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Gout Friendly Foods that Reduce Urate - Review

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Abstract

Dietary treatment for patients with gout/hyperuricemia places emphasis on avoidance of excess intake of certain types of food. However, foods that help to reduce serum uric acid levels and gout risk have recently been recognized: thus should be considered for their positive influence. In the present study, food factors known to decrease serum uric acid level and gout flare risk were reviewed. The "Mediterranean diet" is recommended for gouty patients, as it may help to prevent hyperuricemia, while the "DASH diet" and a high protein diet have also been reported to decrease serum uric acid levels. Dairy products, especially low-fat types, have been shown to lower serum uric acid levels as well and are associated with a lower risk of gout. Furthermore, coffee, tea, vitamin C, and some types of polyphenol supplementation can be considered for gout prevention, as they might also lower the level of serum uric acid.

Keywords: Uric Acid; Gout; Beneficial Diet

Introduction

Gout is an acute mono- or oligoarthritis condition triggered by monosodium urate (MSU) shedding within the articular space. The main cause is the presence of too much uric acid in the body, which is an end-product of the metabolic breakdown of purine nucleotides. In addition to gout, a high level of serum uric acid is also associated with a variety of metabolic disorders, including insulin resistance, hypertension, and dyslipidemia. Several factors can increase the likelihood of hyperuricemia and gout, including age, gender, genetics, medication, lifestyle choices, obesity, and other health problems, among which the most important factors are considered to be genetics and daily lifestyle. Generally, gout is not considered to be curable, though can be controlled by adequate medication and self-management strategies.In contrast to genetic factors, diet components do not generally have large effects on serum uric acid levels in the general population [1]. Nevertheless, it is important to pay attention to daily food intake so as to not increase serum uric acid concentration and associated gout risk, especially in individuals with mild hyperuricemia.

Previously, diets recommended for patients with gout (hyperuricemia) have focused on avoidance of purine-rich foods, such as red meat and seafood, and excessive alcohol consumption, along with moderate calorie restriction to maintain body weight [2]. However, recent prospective epidemiological and open-labeled dietary studies have provided novel insights into the roles of dietary factors, discretionary items, and various supplements that decrease serum uric acid levels and reduce the risk of gout flare. The present study was conducted to review food factors that demonstrate such activities.

Food

A diet consisting of calorie restriction to 6690 kJ (1600 kcal) a day for 16 weeks, with 40% derived from carbohydrates, 30% from protein, and 30% from fat, has been reported beneficial for alleviating insulin resistance, decreasing serum uric acid concentration, and reducing the frequency of gut flare [3].

According to the report of Choi HK, et al., a high-protein diet is associated with increased urinary uric acid excretion and may reduce its level in blood [4]. Also, in a small study of overweight and obese subjects, consumption of the "Atkins diet" (i.e., high protein diet without calorie restriction) for six months was found to reduce serum uric acid levels despite substantial purine loading [5].

The "Mediterranean diet", acknowledged by the United Nations Educational, Scientific and Cultural Organization (UNESCO) as an intangible cultural heritage of humanity in 2010, is composed of daily consumption of cereals (bread, oats, wholegrain cereal, groats), fruits, vegetables, nuts, and legumes, which are rich in fiber and flavonoids. As a source of oil in that diet, consumption of olive oil replaces other forms of saturated fat, such as animal butter and margarine. Dairy products, especially yoghurt and cheese, are taken on a daily basis, while consumption of fish and poultry is recommended up to twice a week, while 4-7 eggs per week can be eaten. Researchers have noted decreased uric acid levels in subjects with better adherence to a Mediterranean style diet [6,7]. Furthermore, a prospective cross-sectional analysis of 4449 elderly participants with high cardiovascular risk showed an inverse association between increasing level of adherence to the Mediterranean diet and decreasing incidence of hyperuricemia ($P < 0.001$) [8]. Also, in the ATTICA study that utilized MedDiet scoring, Kontogianni, et al. found that greater compliance to the Mediterranean diet resulted in better outcomes regarding serum uric acid and consumption of dairy products also seemed to reduce that level [9]. Moreover, in elderly individuals without known cardiovascular disease, linear regression analysis revealed that MedDiet scores were inversely associated with uric acid level [10].

Another termed the "Dietary Approaches to Stop Hypertension (DASH)" diet emphasizes adequate intake of fresh fruits and vegetables, as well as whole grains and low-fat dairy products. However, the effects of the DASH diet on serum uric acid concentration are controversial. Randomized control trial (RCT) results showed that the DASH diet lowers serum uric acid concentration [11,12], while another report suggested that this diet is associated with a lower risk of gout, thus supporting its urate lowering effect in individuals with hyperuricemia [13]. In contrast, findings of another RCT indicated that the DASH diet does not lower serum uric acid [14]. The reason for this discrepancy is not clear, though salt in the diets of the subjects may have been an underlying factor. While these findings are promising, the data are limited and additional studies may be required.

Food items

Types of foods and drinks that raise the concentration of serum uric acid in serum and often trigger gout attacks include red meats and some varieties of fish, as well as fruit juice, sugary drinks and alcohol. On the other hand, whole fruits, vegetables, whole grains, coffee, black and green tea, and low-fat dairy products may help to prevent gout attacks by lowering uric acid level.

Coffee

Coffee is a beverage commonly consumed in Western countries as well as in Japan, and has been shown to be associated with lowered serum uric acid and hyperuricemia frequency [15]. Another report noted inverse associations of coffee consumption with serum uric acid concentration and hyperuricemia in men regardless of adjustment for covariates [16]. According to Choi HK, et al., drinking more than four cups of coffee (including decaffeinated) a day significantly lowered serum uric acid levels up to a maximum of about 8% [17]. They also prospectively evaluated the relationship between coffee intake and risk of incident gout in a large cohort of men, and those findings suggested that long-term coffee consumption is associated with a lower risk of incident gout [18,19].

A systematic review and meta-analysis of the effects of coffee intake, including nine studies published between 1999 and 2014, demonstrated that coffee has a significant effect to reduce serum uric acid. Therefore, moderate coffee intake might be recommended for primary prevention of hyperuricemia and gout in both genders [20]. Another systematic review and meta-analysis of the effects of coffee intake on serum uric acid, including six cross-sectional, three cohorts, and two case-control studies, found no significant difference between the highest and lowest coffee intake categories, while the overall multivariable adjusted relative risk for gout showed a significant inverse association between coffee consumption and incidence of gout [21]. Therefore, further well-designed RCTs are needed to investigate these issues in greater detail.

Although the mechanisms of the urate-lowering effect remain to be clarified, a single cup of coffee contains approximately 280 mg of polyphenols and the beverage is known to be major source of the phenol chlorogenic acid, which has been suggested to inhibit xanthine oxidase in results of *in vitro* studies [22,23]. Oral administration of chlorogenic acid (2 g) was found to decrease serum uric acid concentration (5.43±0.91 *vs.* 5.33±0.92 mg/dL, $p<0.05$) (Y. M., personal observation). More recently, pyrogallol contained in hot-water extracts of roasted beans was suggested to be the main contributor to the xanthine oxidase inhibitory activity of coffee [24].

Black tea and green tea

Although the study by Choi HK, et al. showed that ingestion of black tea had no effect on serum uric acid concentration [17], Bahorun, et al. found that black tea intake significantly decreased the level of serum uric acid level by 9.4% in males and 7.1% in females with the highest baseline values [25] Moreover, a recent study demonstrated that ingestion of black or green tea decreased the serum level of uric acid in hyperuricemia model mice [26].

Polyphenols such as catechin (10-18%), teanin (0.6-2%), and flavonoids (0.6-0.7%) are abundant in green tea. In an *in vivo* experiment using hyperuricemia model mice, administration of green tea polyphenols decreased the concentration of uric acid in serum, and suppressed the activity and expression of xanthine oxidase as well as expression of URAT1, while it increased the levels of expression of OAT1 and OAT3 [27]. Therefore, it is considered that green tea polyphenols decrease uric acid production and also increase uric acid excretion. In addition, it has been reported that administration of tea extract (2 g) to 30 healthy individuals for two weeks decreased uric acid clearance and serum uric acid levels, though the differences were not significant [28].

Dairy products

Dairy products, recognized as important dietary factors for reducing serum uric acid and risk of gout development, are low in purine content. Thus, dairy protein may exert a urate-lowering effect without providing the concomitant purine load contained in other protein sources, such as meat and seafood. Choi HK, et al. studied the relationship between serum uric acid level and dairy products, including milk and yogurt, and found a significant inverse relationship between milk consumption and serum uric acid level. They also reported significantly lower serum uric acid levels in subjects who consumed milk one or more times per day or yogurt at least

once every other day as compared with those who did not consume either [29]. In another prospective study of subjects over a 12-year period, they also reported that a higher level of consumption of dairy products was associated with decreased risk of gout [4]. Thus, milk products have been recognized as an important dietary factor for reducing serum uric acid level as well as risk of gout development.

Dalbeth N, et al. examined the acute effect of milk on serum uric acid levels and showed that intake of 800 mL (80 g protein) of skim milk decreased its concentration by 10% at three hours after ingestion [30]. Furthermore, Kurajoh M, et al. administered bovine milk (15 ml/kg body weight) to six healthy subjects and found that its ingestion promoted urinary excretion of uric acid by increasing amino acid concentration [31]. Although the underlying mechanism is not clear from those studies, the mechanism of the urate-lowering effect of milk may be explained, at least in part, from findings of studies showing that orotic acid, casein, and lactalbumin, which have been reported to decrease serum uric acid level by decreasing reabsorption of uric acid, promotes its excretion from the kidneys [32,33].

Dietary fiber

Studies of Wistar rats fed dietary fiber have shown that it lowers serum uric acid and allantoin concentrations, as well as the urinary excretions of their compounds, suggesting dietary fiber intake decreases absorption of uric acid, and can be used for prevention or suppression of hyperuricemia [34,35]. Additionally, it has been suggested that a high-fiber diet may alleviate inflammation caused by gout [36]. These findings have important implications for treatment of hyperuricemia and gout patients.

Vegetables and Fruits

Vegetables

A number of reports have shown reduced risk of hyperuricemia and gout with vegetarian, especially lacto-vegetarian, diets. Two cohort studies also suggested an association of a vegetarian diet with a lower serum uric acid level, and reduced risk of hyperuricemia and gout [37,38]. In addition, two prospective cohort studies presented by Chiu THT, et al. (Tzu Chi Health Study, Tzu Chi Vegetarian Study) showed that a vegetarian diet is associated with lower gout risk [39]. In contrast, Schmidt JA, et al. reported that vegan subjects who strictly abstained from animal products, such as meat, poultry, game, fish, and shellfish, had higher serum concentrations of uric acid as compared to meat and fish eaters, and vegetarians, especially among men [40]. The higher uric acid concentration present in vegans might be ascribable to lack of consumption of dairy products, which are thought to lower uric acid, while the low calcium content of a vegan diet may contribute to raise uric acid concentration.

Findings of the Singapore Chinese Health Study, a large prospective cohort study that included 63,257 Chinese adults, suggested that soy and non-soy legumes are associated with reduced risk of gout [41]. Purple sweet potato is a type of sweet potato that has abundant anthocyanins and administration of 100 mg/kg of anthocyanin extracts from purple sweet potato in hyperuricemia model mice resulted in decreased serum uric acid concentrations [42]. Later, it was clarified that anthocyanin extract from purple sweet potato suppressed xanthine oxidase activity as well as expressions of URAT1, GLUT9 [43].

Fruits

Recent research has found that fructose, purine, polyphenols, vitamin C, dietary fiber, and minerals present in fruits may influence serum uric acid levels. Although ingestion of fruits will theoretically increase the concentration of serum uric acid, since they contain abundant fructose, their effects on serum uric acid and gout are complex. Some studies have found that fruit ingestion lowered serum uric acid levels and possibly reduced the risk of gout [44,45], while others have reported that fruit in the diet was associated with increased incidence of gout flares [46,47]. These discrepancies may be ascribable to the several different nutrients existing in fruits, such as fructose, vitamin C, epicatechin, flavonoids, fiber, and potassium [48].

Cherries have long been recommended for gout patients, largely based on anecdotal evidence showing them useful as complementary and alternative medical therapy. Intake of a large amount of cherries may reduce the level of serum uric acid. Ten healthy females who

ate two servings of Bing cherries had plasma uric acid decreased by 15% at five hours after consumption, as compared with the pre-consumption baseline ($P < 0.05$), along with an increase in urinary uric acid excretion [49]. In another report, 26 subjects (18 women, 8 men; 41±11 years old; BMI 31.3±6.0; 12 obese, 14 overweight) who consumed 240 mL/day of tart cherry juice for four weeks had serum uric acid levels reduced by 19.2% ($p < 0.05$) [50]. Other recent evidence supports an association between cherry intake and reduced risk of gout attacks, as a study of 633 patients with confirmed gout for at least one year found that those who consumed cherries (1/2 cup serving or equivalent to 10-12 cherries) or a cherry-based extract for two days had their risk of recurrent gout attack reduced by 35% [51]. On the contrary, it was also reported that tart cherry concentrate had no effect on serum uric acid level [52].

A relevant meta-analysis investigation has yet to be performed due to lack of relevant reports, and there is a high degree of variation in the methodologies and metrics used in previous studies. Therefore, further comprehensive trials or long-term follow-up studies will be required to evaluate the efficacy of cherry intake for patients with gout or hyperuricemia [53].

Food items that decrease the level of serum uric acid are listed in Table 1.

Food items	Ingredients	Supposed mode of action	References
Coffee	Chlorogenic acid	XO inhibition	22, 23
	Pyrogallol	XO inhibition	24
Black and green tea	Polyphenols	XO inhibition	27
		Decreased expression of URAT1	27
		Increased expression of OAT1 and OAT 3	27
Dairy products	Orotic acid, casein, and lactalbumin	Not specified (decreased reabsorption, increased urinary excretion)	32,33
Dietary fiber	-	Not specified (decreased absorption of uric acid)	34,35
Purple sweet potato	Anthocyanin	XO inhibition	43
		Decreased expression of URAT1 and GLUT9	43
Red onion	Quercetin	Decreased expression of URAT1 and GLUT9	91
Cherry	-	Not specified (increased urinary excretion)	49

XO denotes xanthine oxidase

Table 1: Food items that decrease serum uric acid level

Supplements and polyphenols

Vitamins

Vitamin C: In the Health Professional Follow-up Study, Gao, et al. demonstrated that a high amount of vitamin C intake (>1000 mg/day) significantly decreased serum uric acid concentration [54]. Also, Sun, et al. clarified an inverse association between vitamin C intake and risk of hyperuricemia in an adult population in the USA [55]. Most epidemiological studies have indicated a significant correlation between high vitamin C intake and lower serum uric acid levels, whereas a pilot randomized controlled trial showed that vitamin C (500 mg/day) for eight weeks had no clinically significant urate-lowering effects in patients with gout, suggesting that the effect of modest-dose vitamin C is small [56]. Several studies have described biological mechanisms by which vitamin C reduces uric acid in serum, such as increased glomerular filtration and/or competition for renal reabsorption [57]. In addition, vitamin C appears to induce uricosuria *via* action on the renal proximal tubules [58,59]. Other studies have also noted that vitamin C may act specifically at uric acid reabsorption sites in the apical brush border of the proximal tubule, such as urate transporter 1 (URAT1) [60], and towards the sodium-dependent anion cotransporter SLC5A8/SLCA12 [61].

Supplemental vitamin C intake of 1500 mg/day or greater was shown to reduce the multivariate relative risk of gout by 0.55 as compared with subjects whose vitamin C intake was less than 250 mg/day [62]. In contrast, a literature review showed that such studies have not clearly defined the benefits of a high daily intake of vitamin C for preventing development and recurrence of gout [63]. The exact anti-gout mechanism of vitamin C remains unknown, though its antioxidative property has been widely reported [64].

Folate, vitamin B6, and vitamin B12: The relationships of folate, vitamin B6, and vitamin B12 with serum uric acid are controversial. In an observational study, in females a lower risk of hyperuricemia with higher intake of folate was found, while there was no association of intake of vitamin B6 and B12 with the risk of hyperuricemia for females [65]. On the other hand, it has also been reported that long-term supplementation with folic acid and vitamin B12 had no effects on serum uric acid concentrations [66]. Therefore, further comprehensive trials will be required to evaluate the effects of these vitamins on level of serum uric acid in serum.

Polyphenols

Polyphenols, a large family of natural compounds widely distributed in plant foods and wine that have attracted a great deal of medical attention, possess anti-inflammatory and anti-carcinogenicity properties, as well as antimicrobial and antioxidant activities. Polyphenols with antioxidant properties contained in wine may play a role in alleviating the uric acid-raising effect of alcohol, since uric acid is considered to be an indicator of oxidative stress and antioxidants affect serum uric acid concentration [67]. The relationships of some polyphenols with uric acid metabolism have been investigated, with the results revealing hypouricemic effects.

Oligomerized polyphenol (Oligonol®): Oligomerized polyphenol (Oligonol®) is a phenolic compound formulated from lychee fruit that contains a mixture of 15.7% polyphenol monomers (catechin, epicatechin, *etc*.) and 13% polyphenol dimers (proanthocyanidins), with the remaining 71.3% other polyphenols produced by polyphenol polymerization. In a study of six healthy male subjects, Oligonol® significantly decreased the serum concentration of uric acid from 5.3±0.9 to 5.1±0.9 mg/dL after 3.5 hours [68]. It has also been suggested that several catechins contained in Oligonol®, such as epicatechin gallate and epigallocatechin gallate, as well as theaflavins act as xanthine oxidase inhibitors [67], thereby decreasing uric acid production and oxidative stress. Thereafter, Oligonol® was found to inhibit buttermilk-induced xanthine oxidase activity in a dose-dependent manner [68]. The uric acid lowering effect through inhibition of xanthine oxidase by Oligonol® may be partially explained by the results of epidemiological studies showing that moderate consumption of wine, abundant in polyphenols, does not have effects on serum uric acid concentration and or increase the risk of gout as compared with that of beer or liquor [69].

Chrysanthemum flower polyphenols: According to Peng A, et al., a *chrysanthemum morifolium Ramat 'Boju'* extract demonstrated strong xanthine oxidase inhibitory activities and also showed a significant hypouricemic effect in experimental hyperuricemia model rats by regulating expression of renal uric acid transport-related proteins (ABCG2, URAT1, GLUT9) [70]. Similar effects by extracts of *Chrysanthemum indicum* L. (Ci) were also recently identified [71]. Various reports have noted that intake of extracted chrysanthemum flower polyphenols inhibits liver xanthine oxidase activity and also promotes urinary uric acid excretion, thus inhibiting a rise in serum uric acid level. Comprehensive gene expression analysis of kidney specimens using a DNA microarray method showed increases in gene expression of the uricosuric transporters ABCG2 and SLC17A1 [72], thus the uricosuric action of chrysanthemum flower polyphenols may be ascribed to those genetic changes. In another study, co-administration of foods rich in chrysanthemum flower polyphenols and purines alleviated an increase in serum uric acid level in pre-hyperuricemia subjects [73].

Catechins and procyanidins: An investigation of the inhibitory effects of five catechins contained in tea on xanthine oxidase activity and their mode of action, inhibitory constant, and mode of inhibition, including catechin (Ki = 303.95 μM, noncompetitive type), epicatechin (Ki = 20.48 μM, mixed type), epigallocatechin (Ki = 10.66 μM, mixed type), epicatechin gallate (Ki = 2.86 μM, mixed type), and epigallocatechin gallate (Ki = 0.76 μM, competitive type), noted that the inhibitory constant of epigallocatechin gallate was comparable to that of allopurinol (Ki = 0.30 μM, mixed type) [74]. It has also been shown that epigallocatechin gallate reduces inflammation caused by uric acid [75], while another study found that theaflavin, theaflavin gallate, and theaflavin 3,3'-digallate had xanthine oxidase inhibitory activities [76]. Procyanidin is a polyphenol with extremely strong antioxidant action that develops the structure of a connected catechin. When administered to hyperuricemia model mice, both serum uric acid level and xanthine oxidase activity were decreased, though no relationship between those was found [77].

Resveratrol: Resveratrol, a plant compound that functions like an antioxidant, is strongly associated with red grapes and red wine made from grapes, while in Japan and China, "*itadori*" tea (*Reynoutria japonica*) is another rich source of resveratrol. This compound has multiple biological activities leading to anti-inflammatory, antiproliferative, and antioxidant effects. In addition, a uricosuric action, as well as a urate lowering effect and inhibition of gout flare by resveratrol have been observed in experimental model mice

[78], while other mouse experiments showed that resveratrol suppressed URAT1 and GLUT9 expression [79], and decreased the level of serum urate and recurrence of gout flare [80,81]. Furthermore, resveratrol has been reported to potently inhibit xanthine oxidase activity [82].

Melinjo (*Gnetum gnemon*), which originally came from Indonesia, is rich in resveratrol. Findings of a double-blind trial showed that a Melinjo extract decreased the level of serum uric acid (6.7±1.5 to 6.1±1.4 mg/dL (p=0.009), while that level did not change in the placebo group (6.6±1.1 to 6.6±1.1 mg/dL) [83].

Quercetin: Quercetin, a kind of flavonoid, is abundant in many plants, including citrus fruits, onions, and buckwheat. Previous studies have demonstrated that quercetin reduces serum uric acid levels by inhibiting xanthine oxidase activity [84-86] or increasing uric acid excretion action [87]. Administration of quercetin in experimental hyperuricemia model mice decreased serum uric acid concentration, which was accompanied by increased urinary excretion of uric acid, as well as decreased expressions of GLUT9 and URAT1 [88]. Since the dose used in that study showed no definite adverse effects on humans, it is expected that quercetin can be given as supplementation for patients with hyperuricemia. In addition, a therapeutic effect of quercetin on gouty arthritis was shown in model rats [89] as well as suppression of NLRP3 inflammasome activation [90], suggesting an effect to relieve a gout attack. Furthermore, in a randomized double-blinded placebo-controlled crossover trial, administration of 500 mg of quercetin (red onion, 100 g) to 22 healthy pre-hyperuricemia males (age 19-60 years) for four weeks decreased the concentration of serum uric acid concentration by 26.5 mmol/L (0.4 mg/dL) (p=0.008) [91].

Ferulic acid: Ferulic acid (4-hydroxy-3-methoxycinnamic acid), found in Japanese parsley (*Ferula communis*) and named after the giant fennel plant that grows wild on the Mediterranean Sea coast, is a potent antioxidant that naturally exists in the cell walls of grains, fruits, and vegetables, where it is conjugated with mono-, di-, and polysaccharides, as well as other compounds. Ferulic acid has been reported to have an inhibitory effect on gouty arthritis, which is considered to be caused by inhibition of the NLRP3 inflammasome [92].

Rutin: Rutin, a citrus fruit flavonoid discovered in the Rutaceae family, is used as a medicinal herb and found in abundant quantities in Tartary buckwheat, a type of buckwheat extensively cultivated in Asia. Tartary buckwheat contains 100 times the amount of rutin as compared to the buckwheat present in soba. Administration of rutin to hyperuricemia model mice resulted in decreased serum uric acid concentration and increased uric acid excretion in accordance with inhibition of mRNA expression, as well as protein levels of GLUT9 and URAT1, uric acid reabsorption transporters [93]. Rutin has also been shown to have an inhibitory effect on xanthine oxidase activity [84] and an ameliorative effect on inflammation *via* NLRP3 inflammasome activation [90].

Curcumin: Curcumin is used as a spice and coloring agent in the food industry, along with a yellow polyphenol compound included in turmeric. In an RCT, curcumin was administered to 20 patients with nonalcoholic fatty liver disease (NAFLD) for eight weeks and the level of uric acid in serum was found to significantly decrease from 5.23±1.02 to 4.80±0.85 mg/dL (p<0.001) [94]. In contrast, results of another RCT of 39 patients with asymptomatic hyperuricemia suggested no effects of curcumin on reducing serum uric acid level or increasing uric acid clearance [95]. Thus, the influence of curcumin on serum uric acid remains to be clarified by a more intensive RCT in the future. Curcumin has been shown to possess xanthine oxidase inhibitory action [96]. Furthermore, in rat and mouse models, curcumin ameliorated monosodium urate-induced inflammatory response by inhibition of IκBα degradation, NF-κB signaling pathway activation, mitochondria damage, and the activity of NLRP3 inflammasome [97,98]. In the FAO and FAO/WHO Joint Expert Committee on Food Additives, the daily intake limit of curcumin is considered to 3 mg/kg of body weight, thus careful attention must be paid in regard to excessive intake.

Chrysin: Chrysin is a flavonoid compound that occurs naturally in honey, propolis, and mushrooms, and has anti-inflammatory, anti-hyperuricemia, and antioxidant effects. An *in vitro* study demonstrated its inhibitory action on xanthine oxidase activity [99]. Oral administration of chrysin for four weeks to hyperuricemia model rats decreased the level of serum uric acid along with inhibition of xanthine oxidase activity in the liver. Moreover, chrysin downregulated the expression of the uric acid reabsorption proteins URAT1 and GLUT9, while it upregulated expressions of the uric acid excretion proteins OAT1 and ABCG2 in the kidneys of rats with hyperuricemia [100].

Sinapic acid: Sinapic acid is a type of phytochemical found in various plants, such as spices, citrus and berry fruits, vegetables, cereals, and oilseed crops. It is known to exhibit antioxidant, anti-inflammatory, anticancer, antimutagenic, antihyperglycemic, neuroprotective, and antibacterial activities. In addition, a possible hypouricemic effect has been suggested. Furthermore, sinapic acid was found to inhibit xanthine oxidase activity, and reduce serum and urine uric acid levels, suggesting it as a possible anti-hyperuricemia agent [101].

The effects of polyphenols to lower urate levels, such as uricosuric action and xanthine oxidase inhibition, as well as gout amelioration have mostly been shown in animal and *in vitro* studies. Since clinical studies with humans are sparse, results of future investigations with large cohorts of human subjects are anticipated to provide important findings related to safety and appropriate intake, as well as the usefulness of any urate lowering and/or gout ameliorating effects.

Polyphenols known to decrease uric acid formation and/or increase uric acid excretion are listed in Tables 2 and 3.

Polyphenol	References
Epicatechin gallate, epigallocatechin gallate	67, 74
Oligomerized Polyphenol	68
Chrysanthemum flower Polyphenols	72
Catechin, epicatechin, epigallocatechin	74
Theaflavin, theaflavin gallate, theaflavin di-gallate	76
Procyanidin	77
Resveratrol	82
Quercetin	84,85,86
Rutin	84
Curcumin	96
Chrysin	99
Sinapic acid	101

XO: xanthine oxidase

Table 2: Polyphenols that decrease uric acid formation by XO inhibition

Polyphenol	Urate transporter target	References
Chrysanthemum flower Polyphenols	Suppressed URAT1 and GLUT9 expression Increased ABCG2 and SLC17A1 expression	70, 72
Resveratrol	Suppressed URAT1 and GLUT9 expression	79
Quercetin	Suppressed URAT1 and GLUT9 expression	88
Rutin	Suppressed URAT1 and GLUT9 expression	93
Chrysin	Suppressed URAT1 and GLUT9 expression, increased OAT1 and ABCG2 expression	100

Table 3: Polyphenols that increase uric acid excretion

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