. 1. Flowchart of study selection process.

Table 1
Randomized controlled trial studies included in the systematic review and meta-analysis.

Code Author (year) (country)	Subjects	Age and BMI (mean ±SD)	RCT	Intervention	Placebo	Duration (week)	Variables	Results
1 Aboo Bakkar, Z 2019 UK [41]	Overweight, middle-aged men N = 12	Age: 52.8 ± 5.8 BMI: 28.1 ± 5.3	Randomized, double-blind, placebo controlled, crossover study	1.7 g/d freeze-dried montmorency cherry powder (containing 226 mg anthocyanins and 456 mg total phenolics measures as gallic acid equivalents)	Glucose	4	IL-6, CRP	No significant effect on CRP and IL-6
2 Bowtell, J. L. 2019 USA [42]	overweight and obese participants N = 26	Age: 41 ± 11 BMI: 31.3 ± 6.0	Randomized, placebo-controlled crossover study	240 mL/d TCJ (containing 15.6 mg anthocyanins and 993.6 mg total phenolics)	Color, carbohydrate- and calorie-matched beverage	4	CRP	CRP reduced in intervention group
3 Chai SC. 2018 USA [43]	Healthy men and women N = 37	Age: 68–80 BMI: 27.3 ± 4.2	Parallel randomized-controlled double blind clinical trial	480 mL/d TCJ (Containing 95.9 mg tannin and 450.6 mg total phenolics)	Energy and sugar matched drink	12	CRP, TNF-α	CRP decreased significantly. No significant effect on TNF-α
4.1 Hillman A 2021 [50]	Healthy Adults N = 30	Age: 26 ± 7 BMI: 25 ± 3	Parallel randomized-controlled double blind clinical trial	500 mL/d TCJ (containing 454 mg anthocyanins and 1586 mg total polyphenols)	Placebo Juice	4	CRP, TNF-α	No significant effect on CRP and TNF-α
4.2 Hillman A 2021 [50]	Healthy Adults N = 28	Age: 27 ± 12 BMI: 25 ± 4	Parallel randomized-controlled double blind clinical trial	1000 mg/d freeze-dried tart cherries (containing 660 mg anthocyanins and 1520 mg total polyphenols)	Corn starch	4	CRP, TNF-α	No significant effect on CRP and TNF-α
5 Jackman SR. 2018 UK [44]	Healthy older men N = 16	Age: 60–75 y BMI: 26.4 ± 1.7	Parallel randomized-controlled double blind clinical trial	60 mL/d concentrated montmorency cherry (providing 540 mg anthocyanins per day)	Cherry flavored isoenergetic placebo	2	IL6, CRP	No significant effect on TNF-α and IL-6
6 Kimble R, 2021 UK [45]	Middle-aged adults N = 50	Age: 48 ± 6 BMI: 27.6 ± 3.7	Parallel randomized-controlled double blind clinical trial	60 mL/d concentrated montmorency cherry (providing 68–73.5 mg of anthocyanins and 160.8–178.8 mg of total phenolics)	Isocaloric unsweetened black cherry flavored placebo	12	CRP	No significant effect on CRP
7 Lear R. 2019 UK [46]	Middle-aged adults N = 28	Ag: 48.9 ± 5.4 BMI: 25.8 ± 2.3	Parallel randomized-controlled double blind clinical trial	60 mL/d concentrated montmorency cherry (providing 296 mg total anthocyanins and 1040 mg total polyphenols)	cherry flavored placebo	4	IL6, CRP	No significant effect on CRP and IL-6
8 Lynn A. 2014 UK [47]	Healthy adults N = 47	Age: 38.3 ± 6.16 BMI: 24.6 ± 3.63	Parallel open-label randomized placebo controlled study	30 mL/d concentrated tart cherry (providing 273.5 mg total anthocyanin)	Not mention	6	CRP	No significant effect on CRP.
9 Martin, KR. 2018 USA [48]	overweight and obese adults N = 10	Age: 38.1 ± 12.5 BMI: 32.2 ± 4.6	Randomized, placebo-controlled crossover study	240 mL/d TCJ (Providing 1827 ± 113 mg total polyphenols)	Anthocyanin-free fruit punch	4	CRP, TNF-α, IL-6	No significant effect on CRP, IL-6 and TNF-α
10 Schumacher HR. 2013 USA [49]	Non-diabetic patients with Kellgren grade 2–3 osteoarthritis N = 58	Age: 56.7 ± 11.3 BMI: 31.8 ± 6.2	randomized, placebo-controlled crossover study	240 mL/d TCJ (providing 450 mg phenolic compounds and 30 mg anthocyanins)	Unsweetened black cherry	6	CRP	CRP decreased significantly

Abbreviations:
IL-6: Interleukin-6; CRP: C-reactive protein; TNF-α: Tumour necrosis factor alpha; TCJ: Tart cherry juice, BMI: Body Mass Index, RCT: randomized clinical trial.

3.3. Risk of bias assessment

Cochrane guidelines were used to assess the risk of bias in 10 included studies. According to these guidelines, 5 studies were scored as "Good",[41,44,47,49,50] 3 studies as "Fair",[45,46,48] and 2 studies as "Weak".[42,43] Allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome were the sources of high risk of bias in 8,[42–46,48–50] 3,[42,43,47] 4,[42,43,47,48] and 7[42,43,45–49] studies, respectively. Random sequencing and selective reporting were low in 7[41,42,45,47–50] and 5 studies[44,46–49] and unclear in 3[43,44,46] and 5 studies.[41–43,45,50] The quality assessment of included studies is given in detail in Table 2.

3.4. Findings of the meta-analysis

Nine effect sizes from 8 studies were undertaken to assess the total

Table 2
Quality of bias assessment of the included studies according to the Cochrane guidelines.

Author name, year of publication, references	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Aboo Bakkar, 2019[41]	L	L	L	U	U	U	Good
Bowtell, J. L, 2019[42]	L	H	H	H	H	U	Weak
Chai, 2019[43]	U	H	H	H	H	U	Weak
Hilman, 2021[50]	L	H	L	L	L	U	Good
Jackman, 2018[44]	U	H	L	U	L	L	Good
Kimble, 2021[45]	L	H	L	U	H	U	Fair
Lear, 2019[46]	U	H	L	U	H	L	Fair
Lynn, 2014[47]	L	L	H	H	H	L	Good
Martin, 2018[48]	L	H	U	H	H	L	Fair
Schumacher, 2013[49]	L	H	L	U	H	L	Good

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

effect of TC consumption on plasma CRP level (Fig. 2). The total estimation showed that TC had a significant decreasing effect on plasma CRP level compared with the comparison group (WMD = −0.55 mg/L; 95% CI: −1.03, −0.06; p = 0.02). There was a significant heterogeneity between the studies (Cochrane's Q test, p = <0.001; I^2 = 96.5%). Referring to most studied variables, this heterogeneity wasn't decreased in subgroup analysis except for studies with intervention duration < 42 days (p = 0.22; I^2 = 31.7%), studies on male (p = 0.08; I^2 =65.8), and the weak quality studies (p = 0.37; I^2 = 0.00%) (Table 3).

Subgroup analysis revealed that TC had a significant decreasing effect on plasma CRP level in subgroups with parallel study design(WMD = −0.41 mg/L; 95% CI: −0.78, −0.05; p = 0.02) (5 effect sizes), intervention duration < 42 days (WMD = −0.54 mg/L; 95% CI: −0.95, −0.14; p = 0.009) (4 effect sizes), healthy individuals (WMD = −0.52 mg/L; 95% CI: −0.97, −0.07; p = 0.02) (5 effect sizes), sample size < 40 subjects (WMD = −0.52 mg/L; 95% CI: −0.97, −0.07; p = 0.02) (5 effect sizes), both sexes (WMD = −0.58 mg/L; 95% CI: −1.11, −0.06; p = 0.03) (7 effect sizes), participants' age < 51 years old (WMD = −0.36 mg/L; 95% CI: −0.68, −0.04; p = 0.02) (4 effect sizes), fair quality studies (WMD = −0.42 mg/L; 95% CI: −0.81, −0.03; p = 0.03) (2 effect sizes), weak quality studies (WMD = −1.05 mg/L; 95% CI: −1.41, −0.69; p < 0.001) (2 effect sizes) and publication year ≥ 2019 (WMD = −0.67 mg/L; 95% CI: −1.03, −0.31; p < 0.001) (5 effect sizes) (Table 3).

Sensitivity analysis revealed that the exclusion of each trial from the overall analysis had no significant impact on the total effect size of TC consumption on plasma CRP level (Fig. 3).

The funnel plots for the studies on the effect of TC consumption on plasma CRP level were not visually symmetric, but there was not any evidence of publication bias (Egger test p-value= 0.62 and Begg's test p-value= 0.67) (Fig. 4).

The total effect of TC consumption on plasma IL-6 level was evaluated with 4 effect sizes from 4 studies (Fig. 5). The total effect indicated that TC consumption had no significant effect on plasma IL-6 level compared with comparison group (WMD = 0.08 pg/mL; 95% CI: −0.02, 0.17; p = 0.10). There was a significant heterogeneity among the studies (Cochrane's Q test, p = 0.005; I^2 = 76.6%). As only 4 studies evaluated the effect of TC consumption on plasma IL-6 level, sensitivity and subgroup analyses were not performed for this inflammatory mediator.

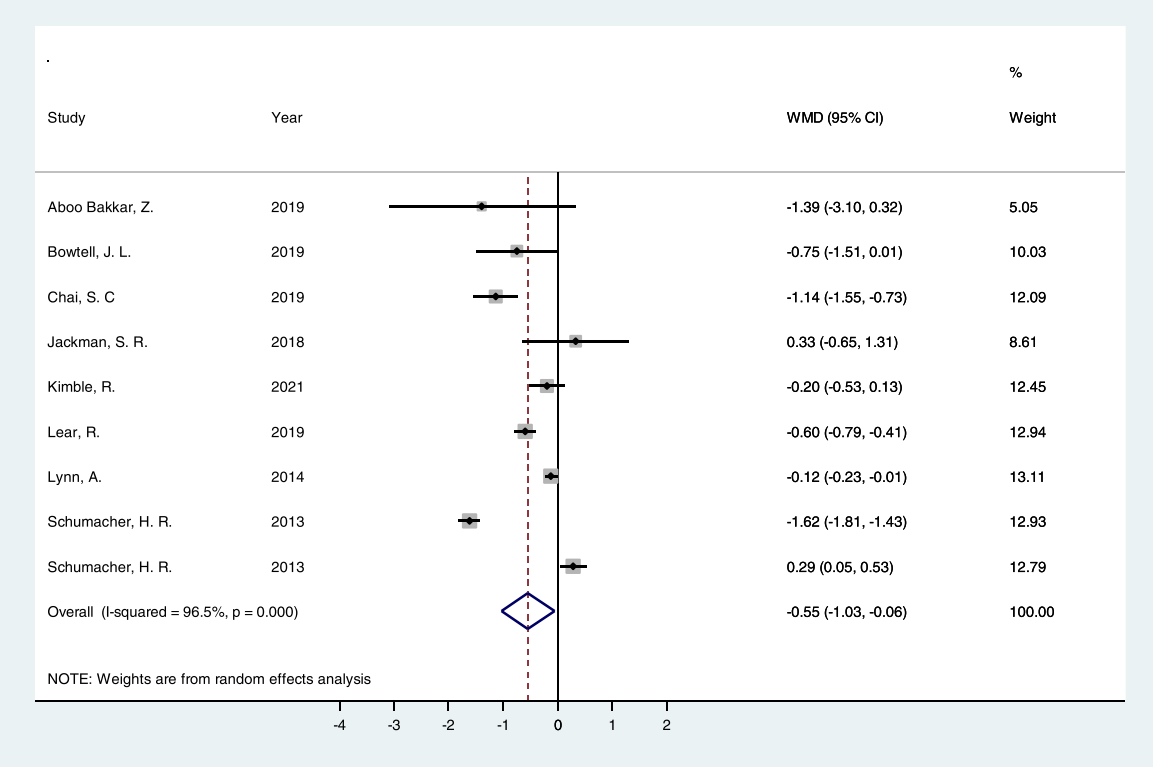

Fig. 2. Forest plot of the effect of tart cherry consumption on plasma concentrations of C-reactive protein.

Table 3
Subgroup analyses for studies evaluating the effect of tart cherry on plasma C-reactive protein.

	Subgroup	No. of trial	Change in CRP (95% CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	–	9	-0.55 (−1.03, −0.06)	0.02	96.5	<0.001
Study design	Parallel	5	-0.41 (−0.78, −0.05)	0.02	89.5	< 0.001
	Cross-over	4	-0.82 (−2.12, 0.47)	0.21	98.0	<0.001
Intervention duration	< 42 days	4	-0.54 (−0.95, −0.14)	0.009	31.7	0.22
	≥ 42 days	5	-0.55 (−1.28, 0.17)	0.13	98.2	< 0.001
Baseline CRP	< 2.3 mg/l	5	-0.29 (−0.61, 0.03)	0.07	81.4	< 0.001
	≥ 2.3 mg/l	4	-0.81 (−1.90, 0.29)	0.15	98.0	< 0.001
Health status	Healthy	5	-0.52 (−0.97, −0.07)	0.02	89.9	< 0.001
	At risk/disease	4	-0.57 (−1.65, 0.51)	0.30	98.1	<0.001
Sample size	< 40 persons	5	-0.52 (−0.97, −0.07)	0.02	89.9	< 0.001
	≥ 40 persons	4	-0.57 (−1.65, 0.51)	0.30	98.1	<0.001
Geographical region	Americas	4	-0.81 (−1.90, 0.29)	0.15	98.0	<0.001
	Europe	5	-0.29 (−0.61, 0.03)	0.07	81.4	< 0.001
Sex	Male	2	-0.38 (−2.04, 1.28)	0.65	65.8	0.08
	Both	7	-0.58 (−1.11, −0.06)	0.03	97.4	0.03
Age	< 51 years	4	-0.36 (−0.68, −0.04)	0.02	85.2	< 0.001
	≥ 51 years	5	-0.68 (−1.74, 0.37)	0.20	97.4	< 0.001
BMI	< 28.5	5	-0.29 (−0.61, 0.03)	0.07	81.4	< 0.001
	≥ 28.5	4	-0.81 (−1.90, 0.29)	0.15	98.0	<0.001
Quality assessment	Good	5	-0.45 (−1.30, 0.40)	0.30	98.1	< 0.001
	Fair	2	-0.42 (−0.81, −0.03)	0.03	74.4	0.03
	Weak	2	-1.05 (−1.41, −0.69)	< 0.001	0.00	0.37
Publication year of article	< 2019	4	-0.32 (−1.32, 0.59)	0.49	98.6	< 0.001
	≥ 2019	5	-0.67 (−1.03, −0.31)	< 0.001	70.2	0.009

BMI: body Mass index, mg: milligram, μg/mL: microgram per milliliter, mg/d: milligram per day, CI: confidence interval

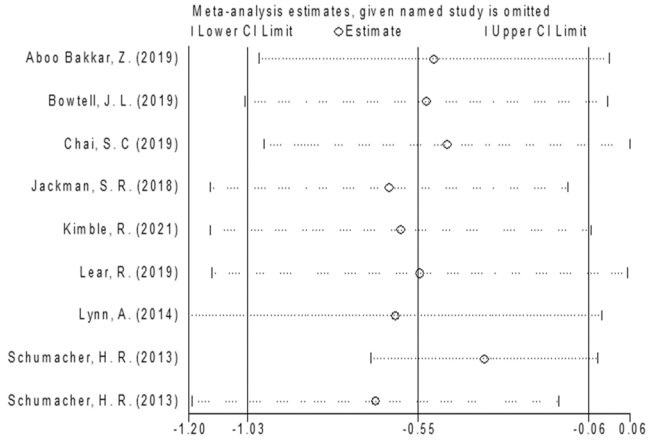

Fig. 3. Sensitivity analysis for C-reactive protein.

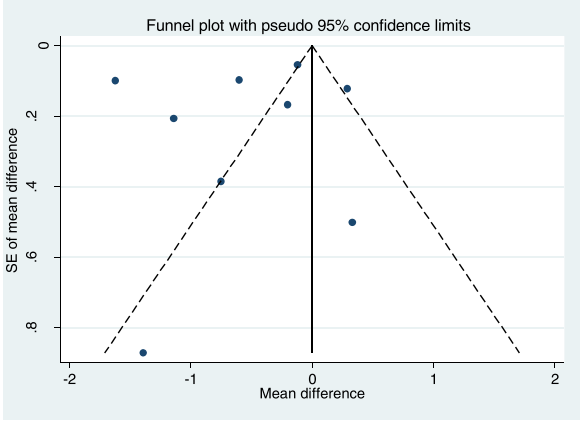

Fig. 4. Funnel plots for the studies of the effects of tart cherry consumption on plasma concentration of c-reactive protein.

4. Discussion

Our study is the first systematic review and meta-analysis on non-exercise RCTs that relieved the effect of TC on circulating CRP, IL-6 and TNF-α levels. Regarding CRP, the present meta-analysis conducted on 9 datasets from 8 studies consisting of 332 participants revealed a significant decrease in CRP concentrations in response to the consumption of TC compared with the control group. According to the results of subgroup analysis, a significant decrease was also indicated in studies with parallel design, intervention duration less than 42 days, sample size smaller than 40, and studies performed on healthy subjects, and subjects aged younger than 51. Furthermore, the results of our meta-analysis from 4 datasets indicated a non-significant enhancement of IL-6 levels after taking TC compared with the control group.

Many chronic diseases such as diabetes,[51] cancers,[52] and CVDs[53] might be caused by inflammation. The inflammation in these diseases might have carcinogenesis effects through reactive oxygen species[31] production.[54] Therefore, taking food ingredients with antioxidant activities might be helpful in these conditions.[55,56]

TC contains a high concentration of flavonoids such as anthocyanins which are responsible for the blue and red colors in vegetables and fruits. It has been shown that anthocyanins possess anti-mutagenic, anti-inflammatory, and antioxidant activities.[57] TC also is a rich source of other phytochemicals such as carotenoids and indolamines that have been revealed to have anti-oxidant and anti-inflammatory activities.[58] Since TC contains antioxidant ingredients,[59] scientists have used them as a potential tool to reduce oxidative stress and its related pathologies such as inflammatory disease.[60] Animal studies reported that TC-enriched diets could reduce inflammation by reducing oxidative stress.[61] The results of several reviews and human studies also revealed that nutrients with antioxidant properties such as green tea,[62] curcumin[63] vitamin E,[64] and selenium[65] could reduce inflammation.

New evidence suggests that flavonoids play an important role in inflammation reduction by decreasing the activity of nuclear factor-kappa B (NF-κB) cells, which is responsible for the control of DNA transcription and cytokine production.[66]

However, the results of our meta-analysis disclosed no significant changes in IL-6 levels. This might be because a small number of studies were included in this meta-analysis and most of them had a small sample size which resulted in unsteady approximates of therapeutic effects.

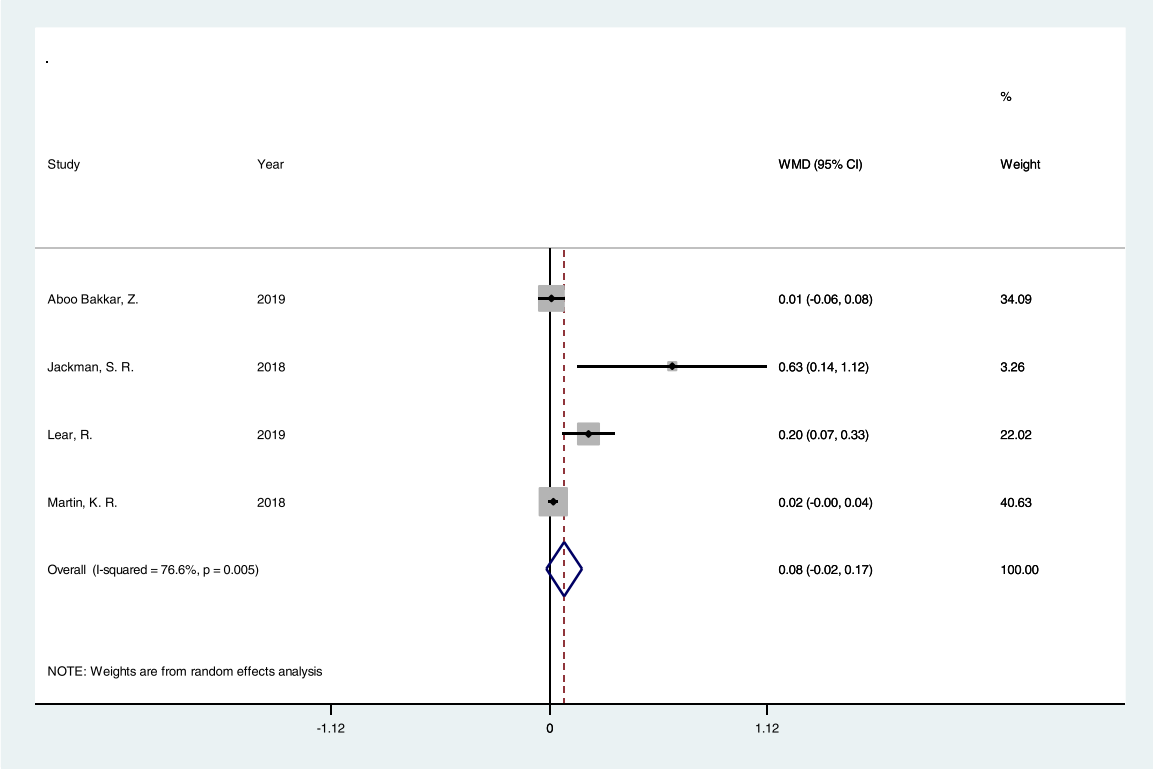

Fig. 5. Forest plot of the effect of tart cherry consumption on plasma concentrations of Interleukin-6.

Conducting all studies on participants with health risk factors or the elderly populations might show why the non-significant results were got. The results of the subgroup analysis concerning CRP showed that TC could not reduce the plasma levels of CRP in these populations; therefore, it would be also possible for IL-6. Furthermore, the low bioavailability of flavonoids might give rise to non-significant results.[67] It should be noticed that because the urine or plasma levels of flavonoids and their metabolites weren't measured in any study, it is difficult to determine the cause of ineffectiveness.

Our results of the subgroup analysis based on health status and age proposed that TC significantly reduced plasma concentration of CRP in healthy subjects and subjects aged younger than 51 years old. One reason posited for non-significant results in unhealthy participants or participants with health risk factors and also in participants with age older than 51 might be high levels of CRP in this population[68,69]; therefore, TC could not be effective enough to decrease CRP among these participants.

Our findings showed a marked effect of TC on CRP in studies with a short-duration intervention (<42 days) and a sample size smaller than 40. We proposed that the non-significant effect in studies with an intervention duration $\geq$ 42 days might be due to poor adherence to the treatment. This is also suggested by the previous studies that short-term interventions might be more efficacious.[70,71] Since most studies with sample size smaller than 40 followed participants for short time period, they also might got significant effect because of short intervention duration. might be the reason for the significant effect in studies with a sample size smaller than 40.

Consistent with the results of our systematic search, three studies assessed the effect of TC on plasma concentration of TNF-α and all of them reported the non-significant effect of TC on TNF-α.[43,48,50] One study was on the elderly population[43] and another one was on overweight and obese participants[48]. Due to the fact that adipose tissue might produce TNF-α 7.5 times more in obese subjects compared with non-obese subjects,[72] TC didn't show to be effective to decrease TNF-α in that study. Increased inflammatory activity in the elderly contributors might be a reason for the non-significant effect in another study.[73]

We had various limitations in this study. Firstly, there were few studies for TNF-α which caused reporting the results only as a systematic review. Given the fact that the number of RCTs for IL-6 and CRP was low, especially in the subgroup analysis for CRP, our results could be biased. Secondly, our results indicated a significant heterogeneity even in most subgroup analyses. Thirdly, there was no information on the absorption and metabolization of flavonoids; therefore, we could not assess whether flavonoid absorption was responsible for non-significant results. Fourthly, purity and potency of TC were not assessed in this study. Next, forasmuch as no study was done on females, the effect of TC on females remained questionable. Because the most of reviewed studies were conducted in the USA and England, we still need more studies on other parts of the world. Finally, the intervention duration in most articles was short, and only two studies followed participants for 12 weeks.

Despite several limitations, our study had some strengths. Our study was the first systematic review and meta-analysis which assessed the effect of TC exclusively on non-exercise RCTs. We did not have any time limitations for our systematic search. The RCTs in which subjects took other nutrients besides TC were removed; therefore, their confounding effects were excluded as well. Finally, we indicated the effects of BMI, age, geographical region, sample size, trial design, health status, intervention duration, publication year, baseline levels of CRP, and quality assessment on the effect of taking TC on the CRP levels.

In conclusion, our results showed that TC reduced plasma concentration of CRP, especially in healthy participants and participants younger than 51 years old. On account of the fact that our results indicated TC reduced plasma CRP in studies with shorter intervention duration, conducting more high-quality and long-term intervention studies is necessary to draw a firm conclusion. We also need more studies on different parts of the world and separately on males and females. Our results suggest that TC cannot reduce the plasma concentration of IL-6. Because we conducted this study using the results obtained from 4 studies, further research is needed. Our systematic review results showed that only three studies were assessing the effect of

TC on TNF-α, thus we still need more studies to come to a firm conclusion.

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Contributors

AGh found keywords and made search strategy. **MH, BA and AGh** searched databases, and found relevant RCTs. They also read the full text of the articles, excluded irrelevant RCTs, and extracted data. **AGh and HRB** were responsible for conducting the statistical analysis. **MH, AGh and BA** wrote the first version of the manuscript. **HRB** approved the final version of the articles.

Conflict of interest

No conflict of interest.

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