Dose-Dependent Effect of Tart Cherry on Selected Cardiometabolic Risk Factors: A GRADE-Assessed Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials

Article · May 2024

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Dose-dependent effect of tart cherry on selected cardiometabolic risk factors: A GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials ☆

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ARTICLE INFO

Keywords:
Tart cherry
Cardiometabolic risk factors
Metabolic syndrome
Natural product
Meta-analysis
Dose-response

ABSTRACT

Aims: This study aimed to clarify the effectiveness of tart cherries on anthropometric, lipid, and glycemic indices. We also aimed to clarify the appropriate dosage for this effect and suggest directions for future studies.
Methods: PubMed, Scopus, and Web of Science were searched until May 2022. Twelve eligible trials were included. The pooled results were reported as weighted mean differences (WMD) and 95 % confidence intervals (CIs). The Cochrane risk of bias and GRADE tools were used to assess the risk of bias and certainty of the evidence, respectively.
Results: Tart cherry generally showed no significant effects on cardiometabolic risk factors. But subgroup analysis revealed that tart cherry significantly lowered total cholesterol (WMD: − 0.33 mmol/l; 95 % CI: − 0.55, − 0.10), triglyceride (WMD: − 0.19 mmol/l; 95 % CI: − 0.26, − 0.12), and low-density lipoprotein cholesterol (WMD: − 0.36 mmol/l; 95 % CI: − 0.58, − 0.14), in unhealthy populations. Additionally, subgroup analysis indicated that the favorable effects of tart cherry were more pronounced in a single dose, longer duration, elderly, and obese individuals. Dose-response analysis revealed that 20 ml concentrate has the greatest effect in reducing total cholesterol (WMD: − 0.40 mmol/l; 95 % CI: − 0.61, − 0.19), triglyceride (WMD: − 0.23 mmol/l; 95 % CI: − 0.33, − 0.13), and elevating high-density lipoprotein cholesterol (WMD: 0.20 mmol/l; 95 % CI: 0.17, 0.22).
Conclusions: Tart cherry supplementation did not have significant effects on anthropometric and glycemic indices, but can improve lipid profile, especially in a single dose, longer duration, and in elderly, obese, and unhealthy individuals.

1. Introduction

Cardiovascular diseases (CVDs) stand as the primary cause of mortality globally [1]. Recently, the prevalence of CVDs has doubled, and by 2030, the CVDs associated costs are expected to reach 1208 billion dollars [1,2]. CVDs are primarily linked to modifiable risk factors like obesity, dyslipidemia, and hyperglycemia [3], emphasizing the requirement for effective management strategies.

Since dietary interventions are safe, affordable, and simple to incorporate into an individual's lifestyle, they provide a promising approach to treating the risk factors associated with CVDs [4,5]. Incorporating fruits and vegetables into individuals' diets is crucial to achieve the dietary balance which is inversely associated with the risk of CVDs incidence and overall mortality [6 – 8]. The bioactive compounds present in fruits and vegetables, such as anthocyanins, play a pivotal role to confer these health benefits. Furthermore, tart cherry (TCH) has gained attention as a prominent source of these active compounds [9, 10].

TCH (*Prunus cerasus* L.) is an abundant source of anthocyanins, flavonols, chlorogenic acid, and melatonin [11]. Also, TCH is superior to sweet cherries in terms of vitamin A content and essential amino acid composition [12]. TCH has a relatively low-calorie content and its

☆ Systematic review registered with PROSPERO, registration number CRD42022334346 (http://www.crd.york.ac.uk/PROSPERO).

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https://doi.org/10.1016/j.dsx.2024.103026
Received 4 May 2023; Received in revised form 28 April 2024; Accepted 30 April 2024
Available online 8 May 2024

ability to inhibit nuclear factor kappa B (*NF-κB*) confers antioxidant properties [13 – 16]. Additionally, apart from enhancing the intestinal microbiome, TCH exhibits superior efficacy to prevent lipid peroxidation compared to other antioxidants [17 – 19]. The consumption of TCH can modulate peroxisome proliferator-activated receptors (*PPARs*), thereby influencing energy metabolism and cardiometabolic factors [9, 10,20,21].

Currently, there is a controversy regarding the effectiveness of TCH in previous trials [22 – 33]. Several studies have shown that TCH supplementation may improve lipid and glycemic profiles [31,34,35], whereas other investigations have shown no significant effect [29,30, 32]. Moreover, despite notable research efforts [36,37], a clear consensus has yet to emerge, leaving unresolved aspects of the relationship between TCH supplementation and cardiometabolic health including the certainty of evidence and the shape of the association between TCH dosage and CVDs risk factors.

Hence, we conducted the first GRADE-assessed pair-wise and dose-response meta-analysis to examine the effect of TCH supplementation on selected CVDs risk factors. Also, to ensure the reliability of our findings, rigorous measures have been implemented, including influence analysis and comparing the results in different pre-defined subgroups.

2. Materials and methods

The present dose-response meta-analysis has been reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement [38]. The protocol of the systematic review was registered in PROSPERO (CRD42022334346).

2.1. Systematic search

To find potential eligible randomized controlled trials (RCTs) for inclusion, we searched PubMed, Scopus, and ISI Web of Science up to May 2022. We supplemented the database search by manually reviewing the reference lists of all existing related reviews. The search in the databases and reference lists was restricted to articles published in English. The complete search strategy is described in Supplementary Table 1. Teams of two reviewers independently screened titles and abstracts according to the pre-defined inclusion and exclusion criteria to identify potentially eligible trials.

2.2. Eligibility criteria

We applied the PICOS (population, intervention, comparator, outcome, and study design) framework to define 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 TCH on the anthropometric measures (body weight (BW), body mass index (BMI), fat mass (FM), fat free mass (FFM), and waist circumference (WC)); glycemic indices (fasting blood glucose (FBG), serum insulin (INS) and homeostatic model assessment of insulin resistance (HOMA-IR)), and lipid profile (total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and TC to HDL-C ratio); 3) Compared the effect of different doses (ml/d) of TCH on anthropometric measures, glycemic indices or lipid profile against a placebo; 4) Considered the change in anthropometric measures, glycemic indices or lipid profile as the primary or one of the secondary outcomes; 5) Provided mean and standard deviation (SD) of change in anthropometric measures, glycemic indices or lipid profile across study arms or reported sufficient information to estimate those values; and 6) Reported the number of participants in each study arm. Trials with non-randomized design, quasi-experimental studies, and trials conducted in adolescents (under 18 years of age), and pregnant and lactating women were excluded.

2.3. Data extraction

Two reviewers (MN-Z and MH-R) independently and in duplicate, screened the full texts of eligible trials and extracted the following data: author and year of publication, population location, study design, study duration, characteristics of the population (baseline mean age, mean BMI, and health status), total sample size, intervention characteristics (type and dose of TCH), comparison groups, outcome measures and main results of the included outcomes.

2.4. Risk of bias assessment

Two reviewers (MN-Z and MH-R) independently and in duplicate, performed the risk of bias assessments using the Cochrane risk of bias tool [39]. An overall quality score was given to the trials based on bias domains: good (≤1 items were unclear and none were high), fair (≤2 items were unclear or at least one high), and high risk of bias (≥2 items were high). Disagreements regarding the risk of bias assessment were resolved by discussion.

2.5. Statistical analysis

We considered weighted mean difference (WMD) and 95 % confidence interval (CI) of change as the effect size for reporting the results of the present study. First, we calculated changes from baseline measures in each study arm. In the absence of mean values and SDs of changes, we computed them using data from measurements taken both before and subsequent to the intervention, in adherence to the procedures outlined in the Cochrane Handbook [40]. When standard error (SE) instead of SD was reported, the former was converted to SD [41]. If the studies reported medians and interquartile ranges, we used the median to impute the missing mean and calculated SDs by dividing interquartile ranges by 1.35 [41]. If none of these options were available, we imputed the missing SDs using pooled SDs obtained from other trials included in our meta-analysis [42]. Second, we used the one-stage approach introduced by Crippa and Orsini et al. [43] to calculate the mean difference and its corresponding SD of the change in studied outcomes for different TCH dosages in the intervention group relative to the control group in each trial. This method requires a dose (ml/d) of TCH, the mean, and its corresponding SD of the change in anthropometric measures, glycemic indices and lipid profile, and the number of participants in each arm. Random-effect models were employed to pool trial-specific outcomes [44]. We performed a series of pre-defined subgroup analyses based on health status (healthy vs. unhealthy which includes individuals with an underlying health condition), mean BMI (<30 vs ≥ 30 kg/m^2), the type of intervention (concentrate vs juice), number of prescriptions in a day (once vs twice), follow-up duration (≤4 vs > 4 weeks), study population (<40 vs ≥ 40 persons), mean age (<50 vs ≥ 50 years), weight category (normal weight vs overweight vs obese) and the risk of bias assessment (good vs fair vs poor). Influence analysis was carried out to test the potential impact of each trial on the pooled effect size. The potential for publication bias was tested using Egger's test [45], Begg's test [46], and by inspection of funnel plots. We assessed heterogeneity quantitatively using I^2 statistics and performed a χ^2 test for homogeneity (P-heterogeneity> 0.10) [47]. Finally, we performed a one-stage weighted mixed effects meta-analysis to clarify the shape of the effect of different doses of TCH on anthropometric measures, glycemic indices, and lipid profiles [43]. Nonlinear dose-response associations were assessed with restricted cubic splines with 3 knots at Harrell's recommended centiles (10 %, 50 %, and 90 %) [43,48]. The significance of the Wald test determined that a non-linear model was the best fit. STATA syntax that was used for the analyses is provided in Supplementary Method 1. Statistical analyses were conducted using STATA software version 16.1. A two-tailed P

value of less than 0.05 was considered significant.

2.6. Grading the evidence

We used the GRADE tool to evaluate the overall certitude of the evidence (CoE) for each outcome [49]. 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 downgrading of the evidence, however, large effect size and dose-response gradient are responsible for upgrading the certainty of the evidence. Also, there is a point to evaluate the imprecision, we used as the recently reported minimal clinically important difference (MCID) threshold for anthropometrics measures, lipid profile, and glycemic indices to rate it. The MCID for BW (4.5 kg), BMI (0.95 kg/m^2), WC (2 cm), LDL-C (0.10 mmol/l), HDL-C (0.10 mmol/l), TG (0.09 mmol/l), TC (0.26 mmol/l), FBG (1.6 mmol/L), HOMA-IR (0.05), INS (5 pmol/l), was set [50 – 52]. In the case of lack of MCID in the literature, half of baseline SD values were considered as MCID [53].

3. Results

3.1. Study selection

The flow diagram for study selection is presented in Fig. 1. Initially, a total of 1341 records were retrieved. After eliminating duplicates, 856 records remained for screening, which was conducted based on the title and abstract reviewing. Subsequently, if required, the full-length article underwent further review. Finally, twelve articles [22 – 33] were included, and the rest were excluded because of the following reasons: 1) Irrelevant; 2) Reviews and experimental studies; 3) Studies excluded due to lack of quality.

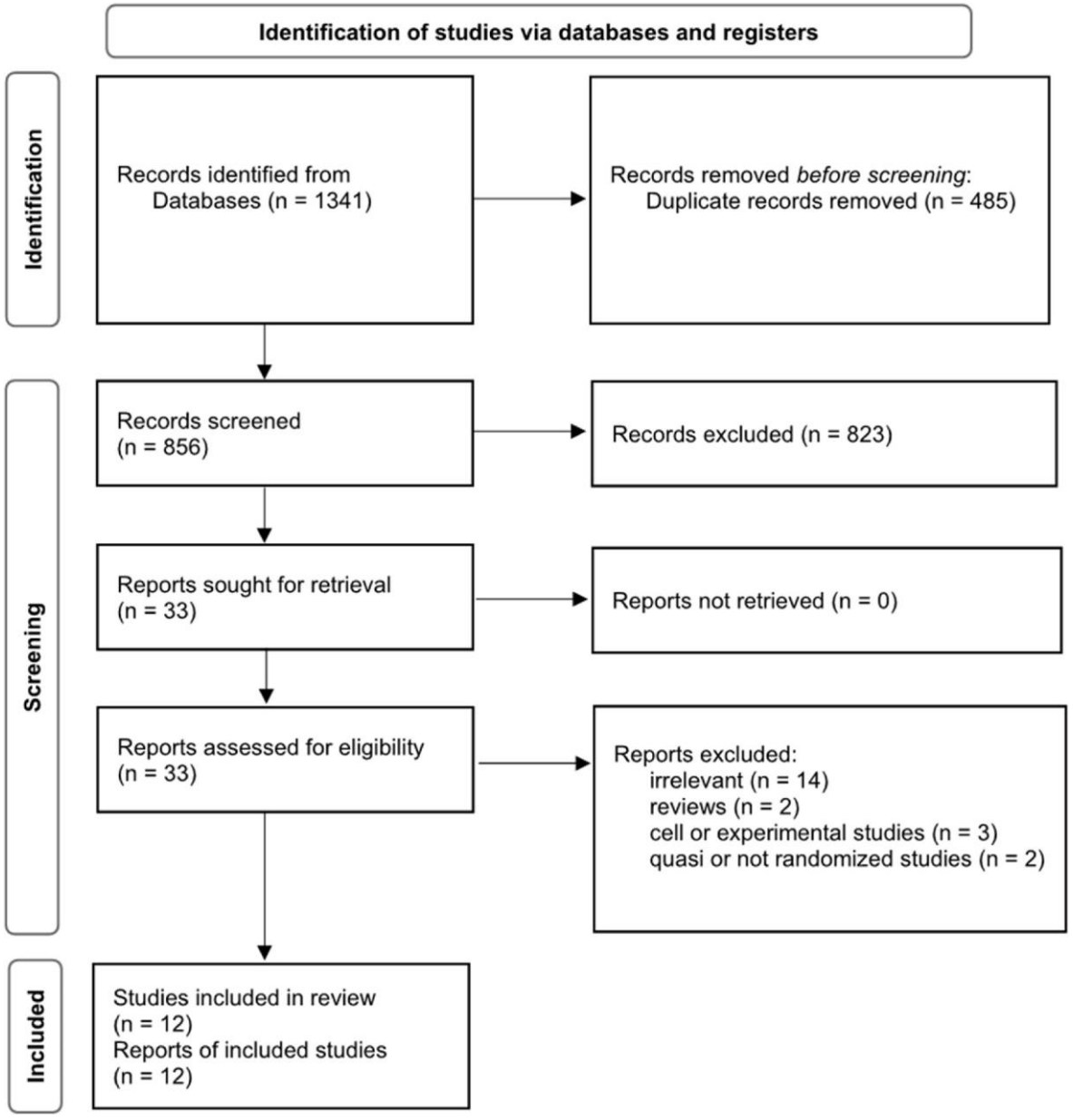

Fig. 1. The PRISMA flow diagram for literature search and study selection.

3.2. Study characteristics

The main characteristics of the included RCTs are summarized in Table 1. The majority of the included studies were conducted in either the United Kingdom (UK) or the United States of America (USA), with only one study originating from New Zealand [25]. Among the included studies, nine studies [22 – 26,28,31 – 33] utilized a parallel design, while three studies [30,32,33] employed a crossover design [27,29,30]. The target group of included studies encompasses both healthy [22,23,28, 29,31,32] and unhealthy [24 – 27,30] individuals. Except for the study by Stamp et al. [28], which exclusively focused on male individuals with gout, all studies included both sexes. The total sample size across the studies ranged from 10 to 56 participants, while the duration of the studies varied from one week [27] to 13 weeks [26]. The baseline mean age of the participants in the studies ranged from 30 to 69.75 years, while the mean BMI varied from 24.05 to 33.9 kg/m^2. Various TCH dosages, ranging from 130 to 596 ml per day, and different varieties (including concentrate, juice, or capsules) were administered. Notably, only one study incorporated exercise [29], while none of the studies implemented calorie restriction as part of the intervention.

3.3. Meta-analysis

3.3.1. Effect of TCH on anthropometric indices

The effect of TCH on anthropometric indices is presented in Table 2 and Supplementary Fig. 1. Our meta-analysis revealed no significant alteration in BW (WMD: 0.31 kg; 95%CI: 1.75, 1.13; I^2 = 0.0 %), BMI (WMD: 0.15 kg/m^2; 95%CI: 0.60, 0.29; I^2 = 0.0 %), FM (WMD: 0.11 kg; 95%CI: 1.32, 1.53; I^2 = 0.0 %), FFM (WMD: 0.03 kg; 95%CI: 2.54, 2.47; I^2 = 0.0 %), and WC (WMD: 0.03 cm; 95%CI: 1.71, 1.76; I^2 = 9.2 %).

3.3.2. Effect of TCH on glycaemic indices

As indicated in Table 2 and Supplementary Fig. 2, TCH supplementation had no significant impact on FBG (WMD: 0.04 mmol/l; 95%CI: 0.08, 0.17; I^2 = 39.2 %), INS (WMD: 0.20 pmol/l; 95%CI: 3.92, 4.32; I^2 = 47.0 %) and HOMA-IR (WMD: 0.16; 95%CI: 0.14, 0.47; I^2 = 61.8 %).

Table 1
The main characteristics of the included studies.

Author [Ref.]	Location	RCT design	Health status	Gender	Sample size	Duration (week)	Mean age (year)	Baseline BMI (kg/m^2)	Intervention		Outcome
									Treatment group	Control group	
Sinclair et al. [22]	UK	Parallel, Three-arm	Adults between 18 and 65 years	Both	45	3	34	28	60 ml concentrate/day (in two equal doses)	Placebo	BW, BMI, FM, WC, TC, TG, LDL-C, HDL-C, TC/HDL-C, FBG
Kimble et al. [23]	UK	Parallel	Middle-aged adults	Both	56	13	48	27.6	60 ml concentrate/day (in two equal doses)	Placebo	BW, BMI, FM, FFM, TC, TG, LDL-C, HDL-C, TC/HDL-C, FBG, INS, HOMA-IR
Desai et al. [24]	UK	Parallel	Individuals with metabolic syndrome	Both	12	1	50	31	30 ml concentrate/day	Placebo	TC, TG, LDL-C, HDL-C, FBG, INS
Stamp et al. [25]	New Zealand	Parallel	Individuals with gout	Male	50	4	58.65	30	60 ml concentrate/day (in two equal doses)	Placebo	BW, BMI
Johnson et al. [26]	USA	Parallel, Single-blind	Individuals with metabolic syndrome	Both	26	12	36.75	33.9	480 ml juice/day (in two equal doses)	Placebo	BW, BMI, FM, WC, TG, LDL-C, HDL-C, FBG, INS, HOMA-IR
Martin et al. [27]	USA	Crossover	Overweight and obese participants	Both	36	4	41	31.3	40 ml concentrate/day	Placebo	BW, BMI, FM, WC, TC, TG, LDL-C, HDL-C, TC/HDL-C, FBG, INS, HOMA-IR
Lear et al. [28]	UK	Parallel	Untrained and non-obese adults	Both	28	4	51.05	24.95	60 ml concentrate/day (in two equal doses)	Placebo	HOMA-IR
Desai et al. [29]	UK	Crossover, Single-blind	Healthy participants	Both	11	4	30	24.43	60 ml concentrate/day (in two equal doses)	Placebo	BW, BMI, FM, FFM, FFM, WC, TC, TG, LDL-C, TC/HDL-C, FBG
Martin et al. [30]	USA	Crossover	Obese subjects	Both	10	4	38.1	32.2	240 ml juice/day	Placebo	BW, BMI, FM, FFM
Chai et al. [31]	USA	Parallel	Older adults	Both	37	12	69.75	27.9	68 ml concentrate/day (in two equal doses)	Placebo	BW, BMI, FFM, TC, TG, LDL-C, HDL-C, FBG, INS, HOMA-IR
Lynn et al. [32]	UK	Parallel	Healthy adults	Both	46	6	37.75	24.05	30 ml concentrate/day	Placebo	TC
Lynn et al. [33]	UK	Parallel	Healthy adults	Both	46	6	37.75	24.05	30 ml concentrate/day	Placebo	TG, LDL-C, HDL-C

Abbreviations: BW, Body Weight; BMI, Body Mass Index; FM, Fat Mass; FFM, Fat-Free Mass; WC, Waist Circumference; TC, Total Cholesterol; TG, Triglyceride; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein ratio; FBG, Fasting Blood Glucose; INS, Serum Insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; Ref, Reference; RCT, Randomized Controlled Trial.

Table 2
Pairwise analysis for the effect of tart cherry on selected cardiometabolic risk factors.

Outcome	Participants (trials)	Mean difference (95 % CI)	GRADE
TC to HDL-C ratio	148 (4)	0.12 (0.04 – 0.20)	Moderate
BW, kg	271 (8)	−0.31 (−1.75 to 1.13)	Low
BMI, kg/m^2	271 (8)	−0.15 (−0.6 to 0.29)	Low
FM, kg	184 (6)	0.11 (−1.32 to 1.53)	Low
FBG, mmol/l	204 (7)	0.04 (−0.08 to 0.17)	Low
INS, pmol/l	167 (5)	0.20 (−3.92 to 4.32)	Low
FFM, kg	113 (4)	−0.03 (−2.54 to 2.47)	Very low
WC, cm	118 (4)	0.03 (−1.71 to 1.76)	Very low
TC, mmol/l	244 (7)	−0.18 (−0.49 to 0.14)	Very low
TG, mmol/l	269 (8)	−0.12 (−0.27 to 0.03)	Very low
LDL-C, mmol/l	269 (8)	−0.17 (−0.49 to 0.15)	Very low
HDL-C, mmol/l	258 (7)	0.02 (−0.06 to 0.11)	Very low
HOMA-IR	183 (5)	0.16 (−0.14 to 0.47)	Very low

Abbreviations: BW, Body Weight; BMI, Body Mass Index; FM, Fat Mass; FFM, Fat-Free Mass; WC, Waist Circumference; TC, Total Cholesterol; TG, Triglyceride; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein ratio; FBG, Fasting Blood Glucose; INS, Serum Insulin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; CI, Confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

3.3.3. *Effect of TCH on lipid profile*

The effect of TCH supplementation on lipid profile is presented in Table 2 and Supplementary Fig. 3. Accordingly, TCH supplementation had no significant impact on TC (WMD: 0.18 mmol/l; 95%CI: 0.49, 0.14; I^2 = 90.9 %), TG (WMD: 0.12 mmol/l; 95%CI: 0.27, 0.03; I^2 = 91.6 %), LDL-C (WMD: 0.17 mmol/l; 95%CI: 0.49, 0.15; I^2 = 90.2 %), HDL-C (WMD: 0.02 mmol/l; 95%CI: 0.06, 0.11; I^2 = 93.8 %). However, we observe a significant elevation in TC/HDL ratio following a TCH supplementation (WMD: 0.12; 95%CI: 0.04, 0.20; I^2 = 0.0 %).

3.3.4. *Subgroup analysis*

According to the findings outlined in Supplementary Table 2, health status, study population, mean age, mean BMI, study duration, risk of bias, number of TCH prescriptions per day, and participant's weight category were identified as sources of heterogeneity across all studied outcomes ($P < 0.05$). In line with the results of pairwise analysis, subgroup analysis also failed to demonstrate a significant impact of TCH supplementation on anthropometric indices across the studied subgroups. However, in studies involving unhealthy participants, individuals with a mean age younger than 50, a mean BMI of 30 kg/m^2 or higher, and a study duration exceeding 4 weeks, TCH supplementation resulted in a significant increase in HOMA-IR ($P < 0.05$).

Furthermore, the subgroup analysis revealed that supplementation with TCH had more favorable effects on the lipid profile in studies focusing on unhealthy, obese, and elderly individuals. Additionally,

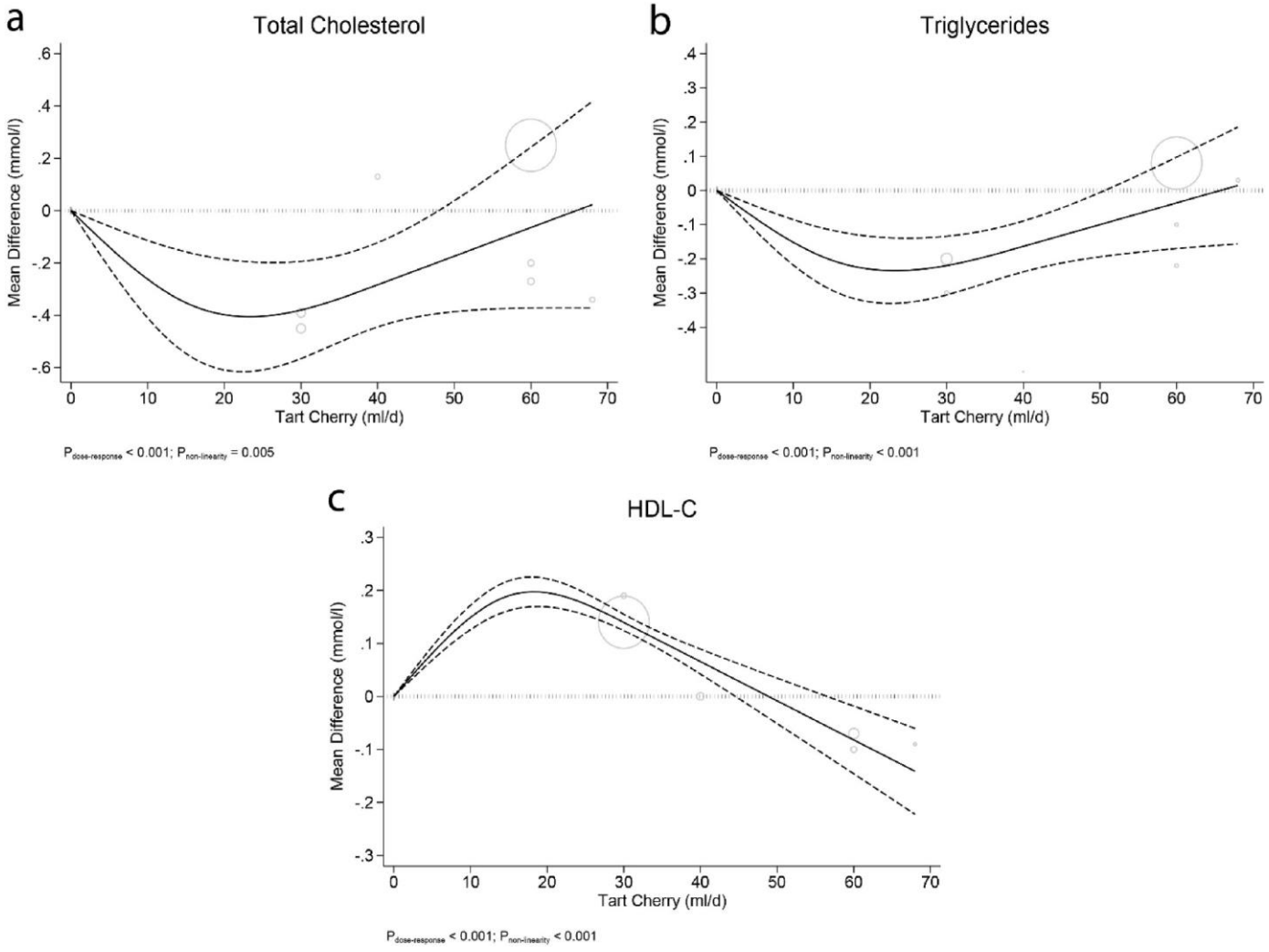

Fig. 2. Dose-response analysis for the effect of tart cherry supplementation on (a) total cholesterol, (b) triglycerides, and (c) high-density lipoprotein cholesterol.

studies with larger sample sizes and longer follow-ups, as well as those prescribing TCH once a day, reported more favorable effects on the lipid profile. Conversely, studies assessed as fair or poor quality indicated that supplementation with TCH led to increases in TC, TG, LDL-C, HDL-C, and the TC to HDL-C ratio.

3.3.5. Dose-response analyses of TCH's supplementation effect on lipid profile

As depicted in Fig. 2, supplementation with TCH at a dosage of 20 ml concentrate per day yielded the most substantial impact on serum TC (WMD: 0.40 mmol/l; 95 % CI: 0.61, −0.19) and TG (WMD: 0.23 mmol/l; 95 % CI: 0.33, −0.13). However, increasing or decreasing the administered dose from 20 ml resulted in diminishing effects, with doses exceeding 60 ml per day eventually leading to null or positive values for these parameters. Also, TCH supplementation at a dose of 20 ml concentrate per day exhibits the most significant impact on serum HDL-C (WMD: 0.20 mmol/l; 95 % CI: 0.17, 0.22). However, variations in the administered dose from 20 ml concentrate per day result in diminishing effects, with doses exceeding 50 ml per day ultimately leading to null or negative values for this parameter.

Additionally, as indicated in Table 3, these changes remain significant up to a dosage of 47 ml and 51 ml of concentrate per day for serum TC and TG, respectively. However, the significance does not apply for HDL-C in the interval of 45 – 56 ml concentrate per day.

3.3.6. Risk of bias assessment

As shown in Table 4, to assess study quality and risk of bias in included trials we used the Cochrane tool [39]. The overall quality of the trials was categorized as follows: five studies [23,26,27,30,31] were of good quality, six studies [24,25,28,29,32,33] were rated as poor, and only one study [22] deemed to have fair quality [25]. Additionally, it was noted that one trial had missing data [31].

3.3.7. Influence analysis

Supplementary Tables 3 – 15 represent the overall effect of TCH by omitting the effect of every single study. While the influence analysis did not reveal a significant effect for studies investigating anthropometric indices, by removing the effect of a study [29], TCH can significantly reduce TC (WMD: 0.31 mmol/l; 95 % CI: 0.45, −0.18), TG (WMD: 0.18 mmol/l; 95 % CI: 0.23, −0.12), and LDL-C (WMD: 0.30 mmol/l; 95 % CI: 0.43, −0.17). Concerning HDL-C, a notable increase was observed across all studies except for one [24]. In contrast to FBG and INS, a noticeable influence was observed for HOMA-IR. With the exclusion of a single study [26], the non-significant elevation in HOMA-IR turns to negative values.

3.3.8. Publication bias

Evaluation of publication bias through visual inspection of funnel plots and Egger's test indicated no evidence for publication bias in the meta-analysis of TCH supplementation on BW (P = 0.694), BMI (P = 0.763), FM (P = 0.979), FFM (P = 0.899), WC (P = 0.614), HDL-C (P = 0.181), TC to HDL-C ratio (P = 0.097), FBG (P = 0.301), INS (P = 0.576) and HOMA-IR (P = 0.686) levels. However, we identified publication bias for serum TC (P = 0.014), LDL-C (P = 0.042), and TG (P = 0.039) levels according to this test, suggesting that smaller, non-significant studies may be missing from the analysis (Supplementary Figs. 4 – 6).

3.3.9. Grading the evidence

Table 4 and Supplementary Table 16 represent the GRADE tool for assessing the CoE. The CoE was in the range of very low to moderate. None of the outcomes didn't reach the threshold of MCID, so they were downgraded by imprecision at least for one reason. The CoE for TC to HDL ratio is moderate and low for BW, BMI, FM, FBG, and INS. The CoE for FFM and WC was very low because, in addition to not receiving the threshold of MCID, the population study didn't surpass the threshold either. Dose-response effect upgraded the CoE for TC, TG, and HDL-C but

Table 3
Non-linear dose-response analysis for the effects of tart cherry on lipid profile[a].

Tart Cherry intake (ml/d)	0 (Ref)	10	20	30	40	47	48	60	70
TC (mmol/l) (95 % CI)	0 (0.00,0.00)	−0.26 (−0.41, −0.11)	−0.40 (−0.61, −0.19)	−0.38 (−0.57, −0.19)	−0.28 (−0.44, −0.12)	−0.21 (−0.40, −0.02)	−0.20 (−0.39, 0.00)	−0.06 (−0.37, 0.24)	0.04 (−0.37, 0.46)
Tart Cherry intake (ml/d)	0 (Ref)	10	20	30	40	51	52	60	70
TG (mmol/l) (95 % CI)	0 (0.00,0.00)	−0.15 (−0.22, −0.09)	−0.23 (−0.33, −0.13)	−0.22 (−0.31, −0.13)	−0.16 (−0.24, −0.09)	−0.09 (−0.19, 0.00)	−0.09 (−0.19, 0.01)	−0.04 (−0.17, 0.10)	0.03 (−0.15, 0.21)
Tart Cherry intake (ml/d)	0 (Ref)	10	26	27	30	40	41	60	70
LDL-C (mmol/l) (95 % CI)	0 (0.00,0.00)	−0.26 (−0.53, 0.01)	−0.39 (−0.78, 0.00)	−0.39 (−0.77, −0.00)	−0.37 (−0.74, −0.01)	−0.27 (−0.55, −0.00)	−0.26 (−0.53, 0.00)	−0.06 (−0.36, 0.25)	0.05 (−0.37, 0.48)
Tart Cherry intake (ml/d)	0 (Ref)	10	30	40	44	45	56	57	70
HDL-C (mmol/l) (95 % CI)	0 (0.00,0.00)	0.15 (0.13, 0.17)	0.14 (0.12, 0.16)	0.07 (0.04, 0.09)	0.04 (0.01, 0.07)	0.03 (−0.00, 0.06)	−0.05 (−0.11, 0.00)	−0.06 (−0.12, −0.00)	−0.16 (−0.24, −0.07)

Abbreviations: Ref, Reference; CI, Confidence interval; TC, Total Cholesterol; TG, Triglyceride; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol.
[a] Data is presented as mean difference (95 % confidence interval).

Table 4
Risk of bias assessment of the included trials using the Cochrane risk of bias tool.

Author [Ref.]	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias	Overall quality
Kimble et al. [23]	L	L	L	L	L	L	L	Good
Johnson et al. [26]	L	L	L	L	L	L	L	Good
Martin et al. [27]	L	L	L	L	L	L	L	Good
Martin et al. [30]	L	L	L	L	L	L	L	Good
Chai et al. [31]	L	L	L	L	L	L	L	Good
Sinclair et al. [22]	L	L	H	L	L	L	L	Fair
Desai et al. [24]	U	L	H	H	L	L	L	Poor
Stamp et al. [25]	U	U	U	U	L	L	U	Poor
Lear et al. [28]	U	L	L	L	H	L	L	Poor
Desai et al. [29]	U	L	H	H	L	L	L	Poor
Lynn et al. [32]	U	L	H	H	L	L	H	Poor
Lynn et al. [33]	U	L	H	H	L	L	H	Poor

Abbreviations: L, Low; H, High; U, Unclear; Ref, Reference.

due to downgrading by imprecision, the conclusion was very low. Also, the CoE for LDL-C and HOMA-IR was very low due to downregulation because of high heterogeneity, non-significant results, and suspected publication bias.

4. Discussion

In general, while the results of pairwise analysis indicated that supplementation with TCH had no significant impact on studied outcomes, further study through influence analysis showed significant reductions in TC, TG, and LDL-C. Moreover, the dose-response analysis revealed a non-linear relationship between TCH dosage and TC, TG, and HDL-C levels. Additionally, subgroup analysis revealed that studies employing TCH for an extended period of time, with a greater number of participants, and in a single dose tended to yield more beneficial results.

Previous studies reported beneficial effects of TCH supplementation on lipid profile [37] and inflammation [54]. Despite mixed findings in a study by Mousavian et al. [37], they reported that TCH may reduce TC levels in the long term. In a dose-response meta-analysis by Norouzzadeh et al. [54], higher TCH dosage showed a linear relationship with lower C-reactive protein levels, Additionally, some studies explored the effects of active ingredients in TCH. A meta-analysis indicated that anthocyanin supplementation may improve lipid profile, especially in studies lasting over 3 months [55].

Based on our findings, a daily dosage of 20 ml of tart cherry concentrate was shown to be the most effective in enhancing the lipid profile. The difference in suggested dosage and the usual prescribed dosage in previous studies (30 – 60 ml concentrate/day) might be in terms of variable active ingredient concentration and participant compliance. Our study showed no significant difference between TCH concentrate and TCH juice in the studied outcomes. Nevertheless, Norouzzadeh et al. [54] found that TCH juice yielded more advantageous outcomes in mitigating inflammation when compared to concentrate. Moreover, polyphenolic content varies between concentrate and juice forms due to cultivation methods, storage conditions, processing techniques, and interactions with other foods [56,57]. Based on the included RCTs, TCH supplements anthocyanin content ranging from 15.6 mg [27] to 640 mg [22]. Additionally, higher doses are typically prescribed twice a day, which may reduce compliance. Eating nutrient-dense foods, like TCH, may increase calorie intake, which can have negative effects if overeating occurs.

By excluding a single-blind poor-quality study [29], which focused on fat oxidation and implemented exercise, TCH was effective in lowering serum lipid levels, including TC, TG, and LDL-C. TCH may improve lipid profile by altering the intestinal microbiome. Five days of TCH juice consumption increased the number of *Firmicutes* isolates, including *Lactobacillus*, *Clostridium*, and *Streptococcus*, in a pilot study [58]. Additionally, anthocyanins and active compounds in TCH were reported to lower cholesterol levels by enhancing HDL-Paraoxonase 1 function [59] and exerting inhibitory effects on plasma cholesterol ester [37], respectively.

Considering TCH supplementation did not significantly affect anthropometric indices and studies did not include calorie restriction, TCH's positive effects on lipid profile seem independent of changes in body weight or fat distribution. Moreover, the favorable effects of TCH supplementation were more pronounced in unhealthy, obese, and elderly individuals. These findings can be interpreted in several ways. First, in healthy individuals, changes may be neutralized by the body's homeostatic system. Second, individuals with underlying health conditions may exhibit greater compliance with study protocols. The underlying mechanism for the better improvement in lipid profiles among obese individuals is not fully understood, but multiple factors may contribute to this effect: 1) Increased *mRNA* expression of *PPARα* and *PPARγ* leads to improved fat oxidation [9,10]; 2) The activation of *PPARγ* coactivator 1-alpha and sirtuin-1 mediated *PPARα* improves skeletal muscle insulin sensitivity [60]; 3) Cholesterol ester transfer

protein inhibition increases cellular cholesterol flow to the serum [61]; 4) Bile acid binding up to 5 % [62].

Mousavian et al. [37] found that TCH supplementation significantly reduced FBG levels (−0.51 mg/dl). They suggested that TCH may regulate the glycemic profile via its long-term impact on insulin release from pancreatic beta cells [37]. However, TCH is unlikely to significantly alter the glycemic profile due to its modest glycemic load. Variations in research methods, participant characteristics, and durations of interventions may account for discrepancies in results. A meta-analysis by Daneshzad et al. [55] on 19 RCTs, suggested that anthocyanin supplementation may reduce HOMA-IR, but did not show significant effects on FBG and INS levels. Therefore, anthocyanin supplementation may affect glycemic profile through long-term weight management [55]. However, our study found no significant effect of TCH on anthropometric indices. Each 480 ml of TCH juice has 34 grams of sugar and provides 181 kilocalories. The average American consumes 209 kilocalories per day from sugar-sweetened beverages [63]. Therefore, TCH juice consumption is unlikely to significantly affect the anthropometric indices. Furthermore, anthropometric measurements were regarded as secondary outcomes in the included studies [30,31] which could have led to an inadequate sample size to identify significant changes in these indices. While some studies have indicated the positive effects of anthocyanins in aiding weight loss, these effects seem to be more pronounced when taken as a supplement or isolated, rather than consumed as part of a fruit with calorie content [64].

The authors suggest more high-quality studies on administering TCH at correct dosages, emphasizing personalizing the dosage (e.g., ml/kg/day). Two approaches to TCH supplementation include consuming it through fruits, juice, or concentrate, and using TCH active ingredient extracts or combinations with compatible supplements which are promising for future studies. Future studies should mitigate the influence of confounding factors such as diet, medication usage, and disease stage on the observed outcomes.

The study's strengths include comprehensive searching, focusing on TCH effects, dose-response analysis, CoE expression, reliability assessment through statistical analysis, and providing a perspective for future studies.

Also, our study faced limitations due to 1) A small number of RCTs, 2) Varied forms of TCH, but we attempted to address them by comparing results across subgroups, 3) Failure of anthocyanin intake measurement from other sources among included studies, 4) Significant publication bias, and 5) Poor quality of half of the included studies.

5. Conclusions

TCH Supplementation did not affect anthropometric and glycemic indices but enhanced lipid profile, particularly with a 20 ml daily dose for over a month. This improvement shows potential for enhancing metabolic health, particularly in elderly, obese, and unhealthy individuals. In conjunction with a healthy diet, individualized dosages and adequate active ingredients in TCH supplements may augment metabolic health benefits. However, caution is advised in terms of low certainty from poor-quality studies, necessitating further high-quality studies for confirmation.

Data availability statement

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

Author contributions

MN conceived the study, carried out the literature search, and wrote the manuscript. MN and MHR carried out data extraction and independent reviewing. MN and MHR assessed the quality of the included studies. MN and HSH performed data analysis and interpretation. STR revised the manuscript. The manuscript has been read and approved by all authors.

Sources of support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial support

None.

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.

Acknowledgments

We appreciate the "Student Research Committee" at Iran University of Medical Sciences for their support of this study. The authors would like to sincerely gratitude Mr. Ali Asghar Norouzzadeh and Miss Fatemeh Niroomand, as well as everyone else who supported the completion of this research project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2024.103026.

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