Original Article

Tart cherry intake and serum uric acid: Meta-analysis of randomized controlled trials and evidence from network pharmacology

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Background and Objectives: Tart cherry products have been proposed to lower serum uric acid and reduce gout risk, but clinical findings are inconsistent. This study evaluated the effect of tart cherry intake on serum uric acid concentration and explored possible mechanisms. **Methods and Study Design:** Randomized controlled trials comparing tart cherry intake with placebo or usual diet and reporting serum uric acid concentration were identified from electronic databases. A random effects meta analysis was used to pool standardized mean differences between groups. In parallel, bioactive compounds in tart cherry were retrieved from public databases, and their potential targets related to serum uric acid and gout were investigated using network based analyses and molecular docking. **Results:** Four randomized trials (eight comparisons; 392 participants) were included. Tart cherry intake was associated with a modest reduction in serum uric acid concentration compared with control (standardized mean difference −0.22; 95% confidence interval −0.43 to −0.01), with substantial heterogeneity. Network and docking analyses suggested that anthocyanins and other polyphenols may act on inflammatory, oxidative stress and metabolic pathways. **Conclusions:** Tart cherry intake may modestly lower serum uric acid concentration, but evidence is limited in quantity and consistency. Larger, rigorously designed randomized trials are needed.

Key Words: tart cherry intake, serum uric acid (sUA), gout, meta-analysis, network pharmacology

INTRODUCTION

Uric acid derives from purine catabolism and may play multiple physiological roles, including functioning as an antioxidant and neuroprotective factor, helping maintain blood pressure under low-salt dietary conditions, and participating in immune regulation.[1] As an important non-enzymatic antioxidant in human plasma, uric acid scavenges reactive oxygen and nitrogen species and is involved in multiple redox reactions, thereby contributing to the maintenance of internal homeostasis.[2] However, serum uric acid (sUA) may remain persistently elevated and exceed the physiological saturation threshold. In such cases, monosodium urate can deposit in the joints and periarticular tissues. This leads to the activation of innate immunity and local inflammation mediated by crystals. Clinically, this presents as a complex inflammatory arthritis with erythema, warmth, marked tenderness, and severe pain—namely, gout.[3-5] Epidemiologically, the global prevalence and incidence of gout have continued to rise. Rates differ across regions and populations. Overlapping metabolic comorbidities and lifestyle factors further complicate management.[4, 6, 7]

For recurrent gout, the effectiveness of urate-lowering therapy (ULT) and anti-inflammatory treatment has been established. International and regional guidelines also emphasize a treat-to-target approach to reduce the risk of recurrence and complications.[7-12] However, in real-world settings, long-term adherence to prescribed ULT is only about 20%–70%. This undermines sustained efficacy and prevention of recurrence.[4] Against this backdrop, adjunctive strategies that fit daily life alongside pharmacotherapy are of practical relevance. Dietary interventions, such as tart cherry products, have attracted attention for their safety and accessibility and are increasingly in the spotlight.[1] Prior short-term interventional and observational studies suggest that intake of tart cherry juice or its concentrates is associated with reductions in sUA, downregulation of inflammatory biomarkers, and a decreased risk of gout flares. However, effect sizes vary with population characteristics (weight, comorbidities), formulation, anthocyanin dose, and intervention duration.[3, 13-16] Given

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suboptimal adherence and a rising disease burden, dietary interventions can act as useful adjuncts to lifestyle management. They are most effective when combined with purine restriction, weight control, limited alcohol intake, and urinary alkalinization for additive benefits.[7, 11, 12]

From a mechanistic perspective, anthocyanins and related polyphenols are the main active constituents of tart cherries. They can inhibit cyclooxygenase (COX) activity, scavenge reactive nitrogen and oxygen species, and modulate inflammatory and oxidative stress pathways. These actions provide biological plausibility for anti-inflammatory and antioxidant effects.[17-20] When adherence falls short and the burden keeps climbing, these interventions can complement routine care.[3]

In vitro and animal studies suggest that tart cherry extracts or principal anthocyanins may inhibit xanthine oxidase (XO). They may also influence uric acid homeostasis by modulating the redox microenvironment and affecting renal and intestinal urate excretion.[1, 19] Genetic and transport pathway studies indicate that urate acid transporter 1 (URAT1), glucose transporter 9 (GLUT9), and ATP binding cassette subfamily G member 2 (ABCG2) are central to renal and intestinal uric acid handling. Altered function of these transporters is closely associated with hyperuricemia and gout risk. This provides a theoretical basis for dietary effects on the transport–excretion axis.[1, 21, 22] Although the biological rationale is robust, human evidence remains heterogeneous. Differences span study populations, sample sizes, product sources, anthocyanin quantification, intervention duration, control design, and outcome measures including sUA, inflammatory biomarkers, and clinical flares. These factors limit the consistency and generalizability of the conclusions drawn from the studies.[3, 13, 15, 16]

Based on these considerations, a systematic review, meta-analysis, and network pharmacology analysis were conducted. Randomized controlled trials were systematically integrated to quantify the effect of tart cherry products on sUA level, and observational and mechanistic evidence was qualitatively summarized. Subgroup analyses were prespecified by population characteristics, formulation and anthocyanin dose, intervention duration, and concurrent lifestyle measures to explore dose–response relationships and heterogeneity. Safety outcomes and long-term sustainability were also evaluated. Our aim was to provide clearer, actionable evidence for clinical practice and for subsequent standardized human trials.

METHODS

Study design

Randomized controlled trials (RCTs) served as the primary evidence for a systematic review and meta-analysis, and cohort and case–control studies were included for qualitative reference. Network pharmacology and molecular docking were integrated to explore mechanisms. The study workflow followed Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines. We placed no restriction on year of publication. The study was registered in PROSPERO under the registration number CRD420261347406.

Search strategy

We conducted in-depth searches in eight databases (Cochrane Library, PubMed, MEDLINE, Embase, EBSCO, Ovid, ScienceDirect, and Web of Science) to identify relevant studies. Medical Subject Headings (MeSH) terms were incorporated to cover all eligible reports from database inception through July 2025. Full search strategies and database query strings are provided in Supplementary Table 1.

Only human studies were included, and English was used as the primary language. After deduplication, titles and abstracts were screened, followed by full-text review to assess eligibility. Publication date was not used as a restriction for searching or inclusion.

Inclusion and exclusion criteria

Inclusion criteria: (1) randomized controlled trials (parallel or crossover) in adults (≥18 years); (2) interventions involving tart cherry products (juice, concentrate, powder, or standardized extract derived from Prunus cerasus L.); (3) a control condition (e.g., placebo, isoenergetic beverage, or no intervention); and (4) usable arm-level sUA data either pre-/post-intervention or between groups at the end of treatment. Cohort and case–control studies addressing tart cherry intake and urate-related outcomes were included only for qualitative context and not pooled quantitatively.

Exclusion criteria: (1) opinions, reviews, case reports, abstracts, or *in vitro* studies; (2) interventions using sweet cherries or studies that could not distinguish tart cherries; (3) no control group or missing key outcome data; and (4) duplicate data or missing sample-size information that rendered data unusable.

Data extraction, synthesis, and analysis

Methods included extraction of the following information: author and publication year; country or region; study design and blinding; sample size and population characteristics; baseline sUA; intervention preparation (formulation, dose, frequency, duration); type of control; measurement time points; and statistics related to sUA. Where unit inconsistency was present, sUA values were standardized to mg/dL (1 mg/dL ≈ 59.5 μmol/L). As needed, authors were contacted or estimates were derived using handbook methods. For crossover designs, measurements after an adequate washout were prioritized. For multi-arm studies, arm-specific doses or formulations were recorded, and pooled data were processed under prespecified rules.

Study characteristics and outcome definitions were summarized in Supplementary Table 2.

Quality assessment and Risk of Bias (RoB)

Risk of bias for randomized controlled trials included in the quantitative synthesis was assessed using the Cochrane Risk of Bias tool, version 2 (RoB 2). Two reviewers independently evaluated each domain (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result). Disagreements were resolved through discussion or consultation with a third reviewer. Study-level RoB judgments are summarized in

Table 1, and domain-level details are provided in the Supplementary Materials.

Certainty of evidence Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment

The GRADE framework was used to assess the certainty of prespecified outcomes. In randomized evidence, certainty starts at a high level and may be downgraded across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (or other concerns). Downgrading decisions follow standardized GRADE criteria and are accompanied by explicit justification for each downgrade. Where appropriate, potential upgrading considerations may also be discussed, but upgrading is uncommon in typical randomized evidence.

Statistical analysis

We pooled effects using random-effects models with restricted maximum likelihood (REML) to estimate between-study variance (τ^2) and applied Hartung–Knapp–Sidik–Jonkman adjustments for confidence intervals. Because trials reported sUA using different summary formats (change-from-baseline versus end-of-treatment values), the primary effect measure was the standardized mean difference (SMD). We report pooled SMDs with 95% confidence intervals (CIs), along with τ^2 and I^2 as measures of between-study heterogeneity. Change-from-baseline values were preferentially used; when unavailable, end-of-treatment between-group differences were analyzed.

Crossover trials were analyzed as paired designs assuming a within-person correlation r = 0.5. For multi-arm trials, we derived separate randomized comparisons by either equally splitting shared control groups or combining similar intervention arms, following Cochrane Handbook guidance, to ensure that each participant contributed only once to each comparison.

Potential small-study effects and publication bias were explored using funnel plots and Egger's regression test, recognizing that these methods are difficult to interpret when fewer than 10 comparisons are available. All meta-analyses were conducted using Stata (meta suite) and cross-checked in RevMan.

Network pharmacology database

Key constituents of tart cherries, primarily anthocyanins along with chlorogenic acid, p-coumaric acid, and quercetin were identified using Simplified Molecular Input Line Entry System (SMILES) strings retrieved from PubChem. Target prediction was conducted with SwissTargetPrediction, Similarity Ensemble Approach (SEA), and TargetNET, followed by deduplication and standardization to UniProt identifiers. Gene sets related to uric acid and gout were retrieved from GeneCards and intersected with the tart cherry–related targets to identify candidate targets associated with tart cherries. We constructed a protein-protein interaction (PPI) network using Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) (human; confidence 70) and visualized it in Cytoscape 3.10.0, where hub genes were identified using CytoHubba. Protein 3D structures were obtained from the Protein Data Bank (PDB), and docking was performed using AutoDock Vina to evaluate binding affinities based on binding energy.

Protocol registration

This review was registered in PROSPERO (CRD420261347406) and followed PRISMA 2020 recommendations.

RESULTS

Study selection

The flow diagram of study selection is shown in Figure 1. According to the inclusion and exclusion criteria, we searched eight English-language databases: the Cochrane Library, PubMed, MEDLINE, Embase, EBSCO, Ovid, ScienceDirect, and Web of Science, identifying a total of 101 records. 36 duplicates were removed, leaving 65 studies for screening. A further 46 studies were excluded after screening titles and abstracts. The remaining 19 studies underwent full-text review, of which 11 were excluded for the following reasons: not retrieved, the intervention involved sweet cherries, non-human study, and the assessed outcome was not sUA level.

Finally, four RCTs met the inclusion criteria and were included in the meta-analysis, contributing eight randomized comparisons in total because some trials had multiple intervention or control arms. Among these four RCTs, three were published within the past 5 years, comprising a total of 392 participants. All studies measured uric acid levels using routine blood sampling. Two trials were double-blind, one was a parallel-group trial, and one used a crossover design. Martin KR used a double-blind, placebo-controlled, two-by-two crossover design in which placebo beverages were masked in color and were equivalent in sugar and energy to the real beverage to allow for the potential for blinding, with crossover through automated online randomization. Gonzalez DE achieved double-blinding by matching cherry powder capsules exactly in size and color to placebo in identically labeled bottles in a randomized, double-blind, placebo-controlled, counter-

Table 1. RoB 2 assessment for included RCTs

RCT Author Name Year [Ref.]	Bias					
	Selection	Performance	Detection	Attrition	Reporting	Other
Gonzalez, 2024[26]	+	+	+	+	+	+
Martin, 2019[3]	+	+	+	+	+	+
Stamp, 2020[25]	+	+	?	+	+	+
Wang, 2022[27]	+	+	+	?	+	+

Risk of bias levels; low RoB (+), high RoB (−), and unknown (?).

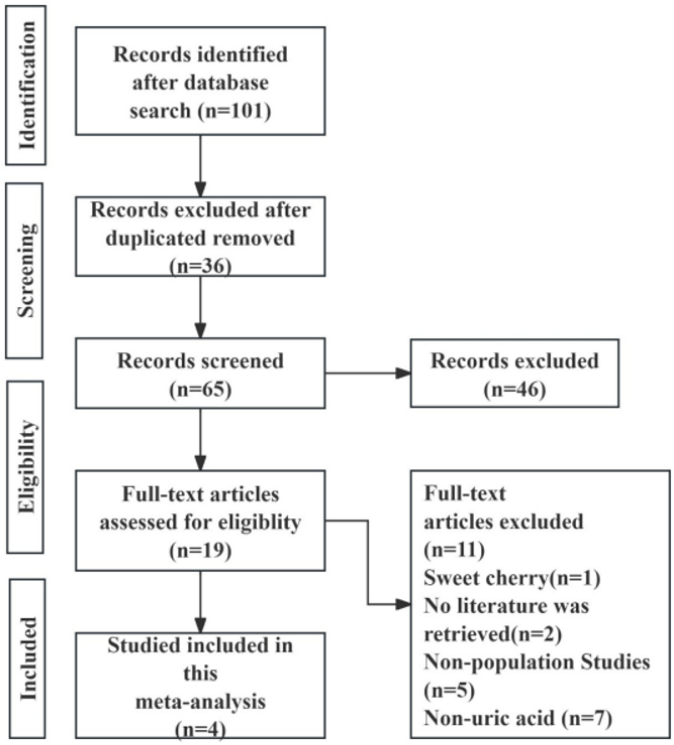

Figure 1. PRISMA flow diagram of study identification, screening, eligibility, and inclusion.

balanced, cross-over study with washout periods. Wang was a parallel controlled open-label randomized controlled trial with a three-arm design. Stamp is also an open-label study.Detailed study characteristics are provided in Supplementary Table 2.

Quality RoB

We used Review Manager 5.4 to implement the RoB 2 tool for the four included RCTs and to summarize study quality.

As shown in Table 1, the RoB assessment was conducted in accordance with the RoB framework. With regard to the randomization process, four studies were at low RoB. Concerning deviations from intended interventions, all four studies were at low RoB, primarily due to minimal and non-differential loss to follow-up. In terms of outcome assessment, four studies were likewise judged to be at low RoB. Nevertheless, several studies did not provide sufficient details regarding blinding of outcome assessors. All included studies demonstrated consistency with prespecified outcomes, with no indication of selective outcome reporting.

Certainty of evidence (GRADE)

GRADE judgments are shown in Table 2. Overall certainty varied by dose and outcome, with notable imprecision at several dose levels. The 7.5 mL dose group had a small sample size and large within-group variation, contributing to imprecise effect estimates and wide CIs. Small sample sizes and mid-range doses increase random error; these uncertainties should be highlighted in the discussion and considered in sensitivity analyses. When dose differences are substantial and samples are small, extrapolation to unstudied doses is limited; dose-subgroup analyses should be presented separately for the highest dose, with explicit emphasis on uncertainty. Some individual studies provided higher certainty for their specific outcomes, but overall certainty remains limited due to imprecision and inconsistency.

Overall effect size

Among the four included RCTs, some trials had multiple intervention or control arms. For the purposes of meta-analysis, we conducted group-wise comparisons within these multi-arm designs, resulting in eight randomized comparisons derived from the four parent trials.

The forest plot indicated statistical significance at the 5% level. Under a random-effects model, the overall SMD for uric acid levels comparing tart cherry intake with control was −0.22 (95% CI: −0.43 to −0.01), suggesting a modest reduction in sUA associated with the intervention (Figure 2). Between-study heterogeneity was substantial (I^2=88%; $Chi^2 = 59.1$, df = 7, $p < 0.01$), indicating marked variability in effect estimates across comparisons. Given the small number of trials and the high heterogeneity, the magnitude of the pooled effect should be interpreted with caution. Funnel-plot inspection and Egger's test ($p < 0.01$) suggested some asymmetry; however, with fewer than 10 randomized comparisons, these findings are exploratory and cannot be considered definitive evidence of publication bias (Figure 3).

Dots represent individual studies; the dashed triangle denotes the 95% confidence limits, and the vertical dashed line indicates the pooled effect (SMD: −0.22). A slight right shift and mild asymmetry suggest the presence of small-study effects or publication bias, although most points fall within the contours.

Testing of sensitivity

In the leave-one-out analysis, each study was sequentially omitted and the remainder re-pooled. The pooled effect did not reverse direction, and statistical significance was

Table 2. GRADE certainty of prespecified outcomes in RCTs

	Num. of studies	Certainty assessment						Num of patients	
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Walnut	Control
Stamp, 2020[25] (7.5 mL)	1	randomised trials	not serious	not serous	not serious	serious [a]	none	9	9
Stamp, 2020[25] (15 mL)	1	randomised trials	not serious	not serious	not serious	serious [b]	none	9	9
Stamp, 2020[25] (22.5 mL)	1	randomised trials	not serious	not serious	not serious	serious [c]	none	9	9
Stamp, 2020[25] (30 mL)	1	randomised trials	not serious	not serious	serious [d]	serious [e]	none	9	9
Gonzalez, 2024[26] (acute)	1	randomised trials	not serious	not serious	not serious	not serious	none	25	25
Gonzalez, 2024[26] (A week)	1	randomised trials	not serious	not serious	not serious	not serious	none	25	25
Wang, 2022[27]	1	randomised trials	not serious	not serious	not serious	not serious	none	26	26
Martin, 2019[3]	1	randomised trials	not serious	not serious	not serious	not serious	none	82	86

	Num. of studies	Effect		Certainty	Importance
		Relative (95% CI)	Absolute (95% CI)		
Stamp, 2020[25] (7.5 mL)	1	-	SMD 0.32 lower (1.25 lower to 0.61 higher)	⨁⨁⨁◯ Moderate[a]	
Stamp, 2020[25] (15 mL)	1	-	SMD 0.35 SD higher (0.59 lower to 1.28 higher)	⨁⨁⨁◯ Moderate[b]	
Stamp, 2020[25] (22.5 mL)	1	-	SMD 0.09 SD lower (1.01 lower to 0.84 higher)	⨁⨁⨁◯ Moderate[c]	
Stamp, 2020[25] (30 mL)	1	-	SMD 0.1 lower (1.03 lower to 0.82 higher)	⨁⨁◯◯ Low[d,e]	
Gonzalez, 2024[26] (acute)	1	-	SMD 0.18 lower (0.74 lower to 0.37 higher)	⨁⨁⨁⨁ High	
Gonzalez, 2024[26] (A week)	1	-	SMD 0.14 lower (0.69 lower to 0.42 higher)	⨁⨁⨁⨁ High	
Wang, 2022[27]	1	-	SMD 3.63 lower (4.54 lower to 2.72 lower)	⨁⨁⨁⨁ High	
Martin, 2019[3]	1	-	SMD 0.05 higher (0.25 lower to 0.35 higher)	⨁⨁⨁⨁ High	

[†]Items involving the 7.5 mL dose had a relatively small sample size and differences in within-group variation compared with the other doses. Together, these factors reduce the precision of the effect estimates, and confidence intervals can be wide; caution is needed in interpreting the direction and magnitude of the overall effect.
[‡]If some comparisons involve both small-sample and moderate-dose groups, there is an increased risk of random error that may amplify or attenuate the observed effect and reduce the stability and reproducibility of the results. Consider inclusion in sensitivity analyses or subgroup analyses.
[§]In the presence of significant dose differences and small sample sizes, additional indirect effects may occur when extrapolated to unstudied dose intervals, thereby reducing direct applicability to the target population. Define this clearly in the discussion and limit clinical decision making to stratified dose-subgroup analyses if necessary.
[¶]The high-dose group may carry a higher indirect risk if the study's dose interval does not overlap with the target interval. Interpret the dose-response relationship with caution; perform dose-group independent analyses as needed; report the strength of evidence for each subgroup.
[††]Highest-dose groups tend to have minimal sample sizes; random fluctuations may be large. Present separate effects and CIs for the highest-dose subgroup and emphasize strength of evidence and potential bias in the discussion.

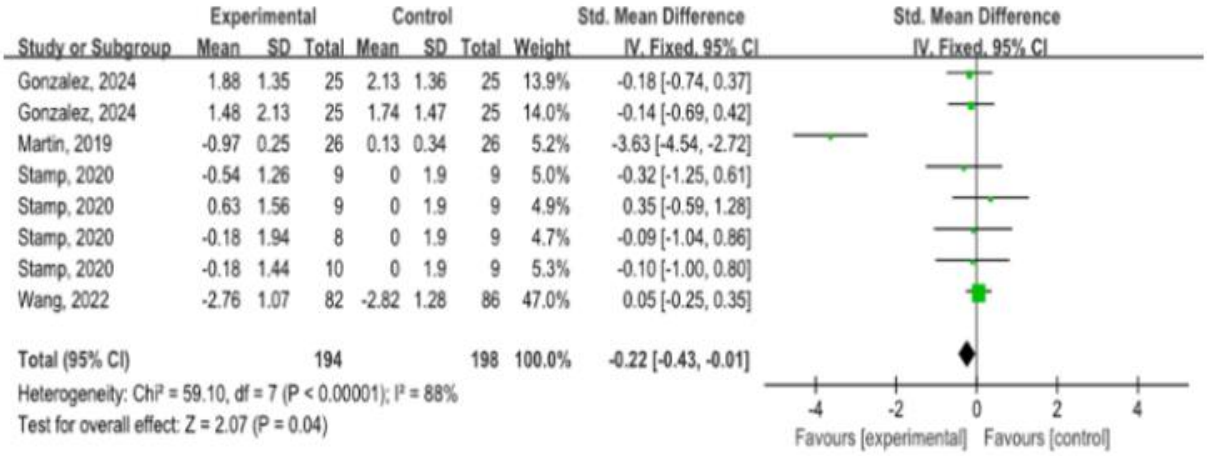

Figure 2. Forest plot of the effect of tart cherry intake on sUA levels

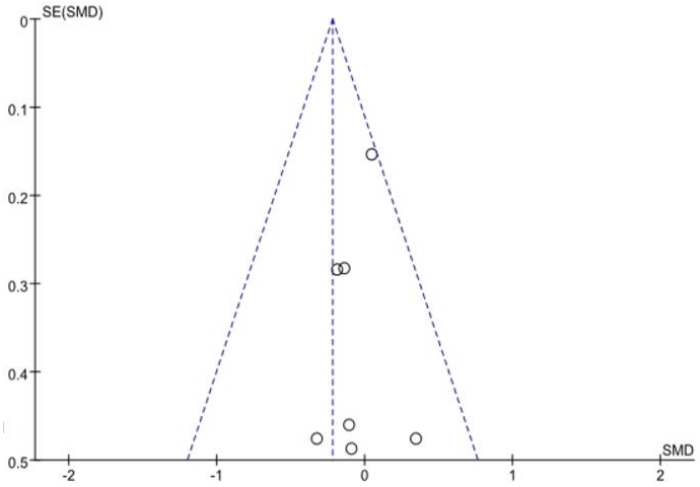

Figure 3. Funnel plot of SMD for serum uric acid levels

largely maintained. No single study with a decisive influence on the overall result was identified (Figure 4A). The funnel plot showed mild asymmetry consistent with Egger's test.

Network pharmacological analysis

All putative targets collected from each platform were subsequently deduplicated and merged, ultimately yielding 131 high-confidence targets. Finally, gene symbols of the predicted targets were retrieved from the UniProt database. Meanwhile, sUA-related targets were identified using the GeneCards database and were intersected with the tart cherry–related targets, yielding 78 common targets. These targets were defined as those related to tart cherry's effect on lowering sUA level. To further identify key functional regulatory targets, the aforementioned sUA-lowering tart cherry–related targets were imported into the STRING database to construct a PPI network (Figure 5A).

After construction, the network was imported into Cytoscape for visualization, and the CytoHubba plugin was used to perform topological analysis of the PPI network. Using algorithms such as Degree and Maximal Clique Centrality (MCC) to score the nodes, top 7 genes were ultimately identified as hub genes, namely interleukin 6 (IL6), tumor necrosis factor (TNF), AKT serine/threonine kinase 1 (AKT1), peroxisome proliferator activated receptor gamma (PPARG), tumor protein p53 (TP53), insulin (INS), and adiponectin (ADIPOQ) (Figure 5B).

Finally, we performed docking between the above 7 hub targets—IL6, INS, PPARG, AKT1, TNF, TP53, and ADIPOQ and anthocyanins, chlorogenic acid, p-coumaric acid, and quercetin (Figure 6). The molecular docking results showed binding energies below -5.0 kcal/mol between the four classes of compounds and the selected hub targets. Among them, anthocyanins with ADIPOQ exhibited the strongest docking ability, followed by quercetin with IL6, and anthocyanins with both IL6 and PPARG (Figure 7). This suggests that tart cherry compounds may target these hubs to modulate sUA level in humans.

DISCUSSION

Prespecified dose-group analyses did not eliminate substantial between-study heterogeneity ($I^2 \approx 88\%$). Across eight randomized controlled trials, tart cherry products were associated with a small and unstable reduction in sUA.[3] Variation in baseline characteristics, product formulation/anthocyanin content, dosing and timing, control design, and outcome definitions likely underlie this inconsistency.[23] Future work should standardize exposure, increase sample sizes, and harmonize outcomes to identify sources of heterogeneity and strengthen the evidence

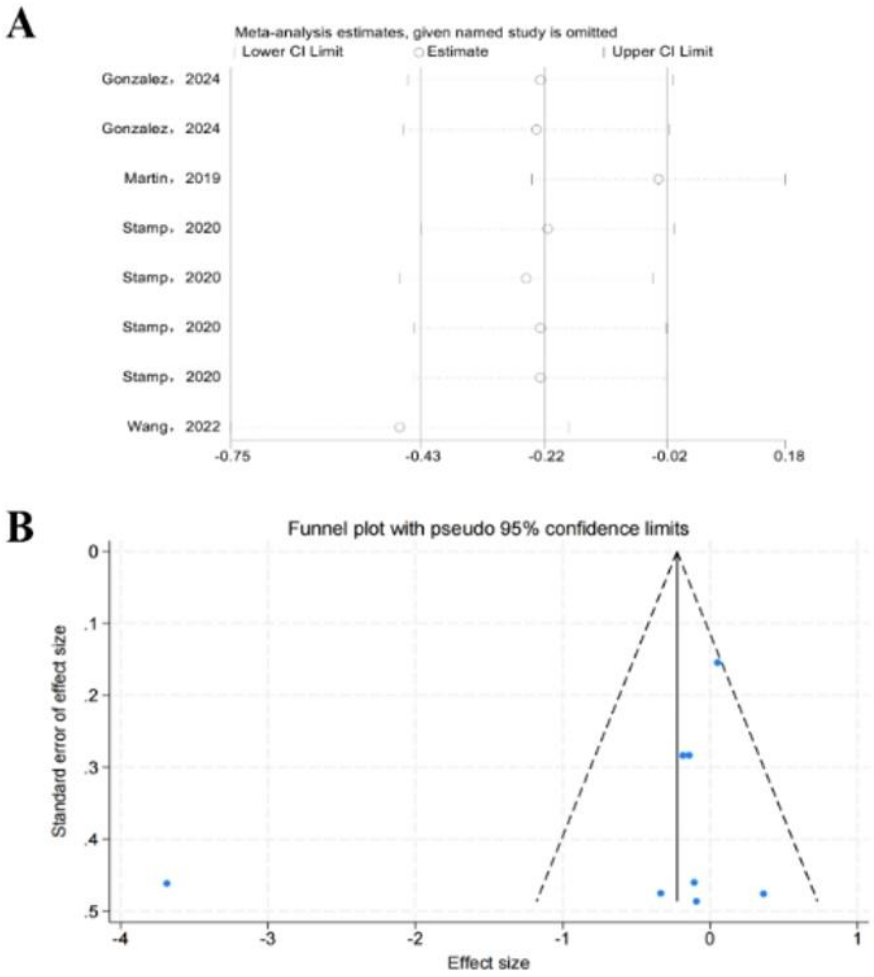

Figure 4. Sensitivity analysis and publication bias assessment. (A) Sensitivity analysis was performed by excluding studies one by one, (B) Funnel plots and their pseudo 95% confidence limits

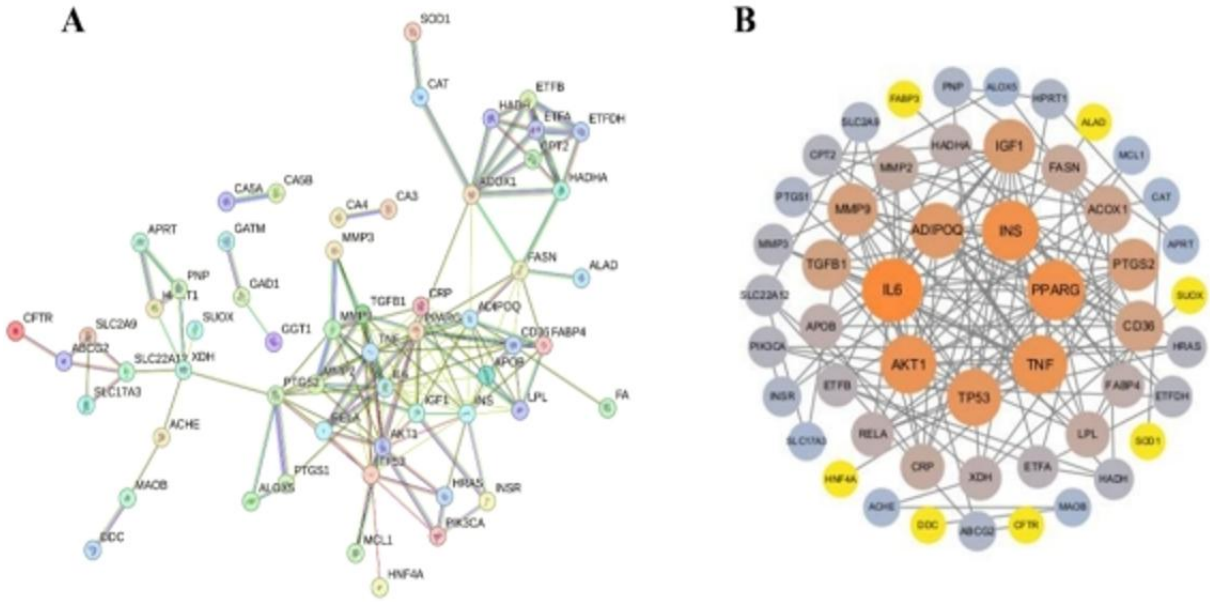

Figure 5. Network pharmacology of tart cherry for sUA reduction: (A) PPI network (STRING); (B) Hub genes (Cytoscape/CytoHubba)

base.[24] Nevertheless, integrating RCT data with network pharmacology and molecular docking analyses provides a framework to explore potential mechanisms and assess concordance and discordance across evidence streams.[5]

Based on a systematic integration of four randomized controlled trials contributing eight randomized comparisons.[3, 25-27] this study incorporated network pharmacology and molecular docking results,[28, 29] to re-evaluate the relationship between tart cherry intake and serum uric acid.

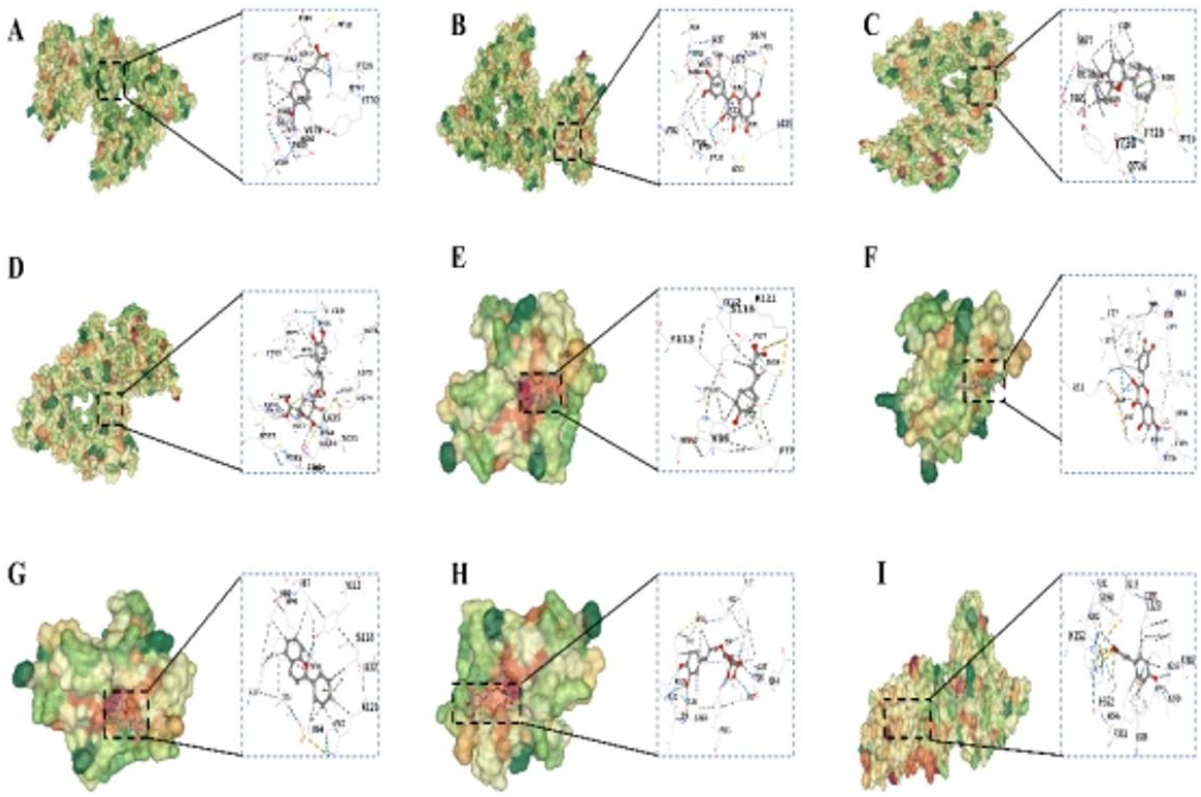

Figure 6. Molecular docking results. IL6 and anthocyanin (A), IL6 and chlorogenic acid (B), IL6 and p-coumaric acid (C), IL6 and quercetin (D), AKT1 and anthocyanin (E), AKT1 and chlorogenic acid (F), AKT1 and p-coumaric acid (G), AKT1 and quercetin (H), ADIPOQ and p-coumaric acid (I). The remaining docking results are presented in the Supplementary material

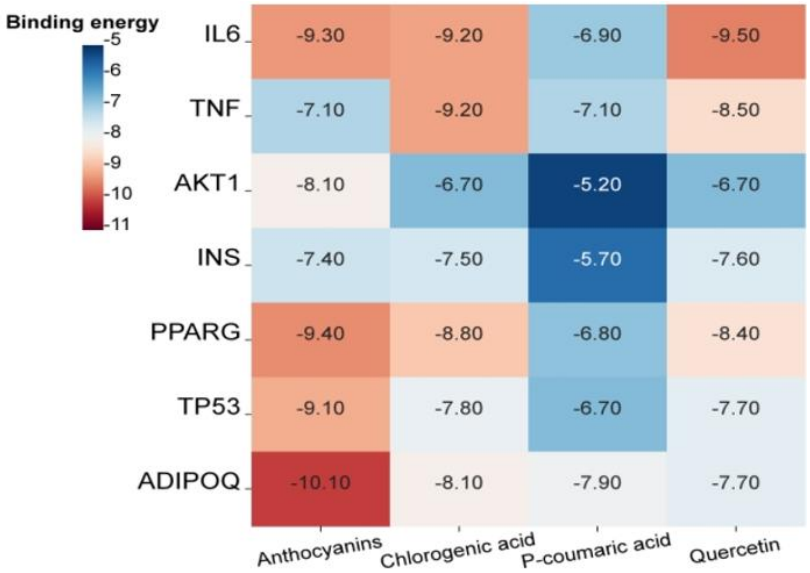

Figure 7. Binding-energy heatmap of tart cherry constituents and target proteins

Overall, tart cherry intake was associated with lower sUA in our pooled analysis (SMD: −0.22; 95% CI: −0.43 to −0.01), but between-study heterogeneity was very high (I^2 = 88 %). Egger's test and slight funnel-plot asymmetry suggested possible small-study effects and publication bias, although such tests are difficult to interpret with so few comparisons. While most comparisons trend toward lower sUA with tart cherry intake, wide confidence intervals and marked heterogeneity mean that both the magnitude and the consistency of the effect remain uncertain.[31]

Although tart cherry intake was associated with lower sUA, the evidence varied by dose and was highly heterogeneous across studies.[25] Thus, conclusions should be interpreted with caution, and tart cherry should be viewed as an adjunct to lifestyle management rather than a replacement for therapy.[32] Future studies should standardize dose/formulation, increase sample sizes, and include mechanistic endpoints to clarify dose–response relationships and long-term safety.[12]

When compared to existing literature, two noteworthy trends emerge for interpretation.[16, 33] Initially, real-world observational studies indicate a correlation between cherry consumption and a reduced risk of gout recurrence.[34] Conversely, the findings from rigorously randomized

trials exhibit inconsistencies, as short-term interventions result in decreased sUA level in healthy individuals or those with metabolic abnormalities.[3,35] However, among gout patients who are particularly undergoing standard ULT or following strict dietary guidelines, the results often demonstrate a diminished effect.[35] The observed discrepancies arise from systematic differences across several factors, including study populations, intervention preparations, and measurement protocols.[33,36] Population characteristics, including healthy individuals, asymptomatic hyperuricemia, and various phases of gout both intercritical and acute, influence baseline sUA, renal, and intestinal clearance capacities, body weight, insulin sensitivity, and concurrent medications (e.g., allopurinol/febuxostat, uricosurics, urinary alkalinizers), thereby affecting the response magnitude.[7,37-39] Likewise, significant differences exist at the preparation level, as juices, concentrates, and capsules vary in terms of anthocyanin/polyphenol equivalents, bioavailability, and matrix components (including sugars, organic acids, and minerals).[40] Moreover, at the design and measurement level, studies often employ short-duration or acute observations. These can be influenced by factors such as blood sampling timing, fasting status, control of purine and alcohol intake, physical activity, and circadian rhythm. Additionally, crossover designs are susceptible to carryover effects if the washout period is insufficient.[41] It is important to note that the fructose content in juice formulations may elevate uric acid levels.[34,42] In contrast, components like citrate or malate can aid in uric acid excretion by raising urinary pH.[43-45] The interaction of these opposing factors varies across studies and affects the overall results.35 This combination of factors largely accounts for the considerable variability and slight signs of publication bias in the pooled analysis.[30, 46] Future studies are likely to benefit from including healthy or hyperuricemic individuals without gout. Utilizing low-sugar standardized preparations with clearly defined anthocyanin levels and consistent sampling methods will likely reduce variability and improve the relevance of the findings.

The network pharmacology results provide biological support for "why it may be effective".[24,47,48] Beginning with the main active components of tart cherry, primarily anthocyanins, along with chlorogenic acid, p-coumaric acid, and quercetin, we identified overlapping targets related to uric acid metabolism and the inflammation–metabolism network. IL6, TNF, AKT1, PPARG, TP53, INS, and ADIPOQ are located at the hubs of the PPI network.[47,49,50] Furthermore, molecular docking suggests that most compounds have a strong affinity for these targets, with binding energies all less than −5 kcal/mol.[51,52] These signals are highly consistent with the pathophysiology of gout/hyperuricemia: on the one hand, inflammation amplification mediated by the nuclear factor κB (NF κB)/NLR family pyrin domain containing 3 (NLRP3) axis and oxidative stress can drive purine catabolism and enhance XO activity.[53,54] On the other hand, insulin resistance and disordered lipid metabolism can affect the expression or function of proximal tubule transporters (URAT1/SLC22A12, GLUT9/SLC2A9, ABCG2), thereby altering uric acid reabsorption and excretion.[55,56] Existing *in vitro* and animal studies indicate that anthocyanins possess COX-inhibitory and antioxidant activities. Quercetin and chlorogenic acid can inhibit XO under certain conditions.[57,58] If they act together with citrate salts in raising urinary pH, the clinically observed "modest decrease" becomes explicable.43 Molecular docking provides affinity-level evidence but cannot substitute for *in vivo* efficacy. These mechanistic findings are inherently hypothesis-generating and do not compensate for the limitations of the clinical evidence base. The parent forms of anthocyanins have low exposure in circulation, and their metabolites, such as protocatechuic acid, are more likely the actual effector molecules.[59] Future work is needed within a pharmacokinetics–metabolomics framework, combining functional experiments to validate key circuits, tissue specificity, and dose thresholds.[60, 61]

From a practical standpoint, tart cherry should be positioned as an adjunct. It reinforces lifestyle management rather than replacing first-line urate-lowering medications.[3,11,32] In individuals who are overweight or insulin resistant, have higher purine or alcohol exposure, elevated inflammatory burden, or limited tolerability to conventional therapy, clinically perceptible marginal benefits are more likely to be observed.[36,57,62] In patients who have already achieved targets with medication or have good dietary control, the net effect may be smaller.[3] Practical recommendations include prioritizing preparations with transparent composition, labeled anthocyanin equivalents, and controllable sugar content. Capsules or low-sugar concentrates are preferable when needed.[63] It is important to coordinate intake with weight management, restrict purines and alcohol, ensure adequate hydration, and promote urinary alkalinization.[64] For patients with chronic kidney disease or glycemic concerns, monitoring potassium and sugar loads and regularly checking sUA and renal function is essential.[63,65,66] Furthermore, patients using allopurinol or febuxostat should not reduce or discontinue these medications because of increasing tart cherry intake or when adding tart cherry products to the diet.[11, 12] When communicating expectations, it should be emphasized that the "average reduction is limited and inter-individual variability is pronounced" to avoid misinterpreting it as a substitute for medication.[3,57]

This study has several notable strengths. First, it effectively integrates recent randomized evidence and conducts robustness checks, including leave-one-out analyses and bias assessments.[23,67-69] Second, it aligns clinical observations with network pharmacology and docking results, creating a feedback loop between clinical signals and molecular mechanisms.[51,70] Furthermore, it differentiates between "stability in direction" and "uncertainty in magnitude" to avoid over-extrapolation in the presence of substantial statistical heterogeneity.[69,71] However, there are also significant limitations. Most of the trials included in this study have small sample sizes and short durations, and they lack supporting dose–response and exposure–response evidence.[72-74] Additionally, there is a lack of uniformity in formulations and dosing conventions. The reporting of anthocyanin equivalents and raw material profiles, such as high performance liquid chromatography (HPLC) polyphenol profiles, is insufficient.[40,75,76] Moreover, inconsistencies in dietary control, concomitant medications, and adherence records may introduce noise that

does not differ between groups.[77] Lastly, the reliance on database inference in network pharmacology results in a lack of direct evidence regarding the in vivo regulation of key transporters and XO in human subjects.[47,56,60] Overall, these factors suggest that the certainty of the current evidence falls within a "limited to moderate" range.[78]

Overall, tart cherry intake (including derived products) is associated with reductions in sUA, showing a generally consistent direction across most comparisons but a modest magnitude and considerable uncertainty. The effect size is markedly influenced by population characteristics, formulation differences, and intervention protocols.[3,36,79,80] Its biological basis includes anti-inflammatory and antioxidant actions mediated by anthocyanins/polyphenols, potential inhibition of XO, and indirect modulation of urate transport processes and urinary pH.[53,55] Clinically, it should be used as a complement to lifestyle management, in combination with a purine-restricted diet, weight management, and urine alkalinization.[11,12,64] Future research should be based on standardized dose and composition, ensure adequate follow-up, and include mechanistic endpoints to define actionable dosing, responder populations, and long-term safety.[36,67,80,81]

Conclusion

In summary, this study integrated a meta-analysis of 4 RCTs with network pharmacology findings. Tart cherry intake (and its preparations) was associated with reductions in sUA. The leave-one-out analysis supported a consistent direction. Heterogeneity was high ($I^2 = 88\%$), and Egger's test and the funnel plot indicated possible small study or publication bias. Anthocyanin-dominant polyphenols may regulate inflammation and metabolism via pathways involving IL6, TNF, AKT1, PPARG, and ADIPOQ, inhibit XO, and influence URAT1, GLUT9, ABCG2, and urinary pH, constituting multi-target modulation. Given the small number and heterogeneity of available RCTs, the overall certainty of evidence remains limited. Tart cherry intake is therefore best used as a complement to lifestyle management rather than a replacement for first-line urate-lowering medications. Individuals with a higher metabolic burden may derive greater marginal benefit. Future work should include well-designed randomized studies with standardized tart cherry formulations and dosing, adequate follow-up, and mechanistic endpoints to define actionable dosing, responder populations, and long-term safety.

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

No AI-assisted technologies were used in the preparation of this manuscript. The authors reviewed and approved the final manuscript and take full responsibility for its content.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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