Is there a role for cherries in the management of gout?

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Abstract: Despite the availability of effective urate-lowering therapy (ULT) and anti-inflammatory drugs for the treatment of gout, there is considerable interest in novel treatment approaches. Patients with gout often have a multitude of comorbidities, leading to concern over drug–drug interactions and medication adverse events. The cherry is a small nutrient-rich fruit that has garnered a great deal of attention in recent years as a nonpharmacologic option for the treatment of a multitude of disease manifestations. Perhaps a quarter of patients with gout try cherries or cherry products to treat their gout, which have antioxidant and anti-inflammatory (IL-6, TNF-α, IL-1β, IL-8, COX-I and -II) properties, hypouricemic effects, and the ability to downregulate NFkB-mediated osteoclastogenesis. Based on these properties, cherries may reduce both the acute and chronic inflammation associated with recurrent gout flares and its chronic destructive arthropathy. In this review, we explore the potential benefits of cherries and cherry products as a nonpharmacologic option for the treatment of gout.

Keywords: anthocyanins, anti-inflammatory, cherries, gout, serum urate, quercetin, tart cherry

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Introduction

Gout is a chronic and often debilitating disease associated with recurrent flares of inflammatory arthritis, manifesting as severe pain and joint dysfunction, which, if untreated, can lead to joint damage and significant morbidity. Once thought of as the disease of kings, gout has a prevalence of 3.9% in the US, affecting 8.3 million adults,[1,2] with a doubling of incidence seen in both men and women over the past 20 years.[3] Several urate-lowering therapies (ULTs) successfully decrease the burden of gout; however, they are not without potential risks. Patients with gout often have a multitude of comorbidities,[4–6] leading to concern over drug–drug interactions and medication adverse events[7] including skin rash, gastrointestinal side effects, infusion reactions, and rare life-threatening hypersensitivity reactions to certain gout drugs.[8,9] In fact, patients ranked interaction of gout medication with medications for other medical conditions as one of their biggest concerns when treating gout.[7] Therefore, it is no wonder that many patients afflicted with gout find themselves seeking complementary or alternative therapies.

Qualitative research suggests that approximately a quarter of gout patients use cherry products (cherries, cherry extract, or cherry juice) to treat their gout.[7] An internet-based survey of patients with self-reported, physician-diagnosed gout found that 24% preferred cherry extract as a potential means for chronic ULT.[10] Providers and patients believe that more ULT options are needed, since a proportion of patients with gout cannot be treated with the currently available ULTs due to low medication adherence, contraindications, inefficacy or partial efficacy, or adverse events.[11] Patients also prefer disease self-management strategies such as diet modification, exercise, weight reduction, medication self-management, as well as use of natural therapies as management options for their chronic diseases.[12,13] This implies that additional treatment options for gout, including complementary medicines such as cherries, are of high interest to patients and possibly to healthcare providers as well.

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Table 1. Nutrients found in sweet raw cherries and mean cyanidin content in cherry products.

Cherry product	Mean cyanidin content** (mg/100 g edible portion)
Sour, dry, unsweetened	6.83
Sour, dry, sweetened	2.27
Sour powder	31.42
Sour, red, frozen, unsweetened	10.13
Sour, red, raw (*Prunus cerasus*)	32.57
Sweet, raw (*Prunus avium*)	30.21
Sour cherry juice concentrate	10.39
Nutrient*	**Value (per 100 g edible)**
Energy (kcal)	63
Protein (g)	1.06
Total lipid (g)	0.2
Carbohydrate (g)	16.01
Fiber, total dietary (g)	2.1
Calcium (mg)	13
Magnesium (mg)	11
Phosphorus (mg)	21
Potassium (mg)	222
Vitamin C (mg)	7
Vitamin A (IU)	64
Vitamin E (mg)	0.07
Vitamin K (µg)	2.1
Carotene, beta (µg)	38

* Adapted from the USDA database for the flavonoid content of selected foods, release 3.1.[34]
** Adapted from the national nutrient database for standard reference legacy release.[35]
USDA, US Department of Agriculture.

Cherries

The cherry is a small nutrient-rich fruit garnering a great deal of attention as a nonpharmacologic option for the treatment of a multitude of disease manifestations in recent years. Cherries contain vitamins A, C, E, and phenolics such as anthocyanins[14,15] (Table 1). The recognition of antioxidant and anti-inflammatory properties of cherries has prompted numerous studies examining their benefits in patients with gout,[16] insomnia,[17] muscle endurance and recovery,[18] and potential benefit in cardiovascular disease,[19,20] diabetes,[20,21] and cancer.[22] Cherries are typically grouped into two major categories, sweet (*Prunus avium*) and tart /sour (*Prunus cerasus*). The most commonly grown cultivar of sweet cherry in the US is the Bing, while the most common for tart cherry is the Montmorency cherry.[14] The stage of ripening, among other things, plays a role in the content of potentially therapeutic compounds found in cherries, with ascorbic acid, total phenolics, antioxidant activity, and total anthocyanins increasing as

the fruit ripens.[23] In addition to raw cherries, numerous cherry products including juices, powders, concentrates, and extracts are commercially available. For example, one 8 oz bottle of a tart cherry juice blend is equivalent to 50 cherries.[24] One tablespoon (0.5 oz/~15 ml) of cherry juice concentrate made from fresh cherries is equivalent to 45–60 cherries,[25] with a 30 ml (1 oz) dose of Montmorency tart cherry concentrate equivalent to 90 whole Montmorency cherries.[26] Most tart cherry extracts and powders are available as oral capsules, for which one of the available commercial products contains 480 mg of tart Montmorency cherry powder, roughly equivalent to 16 ounces of tart cherry juice.[27]

Anthocyanins, phenolic compounds belonging to the family of flavonoids, are water-soluble pigments found in cherries that possess both antioxidant and anti-inflammatory properties,[28–31] characteristics attracting increasing interest over their potential health benefits. Cherries contain high amounts of anthocyanins as compared with other fruits. The major anthocyanins found in edible fruits like cherries are cyanidin, pelargonidin, peonidin, delphinidin, petunidin, and malvidin, with cyanidin being the most abundant.[15,28,32] The mean cyanidin content of the various cherry products can be seen in Table 1. The highest anthocyanin concentration in cherries is found in Bing cherries (40% higher content in the skins of Bing cherries, and nearly three times the anthocyanin content in the edible portion compared with Montmorency), with the majority of bioactive substances concentrated in the skins of both.[33] The anthocyanin content of cherries can be affected by processing, with canning leading to 50% transfer of anthocyanins and total phenolics from fruit to syrup, with varying degrees of degradation with frozen storage.[33]

Cherries as antioxidants

Through the process of metabolism in normal cells, toxic reactive oxygen and nitrogen species are produced, leading to oxidative stress that can result in severely compromised cell functioning, direct cell injury, and even cell death.[36] Oxidative stress plays a role in the manifestations of gout, precipitated by the generation of reactive oxygen species (ROS) and pro-inflammatory cytokines.[37] The enzyme xanthine oxidoreductase, responsible for the conversion of hypoxanthine to xanthine to urate in the final process of purine metabolism, also leads to the generation of ROS.[38] Anthocyanins and other phenolics found in cherries have antioxidant properties.[31,33,39–42] Phenolic antioxidants appear to interfere with the oxidation process as free radical terminators, and ultimately decrease the formation of volatile decomposition products.[43]

Cherry skins have the highest in antioxidant activity, with Montmorency tart cherry skins carrying the highest in total phenolics and antioxidant activities among the cherries tested.[33] Tart cherry juice concentrate has the highest oxygen radical absorbance capacity (ORAC), followed by dried cherries, frozen cherries, and canned cherries.[39] Two animal models evaluated the effect of anthocyanins on the markers of oxidative stress, showing an increase in total antioxidant capacity and superoxide dismutase in rats with adjuvant-induced arthritis,[29] and lower levels of nitrotyrosine and inducible nitric oxide synthetase in the joints of mice with collagen-induced arthritis treated with anthocyanin, when compared with untreated controls.[44] Twenty recreational marathon runners had a significant increase (about 10%) in total antioxidative status after 5 days of tart cherry juice use *versus* placebo, with lower thiobarbituric acid reactive species, a marker of oxidative stress, 48 h postrace.[45]

Anti-inflammatory effects of cherries and anthocyanins

Cytokine inhibition

Gout is associated with the tissue deposition of urate crystals in the setting of hyperuricemia, with a subsequent crystal-induced inflammatory response. Urate crystals stimulate monocyte and synovial cell production of interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α),[46,47] as well as chemotactic IL-8.[48] When stimulated by IL-1, IL-6, and IL-23, T-helper 17 (Th17) cells produce pro-inflammatory cytokines including IL-6, IL-17, and TNF-α.[49] Recent work has also shown that urate crystals activate the NACHT, leucin-rich repeat and pyrin domains containing protein (NALP3) inflammasome,[50] resulting in the production of IL-1β, whose inhibition has been shown to prevent the pain and inflammation response to urate.[51]

Despite positive results from studies of the anti-inflammatory effects of both cherries and anthocyanins, the data are limited at best. In a murine

model examining the effects of anthocyanins on collagen-induced arthritis, joints from mice treated with anthocyanins had lower levels of IL-1β, IL-6, IL-17, and TNF-α, as well as the cell populations secreting them. Furthermore, treated mice had fewer Th17 cells, as well as suppressed Th17 differentiation.[44] Rats with adjuvant-induced arthritis treated with anthocyanins extracted from tart cherries had lower levels of both TNF-α and prostaglandin E2 (PGE_2) in the paws.[29] IL-6 production was inhibited by 41–96% in an *in vitro* study using cluster of differentiation 40 ligand (CD40L)-stimulated vascular endothelial cells treated with anthocyanin metabolites.[19] Vascular cell adhesion molecule-1 (VCAM-1), whose expression during an inflammatory state mediates leukocyte adhesion,[52] was reduced by up to 65% with anthocyanins extracted from tart cherries,[19] indicating that anthocyanins may also play a role in leukocyte migration. Despite evidence of significant anti-inflammatory effects of anthocyanins from *in vitro* and animal models, there is a lack of studies examining its clinical benefit in humans. A randomized, double-blind, placebo-controlled trial investigating the anti-inflammatory effect of 320 mg/day of purified anthocyanin in 150 hypercholesterolemic adults found that patients treated with purified anthocyanin had significantly decreased plasma levels of IL-1β and soluble VCAM-1 compared with placebo controls.[53] Interestingly, no significant changes were seen in levels of TNF-α between the two groups,[53] which may relate to the absence of induced inflammation in this study population when compared with the animal models above.

In studies using cherry products, cherry juice concentrate inhibited IL-1β secretion by 60% and TNF-α by 45% in an *in vitro* study examining the secretion of ILs in monosodium urate (MSU)-stimulated monocytes.[25] Lower postrace levels of IL-6 (49%) were seen in a small study of 20 recreational marathon runners treated with 16 oz/day of tart cherry juice when compared with placebo controls.[45] However, the small study size and limited/no generalizability to patients with gout are major limitations, indicating that more studies are needed.

Effect on COX-I and COX-II pathways

Prostaglandins, inflammatory instigators whose production is mediated by cyclooxygenases (COXs), are also produced as a result of crystal-induced inflammation.[54] An *in vitro* study evaluating the COX inhibitory activity of sweet and sour cherries found that red sweet cherries showed the greatest COX-II inhibitory capacity among those tested, with sweet and tart cherries showing similar COX-I inhibition, as seen in Table 2 below.[30] Positive controls in this study were aspirin, celecoxib, and rofecoxib, with rofecoxib showing similar COX-II inhibition to the cherries tested.[30] Tart cherry juice concentrate showed the greatest COX-I inhibitory activity when compared with frozen, dried, and canned tart cherries,[39] with tart cherry extract associated with inhibition of COX-I and COX-II by 65% and 38%, respectively.[20]

Anthocyanins from sweet and tart cherries showed similar COX-I inhibition, with greater COX-II inhibition seen in sweet cherries which compared favorably to NSAID controls using ibuprofen and naproxen.[31] These studies would suggest that both sweet and tart cherries contain the ability to inhibit the COX enzymes, with sweet cherries showing superior COX-II inhibition when compared with tart cherries, nevertheless it is important to note that these are all *in vitro* studies. In human chondrocytes, the anthocyanin delphinidin was shown to inhibit IL-1β-induced expression of COX-II, known to be increased during inflammatory states,[56] as well as the production of PGE_2[55] indicating that even the less-abundant anthocyanins may play a crucial role in decreasing inflammation.

Impact of anthocyanins on osteoclastogenesis

To understand the impact cherries may have in managing patients with gout, we first need to appreciate the pathophysiology of gout. Osteoclasts are important modulators of bone resorption and erosive damage in gout patients.[57] Patients with severe erosive and tophaceous disease have enhanced osteoclastogenesis.[58] Tartrate-resistant acid phosphatase (TRAP), expressed by osteoclasts, is secreted during bone resorption and has been linked to osteoclast activity.[59] TRAP-positive osteoclasts and multinucleated cells are present around tophi and in osteolytic lesions in gout.[58,60] Their differentiation is regulated by macrophage colony-stimulating factor (M-CSF) and the interaction between nuclear factor kappa-B (NFκB)/receptor activator of NFκB (RANK) on osteoclast precursor cells and RANK ligand (RANKL) expressed on or secreted by mature osteoblasts.[57,61] Higher circulating levels of RANKL and M-CSF,[58]

as well as IL-1, IL-6, and TNF-α produced by infiltrated mononuclear cells, have been reported in gout.[60] RANKL is also strongly expressed in T cells, and the significantly reduced number of TRAP-positive cells seen in T-cell-depleted cultures shows the important role played by T cells in osteoclastogenesis.[60]

A study examining the effects of anthocyanin on both collagen-induced arthritis in mice and human peripheral blood mononuclear cells found that the use of anthocyanin resulted in lower levels of IL-1β, TNF-α, IL-6, and IL-17 in the affected joints, with fewer Th17 cells, suppressed NFκB signaling, and decreased numbers of

Table 2. Anti-inflammatory properties of cherries and anthocyanins.

Author	Study	Treatment	Cytokine	Major findings	Comments
			***In vitro* studies**		
Amin et al.[19]	*In vitro* study examining effects of metabolites of C3G on IL-6 and VCAM-1 in CD40L stimulated endothelial cells	Cyanidin-3-glucoside and metabolites at 0.1, 1, and 10 μmol/l	IL-6	41–96% decreased production of IL-6 ($p \leqslant 0.03$/$p \leqslant 0.001$)	Greatest reduction in IL-6 seen from anthocyanin metabolites
Schlesinger et al.[25]	*In vitro* study testing the effect of cherry juice concentrate on secretion of IL by MSU-stimulated monocytes	Cherry juice concentrate, at concentration with no cytotoxic effect on monocytes	TNF-α IL-1β	Secretion of TNF-α inhibited by 45% Secretion of IL-1β inhibited by 60%	TNF-α inhibited at dilution of 1:4000; IL-1β inhibited at dilution of 1:1600
			Animal studies		
Min et al.[44]	*In vitro* and *in vivo* studies investigating the therapeutic effects of anthocyanin in a murine model of collagen-induced arthritis	Anthocyanin from black soybean seed coats, 60 mg/kg/day for 7 weeks (cyanidin-3-O-glucoside, delphinidin-3-O-glucooside, petunidine-3-O-glucoside)	IL-1β TNF-α IL-6 IL-17	Joints from treated mice had lower levels of IL-1β, IL-6, IL-17, TNF-α, and the cell populations secreting them ($p < 0.05$)	Also showed decreased Th17 cells, lower levels of nitrotyrosine and inducible nitric oxide synthetase, and osteoclastogenesis inhibition
			Human studies		
Howatson et al.[45]	Examine the effects of tart cherry juice on markers of oxidative stress, inflammation, and muscle damage, in 20 recreational marathon runners	T. cherry juice, two 8 oz bottles/day given 5 days before, day of, and 48 h postrace in 10 runners	IL-6	Significantly lower (49%) postrace IL-6 elevation in cherry juice group *versus* placebo (41.8 *versus* 82.1 pg/ml, $p < 0.001$)	34% lower CRP elevation in cherry juice group; cherry juice inhibited postrace SU elevation compared with placebo
Zhu et al.[53]	Randomized, double-blind, placebo-controlled trial examining if long-term anthocyanin supplementation inhibits the inflammatory response in 150 patients with hypercholesterolemia	Purified anthocyanin extracted from bilberries and blackcurrants, 320 mg/day for 24 weeks	IL-1β TNF-α	Significant decrease in IL-1β (–12.8% *versus* –1.3%, $p = 0.019$) *versus* placebo No significant change in TNF-α (–1.6%, $p = 0.673$)	Significant increases in HDL, with decreases in LDL, VCAM-1, hsCRP, IL-6, and IL-1β induced CRP production *versus* placebo.

(Continued)

Table 2. (Continued)

Author	Study	Treatment	Findings		Comments
			COX-I inhibition	COX-II inhibition	
Haseeb et al.[55]	*In vitro* study examining the effects of delphinidin on IL-1β mediated expression of COX-II and production of PGE_2 in OA chondrocytes	Delphinidin 50 μg/ml to study NFκB; 10 μg/ml to study COX-II	Delphinidin inhibited IL-1β induced expression of COX-II mRNA in OA chondrocytes		The anthocyanin delphinidin inhibited IL-1β, production of PGE_2, and induced activation of NFκB
Kirakosyan et al.[20]	*In vitro* study examining the effects of tart cherry extract on enzymes related to diabetes and cardiovascular disease	T. cherry extract Cyanidin 3-gluc Cyanidin-3-rut Quercetin	65% 47% 45% 53%	38% 36% 38% 42%	T. cherry extract inhibited xanthine oxidase by 26%
Mulabagal et al.[30]	*In vitro* study examining the anthocyanin content, lipid peroxidation, and COX enzyme inhibitory activities of sweet and sour cherries	Cherries (assayed at 250 μg/ml) Red sweet Balaton tart Montmorency tart	80–89% 84% 86%	93–96% 91% 87%	Controls using ASA, celecoxib, rofecoxib (assayed at 60 μmol/l, 26 nmol/l, 32 nmol/l respectively) showed COX-I inhibition at ~70%, 40%, 1%; COX-II at 30%, 75%, 90%
Ou et al.[39]	*In vitro* study comparing the antioxidant and anti-inflammatory activity in processed T. cherry products	T. cherry products, to include cherry juice concentrate, frozen, canned, and dried	T. cherry juice concentrate showed the greatest COX-I activity inhibition, followed by frozen and canned		Total phenolics and ORAC were highest in juice concentrate Total anthocyanins highest in frozen cherries
Seeram et al.[31]	*In vitro* study examining the antioxidant and COX inhibitory activity of anthocyanins from tart and sweet cherries	Balaton Montmorency Sweet cherries Cyanidin	27% 25% 29% 39%	38% 37% 47% 47%	NSAID controls using ibuprofen and naproxen showed COX-I inhibition at 47.5% and 54.3%, COX-II at 39.8% and 41.3%

COX, cyclooxygenase; CRP, C-reactive protein; T. cherry, tart cherry; cyanidin 3-gluc, cyanidin 3-glucoside; cyanidin-3-rut, cyanidin-3-rutinoside; C3G, cyanidin 3-glucoside; MSU, monosodium urate; OA, osteoarthritis; ASA, aspirin; NSAID, nonsteroidal anti-inflammatory drug; hsCRP, ; mRNA, messenger ribonucleic acid; ORAC, oxygen radical absorbance capacity; PGE_2, prostaglandin E2; IL, interleukin; mRNA, messenger ribonucleic acid; NFκB, nuclear factor kappa B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VCAM, vascular cell adhesion molecule; TNF, tumor necrosis factor; SU, serum urate; Th, T helper cell.

RANK or TRAP-positive multinucleated cells compared with untreated controls.[44] *In vitro* studies using the anthocyanin cyanidin showed a dose-dependent inhibitory effect on RANKL-induced osteoclastogenesis,[62] inhibition of RANKL-mediated osteoclast differentiation and formation, decreased total TRAP activity, and downregulated expression of osteoclast differentiation marker genes.[63] Pretreatment with cyanidin-3-glucoside also reduced induction of transcription factors important for osteoclast differentiation,[63] with similar results using the anthocyanin delphinidin, which showed a strong inhibitory effect on NFκB activation in chondrocytes.[64] Cyanidin-3-glucoside enhanced genes related to osteoblast differentiation, suggesting cyanidin may also augment bone formation.[63] This suggested that the use of anthocyanins

could potentially ameliorate osteoclastogenesis in patients with gout, yet is again difficult to draw accurate conclusions when the available studies are of predominantly *in vitro* design.

Other bioactive components in cherries

Vitamin C

Vitamin C, a water-soluble antioxidant found in cherries, has been studied as a potential treatment for gout. Using data from the Health Professionals Follow-up Study, vitamin C intake over a 20-year period in people with no prior history of gout lowered the risk of incident gout by 17% with vitamin C intake of greater than 500 mg/d, with a 45% lower risk for those taking over 1500 mg/day.[65] A second study from the same cohort evaluated the effect of vitamin C intake on serum urate (SU) in men with a body mass index (BMI) $< 30\,kg/m^2$ and no history of hypertension.[66] Vitamin C intake of 500 mg/day or higher was associated with ~0.7 mg/dl lower level of SU when compared with subjects taking less than 90 mg/day.[66] This study lacked the information on the use of ULT, though a similar result was obtained when gout patients were excluded. A strength of these studies is that they were well powered given the large sample size, though the cohort of male health professionals would not be generalizable to all men. In comparison with the first two studies, doses of 500 mg/day for 8 weeks did not show significant urate-lowering effects in patients with gout already taking allopurinol,[67] but the short follow up and lower dose might explain the absence of an association. Though vitamin C may have a role in lowering SU levels, possibly *via* a uricosuric effect,[68] one would need large quantities of cherries to glean an overall benefit from a potentially therapeutic dose of vitamin C. The ascorbic acid concentration of sweet cherries is about 28 mg per 100 g,[23] indicating that > 2 kg of cherry intake would be needed to observe an effect similar to the first study noted above.[65]

Quercetin

Quercetin, a flavonol and member of the flavonoid family of phenolics,[43] is found in a variety of fruits including cherries. According to the United States Department of Agriculture (USDA) database, sour (tart) cherry powder has the highest quercetin content when compared with other cherry products.[34] Quercetin has been well studied for its antioxidant and anti-inflammatory properties,[69–72] and may be yet another active compound in cherries with beneficial properties for treating gout. Protection against oxidative DNA damage was observed in a dose-dependent manner in a study using quercetin *in vitro*, with a significant increase in total antioxidant capacity in eight healthy females treated with quercetin-rich fruit juice for 4 weeks.[72] Quercetin inhibited *in vitro* COX-I and II activity by 52.8% and 42.3%, respectively,[20] reduced COX-II mRNA expression in both unstimulated and IL-1β-stimulated colon cancer cells,[73] and significantly decreased COX-II activity in rats with crystal-induced inflammation.[70] Improved arthritis scores, decreased joint circumference, and significantly decreased levels of TNF-α and IL1-β have also been observed in animal models,[70,71] which compared favorably with 3 mg/kg of indomethacin[70] in rats with crystal-induced inflammation. Quercetin reversibly inhibited the formation of urate and superoxide radicals catalyzed by xanthine oxidase (XO) in a concentration-dependent manner similar to that of allopurinol *in vitro*,[74] suggesting a dual role in gout. Unfortunately, studies evaluating the effects of quercetin in humans are sparse. In a randomized, double-blinded, placebo-controlled, crossover trial evaluating the use of quercetin on plasma urate in 22 healthy prehyperuricemic males, a significant decrease in plasma urate of 8% with daily supplementation for 4 weeks was noted, with a greater urate-lowering effect in patients with higher urate levels when compared with untreated controls.[75] Studies using quercetin can be seen in Table 3 below.

Clinical evidence for cherries in gout: effect on gout flares

In a large case-crossover study using an online gout survey ($n = 633$), cherry intake over a 2-day period was associated with a 35% lower risk of gout attack/flare, and any cherry extract use lowered the risk by 45%.[16] In combination with allopurinol, cherry intake was associated with a 75% risk reduction in gout flares. Cherry effects were independent of sex and race, as well as purine intake and alcohol consumption, which are risk factors for gout flares. The antigout benefits of cherries peaked around three servings over a 2-day period.[16]

In one research report, a series of three small studies evaluated the use of cherry juice concentrate for gout flare prophylaxis.[25] The first study was a small randomized controlled trial (RCT)

Table 3. Anti-inflammatory, antioxidant, and hypouricemic effects of quercetin.

Author	Study	Treatment	Findings	Comments
		***In vitro* studies**		
Kirakosyan et al.[20]	*In vitro* study examining the effects of tart cherry on enzymes related to cardiovascular disease and diabetes	Quercetin (0.1 mg/ml) extracted from tart cherry powder	Enzymatic activity inhibition: COX-I by 52.8%; COX-II by 42.3%; XO by 10%; lipoxygenase by 67%	Tart cherry extract with 65.1% and 37.8% inhibition on COX-I and II, XO by 26%
O'Leary et al.[73]	Examine the effect of flavonoids and vitamin E on COX-II transcription and COX activity *in vitro*	Quercetin and quercetin conjugates at 0.1, 1.0, and 10 μmol/l concentrations	Quercetin and its conjugates reduced COX-II expression in both unstimulated and IL-1β stimulated colon cancer cells; COX-II activity inhibited by up to 85%	Effect was not dose dependent
Wilms et al.[72]	Examine the protective effects of quercetin against oxidative DNA damage and formation of bulky DNA adducts *in vitro* and *in vivo/ex vivo* in human lymphocytes	*In vitro*: quercetin at various concentrations (0–100 μmol/l) *In vivo*, 8 female volunteers consumed 1 l of quercetin-rich juice daily for 4 weeks	*In vitro*: significant ($p < 0.01$) dose-dependent protection against formation of oxidative damage and BPDE-DNA adducts ($p < 0.05$). *In vivo*: TEAC increased from 773 to 855 μmol/l TE ($p = 0.04$) at 4 weeks	*Ex vivo*: oxidative damage nonsignificantly ($p = 0.07$) decreased by 41%, BPDE-DNA adduct level nonsignificantly ($p = 0.24$) decreased by 11%
Zhang et al.[74]	*In vitro* study exploring the inhibitory action of quercetin on xanthine oxidase	Quercetin dissolved in absolute ethanol and diluted to different concentrations	Quercetin reversibly inhibited the generation of urate and superoxide radicals Concentration of quercetin resulting in 50% loss of enzyme activity was $2.74 \pm 0.04 \times 10^{-6}$ mol/l	Inhibition was dose dependent Allopurinol concentration resulting in 50% loss of enzyme activity was $2.69 \pm 0.02 \times 10^{-6}$ mol/l
		Animal studies		
Jingqun-Huang et al.[70]	Animal model examining the effects of quercetin on MSU crystal-induced inflammation in rats	Quercetin at 100, 200, and 400 mg/kg given orally daily for 7 days.	Dose-dependent improvement in joint circumference, decreased synovitis at 200 or 400 mg/kg, and significantly decreased levels of TNF-α ($p < 0.01$), IL1-β ($p < 0.01$), and COX-II ($p < 0.05$)	Similar effect seen in rats treated with indomethacin at 3 mg/kg Statistically significant improvement in antioxidant status (SOD, catalase, malondialdehyde)
Mamani-Matsuda et al.[71]	*In vivo* and *in vivo/ex vivo* study examining the effects of quercetin on macrophage activation and inflammatory mediators in chronic adjuvant-induced arthritis in rats	Quercetin 150 mg/rat by gavage; 25 and 50 mg/rat IC, every 2 days x5 doses	Oral quercetin at 150 mg/rat ($p < 0.0004$) and IC quercetin at 50 >25 mg/rat significantly reduced arthritis scores, and significantly decreased levels of TNF-α ($p < 0.02$), IL1-β ($p < 0.003$), and MCP1 ($p < 0.014$)	PGE_2 production unchanged
		Human studies		
Shi et al.[75]	Randomized, double-blinded, placebo-controlled, crossover trial examining the effects of quercetin on plasma urate, BP, and fasting glucose in 22 healthy males without gout	One tablet containing 500 mg quercetin daily for 4 weeks	After 4 weeks, plasma urate levels decreased from baseline of 330 ± 56 μmol/l (5.55 ± 0.94 mg/dl) to 304 ± 48 μmol/l (5.11 ± 0.81 mg/dl), $p < 0.008$	Fasting glucose, urinary excretion of urate, and BP were unchanged

BPDE, benzo(a)pyrene [B(a)P] diolepoxide; COX, cyclooxygenase; DNA, deoxyribonucleic acid; MCP1, monocyte chemoattractant protein-1; MSU, monosodium urate; BP, blood pressure; TE, Trolox equivalent; TEAC, Trolox-equivalent antioxidant capacity; XO, xanthine oxidase; IL, interleukin; TNF, tumor necrosis factor; SOD, superoxide dismutase; PGE_2, prostaglandin E2; IC, intracutaneous.

comparing cherry juice concentrate and pomegranate juice. Cherry juice concentrate (Brownwood Acres Foods, Michigan, MI, US) at a dose of 1 tablespoon twice daily for 4 months reduced the number of flares from about 5 to 1.5 over a 4-month period (9 patients), with 55% of patients in the cherry group flare free at 4 months when compared with 20% in patients taking pomegranate juice (control group; 5 patients). Additionally, 55% taking nonsteroidal anti-inflammatory drugs (NSAIDs) chronically in the cherry juice group discontinued the use of their NSAIDs within 2 months. In another study of 24 patients with gout who took cherry juice concentrate for 4 months or longer as chronic flare prophylaxis, the number of gout flares per year decreased from nearly seven to two with the use of cherry juice concentrate. Of those patients, 45% were not on chronic ULT, but gout flare rate decreased both in patients with *versus* without concomitant ULT use. The average SU in cherry-juice-treated patients also taking allopurinol decreased significantly after 4–6 months of treatment (8.4 to 6.2 mg/dl), as compared with the SU level in patients not taking ULT that remained relatively unaltered (9.0 to 8.7 mg/dl), suggesting complementary effects when using with allopurinol. After 4–6 months, 50% of all patients consistently consuming cherry juice concentrate were flare free; 62% of patients additionally on ULT were flare free at 4–6 months, and 36% of patients not on ULT were flare free despite an average SU of 8.7 mg/dl.[25]

Urate-lowering potential of cherries and anthocyanins

The recognition of cherries as beneficial in gout management dates back to 1950. An article reported the lowering of SU to baseline with resolution of recurrent gout flares after consuming 0.5 lb of cherries daily in 12 patients with gout.[76] Unfortunately, there is a paucity of data examining the urate-lowering potential of cherries and cherry products. In an animal model evaluating the effects of tart cherry juice in normal and hyperuricemic rats, 14 days of treatment with tart cherry juice (5 ml/kg) significantly decreased (20%) SU in hyperuricemic rats, a finding not seen in normal controls. Hepatic XO was inhibited by 20% in hyperuricemic rats, suggesting a potential, though limited role in lowering SU through XO inhibition. In comparison, allopurinol 5 mg/kg showed 58% XO inhibition.[77]

Significant urate-lowering effects were also seen in two studies using healthy human participants, with a notable difference between the two cherry products used. The plasma urate concentration decreased by 14% 5 h after consuming two servings of sweet Bing cherries (~45 cherries), with a 73% increase in urinary urate at 3 h.[78] This compares with 30 ml (1 oz) of tart cherry concentrate (equivalent to 90 cherries), which was associated with ~36% decrease in SU, and ~250% increase in urinary urate excretion,[26] with similar results seen with 60 ml tart cherry concentrate. In contrast, two small studies using cherry juice concentrate for gout flare prophylaxis in patients with crystal-proven gout, also at a dose equivalent to ~90 cherries, showed a decrease in gout flare rate despite no significant change in SU from baseline.[25] These studies had small sample sizes, with the major difference between these studies being: (a) healthy subjects as compared with those with crystal-proven gout; (b) duration of treatment (hours *versus* months); and (c) the time of assessment, with the latter study measuring SU at day 0 and 120. These studies suggest that cherries may have urate-lowering properties, possibly through inhibition of XO or increased renal clearance, which were noted in healthy participants, but not in people with gout. However, the conflicting data, potential for publication bias (namely, negative studies less likely to be published), and lack of consensus as to which active compound in cherries lowers urate reiterates the need for future studies. Details of the studies examining the urate-lowering potential of cherries are shown in Table 4.

Three small studies using anthocyanin extract (proposed active ingredient in cherries and cherry extracts) in animal models showed positive results suggesting anthocyanins may be beneficial in managing gout (Table 2). A study examining the effects of a single dose of 100–300 mg/kg anthocyanin extracts from purple sweet potato on hyperuricemic mice[79] and rats[81] found that compared with hyperuricemic controls, SU decreased by 29–60%,[79,81] as compared with 5–10 mg/kg of allopurinol, which resulted in 82% reduction to undetectable SU levels.[79,81] Anthocyanin extract was also found to inhibit XO up to 91% when compared with hyperuricemic controls in a dose-dependent manner both *in vivo* and *in vitro*.[81] Extract from *Hibiscus* anthocyanins reduced SU by 70%.[80] These studies were limited, since none of them used anthocyanins extracted from cherries, raising the question of whether these

Table 4. Studies evaluating cherries and anthocyanins on serum urate.

Author	Study	Treatment	Serum urate		Comments
			Control	Treated; *p* value	
Cherries and anthocyanins *versus* **control (or before and after)** Animal studies					
Haidari et al.[77]	Animal model examining the effect of tart cherry juice on SU, xanthine oxidoreductase activity, and markers of oxidative stress in rats	14 days of oral tart cherry juice (5 ml/kg)	Hyperuricemic control 214.36 ± 26.42 μmol/l (3.60 ± 0.44 mg/dl)	171.95 ± 25.78 μmol/l (2.89 ± 0.43 mg/dl); $p \leqslant 0.05$	XO inhibited by 20% SU after 14 days of allopurinol (5 mg/kg) was 72.38 ± 19.24 μmol/l (1.22 ± 0.32 mg/dl), with 58% XO inhibition
Hwa et al.[79]	Animal model examining the hypouricemic effects of anthocyanin extracts from purple sweet potato (APSP) extract on hyperuricemic mice	Single dose of 100 mg/kg of APSP	Hyperuricemic control 10.25 ± 0.63 mg/dl	4.1 ± 0.04 mg/d; $p < 0.01$	Reduction of 60% in SU One dose of allopurinol 10 mg/kg reduced SU to 1.84 ± 0.13 mg/dl (82%)
Tsai et al.[80]	Animal model exploring the antitumor effect of anthocyanin extract from *Hibiscus sabdariffa* in leukemic rats	*Hibiscus* anthocyanin extract at 0.2 g/kg/day for 220 days	Leukemic rat control 3.07 ± 0.89 mg/dl	0.87 ± 0.22 mg/dl; $p < 0.005$	Reduction of 72% in SU Significant SU reduction ($p < 0.05$) also seen in rats treated with 0.1 g/kg/d
Zhang et al.[81]	Animal model examining the effects of anthocyanin-rich purple sweet potato extract (APSPE) on XO activity *in vitro*/ *in vivo*, as well as SU in hyperuricemic mice	Single dose of 300 mg/kg of APSP (anthocyanin content of 3.53 × 10^4 cyanidin 3-glucoside equivalent per 100 g APSPE)	Hyperuricemic control 134.67 μmol/l (2.26 mg/dl)	95.50 μmol/l (1.61 mg/dl); $p < 0.001$	Reduction of 29% in SU Positive control with allopurinol 5 mg/kg lowered SU to nearly undetectable level Significant inhibitory activity on XO
Human studies					
Bell et al.[26]	Single-blind, two-phase, randomized, crossover study examining the effects of tart cherries on urate activity and inflammation in 12 healthy participants	Montmorency tart cherry juice concentrate at 30 or 60 ml (30 ml tart cherry juice ~90 cherries)	Baseline: ~494 μmol/l (8.3046 mg/dl)	8 hr postsupplementation: ~316 μmol/l (5.31 mg/dl); $p < 0.0001$	Reduction of 36% (178 μmol/l/ 2.99 mg/dl) in SU, 250% (178 μmol/mmol creatinine) increase in urinary urate at 2 h Change independent of dose
Jacob et al.[78]	Examining the effects of cherry consumption on plasma urate, antioxidant, and inflammatory markers in 10 healthy women	280 g of sweet Bing cherries (~45 cherries)	Baseline: 214 ± 13 μmol/l (3.60 ± 0.22 mg/dl)	5 h postcherry consumption: 183 ± 15 μmol/l (3.07± 0.25 mg/dl); $p < 0.05$	Reduction of 14% in SU Urinary urate increased from 202 ± 13 to 350 ± 33 μmol/mmol creatinine (73%) after 3 h

Table 4. (Continued)

Author	Study	Treatment	Serum urate		Comments
			Control	Treated; *p* value	
Schlesinger et al.[25]	Randomized controlled trial of cherry *versus* pomegranate juice concentrate for gout prophylaxis in 14 patients with crystal-proven gout	1 Tbsp (~45–60 cherries) of cherry juice concentrate twice daily for 4 months	Pomegranate juice 7.45 ± 1.62 to 6.14 ± 1.07 mg/dl	Cherry juice 8.37 ± 0.82 to 8.17 ± 1.1 mg/dl; *p* value not provided	No significant change in serum urate
Schlesinger et al.[25]	Retrospective study evaluating cherry juice concentrate, taken for over 4 months, on gout flare prophylaxis in 24 crystal-proven gout patients	1 Tbsp (~45–60 cherries) of cherry juice concentrate twice daily for 4–6 months	Baseline: 9.0 ± 1.1 mg/dl	After cherry juice: 8.7 ± 1.4 mg/dl; $p = 0.5943$	Baseline SU in patients receiving allopurinol was 8.4 ± 0.6 mg/dl and decreased to 6.2 ± 0.4 mg/dl ($p = 0.0052$)

APSP, anthocyanin extracts from purple sweet potato; APSPE, anthocyanin-rich purple sweet potato extract; Tbsp, tablespoon; SU, serum urate; XO, xanthine oxidase.

properties are truly generalizable to the family of anthocyanins, regardless of the fruit of origin. Thus anthocyanins, an active ingredient in cherries, may have urate-lowering properties.

Gout treatment guidelines: how do they define the role of cherries in gout management?

According to the 2012 American College of Rheumatology (ACR) guidelines for management of gout, an acute gouty arthritis attack should be treated with pharmacologic therapy, for which the three preferred options are NSAIDs, systemic corticosteroids, or oral colchicine.[82] Pharmacologic prophylaxis against flares is recommended when initiating or titrating ULT, preferably with colchicine or NSAIDs, should be initiated for the greater of: 6 months' duration, 3 months after achieving target SU in people without tophi, or 6 months after achieving target SU with resolution of prior tophi.[83] Cherry juice or extract was voted as inappropriate for the treatment of an acute gout attack.[82] Recommendations to avoid naturally sweet fruit juice were also included.[83] However, the guideline noted '…more research is needed in diet and lifestyle modifications for gout, especially direct intervention studies.'[83] The common occurrence of comorbidities in gout, including chronic kidney disease (CKD) and diabetes, as well as the CYP3A4 medication interactions, make it difficult to provide safe anti-inflammatory options for patients with active gout. NSAIDs inhibit prostaglandin synthesis through COX inhibition,[84] whereas colchicine exerts its beneficial effects *via* inhibition of microtubule polymerization and the NLRP3 inflammasome that contributes to the disruption of chemokine and cytokine secretion, as well as neutrophil migration.[85] The use of cherries was associated with a reduction of gout flares[16,25] and inhibition of inflammatory processes related to the inhibition of pro-inflammatory cytokines[19,25,29,44,45,53] or COX enzymes[20,30,31] in a manner similar to that of the current standard of care. Whether cherry extract or products can play an adjunctive role to ULT in the long-term management of gout needs to be examined using rigorous RCT, placebo-controlled designs. The ACR also recommends that patients with an established diagnosis of gout should be treated with chronic ULT if there is evidence of tophi, frequent attacks (at least two attacks per year), CKD II or worse, or history of urolithiasis.[83] Treatment should be initiated with the use of an XO inhibitor such as allopurinol or febuxostat as first-line therapy. Unfortunately, medication side effects, including the rare possibility of life-threatening hypersensitivity reactions with allopurinol and the recent data showing that febuxostat was associated with higher cardiovascular mortality and overall mortality,[86] have heightened the concern with the use of these ULTs. Cherries and their associated compounds may have inhibitory effects, often in a dose-dependent manner, on XO,[20,77,79,81,74] and therefore could be used as

Table 5. Knowledge gaps.

Current knowledge gaps
Do cherries have complementary effects when combined with allopurinol or febuxostat?
At what dose do the various cherry products (juice, concentrate, extract) provide the most benefit in treating gout?
At what dose do cherries or their contents compare with the available NSAIDs?
Which cherry components (anthocyanins or quercetin) have beneficial effects on gout?
Is there a dose at which cherries or cherry products have a detrimental effect?
Which gout subpopulation can best benefit from the use of cherries, or cherry products?
At what dose are cherries, cherry products, or their contents comparable to allopurinol and febuxostat?

NSAIDs, nonsteroidal anti-inflammatory drugs.

complementary treatments, in addition to the use of traditional ULT.

Knowledge gaps: cherries and gout

There is a paucity of data to currently support the use of cherries or cherry products in the treatment of gout. Numerous questions remain regarding the use of cherries and the role they could conceivably play in the management of gout (Table 5). For instance, at what dose would cherries and their contents be comparable with the currently available XO inhibitors? In a study using hyperuricemic mice, anthocyanin extract at a dose of 100 mg/kg inhibited XO by 62% compared with 80% inhibition with 10 mg/kg of allopurinol.[79] An *in vitro* study found that 10 mg/ml of anthocyanin extract inhibited XO activity by nearly 90%, as compared with allopurinol 100 mg that caused 60% inhibition in XO activity.[79] Another important question arises as to whether or not cherries may also have complementary effects when used in combination with allopurinol, an outcome seen in a study evaluating cherry consumption on recurrent gout attacks that noted a 75% risk reduction in gout attacks when combined with allopurinol.[16] Similarly, a study using cherry juice concentrate for gout flare prophylaxis observed that 62% of patients on ULT were flare free at 4–6 months when combined with cherry juice concentrate, as compared with only 36% of patients not on ULT that were flare free.[25]

Summary and conclusions

Despite the availability of effective ULT and anti-inflammatory drugs for the treatment of gout, there is considerable interest in novel treatments and approaches to the management of gout. In a patient-centered approach, given the common use of cherries and related products by patients with gout, we provide a focused review examining the current evidence. Data indicate that cherries and their products have antioxidant properties, the capacity to inhibit several processes involved in the acute inflammatory response to the urate crystals, and the ability to decrease bone resorption that is characteristic of gouty bone erosions. Phenolics, and more specifically, the anthocyanins found abundantly in cherries, have been linked to the inhibition of IL-6, TNF-α, IL-1β, IL-8, COX-I and COX-II, as well as the downregulation of NFkB-mediated osteoclastogenesis, suggesting that cherries may have the ability to reduce both acute and chronic inflammation that play a role in recurrent gout flares and chronic destructive arthropathy. Additionally, cyanidin-3-glucoside enhanced genes related to osteoblast differentiation, suggesting that anthocyanins may also play a role in bone formation. The flavonol quercetin has also emerged as yet another beneficial component found in cherries, not only in its capacity as an antioxidant, but also through inhibition of XO and inflammatory cytokines. Though there is evidence that cherries may lower SU and inhibit XO, possibly mediated by anthocyanins or quercetin, the data comparing cherries with traditional ULT are lacking, and it is likely through inhibition of acute and chronic inflammation that cherries may have a future as a nonpharmacologic option in the management of gout. There are data, however, suggesting that cherries may have complementary effects on SU when combined with allopurinol, indicating yet another area in need of further examination.

Given the potential beneficial effects of cherries, this powerful fruit is becoming a more attractive option, and clearly has a role in the management of gout. Unfortunately, there are no large RCTs on the use of cherries in the treatment of gout. It would seem that this is long overdue and may provide additional evidence as to the role cherries could play in the future management of a burdensome disease. Additionally, a number of questions still remain when it comes to using cherries in the management of gout, and the answers to these questions may provide substantial insight into the future role cherries may best fit into. Based on the data presented here and new data generated with rigorous RCTs and other translational studies, one potential future option might be to manage gout using ULT with 'a cherry on the top.'

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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