Review

The effect of sour cherry consumption on blood pressure, IL-6, CRP, and TNF-α levels: A systematic review and meta-analysis of randomized controlled trials sour cherry consumption and blood pressure

Baizhi Han [a], Akshaya Srikanth Bhagavathula [b], Muhammed Rashid [c], Manik Chhabra [d], Cain Clark [e], Hebatullah M. Abdulazeem [f], Mohamed Abd-ElGawad [g], Hamed Kord Varkaneh [h], Jamal Rahmani [i], Yong Zhang [j,*]

[a] Department of General Medicine, Affiliated Hospital of Weifang Medical University, No. 2428 Yuhe Road, Kuiwen District, Weifang, Shandong Province 261031, China
[b] Department of Internal Medicine, College of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates
[c] Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, BG Nagar 571448, Karnataka, India
[d] Department of Pharmacy Practice, Indo-Soviet Friendship College of Pharmacy, Moga 142001, Punjab, India
[e] School of Life Sciences, Coventry University, Coventry CV1 5FB, United Kingdom
[f] Arab Diploma in Family Medicine, AICPD, Egypt
[g] Department of Neurology, Fayoum University, Al Fayyūm, Egypt
[h] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[i] Department of Community Nutrition, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[j] School of Public Health and Health Management, Chongqing Medical University, Chongqing 400016, China

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ABSTRACT

Objectives: Cherries are rich in polyphenols and anthocyanins and are believed to possess strong anti-inflammatory activity and cardio-protective effects. This study aim was to summarize the overall effect of sour cherry consumption on blood pressure and biomarkers associated with the inflammation.
Methods: MEDLINE/PubMed, Cochrane, and Scopus were searched to find relevant papers up to April 2019. There were no time and language restrictions. This systematic review and meta-analysis was performed in accordance with the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Results: Eleven studies with 275 participants were included in this meta-analysis. Mean dose of the sour cherry was 170 mL/day, whilst mean duration of interventions was six weeks. Combined the results using random-effects model showed significant reductions in diastolic blood pressure levels following sour cherry consumption (WMD: −2.32 mmHg, 95% CI: −4.45, −0.19, I^2 = 39%), but there were no significant changes in systolic blood pressure (WMD: −2.64 mmHg, 95% CI: −5.84, 0.56, I^2 = 33%), IL-6 levels (WMD: 0.12 pg/mL, 95% CI: −0.13, 0.36, I^2 = 49%), hs-CRP (WMD: −0.13 mg/mL, 95% CI: −0.47, 0.22, I^2 = 49%) or TNF-α (WMD: −0.07 pg/mL, 95% CI: −0.18, 0.05, I^2 = 00%).
Conclusion: Sour cherry supplementation results a decrease in diastolic blood pressure, but elicits no significant effect on systolic blood pressure, IL-6 levels, CRP levels and TNF-α.

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Contents

1. Introduction

Globally, cardiovascular diseases (CVDs) persist as one of the primary causes of mortality and morbidity among non-communicable diseases (Roth et al., 2017). Annually, 17.9 million deaths are attributed to CVDs, approximating 31% of the world's deaths. Furthermore, CVDs are estimated to directly cause 80% of deaths in Americans who are over 64 years of the age (Benjamin et al., 2019), and whilst in 2015, USA health care expenditure for CVDs was around 656 billion dollars, it is expected to be double by 2030, and reach 1208 billion dollars (Benjamin et al., 2019). High blood pressure, or hypertension, and inflammation are the two major factors in the development of CVDs and atherosclerosis (Gupta et al., 2013).

Typically, the treatment of high blood pressure and inflammation consists of medications, primarily consisting of calcium channel blockers, angiotensin converting enzyme inhibitors, lipid-lowering agents, diuretics, beta-blockers, and non-steroid anti-inflammatory drugs (NSAIDs) for inflammation (Chai et al., 2018). These medications are shown to be somewhat beneficial in reducing cardio-vascular risks. Although these agents lower the risk of CVDs, they are associated with side effects, such as angiotensin converting enzyme inhibitors-induced dry cough, NSAIDs induced hepato-toxicity and nephrotoxicity, and lipid-lowering agents induced muscle damage(rhabdomyolysis), which cause harm and, in some cases, are fatal (Banach et al., 2015).

Concomitant to traditional pharmacotherapies, there is a growing evidence base to suggest that natural resources, such as phytochemicals within fruits and vegetables, may act to reduce risk CVDs, and conceivably reduce health care burdens (Miller et al., 2017). However, there is equivocality with regard to whether natural resources are sufficient to treat and prevent cardiovascular risk factors. Indeed, various epidemiological studies state that a diet rich in fruits and vegetables serves as a protective agent against CVDs. Furthermore, fruits, which are rich, source of polyphenolic compounds, especially, anthocyanin, possess potentially cardio-protective properties (Aune et al., 2017). Cherries are fruits which are rich in polyphenols and anthocyanin, and are believed to possess strong anti-inflammatory activity and cardio-protective effects. Moreover, cherries increase the activity of nitric oxide synthase, which serves to be efficient in arterial stiffness, and thus, they may be potentially beneficial in preventing atherosclerosis, by helping to maintain proper endothelial functions (Chai et al., 2018). In addition, cherries possess anti-oxidant properties as well as lipid reducing power. Furthermore, there are no known adverse side effects associated with cherries, and their consumption can ameliorate post-exercise induced inflammation, improve muscle recovery, and enhance circulatory melatonin levels (Lynn et al., 2014b). Therapeutic application of cherries has also yielded beneficial responses in inflammation-associated diseases, especially in osteoarthritis and gout (Schumacher et al., 2013b). A number of observational studies exploring the effect of raw cherries on blood pressure, C-reactive protein (CRP), Tumor Necrotic Factor (TNF), and Interleukin-6 (IL-6) (Chai et al., 2018; Lynn et al., 2014b) have recently been conducted, however, to date, there exists no summative assessment available. Therefore, the aim of the present study was to summarize the overall effect of sour cherry consumption on blood pressure and the biomarkers associated with inflammation.

2. Methods

PRISMA statement used to conduct present meta-analysis (Moher et al., 2015).

2.1. Search strategy

A search was performed in PubMed/MEDLINE, Cochrane and SCOPUS by two reviewers, from database inception until April 2019. Details of the comprehensive search strategy are presented in supplementary Table 1.

2.2. Selection criteria and data extraction

The PICOS criteria was used to conduct this studies. Two authors evaluated the title and abstract of all articles, independently. The inclusion criteria for including were: Intervention using Sour Cherry, RCT studies reporting our outcome measures in the form of mean differences (MD) with the confidence intervals. Studies that did not report relevant outcomes, were animal-based or review studies and non-randomized studies were excluded. Furthermore, studies without a control group, conference, commentaries, and case-reports studies were also excluded.

Data extraction from the included studies as performed by two reviewers, independently.

2.3. Quality assessment

Cochrane tool was used for the assessment of quality of the included studies (Higgins et al., 2011).
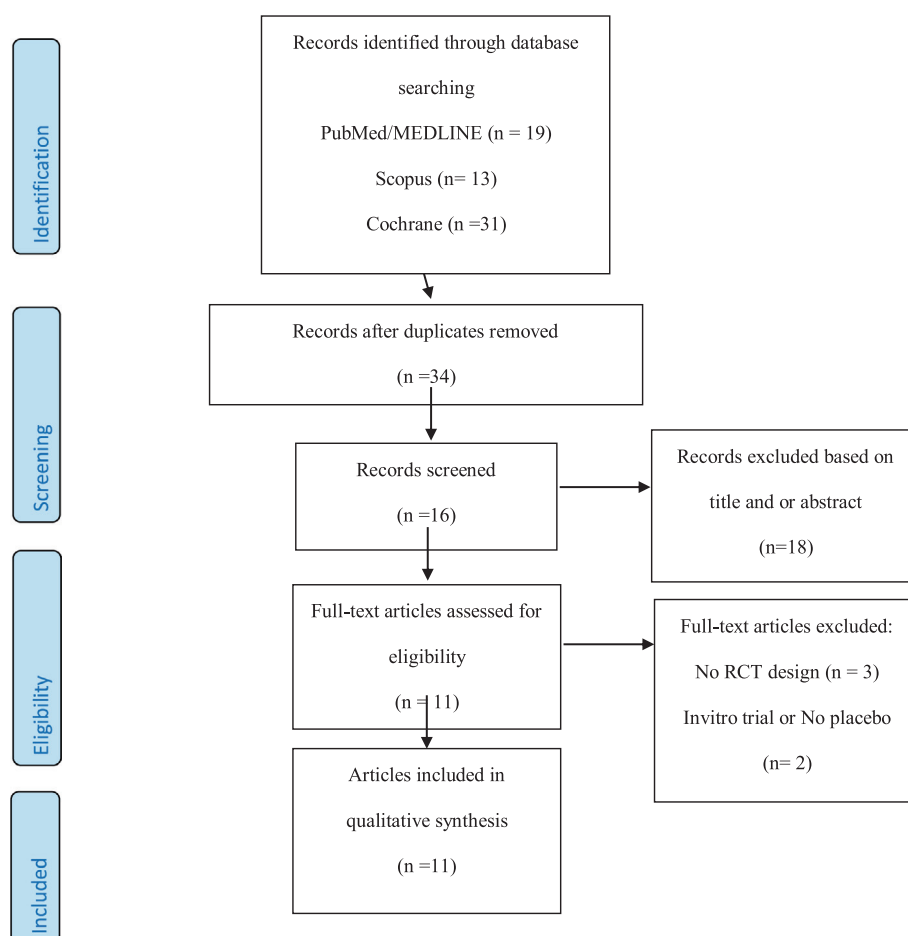
Table 1
Characteristics of included studies.

Author	Location	year	Participants (n)	Gender(1women, 2men, and 3 both	Age (year)	dose (mg or ml/ day)	Duration of study (week)
Sheau C. Chai	USA	2019	37	3	65–80	480	12
Brown, M. A.	UK	2019	20	2	19	30	1
Bakkar, Z. A.	UK	2019	12	1	54	1.7	4
Martin, K. R.	USA	2018	10	3	38	240	10
Jackman, S. R.	UK	2018	16	1	60–75	30	3
Desai, T.	UK	2018	11	3	30	30	10
Chai, S. C.	USA	2018	37	3	65–80	480	12
Bell, P. G.	UK	2016	16	1	25	30	1
Levers, K.	USA	2015	23	1	20	480	2
Lynn, A.	UK	2014	47	3	30–50	30	6
Naruszewicz, M.	Poland	2007	44	3	56	255	6

2.4. Statistical analysis

All statistical analyses were conducted using the STATA 14 (StataCorp LP, College Station, USA). Weighted mean difference (WMD) with the 95% CI was used to measure effects of Sour Cherry on outcome measures. DerSimonian and Laird method random effects model was used to calculate the pooled effects. Heterogeneity across the included studies was evaluated by the I-squared and an alpha of 0.05 for p heterogeneity. Sensitivity analysis was run to examin effect of each studies. The publication bias evaluated by funnel plot, Egger's and begg's weighted tests.

3. Results

Following comprehensive systematic searching, 63 studies were retrieved (Fig. 1). After removing duplicates and title and abstract screening, 16 articles remained for full text examination. In full text screening, 5 studies were excluded because they did not meet our inclusion criteria such as they was not RCTs or was not on human, and finally, 11 studies were included in this meta-analysis(Bakkar et al., 2019; Bell et al., 2016; Brown et al., 2019; Chai et al., 2018; Chai et al., 2019a,b; Desai et al., 2018; Jackman et al., 2018; Levers et al., 2015; Lynn et al., 2014a; Martin et al., 2018; Schumacher et al., 2013a).

Fig. 1. Flow chart of included studies.

Table 2
Risk of bias assessment.

Study name	Year	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance bias Blinding	Detection bias Blinding	Attrition bias Incomplete outcome data	Reporting bias Selective reporting	Other bias Other sources of bias
Chai, S.C.	2019	Low	Unclear	Unclear	Low	Low	Low	Low
Brown, M. A.	2019	Low	Unclear	Low	Low	Low	Low	Low
Bakkar, Z.A	2019	Low	Low	Low	Low	Low	Low	Low
Martin, K.R.	2018	Low	Unclear	Low	Low	Low	Low	Low
Jackman S.R.	2018	Low	Unclear	Low	Low	unclear	Low	Low
Desai, T	2018	Low	Unclear	Low	Low	Low	Low	Low
Chai, S.C.	2018	Low	Unclear	Low	Low	Low	Low	Low
Bell, P.G	2016	Low	Unclear	Low	Low	Low	Low	Low
Levers, K.	2015	Low	Unclear	Low	Low	Low	Low	Low
Lynn A	2014	Low	Low	Low	Low	Low	Low	Low
Schumacher, H.	2013	Low	Unclear	Low	Low	Low	Low	Low

3.1. Study characteristics

Table 1 details characteristics of the included studies, which were published between 2013 and 2019 and conducted in the US (Chai et al., 2018; Chai et al., 2019a,b; Levers et al., 2015; Martin et al., 2018; Schumacher et al., 2013a) or UK (Bakkar et al., 2019; Bell et al., 2016; Brown et al., 2019; Desai et al., 2018; Jackman et al., 2018; Lynn et al., 2014a). The total sample size was 275 participants with a men age of 45 years. Mean dose of the sour cherry was 170 mL/day, whilst mean duration of interventions was six weeks, ranging from one to 12 weeks. The risk of bias in included randomized control trials was low (Table 2).

3.2. Results of meta-analysis

Three studies with 102 participants reported blood pressure as an outcome measure (Chai et al., 2018; Desai et al., 2018; Lynn et al., 2014a). The random-effects model demonstrated significant reductions in diastolic blood pressure levels following sour cherry consumption (WMD: -2.32 mmHg, 95% CI: -4.45, -0.19, $I^2 = 39\%$) (Fig. 1), but there was not any significant change in systolic blood pressure (WMD: -2.64 mmHg, 95% CI: -5.84, 0.56, $I^2 = 33\%$).

Three studies, providing 60 participants, reported IL-6 as an outcome measure (Bakkar et al., 2019; Jackman et al., 2018; Levers et al., 2015). Pooled data showed not reduction in IL-6 levels in the intervention group compared with the placebo group (WMD: 0.12 pg/mL, 95% CI: -0.13, 0.36, $I^2 = 49\%$).

Results from the random-effects model on seven studies (Bakkar et al., 2019; Bell et al., 2016; Brown et al., 2019; Chai et al., 2019a,b; Jackman et al., 2018; Lynn et al., 2014a; Schumacher et al., 2013a) containing 195 participants (104 participants in intervention group and 91 participants in placebo groups) indicated that sour cherry did not have significant reduction in hs-CRP levels (WMD:-0.13 mg/mL, 95% CI: -0.47, 0.22, $I^2 = 49\%$) (Fig. 2.).

We analyzed the results from five studies containing 106 participants that reported TNF-α as an outcome measures (Bell et al., 2016; Chai et al., 2019a,b; Jackman et al., 2018; Levers et al., 2015; Martin et al., 2018) using a random-effects model. The results did not show any significant change in the intervention group compared to the placebo group (WMD: -0.07 pg/mL, 95% CI: -0.18, 0.05,$I^2 = 00\%$).

3.3. Publication bias and sensitivity analysis

Publication bias is illustrated in Supplementary Fig. 1. The Egger's and Begg's tests show not publication bias for systolic blood pressure (p = 0.82, p = 0.60), diastolic blood pressure (p = 0.35, p = 0.52), CRP (p = 0.81, p = 0.65), TNF-α (p = 0.31, p = 0.49), and IL-6 (p = 0.27, p = 0.11). The sensitivity analysis shows not significant differences beyond the limits of 95% CI of calculated pooled results.

4. Discussion

Sour cherry is the result of the hybridization of sweet cherry and the European dwarf cherry, and belongs to the Rosaceae family. Sour cherry (*Prunus cerasus L.*) is shown to possess anti-oxidant, anti-inflammatory and anti-mutagenic activity, which is attributable to a high flavonoid content. Moreover, sour cherry is considered to have the capacity to control hypertension because of the presence of components like anthocyanins and some flavone and flavan-3-ol compounds, although it is difference between hemodynamic process and inflammatory/oxidative processes (Nemes et al., 2018; Solak et al., 2016).

Anthocyanins are natural water-soluble flavonoids, and chemically they are polydroxy and polymethoxylated glycosides of anthocyanidins bound to several moieties. Anthocyanins exhibit a wide variety of biological effects, including vasodilators, and attributed to act as free radical scavenging and antioxidant activity (Soobrattee et al., 2005). However, the major correlation was found with vasodilatory capacity (Nile et al., 2015). Evidence from the reviews showed that anthocyanins condensed tannin-containing fractions that showed to have vasodilation activity compared to other polyphenols (Reis et al., 2016). In a rat model study, hypertensive stroke-prone rats are treated with anthocyanins rich blueberries for 8 weeks demonstrated significant reduction in the systolic blood pressure. Anthocyanins showed nitric oxide-dependent vasodilation via endothelium induced by acetylcholine through the nitric oxide metabolism pathway — furthermore, the other vasodilator effect of anthocyanins in the endothelium-dependent relaxation (Kalea et al., 2009).

Clinical trials have yielded evidence that sour cherry can significantly reduce hypertension, were such effects are likely manifest due to the circulating phenolic content of the cherries (Keane et al., 2016). Moreover, Chai et al. suggested that the anti-hypertensive ability of sour cherry can be due to its anti-oxidant and anti-inflammatory activity (Chai et al., 2019a,b).

We analyzed eleven studies and found that sour cherry consumption can significantly reduce diastolic blood pressure, but elicited no significant effect on systolic blood pressure, IL-1 levels, hs-CRP levels, and TNF-α. We observed that sour cherry consumption can significantly reduce diastolic blood pressure but the reduction in the systolic blood pressure, was found to be non-significant. Sour cherry has a high flavonoid content (Nemes et al., 2018), which are well linked with the prevention of CVDs (He & Giusti, 2010). Moreover, a previous meta-analysis of seven prospective cohort studies revealed that flavonol intake can significantly
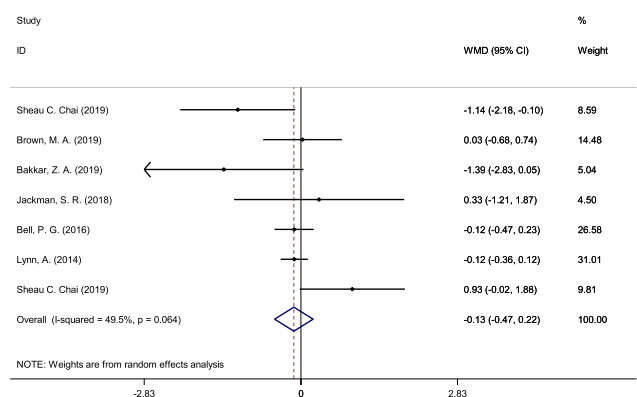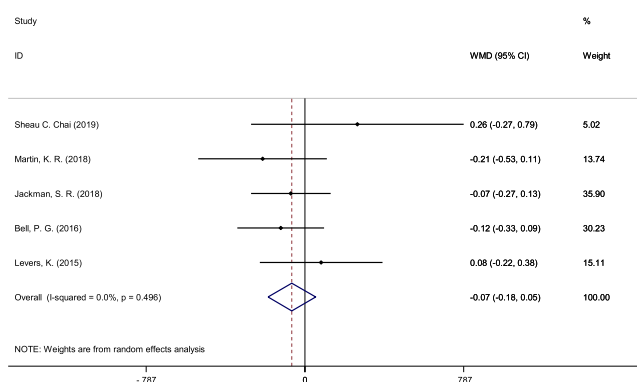
(a) Systolic blood pressure
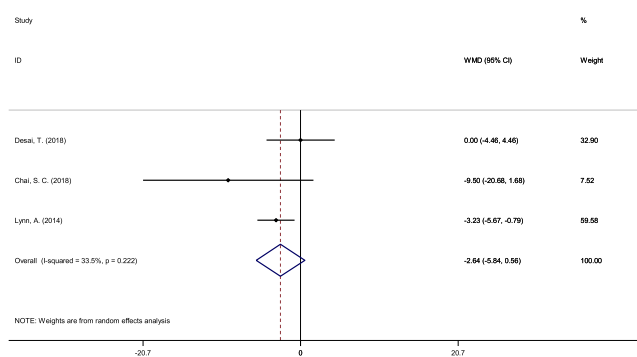
(b)Diastolic blood pressure
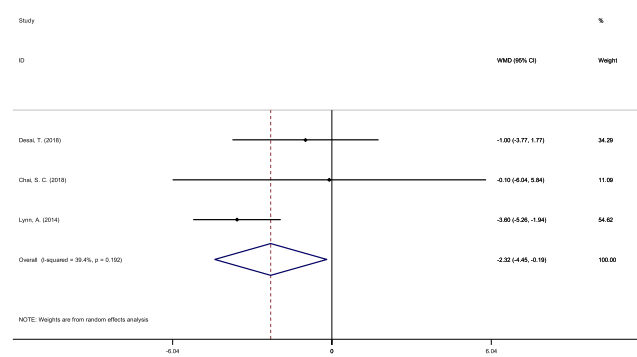
(c) CRP

(d) TNF

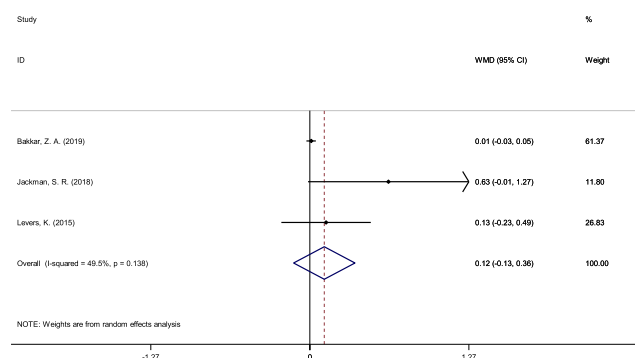(e) IL-1

Fig. 2. Meta-analysis of effect of Sour Cherry on (a) Systolic blood pressure, (b) Diastolic blood pressure, (c) CRP, (d) TNF, and (e) IL-1.

reduce the cardiovascular mortality risk (Huxley & Neil, 2003), whilst a significant reduction in blood pressure, HbA1c and body weight was observed among diabetic woman (Ataie-Jafari et al., 2008). However, our study revealed that there is no significant reduction in systolic BP, which has previously been reported (Anthony Lynn et al., 2014). Thus, there is a need to assess the exact chemical constituency of sour cherries, to ascertain what is contributing to its cardioprotective effect. However, evidence from seven studies included in the present meta-analysis demonstrated that there was no significant reduction in CRP level after consumption of sour cherry, when compared to the placebo group. CRP can inhibit nitric oxide (NO) production and bioavailability, which, in turn, leads to the process of inflammation, atherogenesis and scle-

rosis (Chai et al., 2019a,b). CRP is strongly recommended as an inflammatory response mediator, and a rise in CRP level can indicate an increased cardiovascular risk (Willerson & Ridker, 2004). Previously, it has been reported that patients who have low CRP levels have better clinical outcomes than those with higher CRP levels, and a 75% higher risk in those in the highest quartile of CRP,when compared to those who are in the lowest quartile range of CRP (Ridker et al., 1998). However, our analysis revealed that sour cherry consumption did not reduce the levels of CRP, and thus, may not represent a viable strategy in reducing CRP levels.

In the present study, pooled analysis of studies revealed that sour cherry juice consumption was not significantly associated with IL-6 and TNF-α reduction, when compared to the placebo

group. It is evident that an increase in IL-1β and IL-18 levels will be observed in cases of hypertension, and subsequently lead to renal and vascular inflammation (Krishnan et al., 2014). TNF-α and IL-1β are heavily involved in the pathogenesis of inflammatory bowel disease, and empirical studies have shown that anthocyanin extract of pure sour cherry can significantly reduce the production of TNF-α and IL-1β. Moreover, sour cherry extract can significantly inhibit the production of IL-6 and IL-8, and shown to be beneficial in controlling inflammatory bowel disease monolayers (Le Phuong Nguyen et al., 2018).

A recent review by Ahmed et al. highlighted that sour cherries are widely used in the Unani and Ayurvedic system of medicine, and it is quoted as essential in the treatment of urinary tract infections and other urinary diseases. Furthermore, Amhed et al asserted that sour cherry contains heptatonic, lithotriptic, diuretic, antipyretic, astringent, detergent, demulcent, spermatogenic, aphrodisiac, brain-tonic, anti-inflammatory, sedative and antioxidant properties (Shamsi, 2017). Constituents, like cyanidin-3-glucosyl-rutinoside and cyanidin-3-rutinoside, have been shown to exhibit an anti-oxidant and anti-inflammatory effect, which can be attributed to the cardioprotective effect of the sour cherry fruit and its byproducts (Yılmaz et al., 2018).

The strength of the current meta-analysis that we have used the highest level of evidence available, randomized controlled trials, to assess the effect of sour cherry on hypertension and inflammatory biomarkers, whilst there was no heterogeneity observed among all the studies. However, there was some limitation to the study. Even though we have performed a comprehensive electronic database literature search, we elected to omit grey literature, which may conceivably contain some relevant findings.

5. Conclusion

Sour cherry decrease diastolic blood pressure, but elicits no significant effect on systolic blood pressure, IL-6 levels, hs-CRP levels and TNF-α. Although, results show reducing effect of cherry but use from it in practice dependent to individual and country price and conditions.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jksus.2020.01.002.

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