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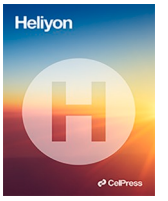

Review article

Dose-dependent effect of tart cherry on blood pressure and selected inflammation biomarkers: A GRADE-assessed systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: As a nutritious food, Tart cherries (*Prunus cerasus* L) benefit cardiovascular health. This study aims to clarify the effectiveness of Tart cherry in controlling blood pressure, heart rate, and inflammatory biomarkers, the appropriate dosage for this effect, and suggest directions for future studies.

Methods: PubMed, Scopus, and Web of Science were searched (up to May 2022), to identify eligible randomized controlled trials. It measured publication bias and was assessed for all outcomes. Evidence quality was evaluated using the Cochrane risk of bias tool and GRADE (Grades of Recommendations, Assessment, Development, and Evaluations).

Results: Regarding the 21 included trials, Tart cherry didn't affect blood pressure, heart rate, high-sensitive C-reactive protein, and interleukin-6 ($P > 0.05$). In contrast, with moderate certainty, it can reduce serum C-reactive protein (WMD: - 0.39 mg/l; 95% CI: - 0.74, - 0.05; $P = 0.024$) and with very low certainty can decrease tumor necrosis factor-alpha (WMD: - 0.14 pg/ml; 95% CI: - 0.27, - 0.02; $P = 0.026$). In addition, dose-response analysis implies that with each 30 ml elevation in dose, CRP reduces by 0.19 mg/l (95% CI: - 0.37, - 0.01).

Conclusions: Tart cherry can control inflammation by administering the proper dose. Even though tart cherry generally doesn't affect blood pressure and heart rate, further high-quality studies are needed to determine its effect.

1. Introduction

Cardiovascular diseases (CVD) are responsible for most premature deaths and their mortality rate is increasing, highlighting the need to address CVD risk factors [1]. Hypertension is the primary risk factor for CVD-related deaths [2]. Hypertension prevalence has doubled from 1990 to 2019 affecting 1.2 billion people, and responsible for 8.5 million deaths annually [3]. In addition, research in recent years has shown that inflammation is the primary risk factor in the pathogenesis of chronic diseases like CVDs [4]. Thus, controlling inflammation may be a source of recovery [5].

The efficacy and long-term side effects of existing therapies for blood pressure control like calcium antagonists, diuretics, and

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angiotensin-converting enzyme inhibitors limit their use. These treatments can delay the transformation of high blood pressure into hypertension, but their long-term effectiveness in controlling blood pressure is still questionable. Complications such as dry cough, dizziness, bradycardia, peripheral edema, and insomnia become more apparent when these drugs are taken regularly for a long time, a condition that is seen in most of the elderly. So, there is a need for proper therapy [6,7].

It can control CVD risk factors through diet interventions effectively and safely [8]. Dietary benefits are often attributed to natural ingredients found in foods, such as phytochemicals [9,10], which act as anti-inflammatory agents [11,12]. Anthocyanin is one of them located in red-orange to blue-purple food pigments. Besides their efficacy in controlling CVD risk factors like lipid profile, they are at the center of attention because of their presence in the daily diet [13].

Tart cherry (TC) belongs to the Rosaceae family and is a rich source of anthocyanins. Meanwhile, TC contains phytochemicals like flavonols, melatonin, and carotenoids which by synergistic effect, might affect its features like anti-inflammatory actions [14–16].

Recently, TC consumption increased due to its unique characteristics. TC is a low-calorie and nutrient-dense food with high antioxidant properties, cyanidin content, and vitamin A content, making it superior to red wine, dark chocolate, and orange juice [10, 17–19]. Tart cherry juice concentrate, with high phenolic compound and oxygen radical absorbance capacity, can alter PPAR receptors and have a beneficial effect on chronic diseases [11,12,20,21]. However, dose-response studies are needed to determine its health benefits [10].

While recent studies imply an increase in TC dose to have significant results [22], this is the first study that examines the GRADE-assessed pairwise and dose-response association of TC on blood pressure, heart rate, and inflammation.

2. Methods

The current dose-response meta-analysis has been documented following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA statement) [23]. The protocol of the systematic review was registered in PROSPERO (CRD42022334346).

2.1. Systematic search

To identify eligible RCTs, we conducted an extensive search on PubMed, Scopus, and ISI Web of Science until May 2022. Furthermore, to enhance our search approach, we conducted a rigorous manual review of the reference lists of all pertinent previous reviews. Our search strategy was confined to scholarly articles published in English. We combined keywords related to intervention, outcome, and study design to find potential eligible RCTs. The complete search strategy is described in Supplementary Table 1. Teams comprising two reviewers conducted an independent screening of titles and abstracts. The screening process involved adhering to pre-defined inclusion and exclusion criteria, intending to identify eligible trials.

2.2. Eligibility criteria

We utilized the PICOS (population, intervention, comparator, outcome, and study design) framework to establish our inclusion and exclusion criteria. Published human intervention studies were considered eligible for inclusion in the present meta-analysis if they had the following criteria: 1) RCTs, either with parallel or cross-over design, conducted in adults aged 18 years or older, regardless of health status; 2) evaluated the effect of TC on heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α; 3) compared the effect of different doses (ml/d) of TC on heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α against a placebo; 4) considered the change in heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α as the primary or one of the secondary outcomes; 5) provided mean and standard deviation (SD) of change in heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6 and TNF-α across study arms or reported sufficient information to estimate those values, and; 6) reported the number of participants in each study arm. Trials possessing non-randomized designs, quasi-experimental studies, and trials conducted among adolescents (below 18 years of age) and pregnant as well as lactating women were excluded.

2.3. Data extraction

Two reviewers (MN-Z and MH-R) conducted a thorough screening of the full texts of qualified trials in duplicate and extracted the following data: author and year, population, location, study design, and duration, characteristics of the population (mean age $\pm$ SD, baseline BMI, health status), total sample size, intervention characteristics (type and dose of TC), comparison group, outcome measures and main results for the outcomes included. The disagreements of opinions between the two reviewers were settled through discussion.

2.4. Risk of bias (quality) assessment

Two reviewers (MN-Z and MH-R) carried out the Risk of bias evaluations using the Cochrane risk of bias tool in duplicate and independently [24]. The subject provided an overall quality rating to the trials based on bias domains, which were categorized as good, fair, and high risk of bias. Good was indicated by $\leq 1/5$ items being unknown and none being high, fair was indicated by $\leq 2/5$ items being unclear or at least one high, and high Risk of bias was indicated by $\geq 2/5$ items being high. Any discrepancies in the Risk of bias evaluation were resolved through discussion.

2.5. Statistical analysis

We considered the weighted mean difference (MD) and 95% confidence interval (CI) of change in SBP and DBP as the effect size for reporting the results of the present systematic review. First, we calculated changes from baseline heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α in each study arm. If the mean values and SDs of changes were unavailable, we computed these values by utilizing data from measures before and after the intervention, following the directives of the Cochrane Handbook [25]. When standard errors instead of SDs were presented, the former was converted to SDs [26]. When studies presented medians and interquartile ranges, the missing mean is estimated using the median, and the standard deviations are computed by dividing the interquartile ranges by 1.35 [26]. If none of the aforementioned alternatives were available, to assign the missing SDs we utilized pooled SDs from other trials included in our meta-analysis [27]. Second, We utilized the methodology proposed by Crippa and Orsini [28] to assess the mean difference (MD) and its corresponding SD of change in heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α for every 20 ml/d increments in TC in the intervention group relative to the control group in each trial. The current methodology requires a specific dosage (ml/day) of TC in each study arm, accompanied by the respective mean and SD of the change in anthropometric measures, heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α in each study arm, and the number of participants in each arm. Trial-specific results were pooled using a random-effects model [29]. Series of pre-defined subgroup analyses were conducted based on health status, baseline BMI (<30 or ≥ 30) as well as the type of intervention (concentrate vs. juice), number of prescriptions in a day (once vs. twice), follow-up duration, number of the study population, mean age and risk of bias assessment. To assess the potential impact of each trial on the overall effect size, an influence analysis was conducted. The probability of publication bias was assessed via the utilization of Egger's test [30], Begg's test [31], and visual inspection of funnel plots. We assessed heterogeneity quantitatively using the I^2 statistic and performed a χ^2 test for homogeneity (P-heterogeneity$>$ 0.10) [32]. Finally, we performed a dose-response meta-analysis to clarify the effect of different doses of TC on anthropometric measures, heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α [28]. Statistical analyses were conducted using STATA software version 16.1. A two-tailed P value of less than 0.05 was considered significant.

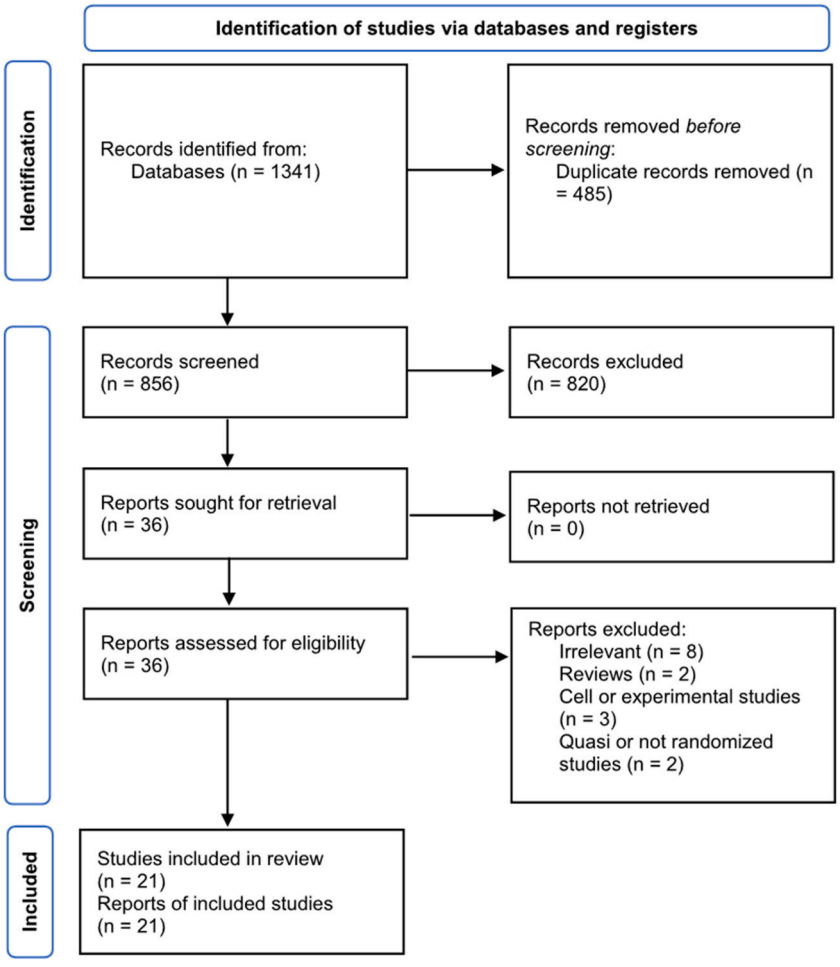

Fig. 1. The PRISMA flow diagram for literature search and selection.

Table 1
Demographic characteristics of the included studies.

First Author (year)	Location	RCT Design	Health status	Gender	Sample size	Duration (week)	Mean age (year)	Baseline BMI (kg/m^2)	Intervention		Outcome
									Treatment group	Control group	
J. Sinclair (2022)	UK	Three-Arm	adults between 18 and 65 years	both	45	3	34	28	60 ml concentrate/day (in two equal doses)	placebo	SBP, DBP, HR
R. Kimble (2021)	UK	Parallel	healthy individuals	both	23	4	23.35	24.6	60 ml concentrate/day (in two equal doses)	placebo	SBP, DBP, HR
R. Kimble (2021)	UK	Parallel	middle-aged adults	both	56	13	48	27.6	60 ml concentrate/day (in two equal doses)	placebo	SBP, DBP, HR, hs-CRP
T. Desai (2020)	UK	Parallel	metabolic syndrome patient	both	12	1	50	31	30 ml concentrate/day	placebo	HR
L. K. Stamp (2020)	New Zealand	Parallel	people with gout	male	50	4	58.65	30	60 ml concentrate/day (in two equal doses)	placebo	SBP, DBP
S. A. Johnson (2020)	USA	Single-blinded, Parallel	people with metabolic syndrome	both	26	12	36.75	33.9	480 ml juice/day (in two equal doses)	placebo	SBP, DBP, HR
R. Quinlan (2020)	UK	Single-blinded, Parallel	team-sport players (football, hockey, or netball)	both	20	1	26	22.81	60 ml concentrate/day (in two equal doses)	placebo	CRP
K. R. Martin (2019)	USA	crossover	overweight and obese participants	both	36	4	41	31.3	40 ml concentrate/day	placebo	SBP, DBP, HR
Z. A. Bakkar (2019)	UK	crossover	inactive overweight middle-aged	men	14	4	52.8	28.1	1.7 gr powder/day (6capsules/day)	placebo	CRP, IL-6
M. A. Brown (2019)	UK	Parallel	physically active females	female	20	1	19	22.01	60 ml concentrate/day (in two equal doses)	placebo	hs-CRP
S. C. Chai (2019)	USA	Parallel	normal people	both	37	12	69.75	26.4	68 ml concentrate/day (in two equal doses)	placebo	CRP, TNF-α
R. Lear (2019)	UK	Parallel	untrained and non-obese adults	both	28	4	51.05	24.95	60 ml concentrate/day (in two equal doses)	placebo	CRP, IL-6
T. Desai (2018)	UK	Single-blinded, cross over	healthy participants	both	11	4	30	24.43	60 ml concentrate/day (in two equal doses)	placebo	SBP, DBP, HR
S. C. Chai (2018)	USA	Parallel	older adults	both	37	12	69.75	27.9	68 ml concentrate/day (in two equal doses)	placebo	SBP, DBP
S. R. Jackman (2018)	UK	Parallel	men aged 60–75 years	male	16	3	67	25.4	60 ml concentrate/day (in two equal doses)	placebo	CRP, IL-6
P. G. Bell (2016)	UK	Parallel	Semi-professional male soccer players	male	16	1	25	25.27	60 ml concentrate/day (in two equal doses)	placebo	hs-CRP, TNF-α
K. Levers (2016)	USA	Parallel	Endurance-trained runners or triathletes	both	34	1.5	21.8	22.4	51.3 ml concentrate/day	placebo	IL-6, TNF-α
K. Levers (2015)	USA	Parallel	healthy, resistance-trained males	male	30	1.5	20.9	25.9	51.3 ml concentrate/day	placebo	IL-6, TNF-α
A. Lynn (2014)	UK	Parallel	healthy adults	both	46	6	37.75	24.05	30 ml concentrate/day	placebo	hs-CRP
A. Lynn (2013)	UK	Parallel	healthy adults	both	46	6	37.75	24.05	30 ml concentrate/day	placebo	SBP, DBP, CRP
A. E. Sleigh (2012)	USA	Parallel	osteoarthritis patients	female	20	3	54.1	29.49	596 ml juice/day (in two equal doses)	placebo	CRP, IL-6, TNF-α

Abbreviations: SBP, Systolic Blood Pressure; **DBP,** Diastolic Blood Pressure**; HR,** Heart Rate**; CRP,** C-reactive Protein**; hs-CRP,** High-sensitive C-reactive Protein**; IL-6**, Interleukin 6**; TNF-a,** Tumor necrosis factor-alpha.

2.6. Grading the evidence

We used the GRADE tool to appraise the overall certainty of the evidence for each outcome [33]. The aforementioned tool categorizes the level of evidence as high, moderate, low, or very low for each outcome. MN-Z and MH-R, two pairs of authors, independently utilized the GRADE assessment and then consensus to reach a single result. There are groups of criteria responsible for downgrading or upgrading the evidence. Risk of bias, inconsistency, indirectness, imprecision, and publication bias cause devaluing of the evidence. However, significant effect size and dose-response gradient are responsible for upgrading the certainty of the evidence. So, because our study is a dose-response meta-analysis, we were able to upgrade the evidence when the dose affected the outcomes significantly. Also, there is a point to evaluate the imprecision, which we used as the recently reported minimal clinically important difference (MCID) threshold for heart rate, blood pressure (SBP or DBP), CRP, hs-CRP, IL-6, and TNF-α to rate it.

3. Results

3.1. Study selection

Our search led to 1341 records that after excluding duplicates, 856 records screened, first from the title and abstract, and then if needed, the original article underwent full review. As shown in Fig. 1, articles were excluded because of the following reasons: 1. Irrelevant (include not relevant intervention) 2. Reviews and experimental articles 3. unfit quality (Including duration of less than a week, lack of a control group, the supplement was not quite TC, or inappropriate outcome investigation). Finally, 21 RCTs were included in the meta-analysis.

3.2. Study characteristics

As indicated in Table 1, of included RCTs, three have cross-over designs [34–36], and three were single-blinded [36–38]. Neither study implemented calorie restriction, but 7 RCTs implemented exercise in their intervention plan [35,36,38–42]. The target group of included studies varies from a healthy population [36,39,43–50] and athletes [38,40–42] to gout [51], osteoarthritis [52], metabolic syndrome [37,53], and overweight patients [34,35]. TC was administered in different doses (ranging from 130 to 596 ml juice) and types like concentrate, juice, or capsule, and in this context juice concentrate was the dominant form. Two studies specifically work on females [39,52] and five studies just work on males [35,40,41,48,51]. Their sample size varied between 10 and 56 persons. Studies, last at least one week [38–40,53] to 13 weeks [43]. Most of the studies were done in the UK or USA and just one was done in New Zealand [51].

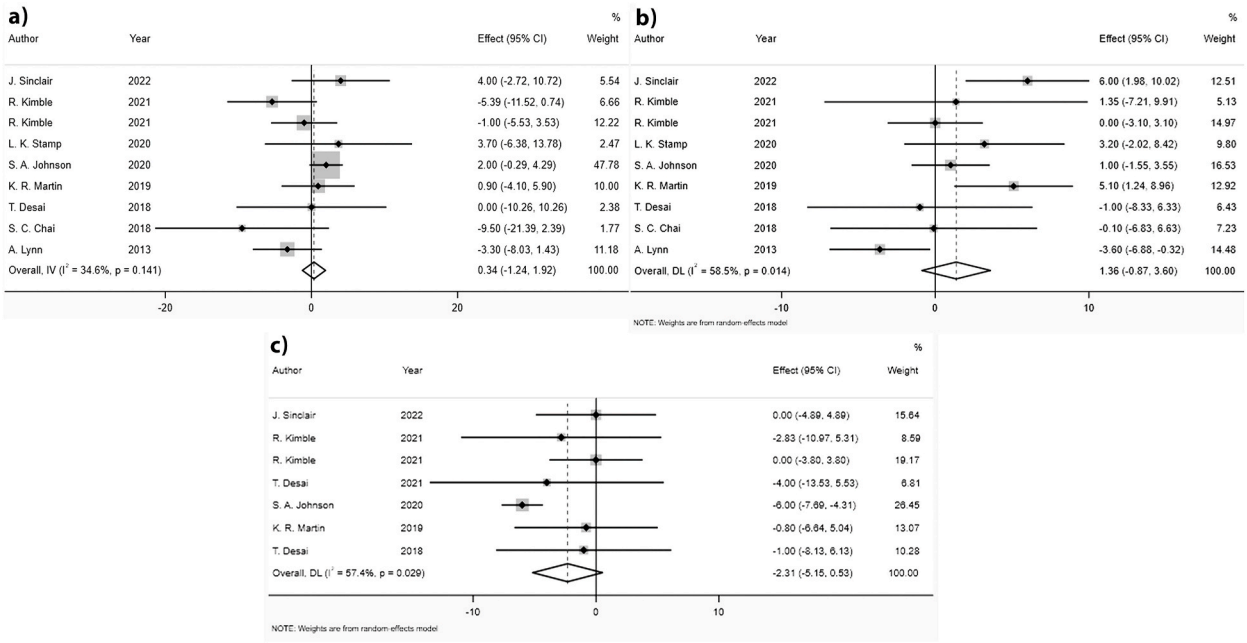

Fig. 2. Forest plots investigating the effect of tart cherry consumption on (a) SBP, (b) DBP, and (c) HR.

3.3. Meta-analysis

3.3.1. Effect of tart cherry on heart rate and blood pressure

The effect of TC consumption on SBP, DBP, and HR is presented in Fig. 2a–c. TC has no significant impact (clinically or statistically) on SBP (WMD: 0.34 mmHg; 95% CI: - 1.24, 1.92; P = 0.674; I 2 = 34.6%), DBP (WMD: 1.36 mmHg; 95% CI: - 0.87, 3.60; P = 0.0.231; I 2 = 58.5%) and HR (WMD: - 2.31 Beats/min; 95% CI: - 5.15, 0.53; P = 0.0.111; I 2 = 57.4%).

Subgroup analysis **(**Supplementary Table 2**)** indicates that health status and mean BMI significantly modify the effect of TC consumption on SBP (P = 0.018) and mean BMI is a source of heterogeneity.

To continue, subgroup analysis suggests that health status (P = 0.09), mean BMI (P = 0.09), and study duration (P = 0.001) significantly modify the effect of TC consumption on DBP. Health status, study population, mean age, mean BMI, study quality, and the number of prescriptions per day are known as a source of heterogeneity. Besides this, studies worked on unhealthy participants, with mean BMI ≥30, duration ≤4 weeks, and prescribed 2 doses per day indicated a significant rise in DBP (P < 0.05).

Health status (P = 0.001), study population (P = 0.002), mean BMI (P = 0.001), study duration (P = 0.02), and quality (P = 0.06), significantly modify the effect of TC consumption on HR. Study duration, study quality, and the number of prescriptions per day are known as a source of heterogeneity. Prescription of TC in 2 doses per day and for unhealthy participants, study population <40, mean BMI ≥30, study duration >4 weeks, and good quality studies lead to a significant reduction in HR (P < 0.05).

3.3.2. Effect of tart cherry on inflammatory biomarkers

Tart cherry consumption has no significant impact on hs-CRP (WMD: - 0.14 mg/l; 95% CI: - 0.34, 0.07; P = 0.200; I 2 = 0.0%) and IL-6 (WMD: - 0.0 pg/ml; 95% CI: - 0.13, 0.12; P = 0.952; I 2 = 0.0%) respectively **(**Supplementary Fig. 1**)**. But our analysis of serum CRP and TNF-α **(**Supplementary Fig. 2**)** indicated that TC could significantly reduce serum CRP (WMD: - 0.39 mg/l; 95% CI: - 0.74, - 0.05; P = 0.024; I 2 = 10.7%) and TNF-α concentration (WMD: - 0.14 pg/ml; 95% CI: - 0.27, - 0.02; P = 0.026; I 2 = 20.0%).

Results for subgroup analysis indicate no significant effect of subgroups on the correlation of TC consumption and CRP, hs-CRP. IL-6 and TNF-α (P > 0.1); therefore, there is no known source of heterogeneity. It's noticeable that studies with good quality, mean age ≥50, or combined exercise with TC consumption significantly reduce serum CRP (P < 0.05). In addition, studies with mean age ≥50 that didn't include training in their intervention, indicates a significant reduction in TNF-α.

3.3.3. Dose-response analysis of the effect of tart cherry consumption on inflammatory biomarkers

Linear dose-response analysis shows that with each 5-, 20-, 30-, and 100-ml elevation in TC consumption, serum CRP significantly (P = 0.035) reduces by 0.03, 0.13, 0.19, and 0.64 mg/l, respectively **(**Fig. 3a–d**)**. But we did not observe such an effect on blood pressure or other inflammatory risk factors.

3.3.4. Risk of bias assessment

As shown in Table 2, we use the Cochrane tool [24] to assess study quality and risk of bias for included trials. According to this method, we considered study quality in 7 domains: Random Sequence Generation, Allocation concealment, Blinding of Participants and personnel, Blinding of Outcome assessment, Incomplete outcome data, Selective outcome reporting, and other sources of bias, and then we reported the overall quality. From all included studies, just one trial has missing data [50], and therefore, there are eight studies of Good quality [34,35,37,39,43,44,46,47], eight studies of Poor quality [36,38,40,49–51,53,54], and five studies with Fair rate [41,42,45,48,55].

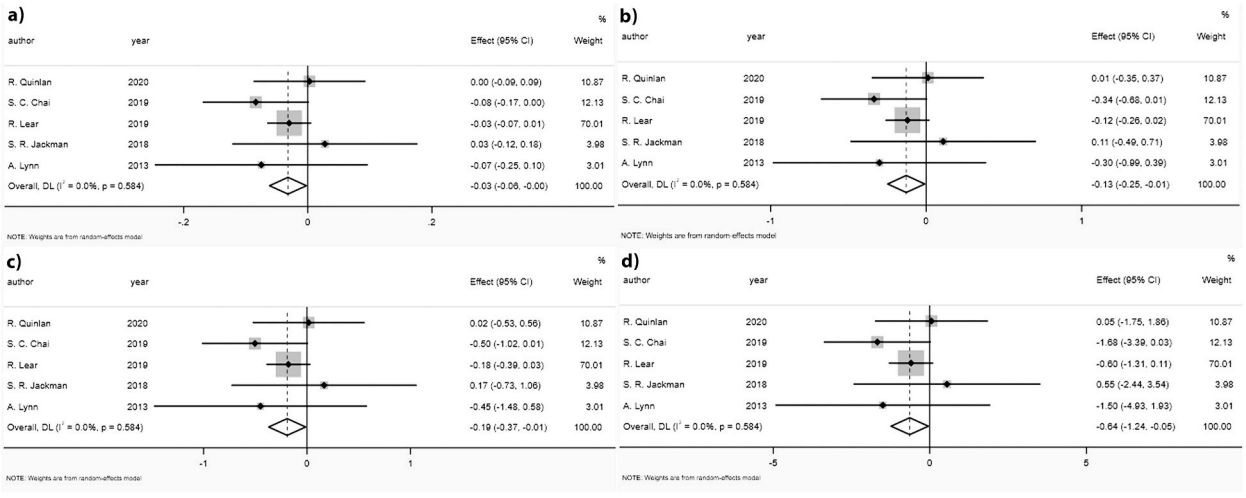

Fig. 3. Forest plots investigating the linear dose-response relationship with each (a) 5 ml, (b) 20 ml, (c) 30 ml, and (d) 100 ml elevation in the received dose.

Table 2
Risk of bias assessment.

Author; Year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of exposure	Bias due to departures from intended exposures	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Jonathan Sinclair et al. (2022)	L	L	H	L	L	L	L	FAIR
Rachel Kimble et al. (2021)	L	L	L	L	L	L	L	GOOD
Rachel Kimble et al. (2021) (Cardiometabolic)	L	L	L	L	L	L	L	GOOD
Terun Desai et al. (2020)	U	L	H	H	L	L	L	POOR
Lisa K. Stamp et al. (2020)	U	U	U	U	L	L	U	POOR
Sarah A. Johnson et al. (2020)	L	L	L	L	L	L	L	GOOD
Quinlan et al. (2020)	U	L	H	U	L	L	U	POOR
Keith R Martin et al. (2019)	L	L	L	L	L	L	L	GOOD
Zainie Aboo Bakkar et al. (2019)	L	L	L	L	L	L	L	GOOD
Meghan A. Brown et al. (2019)	L	L	L	L	L	L	L	GOOD
Sheau C. Chai et al. (2019)	L	L	L	L	L	L	L	GOOD
Rebecca Lear et al. (2019)	U	L	L	L	H	L	L	POOR
Terun Desai et al. (2018)	U	L	H	H	L	L	L	POOR
Sheau C. Chai et al. (2018)	L	L	L	L	L	L	L	GOOD
Sarah R. Jackman et al. (2018)	U	L	L	L	L	L	L	FAIR
Phillip G. Bell et al. (2016)	U	L	L	L	L	L	L	POOR
Kyle Levers et al. (2016)	U	L	L	L	L	L	L	FAIR
Kyle Levers et al. (2015)	U	L	L	L	L	L	L	FAIR
Anthony Lynn et al. (2014)	U	L	H	H	L	L	H	POOR
Anthony Lynn et al. (2013)	U	L	H	H	L	L	H	POOR
A. E. Sleigh et al. (2012)	U	L	L	L	L	L	L	FAIR

All parameters were assessed for their risk by using a scale that classifies them as low, moderate, serious, or critical.
Abbreviations: L, Low**; H,** High**; U,** Unclear.

3.3.5. Influence analysis

Supplementary Tables 3–9 represent the overall effect of TC by omitting the impact of every single study. The influence analysis did not significantly impact studies investigating SBP, HR, CRP, hs-CRP, and IL-6. In all the included studies, IL-6 has minor changes due to TC consumption. But by removing the influence of a single study (49), DBP rises (WMD: 2.05 mmHg; 95% CI: 0.60, 2.50). Also, after omitting the influence of a single study (50), a significant reduction in TNF-α turns to positive and insignificant values (WMD: 0.04 pg/ml; 95% CI: −0.19, 0.27).

3.3.6. Publication bias assessment

Evaluation of publication bias by visual inspection of the funnel plot **(**Supplementary Figs. 3 and 4**)** and Egger's test demonstrated no evidence for publication bias in the meta-analysis of TC consumption on SBP (P = 0.231), DBP (P = 0.727), HR (P = 0.069), CRP (P = 0.300), hs-CRP (P = 0.968), IL-6 (P = 0.991) and TNF-α (P = 0.147) levels. Therefore, there are no unpublished studies since lack of significance, etc.

3.3.7. Grading the evidence

Table 3 and Supplementary Table 10 present the GRADE tool for assessing the certainty of the evidence. The certainty of the evidence was in the range of very low to moderate. None of the outcomes didn't reach the threshold of minimal clinically important differences (MCID), so they were downgraded by imprecision at least for one reason. Dose-response correlation upgraded the certainty of CRP to moderate. Except for low certainty of SBP, certainty for the other outcomes was reported as very low due to insignificant results, low or fair-quality studies, and using different types of TC or combining it with other substances.

4. Discussion

Based on the result of 21 RCTs, including 538 individuals, TC has no impact on blood pressure and heart rate. In contrast, TC significantly decreases inflammation by reducing CRP and TNF-α, and this anti-inflammatory property has a linear relationship with the received dose. With each 30 ml elevation in dosage, CRP reduces by 0.19 mg/l. Since the dominant form of Tart cherry consumption in the dose-response analysis is a 60 ml concentrate per day, it seems that 90 ml concentrate has a potential active ingredient to alter CRP up to MCID (0.5 mg/l). Our findings are generally consistent with previous meta-analyses in this field [22,56], but notable differences exist.

Since implementing exercise alongside TC consumption failed to yield sound effects, discussing the differences between these studies is helpful. Most studies in this area have focused on endurance exercises, which lead to high energy turnover and extraordinary muscle actions, subsequently leading to inflammation following exercise [57–60]. The anti-inflammatory properties of TC used in the studies were not sufficient to control exercise-induced inflammation. Nevertheless, consideration should be given to the short duration and small population of studies included in the analysis.

In addition to the small number of included RCTs, no significant results about hs-CRP are because the benefits of TC can be realized when there is an imbalance in cardio-metabolic function [49,61,62]. Notably, almost half of the included studies implement TC in healthy participants whose baseline mean values of BP, HR, and inflammatory biomarkers are within normal ranges, so any alterations are neutralized by the body's homeostatic system.

In this context, TC is a rich source of anthocyanins, such as aglycon cyanidin [63,64]. The anti-inflammatory properties of aglycon cyanidin are similar to those of NSAIDs like naproxen [65]. Although the overall mechanism of its anti-inflammatory impact is not fully understood, explanations are: 1) limiting the formation of advanced glycation end products (AGEs) [66], 2) inhibition of nuclear factor-κ B (NF-κB) [67], 3) reducing ROS synthesis [68], 4) raise in expression and activity of endogenous antioxidant enzymes like glutathione peroxidase and superoxide dismutase [69], 5) decrease cyclooxygenase activities [64], 6) scavenging of nitric oxide radicals [70], 7) lowering monocyte chemoattractant protein 1 (MCP-1), that involved in the shift of macrophages and lymphocytes to inflammation sites like adipose tissue [71], 8) tryptophan and melatonin content of TC, in addition to improvements in sleep quality, they can act as an antioxidant and antiatherogenic agent [72–74].

The included studies showed no significant alteration in SBP following TC supplementation. But SBP was reduced when TC was implemented in the average BMI population. Of note, three studies show a significant alteration in DBP. Two of these [34,45] report a significant elevation in DBP, which are fair or good quality and works on overweight individuals. Another study that demonstrates a

Table 3
Summary of the effect of tart cherry on blood pressure and inflammatory biomarkers.

outcome	Participants (trials)	Mean difference (95% CI)	GRADE
SBP, mmHg	330 (9)	0.34 (−1.24 to 1.92)	Low
DBP, mmHg	330 (9)	1.36 (−0.87 to 3.60)	Very low
HR, beats/min	209 (7)	−2.31 (−5.15 to 0.53)	Very low
CRP, mg/l	181 (7)	−0.39 (−0.74 to −0.05)	Moderate
hs-CRP, mg/l	139 (4)	−0.14 (−0.34 to 0.07)	Very low
IL-6, pg/ml	142 (6)	−0.00 (−0.13 to 0.12)	Very low
TNF-α, pg/ml	137 (5)	−0.14 (−0.27 to −0.02)	Very low

Abbreviations: SBP, Systolic Blood Pressure; **DBP,** Diastolic Blood Pressure**; HR,** Heart Rate**; CRP,** C-reactive Protein**; hs-CRP,** High-sensitive C-reactive Protein**; IL-6**, Interleukin 6**; TNF-α,** Tumor necrosis factor-alpha.

significant reduction in DBP, is poor quality, which works on healthy individuals [54]. These results may indicate that TC, can decrease blood pressure, but not to the extent effective in people with metabolic dysregulation like obese or metabolic syndrome individuals.

By the way, we observed an elevation in DBP due to influence analysis. Since this elevation reaches MCID, our conclusion is that usage of TC has no benefit in reducing blood pressure, especially on DBP. Also, due to this property, it would be interesting for future studies to use it in the context of a need for elevating DBP. Pulse pressure which is a better predictor of CVD risk than SBP raising alone calculates by subtracting SBP-DBP [75]. By increasing the age after 60, SBP still increases, but DBP turns to fall and subsequently increases pulse pressure [75]. If TC increases diastolic blood pressure in the elderly population, it may reduce pulse pressure, which may, in turn, reduce the risk of cardiovascular disease.

In addition, only one study [55] reported significant reductions in CRP and TNF- α levels. This research studied women suffering from osteoarthritis; unlike most studies, they chose TC juice rather than TC concentrate. Furthermore, only a single study (32) using TC juice showed a statistically significant decrease in HR. In this context, the processing may adversely affect TC active ingredients.

It has been suggested that polyphenolic compounds in TC may lower blood pressure due to their effects on nitric oxide synthesis and the relaxation of blood vessels [76]. Additionally, anthocyanin metabolites, such as protocatechuic acid and vanillic acid, modulate the smooth vascular muscle cells essential for normal vascular tone [15,77,78]. But, to observe these actions, a sufficient concentration of the TC anthocyanin content is necessary, which depends on the type of culture, storage, and TC processing methods. In addition, intestinal microflora can affect the polyphenol's bioavailability since good microflora in healthy individuals. It leads to higher bioavailability. Therefore, no reasonable reduction in blood pressure is possibly due to poor culture, storage, and processing methods or even the presence of disturbed intestinal microflora in participants [79,80].

The high-quality studies did not observe any significant correlation. The main reason for poor quality is a lack of blinding. As a result of the grading of evidence, the most common factors are the absence of significant results, and the final effect was lower than the MCID. With this in mind, TC has a statistical effect on inflammation, but correcting the factors that caused the poor quality of evidence is necessary for clinical application.

The strength points of our research are 1) comprehensive searching, 2) specific investigation of TC effects, 3) dose-response analysis, 4) statement of the evidence certainty, and 5) providing a perspective for future studies. Also, our work has limitations like 1) a limited number of RCTs, 2) studies with small sample sizes or combining exercise with TC 3) studies working on a healthy population, 4) different types of TC used in studies like capsules, juice or concentrate 5) existence of heterogeneity in most subgroups. As a result, future studies should eliminate these limitations as much as possible.

Several limitations of this study require caution when interpreting the findings. Also, they provide a point of view for future studies. There is a suggestion to perform high-quality studies with a larger sample size and longer duration (more than a month). Since most of these studies were conducted in the UK and USA, it is encouraged to carry out further research in the different population groups. Meanwhile, as a source of anthocyanins and anti-inflammatory agents, several effects can be considered for tart cherries on blood sugar, lipid profile, inflammation, and sleep quality. Therefore, its application for depression, sleep disorder, or metabolic syndrome may be a question of future studies.

In addition, two ways of consumption of TC are proposed: first, juice concentrate-the most common type - which implements in diet, and its dosage, calorie, polyphenol content, and duration of supplementation should consider. Second, that seems a point of view for future studies is to use TC active ingredient extracts or combine them with consonant substances for a synergistic effect. Specifically, the quantity, bioavailability, serum, urinary metabolites of TC active ingredients, and participant compliance, play a role in the study's outcome. In any case, future studies should eliminate the effects of other factors that affect the disease, such as diet, drug usage, and disease stage. Of note, because of the different nutritional requirements, it is recommended to personalize the received dose according to the individual needs (e.g., ml/kg/day).

In conclusion, the tart cherry has a low-grade anti-inflammatory activity which has a linear relationship with the received dose and establishes its efficacy in its size. The value of this effect depends on its regular use in the diet. In other words, the anti-inflammatory properties of tart cherry are preventive rather than therapeutic. Although TC didn't affect blood pressure and heart rate, due to influence analysis, it can raise DBP to MCID. There is a possibility that should use TC, cautiously in people suffering from hypertension. Also, this provides insight for future studies, in which we should investigate this property in the context of elevated blood pressure. In conclusion, tart cherries are beneficial when eaten as part of a varied diet, with proper processing, adjusted dose, and active ingredients recommended in the background as a source of antioxidants.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon a reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19987.

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