Saudi Pharmaceutical Journal 30 (2022) 918–926

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Review

A review on benefits of quercetin in hyperuricemia and gouty arthritis

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ARTICLE INFO

Article history:
Received 11 December 2021
Accepted 26 April 2022
Available online 30 April 2022

Keywords:
Quercetin
Hyperuricemia
Gout
NLRP3 inflammasome
Antioxidant

ABSTRACT

Hyperuricemia becomes a public health problem worldwide. It is not only a major risk factor for gout but also associated with the development of life-threatening diseases such as chronic kidney disease and cardiovascular diseases. Although there are several available therapeutic drugs, some serious adverse effects and contraindications are concerned. These drive the search for an alternative therapy that is effective and safe. Quercetin is of particular interesting since it has been reported numerous pharmacological activities, especially anti-hyperuricemia, antioxidant, anti-inflammation and amelioration of metabolic syndromes and cardiovascular diseases which are comorbidities of hyperuricemia and gout. In addition, quercetin has been widely used as a health supplement for many diseases however, the use for hyperuricemia and gout has not been indicated. Therefore, this review aims to gather and summarize published data regarding the efficacy in preclinical and clinical studies along with possible mechanism of action, and safety aspect of quercetin in order to support the use of quercetin as a dietary supplement for prevention and management of hyperuricemia and gouty arthritis and/or use as alternative or combination therapy to minimize the side effects of the conventional drugs.

Contents

Peer review under responsibility of King Saud University.
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Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2022.04.013
1319-0164/

1. Introduction

Nowadays, lifestyle and diet changes lead to the rise of hyperuricemia around the world, especially in Western lifestyle countries (Li et al., 2020). It has been reported that the prevalence of hyperuricemia in the United States was 11.3–47%, European was 11.9–25.0%, and Japanese was 26.8% while the prevalence in Chinese was 13.1–13.3% (Butler et al., 2021). Hyperuricemia has gained increasing attention as a public health concern since it is not only a major risk factor for gout, but also associated with the development of life-threatening diseases including chronic kidney disease (CKD) and cardiovascular diseases (CVD) (Sun et al., 2021). Hyperuricemia is defined as a condition where the serum urate level exceeds the normal range which is 1.5 to 6.0 mg/dL in women and 2.5 to 7.0 mg/dL in men (Maiuolo et al., 2016). The elevated serum urate level is the result of overproduction from hepatic metabolism and cell turnover, or underexcretion through the kidney and gastrointestinal tract, or combination process (Dalbeth et al., 2016). Chronic elevation of serum urate above the saturation point, which is approximately 6.8 mg/dL, leads to precipitation of urate into monosodium urate (MSU) crystals (Martillo et al., 2014). In some individuals, the MSU crystals that deposit in joints and connective tissue could interact with the resident macrophages and activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and interleukin (IL)-1β production, resulting in an acute inflammatory response in gouty arthritis. However, hyperuricemia without MSU crystals deposition has been reported to stimulate immune responses and inflammation in gout and comorbidities but different pathway from MSU crystals (Cabău et al., 2020).

The strategies for management of hyperuricemia and gout are to lower serum urate levels by using urate-lowering drugs and treat gout flares by using anti-inflammatory drugs. However, allopurinol, the first-line urate-lowering drug, has been reported to cause a fatal adverse effects and anti-inflammatory drugs including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and colchicine commonly have undesired side effects and contraindications in some patients (Dalbeth et al., 2019, Pillinger and Mandell 2020). Therefore, the search for an effective and safe alternative therapy for management of hyperuricemia and gout is important and needed.

Quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavanone, Fig. 1) belongs to the flavonol subgroup of flavonoids. It is abundantly found in vegetables and fruits, especially onions, apples, berries, dill, fennel leaves, oregano, chili pepper, kale, lettuce and broccoli (Sampson et al., 2002, Dabeek and Marra 2019). By definition, quercetin is an aglycone. It is a yellow color, bitter taste and poorly soluble in water, but quite soluble in alcohol and lipids (Kelly 2011). In diets, quercetin is usually in form of glycosides, in which one or more hydroxyl group is replaced by different types of glycosyl groups (Wang et al., 2016). On the contrary, quercetin as an ingredient of dietary supplements is mostly in form of aglycone (Andres et al., 2018) and utilized as a nutritional supplement for many diseases such as cancer, cardiovascular diseases, diabetic, obesity, and arthritis (D'Andrea 2015). Numerous pharmacological activities have been reported to evidence the health benefits of quercetin such as prevention of cardiovascular and neurodegenerative diseases, anticancer, antidiabetic, antihypertensive, antihyperlipidemic, antibacterial, antiviral, antiallergy, antioxidant, anti-inflammatory, and anti-hyperuricemic activities (Kelly 2011, Anand David et al., 2016). Interestingly, several of these activities are benefits for hyperuricemia and gouty arthritis. However, the use of quercetin as health supplements or alternative therapy for hyperuricemia and gout has not been indicated. Therefore, this review aims to gather and summarize relevant preclinical and clinical studies including anti-hyperuricemic, anti-inflammatory, and antioxidant activities as well as ameliorate effect on comorbidities, possible mechanism of action, and safety aspect of quercetin. The results of this review may provide scientific evidences for further development of quercetin as a dietary supplement for prevention and management of hyperuricemia and gout and/or use as alternative or combination therapy to minimize the side effects of the conventional drugs.

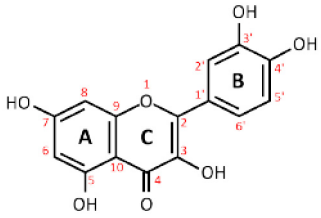

Fig. 1. Chemical structure of quercetin.

2. Effects of quercetin in hyperuricemia and gouty arthritis

2.1. Anti-hyperuricemic effect

Hyperuricemia is caused by urate overproduction and/or underexcretion (Dalbeth et al., 2016). Thus, any compounds that inhibit urate production and/or promote urate excretion are benefit for the treatment of hyperuricemia and gout as well. Quercetin is one of bioactive compounds that has been studied and reported of anti-hyperuricemic effect through several mechanisms including reducing urate production by inhibiting the corresponding enzymes and increasing urate excretion by regulating renal urate transporters.

2.1.1. Reducing urate production

Urate is the end product of purine metabolism pathway, which is involved of many enzymes as demonstrated in Fig. 2. Initially, adenosine monophosphate (AMP) is catalyzed to inosine via two different ways; by using AMP deaminase (AMPD) to form inosine monophosphate (IMP), followed by 5′-nucleotidase (5′NT) to form inosine, or by using 5′NT to form adenosine, followed by adenosine deaminase (ADA) to form inosine. Inosine is further converted to hypoxanthine by purine nucleoside phosphorylase (PNP). Hypoxanthine is converted to xanthine and further to urate by xanthine oxidoreductase (XOR). This enzyme has two different forms, xanthine dehydrogenase (XDH) which prefers NAD^+ and xanthine oxidase (XO) which prefers O_2 (Maiuolo et al., 2016). Among these enzymes, ADA and XOR, in particular XO, are key enzymes in purine metabolism and urate production (Jiang et al., 2020).

Quercetin has been known as effective XO inhibitor for many years (Beiler and Martin 1951) and reported in several studies (Cos et al., 1998, Nagao et al., 1999, Mo et al., 2007, Nile et al., 2017, Gainche et al., 2021). In a comparative study of various diet-

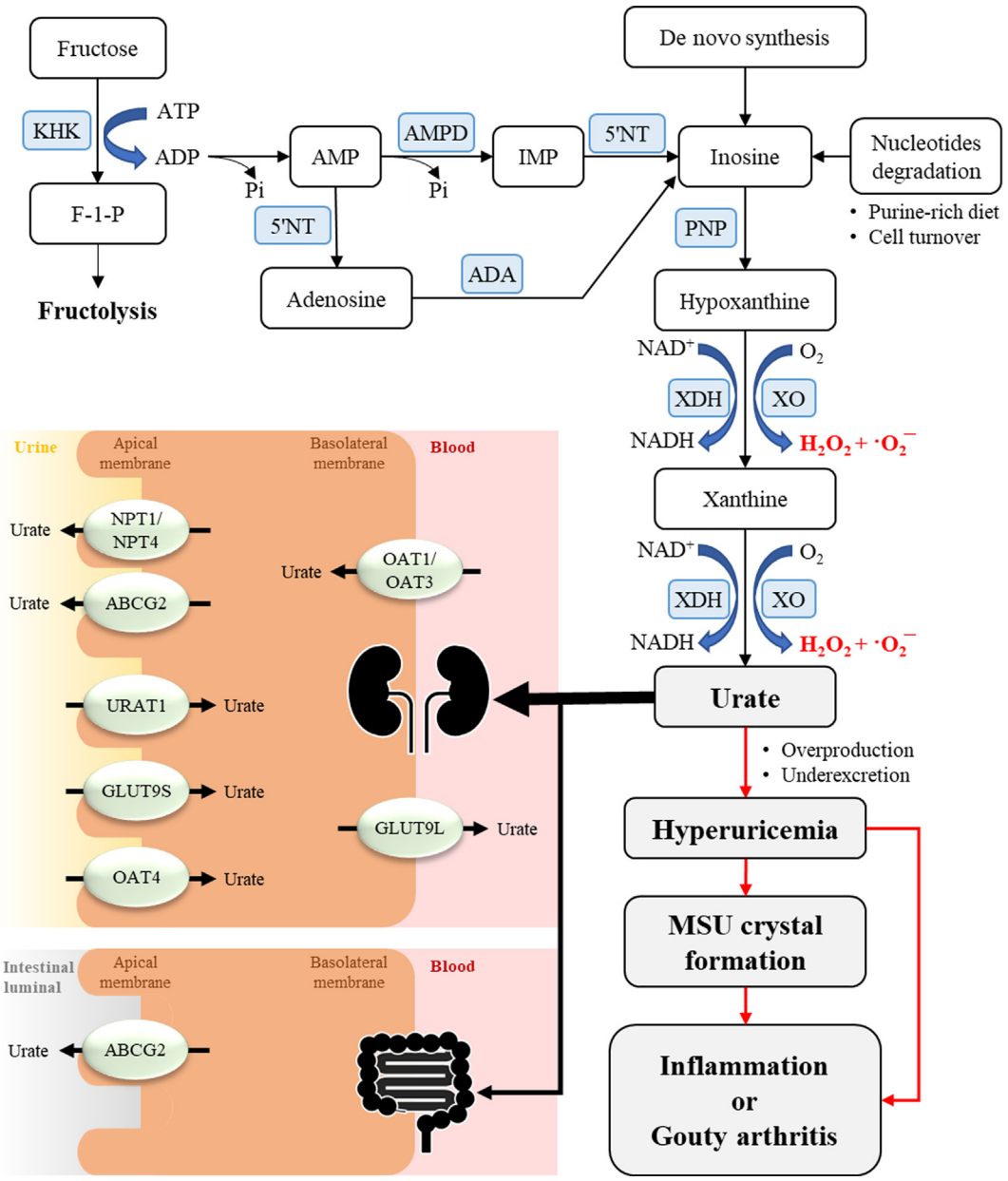

Fig. 2. Urate production and excretion in human body. **5′NT**, 5′-nucleotidase; **ADA**, adenosine deaminase; **AMPD**, AMP deaminase; **KHK**, ketohexokinase; **PNP**, purine nucleoside phosphorylase; **XO**, xanthine oxidase; **XDH**, xanthine dehydrogenase.

ary flavonoids, quercetin showed a potent inhibitory effect on XO with an IC50 value of 0.44 μM which was stronger than the standard allopurinol, an IC50 value of 0.77 μM (Nagao et al., 1999). In another study, quercetin isolated from *Filipendula ulmaria*, a plant traditionally used for gout, inhibited XO with an IC50 value of 1.07 ± 0.06 μg/mL which was also stronger than allopurinol, an IC50 value of 2.0 ± 0.1 μg/mL (Gainche et al., 2021). However, in some studies, quercetin showed less inhibitory effect than allopurinol. For example, quercetin isolated from onion solid waste showed an IC50 value of 10.5 ± 0.06 μg/mL while allopurinol was 6.5 ± 0.05 μg/mL (Nile et al., 2017). In comparative study between quercetin and its glycoside, quercetin showed an IC50 value of 11.0 μM, rutin was 95.0 μM, while allopurinol showed an IC50 value of 0.6 μM which was much stronger than quercetin (Adachi et al., 2021). In animal study, oral administration of quercetin at a dose of 50 mg/kg or above significantly reduced serum urate levels in potassium oxonate-induced hyperuricemic mice by inhibiting the activities of XDH and XO in the liver (Zhu et al., 2004). Another study showed that after treatment with quercetin (200 mg/kg), the serum uric acid levels of hyperuricemic mice were significantly lower by 11.3% in contrast to the normal mice which showed significantly elevated serum uric acid levels. In addition, quercetin treatment significantly decreased liver XO activity in both hyperuricemic mice and normal mice but significantly increased serum XO activity in normal mice which was correlated with the serum uric acid levels (Huang et al., 2011). The *in vitro* structure–activity relationship study suggested that high XO inhibitory effect of quercetin attributed to the presence of OH group at position C-5 and C-7, and the double bond between C-2 and C-3 (Cos et al., 1998). This result correlates with another study in animal model which suggested that the presence of OH group at position C-3, C-5 and C-7 with the double bond between C-2 and C-3 was relevant to the hypouricemic and XO inhibitory effect of quercetin (Mo et al., 2007). In addition, the molecular docking

study demonstrated that quercetin could bind to the site around isoalloxazine ring in the FAD domain of XO in which was involved in the formation of hydrogen peroxide (H_2O_2) indicating the potential of quercetin on inhibiting XO activity and preventing H_2O_2 formation (Zhang et al., 2018).

Adenosine deaminase (ADA) is one of the key enzymes in purine metabolism that irreversibly converts adenosine to inosine (Kutryb-Zajac et al., 2020). Interestingly, quercetin has been reported to inhibit ADA activity of aortic endothelial cells with an IC50 value of 26 μmol/L (Melzig 1996). In another study, quercetin inhibited not only the activity of ADA, but also the activities of XO and PNP with IC50 values of 55.6, 3.0 and 36.9 μM, respectively (Ozyel et al., 2021). However, in another study, quercetin showed weakly inhibitory effect on ADA activity in human plasma, no effect on PNP, and inhibited bovine milk XOR with an IC50 value of 23.6 ± 8.1 μM (Tumova et al., 2021).

Fructose is one of the dietary risk factors for hyperuricemia and gout (Li et al., 2018). High fructose intake contributes to increase urate level by stimulating urate production and reducing urate excretion. Fructose is mainly metabolized in the liver by ketohexokinase (KHK, or fructokinase), an initial enzyme in fructose metabolism. KHK phosphorylates fructose to generate fructose-1-phosphate, resulting in ATP and intracellular phosphate depletion. These stimulate AMPD to convert AMP into IMP and consequently urate production as demonstrated in Fig. 2 (Zhang et al., 2020). KHK consists of two isoforms namely KHK-A and KHK-C. KHK-A is widely expressed but its activity is relatively low due to a low fructose affinity, whereas KHK-C is primarily expressed in the liver, kidney, and intestines with higher affinity (Zhang et al., 2020). It has been reported that serum and hepatic urate of KHK-A/C knockout mice did not increase after receiving high fat diet or high fat high sucrose diet for 15 weeks. This result indicated that lack of fructokinase could prevent the increase in serum and hepatic urate (Ishimoto et al., 2013). In a clinical study of adults with non-alcoholic fatty liver disease, serum urate levels of participants receiving a KHK inhibitor PF-06835919 at a dose of 300 mg for 6 weeks were reduced by 11.5% compared to baseline (Kazierad et al., 2021). Interestingly, quercetin has reported to suppress the mRNA expression level of KHK and several genes of carbohydrate and lipid metabolism enzymes in the liver of rats receiving high-fructose diet (Mzhel'skaya et al., 2019). This result suggests that quercetin might inhibit KHK activity and reduce downstream process of fructose metabolism and urate production which could be another mechanism to reduce serum urate level.

2.1.2. Increasing urate excretion

As mentioned above, hyperuricemia is caused by urate overproduction or renal underexcretion through disturbance of reuptake and secretory transporters or intestinal underexcretion or in combination. Among these causes, renal urate underexcretion is the main cause of hyperuricemia. Most urate is filtered through the renal glomeruli. About 90% of the filtered urate is reabsorbed from the proximal tubules and the remainder is excreted in urine (Dalbeth et al., 2016, Sun et al., 2021). These processes are regulated by urate transporters located at the proximal tubules including urate excretion transporters such as sodium phosphate co-transporter type 1 or NPT1 (SLC17A1), NPT4 (SLC17A3), organic anion transporter 1 or OAT1 (SLC22A6), OAT3 (SLC22A8), ABCG2, and urate reabsorption transporters such as urate transporter 1 or URAT1 (SLC22A12), glucose transporter 9 or GLUT9 (SLC2A9), and OAT4 (SLC22A11) (Sun et al., 2021) as demonstrated in Fig. 2. Among these transporters, serum urate levels are mainly regulated by NPT1, ABCG2, URAT1, and GLUT9. Dysfunction of these transporters are associated with hyperuricemia and increase risk of gout (Dalbeth et al., 2019).

Several studies demonstrated that quercetin could reduce serum urate levels not only by inhibiting enzymes involved in the urate production, but also increasing renal urate excretion. The study in fructose-fed rat induced MetS, hyperuricemia, and renal dysfunction demonstrated that the administration of 100 mg/kg quercetin significantly lowered serum urate levels and attenuated dysregulation of SLC2A9v2, renal-specific transporter (a homolog of human URAT1), organic anion transporters (OAT1 and UAT), and organic cation transporters (OCT1 and OCT2), leading to increase urinary urate excretion (Hu et al., 2009). In another study, potassium oxonate-induced hyperuricemic mice received quercetin at dose of 25, 50 and 100 mg/kg exhibited significantly decreased serum urate and uromodulin levels, renal uromodulin concentration and increased urate and uromodulin excretion by regulating the renal organic ion transporters including OAT1, OCT1, OCT2, OCTN1, OCTN2, URAT1 and GLUT9 and uromodulin (Hu et al., 2012a,b). These results indicate that quercetin could regulate renal transporters by promoting the activity of urate excretion transporters and suppressing the activity of urate reabsorption transporters, resulting in enhancing urate renal excretion and ameliorating hyperuricemia and renal dysfunction.

2.1.3. Clinical studies on anti-hyperuricemic effect

There are many evidences supporting the hypouricemic effect of quercetin from preclinical studies, but human clinical studies proving its efficacy are still lacking. To the best of our knowledge, there is only one clinical study where plasma urate level is a primary outcome. In the randomized, double-blinded, placebo-controlled, cross-over trial, twenty-two healthy male volunteers with high plasma urate level (339 ± 51 μmol/L) who received 500 mg/day quercetin for 4 weeks, exhibited significant lowered levels of plasma urate by 26.5 μmol/L (equivalent to approximately 8%), without affecting urinary urate excretion, BMI, fasting glucose, or blood pressure (Shi and Williamson 2016). However, in other clinical studies where plasma urate level is not a primary outcome, the results are controversial. In double-blinded, placebo-controlled, cross-over trial, ninety-three overweight or obese subjects with MetS traits who received 150 mg/day quercetin for 6-week showed reduction in SBP and plasma oxidized LDL concentrations but did not affect serum urate levels (Egert et al., 2009). In bioavailability study of thirty-five healthy volunteers, supplementation with either 50, 100, or 150 mg/day quercetin for 2 weeks did not significantly affect serum urate levels (Egert et al., 2008). These results suggest that the effect of quercetin on serum urate level might be dependent on the dose, length of treatment time, and clinical characteristics of participants.

Interestingly, there is a study reporting the effect of adding quercetin to antihypertensive and urate-lowering regiments in patients with gout and essential hypertension for 12 months. The results showed that serum uric acid levels of the patients in the treatment group with quercetin were lower and achieved to the target level of uric acid faster than the patients in the treatment group without quercetin. In addition, the patients in the quercetin group showed better echocardiographic parameters of diastolic function left ventricular, renal function, and blood pressure lowering than patients in comparative group. These indicated the potential benefit of adding quercetin in treating patients with gout and essential hypertension (Kondratiuk and Synytsia 2018).

2.2. Anti-inflammatory effect

In hyperuricemic patients, some individuals have evidence of MSU crystal deposition, and in some individuals with MSU crystal deposition have experienced to suffer from gout flares. A gout flare is a clinically evident episode of acute inflammation which causes a

rapid onset of a painful, swollen, hot, and red joint (Dalbeth et al., 2019). The inflammation is known to associate with the interaction between MSU crystals and the resident macrophages activating the NLRP3 inflammasome and IL-1β production. There are two signals required for the inflammasome activation. Firstly, priming signal, MSU crystal, free fatty acids and lipopolysaccharide which act as damage-associated molecular patterns (DAMPs) are able to trigger Toll- like receptor 2 (TLR2) or TLR4 signaling and induce the expression of the inflammasome components and intracellular pro-IL-1β production through TLR-MyD88-NF-κB signaling pathway. The second, activating signal, the uptake of MSU crystals activates NLRP3 inflammasome components assembly, resulting in caspase-1 activation. Activated caspase-1 cleaves pro-IL-1β into its active form, IL-1β which triggers the production of other inflammatory cytokines such as TNF-α, IL-6 and IL-8. Then, IL-8 recruits neutrophils and accelerates the inflammatory process (So and Martinon 2017, Dalbeth et al., 2019, Szekanecz et al., 2019, Cabău et al., 2020). However, apart from MSU crystals, soluble urate has been reported to activate the NLRP3 inflammasome through several mechanisms such as TLR4/MyD88/NF-κB signaling pathway (Xiao et al., 2015) and inducing mitochondrial ROS production (Braga et al., 2017) as demonstrated in Fig. 3. Therefore, inhibition of NLRP3 inflammasome-IL-1β pathway is suggested to be a therapeutic target in treatment of gouty inflammation as well as others similar inflammatory conditions (Szekanecz et al., 2019).

2.2.1. Targeting NLRP3 inflammasome-IL-1β pathway

Quercetin is considered as an anti-inflammatory agent and has been reported to reduce inflammation in several models through different mechanisms, particularly through NLRP3 inflammasome-IL-1β pathway (Carullo et al., 2017). In animal model of spinal cord injury, administration of 100 mg/kg quercetin significantly reduced protein levels of NLRP3, ASC, active-caspase-1, IL-1β, IL-18 and TNF-α in the spinal cord tissue of rat suggesting the inhibitory effect on NLRP3 inflammasome activation and pro-inflammatory cytokine production (Jiang et al., 2016). Moreover, in streptozotocin-induced diabetic nephropathy rat, quercetin treatment at the dose of 25, 50, and 100 mg/kg could ameliorate renal injury and dysfunction by suppressing renal NLRP3 inflammasome activation, and regulating renal urate transport-related proteins (Wang et al., 2012). This result correlates with another study of fructose-fed rats (Hu et al., 2012a,b). Treatment with 50 and 100 mg/kg quercetin ameliorated renal inflammation by suppressing NLRP3 inflammasome activation, and subsequently decreasing pro-inflammatory cytokines including IL-1β, IL-6, IL-18 and TNF-α as well as improved hyperuricemia, dyslipidemia and renal dysfunction. In addition, in MSU-induced gouty arthritis in mice model, quercetin at a dose of 100 mg/kg showed anti-inflammatory and analgesic effects through inhibiting MSU-induced mechanical hyperalgesia and leukocyte recruitment, TNF-α and IL-1β production, NFκB activation, NLRP3 inflammasome components mRNA expression, decrease of antioxidant capacity, superoxide anion production, and inducing Nrf2 and HO-1 mRNA expression (Ruiz-Miyazawa et al., 2017). In another gouty arthritis rat model induced by acute MSU crystal injection, treatment with 200 and 400 mg/kg quercetin inhibited joint edema and histological signs of acute inflammation, suppressed leucocyte recruitment into injected joints, decreased levels of inflammatory mediators including IL-1β, TNF-α, COX-2, PGE2, and NO, decreased levels of malondialdehyde and increased antioxidant enzyme activity of SOD, CAT and GSH-PX (Huang et al., 2012). These results suggest that quercetin effectively suppressed NLRP3 inflammasome activation and IL-1β production which might ameliorate inflammation in gouty arthritis.

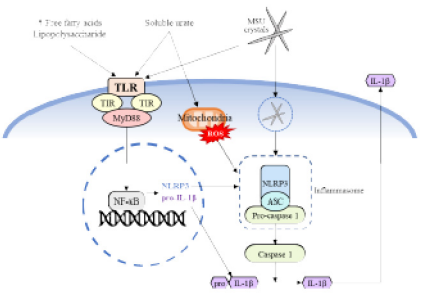

Fig. 3. NLRP3 inflammasome priming and activation in gouty arthritis.

2.2.2. Targeting TLR signaling pathway

Inhibition of TLR signaling is one of the promising therapies for inflammatory diseases including inflammatory arthritis (Gao et al., 2017, Santos-Sierra 2021) and as mentioned above, gouty inflammation is involved with TLR-MyD88-NF-κB signaling pathway (Cabău et al., 2020). In *in vitro* study, quercetin inhibited the ligand-induced activation of TLR2 and TLR4 and suppressed the activation of NF-κB induced by MyD88 overexpression, suggesting that quercetin acts as a TLR signaling inhibitor and affects the TLR-MyD88-NF-κB signaling pathway (Shibata et al., 2014).

2.2.3. Clinical studies on anti-inflammatory effect

To date, there is still lack of clinical study on the effect of quercetin on gouty arthritis, however a clinical study in rheumatoid arthritis has been reported. In double-blind, randomized, placebo-controlled clinical trial, fifty women with rheumatoid arthritis who received quercetin at a dose of 500 mg/day for 8 weeks showed significant improvements in clinical symptoms including early morning stiffness, morning and after-activity pain, disease activity and health assessment questionnaire, as well as plasma hs-TNF-α level (Javadi et al., 2017). However, the use of quercetin with diclofenac might not be recommended for gouty arthritis pain, since there is a study reporting that co-administration of quercetin and diclofenac exhibited antagonistic antinociceptive interaction in pain-induced functional impairment in the rat model (Ventura-Martínez et al., 2021).

2.3. Antioxidant effect

Oxidative stress is one of the early events associated with gout and comorbidities which is triggered by reactive oxygen species (ROS) and pro-inflammatory cytokines (Zamudio-Cuevas et al., 2015). In the last two steps of purine metabolism pathway, XOR, in particular XO form, oxidizes hypoxanthine to xanthine and further to urate, generating H_2O_2 and $\cdot O_2^-$which are ROS. In the presence of iron, $\cdot O_2^-$ is converted to hydroxyl radical (·OH) via the Haber-Weiss and Fenton reactions. Under hypoxic conditions, these ROS can be produced by XDH and $\cdot O_2^-$ can further react with nitric oxide (NO) leading to generate reactive nitrogen species (RNS), particularly peroxynitrite ($ONOO^-$) (Battelli et al., 2016, Maiuolo et al., 2016). In addition, MSU crystals have been reported to induce the release of ROS and RNS in human fibroblast-like synoviocytes which may involve with NADPH oxidase system in THP-1 cells (Zamudio-Cuevas et al., 2016). Moreover, soluble urate has also been reported to induce mitochondrial ROS production, resulting in NLRP3 inflammasome activation (Braga et al., 2017). The overproduction of ROS and RNS causes oxidative stress which not only leads to joint damage and inflammation in gouty arthritis but also pathogenesis of various diseases such as diabetic, hypertension, cardiovascular diseases, and cancer (Zamudio-Cuevas et al., 2015, Battelli et al., 2016). Therefore, antioxidants that

reduce oxidative stress might ameliorate inflammation in gouty arthritis and related diseases.

2.3.1. Free radical scavenging

Quercetin is well known to be a potent antioxidant compound. Several studies demonstrated potent *in vitro* antioxidant activities in various assays such as FRAP, DPPH, ABTS, and OH radicals (Xie et al., 2015, Nile et al., 2017, Zeng et al., 2020). The antioxidant activity of quercetin is suggested to relate to its structure that promotes free radical scavenging capacity including the presence of a 3′, 4′ -catechol structure in the B-ring, a free OH group at C-3, and a double bond between C-2 and C-3 in conjugation with a 4-carbonyl group in the C-ring (Heim et al., 2002).

2.3.2. Strengthening antioxidant defense system

Besides free radicals scavenging capacity, quercetin has been reported to strengthen antioxidant defense system. In oxonate-induced hyperuricemic rats, treatment with 5 mg/kg quercetin not only significantly reduced the serum uric acid levels of hyperuricemic rats by inhibiting liver XO and XDH activities, but also significantly increased serum total antioxidant capacity (FRAP value) in both normal and hyperuricemic rats and significantly reduced the elevated levels of malondialdehyde in hyperuricemic rats (Haidari et al., 2011). In galactose-induced oxidative stress in mice, treatment with 0.3 mmol/kg quercetin increased serum total antioxidative capacity, superoxide dismutase, catalase, and glutathione peroxidase levels as well as enhanced mRNA expression levels of these antioxidant enzymes, and decreased serum contents of malondialdehyde and nitric oxide (Zeng et al., 2020). Another study on monosodium urate crystal-induced inflammation in rats revealed that administration of 200 and 400 mg/kg quercetin decreased malondialdehyde level and increased the activity of antioxidant enzymes, namely superoxide dismutase, catalase, and glutathione peroxidase (Huang et al., 2012). These antioxidant enzymes play a major role in the prevention of oxidative damage by detoxifying ROS and RNS. Superoxide dismutase is the first enzyme that scavenges $\cdot O_2^-$ and catalytically converts into O_2 and H_2O_2, and then catalase converts H_2O_2 to water and oxygen, while glutathione peroxidase converts H_2O_2 into water (Nimse and Pal 2015).

2.3.3. Clinical studies on antioxidant effect

Many *in vitro* and *in vivo* studies have confirmed the antioxidant potential of quercetin. However, there are few clinical studies investigating the effect of quercetin on antioxidant status and oxidative stress markers. In a double-blind intervention study, sarcoidosis patients supplemented with high dose quercetin (2,000 mg) for 1 day showed antioxidant defense improvement indicated by the increased total plasma antioxidant capacity and reduced malondialdehyde levels (Boots et al., 2011). In randomized, placebo-controlled study of type 2 diabetics patients, supplementation with 250 mg/day quercetin for 8 weeks showed improvement in total antioxidant capacity and reduction in oxidized LDL (Mazloom et al., 2014). Moreover, in another randomized, placebo-controlled study, supplementation with 500 mg/day quercetin for 8 weeks increased serum total antioxidant capacity in post myocardial infarction patients (Dehghani et al., 2021). However, some clinical studies have reported no effect of quercetin supplementation on either antioxidant status or oxidative stress markers. In young healthy volunteers, daily supplementation with either 50, 100, or 150 mg quercetin for 2 weeks increased plasma quercetin concentrations but did not alter oxidant/antioxidant status using plasma FRAP, ORAC, and plasma levels of oxidized LDL, compared with baseline (Egert et al., 2008). In overweight or obese subjects, supplementation with 150 mg/day quercetin for up to 6 weeks did not affect plasma ORAC but reduced oxidized LDL levels and systolic blood pressure (Egert et al., 2009). In another study in stage 1 hypertensive, even supplementation with high dose of quercetin (730 mg/day) for 28 days, indices of oxidative stress measured by plasma FRAP and PAR, and urinary 8-isoprostane F2α were not affected (Edwards et al., 2007). Furthermore, in rheumatoid arthritis women, supplementation with 500 mg/day quercetin for 8 weeks did not show effect on oxidative stress markers including plasma total antioxidant capacity, malondialdehyde, and oxidized LDL (Javadi et al., 2014). According to these results, antioxidant effects of quercetin supplementation seem to have controversial outcomes which might depend on the exposure dose and duration of quercetin treatment, and the levels of oxidative stress in participants at baseline.

2.4. Ameliorate effect on comorbidities of hyperuricemia and gout

Besides gout, hyperuricemia is involved with the development and pathogenesis of several diseases including hypertension, hyperglycemia, obesity, dyslipidemia, CVD, and CKD (Wang et al., 2018). The frequencies of these diseases have been increased in gout as its comorbidities (Bardin and Richette 2017). A number of epidemiological studies demonstrated the association between hyperuricemia, gout and comorbidities (Bardin and Richette 2017, Borghi et al., 2020, Singh and Gaffo 2020). In the case-control study investigating the burden of comorbidities before and after diagnosis of gout, the prevalence of hypertension and other CVD, renal diseases, and hyperlipidemia were significantly higher in gout patients than controls, and gout patients without a prior history of comorbidities developed CVD, renal diseases, diabetes, and hyperlipidemia more than controls (Kuo et al., 2016). These results suggest that the presence of these comorbidities contributes to the progression of gout and vice versa. In addition, comorbidities affect the management of hyperuricemia and gout, for example, aspirin used for CVD and insulin used for diabetes increased uricemia by reducing urine urate excretion, colchicine and NSAIDs used for treatment of gouty inflammation should be avoided in patients with renal failure (Bardin and Richette 2017). Therefore, prevention and management of the comorbidities might provide benefits not only for delaying the progression of diseases but also management of hyperuricemia and gout.

Interestingly, quercetin is known to have potential in the treatment of MetS (Hosseini et al., 2021, Yi et al., 2021) and CVD (Mirsafaei et al., 2020) which are common comorbidities of hyperuricemia and gout. MetS including hyperglycemia, obesity (especially central obesity), high blood pressure, low HDL cholesterol, and elevated triglyceride levels, is risk factors for developing CVD (Li et al., 2021). The potential and mechanisms of quercetin on MetS have been reviewed and reported elsewhere (Hosseini et al., 2021, Yi et al., 2021). In summary, quercetin ameliorated MetS through several mechanisms such as promoting insulin secretion, improving insulin resistance, maintaining glucose homeostasis, inhibiting inflammation, inhibiting oxidative stress, inhibiting cholesterol absorption, downregulating the expression of some genes related to lipid metabolism, promoting the expression of PPARα, PPARγ, and LXRα, downregulating angiotensin-1 receptor in the kidney, activating AMPK and inhibiting JNK and MAPK. Recently, there is a randomized, placebo-controlled trial investigating the effect of quercetin on different aspects of MetS in elderly patients. The results revealed that administration of 240 mg/day quercetin for 3 months led to a significant decrease in body weight, BMI, systolic and diastolic blood pressure, levels of total cholesterol and LDL-cholesterol, fasting plasma insulin and 2-hour glucose levels, confirming the effectiveness of quercetin on MetS components (Shatylo et al., 2021). In addition, many preclinical and clinical studies have indicated the effects of querce-

tin on the prevention and treatment of CVD and suggested due to its antioxidant, anti-inflammatory, antidiabetic, antidyslipidemic, antihypertension, antiapoptotic, anti-atherosclerotic, and antiplatelet activities (Mirsafaei et al., 2020). Moreover, since the cohort study has demonstrated that MetS was associated with CVD (OR 1.58; P = 0.002) and CKD (OR 2.17; P < 0.001) (Ferraro et al., 2011), and the case-control study has indicated that MetS was a risk factor for the development of CKD (Kebapci et al., 2013), therapeutic intervention with quercetin in MetS might prevent renal dysfunction and subsequent CVD and CKD.

3. Safety aspects

Quercetin is recognized as Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration (Andres et al., 2018). Although quercetin has been regarded as mutagenic *in vitro*, it did not show *in vivo* mutagenicity or carcinogenicity, short and long-term *in vivo* toxicities, and adverse health effect in humans (Harwood et al., 2007). In addition, a number of clinical studies that used quercetin supplementation at doses of 150 to 1000 mg have not reported of any adverse effects. However, the information of high-dose quercetin (≥1,000 mg/day) with long-term use (>12 weeks) in human is still not available. In addition, some animal studies demonstrated that quercetin might promote the growth of tumor, particular in estrogen dependent types and the high-dose might enhance adverse effects in the pre-damaged kidney (Andres et al., 2018). Moreover, interactions between quercetin and different drugs have been concerned and studied. Since quercetin has been reported to modulate metabolic enzymes such as CYP1A1, CYP2C19, CYP2D6, and CYP3A4, and drug transporters such as OATP1A2, OATP2B1, OAT1, P-gp, MRP1, and BCRP (Rastogi and Jana 2014, Miron et al., 2017, Elbarbry et al., 2018). It might alter the bioavailability of the drugs that are metabolized by these enzymes and/or uptake by these transporters and lead to alter the effectiveness of the drug. Therefore, patients with estrogen-dependent tumor diseases, kidney dysfunction, and take several drugs should be aware and consult a physician prior the use of quercetin as a dietary supplement.

4. Conclusion

Hyperuricemia has become a worldwide public health problem, which is not only associated with gout but also several life-threatening diseases including CVD and CKD. Although there are many effective therapeutic drugs for treatment of hyperuricemia and gout, serious adverse effects and contraindications drive the search for an effective and safe alternative therapy. Based on the results of this review, quercetin demonstrates several activities that have benefits for hyperuricemia and gouty arthritis including 1) Anti-hyperuricemic activity through several mechanisms including inhibiting corresponding enzymes in urate production namely xanthine oxidase, adenosine deaminase, and ketohexokinase and increasing renal urate excretion by promoting the activity of urate excretion transporters and suppressing the activity of urate reabsorption transporters. 2) Antioxidant activity by scavenging free radicals and enhancing antioxidant defense system. 3) Anti-inflammatory activity by targeting NLRP3 inflammasome-IL-1β pathway and TLR signaling pathway. 4) Ameliorating comorbidities of hyperuricemia and gout such as hypertension, hyperglycemia, obesity, dyslipidemia, CVD, and CKD. Accordingly, quercetin seem to have a potential to develop as a dietary supplement for prevention and management of hyperuricemia and gouty arthritis and/or use as alternative or combination therapy to minimize the side effects of the conventional drugs.

The author declares no conflicts of interest.

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.

Acknowledgements

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

References

Adachi, S.-I., Oyama, M., Kondo, S., Yagasaki, K., 2021. Comparative effects of quercetin, luteolin, apigenin and their related polyphenols on uric acid production in cultured hepatocytes and suppression of purine bodies-induced hyperuricemia by rutin in mice. Cytotechnology. 73 (3), 343–351. https://doi.org/10.1007/s10616-021-00452-9.

Anand David, A.V., Arulmoli, R., Parasuraman, S., 2016. Overviews of biological importance of quercetin: a bioactive flavonoid. Pharmacogn. Rev. 10, 84–89. https://doi.org/10.4103/0973-7847.194044.

Andres, S., Pevny, S., Ziegenhagen, R., Bakhiya, N., Schäfer, B., Hirsch-Ernst, K.I., Lampen, A., 2018. Safety aspects of the use of quercetin as a dietary supplement. Mol. Nutr. Food Res. 62 (1), 1700447. https://doi.org/10.1002/mnfr.201700447.

Bardin, T., Richette, P., 2017. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med. 15, 123. https://doi.org/10.1186/s12916-017-0890-9.

Battelli, M.G., Polito, L., Bortolotti, M., Bolognesi, A., 2016. Xanthine oxidoreductase-derived reactive species: physiological and pathological effects. Oxid. Med. Cell. Longev. 2016, 1–8. https://doi.org/10.1155/2016/3527579.

Beiler, J.M., Martin, G.J., 1951. The inhibition of xanthine oxidase by flavonoids and related compounds. J. Biol. Chem. 192 (2), 831–834.

Boots, A.W., Drent, M., de Boer, V.C.J., Bast, A., Haenen, G.R.M.M., 2011. Quercetin reduces markers of oxidative stress and inflammation in sarcoidosis. Clin. Nutr. 30 (4), 506–512. https://doi.org/10.1016/j.clnu.2011.01.010.

Borghi, C., Agabiti-Rosei, E., Johnson, R.J., Kielstein, J.T., Lurbe, E., Mancia, G., Redon, J., Stack, A.G., Tsioufis, K.P., 2020. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. Eur. J. Intern. Med. 80, 1–11.

Braga, T.T., Forni, M.F., Correa-Costa, M., Ramos, R.N., Barbuto, J.A., Branco, P., Castoldi, A., Hiyane, M.I., Davanso, M.R., Latz, E., Franklin, B.S., Kowaltowski, A.J., Camara, N.O.S., 2017. Soluble uric acid activates the NLRP3 inflammasome. Sci. Rep. 7 (1). https://doi.org/10.1038/srep39884.

Butler, F., Alghubayshi, A., Roman, Y., 2021. The epidemiology and genetics of hyperuricemia and gout across major racial groups: a literature review and population genetics secondary database analysis. J. Pers. Med. 11 (3), 231. https://doi.org/10.3390/jpm11030231.

Cabău, G., Crișan, T.O., Klück, V., Popp, R.A., Joosten, L.A.B., 2020. Urate-induced immune programming: Consequences for gouty arthritis and hyperuricemia. Immunol. Rev. 294 (1), 92–105. https://doi.org/10.1111/imr.12833.

Carullo, G., Cappello, A.R., Frattaruolo, L., Badolato, M., Armentano, B., Aiello, F., 2017. Quercetin and derivatives: useful tools in inflammation and pain management. Future Med. Chem. 9 (1), 79–93. https://doi.org/10.4155/fmc-2016-0186.

Cos, P., Ying, L.i., Calomme, M., Hu, J.P., Cimanga, K., Van Poel, B., Pieters, L., Vlietinck, A.J., Berghe, D.V., 1998. Structure−activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J. Nat. Prod. 61 (1), 71–76. https://doi.org/10.1021/np970237h.

D'Andrea, G., 2015. Quercetin: a flavonol with multifaceted therapeutic applications? Fitoterapia. 106, 256–271. https://doi.org/10.1016/j.fitote.2015.09.018.

Dabeek, W.M., Marra, M.V., 2019. Dietary quercetin and kaempferol: bioavailability and potential cardiovascular-related bioactivity in humans. Nutrients. 11, 2288. https://doi.org/10.3390/nu11102288.

Dalbeth, N., Choi, H.K., Joosten, L.A.B., Khanna, P.P., Matsuo, H., Perez-Ruiz, F., Stamp, L.K., 2019. Gout. Gout. Nat. Rev. Dis. Primers. 5 (1). https://doi.org/10.1038/s41572-019-0115-y.

Dalbeth, N., Merriman, T.R., Stamp, L.K., 2016. Gout. Gout. Lancet. 388 (10055), 2039–2052. https://doi.org/10.1016/S0140-6736(16)00346-9.

Dehghani, F., Sezavar Seyedi Jandaghi, S.H., Janani, L., Sarebanhassanabadi, M., Emamat, H., Vafa, M., 2021. Effects of quercetin supplementation on inflammatory factors and quality of life in post-myocardial infarction patients: A double blind, placebo-controlled, randomized clinical trial. Phytother. Res. 35 (4), 2085–2098.

Edwards, R.L., Lyon, T., Litwin, S.E., Rabovsky, A., Symons, J.D., Jalili, T., 2007. Quercetin reduces blood pressure in hypertensive subjects. J. Nutr. 137 (11), 2405–2411. https://doi.org/10.1093/jn/137.11.2405.

Egert, S., Bosy-Westphal, A., Seiberl, J., Kürbitz, C., Settler, U., Plachta-Danielzik, S., Wagner, A.E., Frank, J., Schrezenmeir, J., Rimbach, G., Wolffram, S., Müller, M.J., 2009. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled

cross-over study. Br. J. Nutr. 102 (7), 1065–1074. https://doi.org/10.1017/S0007114509359127.
Egert, S., Wolffram, S., Bosy-Westphal, A., et al., 2008. Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J. Nutr. 138, 1615–1621. https://doi.org/10.1093/jn/138.9.1615.
Elbarbry, F., Ung, A., Abdelkawy, K., 2018. Studying the inhibitory effect of quercetin and thymoquinone on human cytochrome P450 enzyme activities. Pharmacogn. Mag. 13, S895–S899. https://doi.org/10.4103/0973-1296.224342.
Ferraro, P.M., Lupo, A., Yabarek, T., Graziani, M.S., Bonfante, L., Abaterusso, C., Gambaro, for the INCIPE Study Group, G., 2011. Metabolic Syndrome, Cardiovascular Disease, and Risk for Chronic Kidney Disease in an Italian Cohort: Analysis of the INCIPE Study. Metab. Syndr. Relat. Disord. 9 (5), 381–388. https://doi.org/10.1089/met.2011.0040.
Gainche, M., Ogeron, C., Ripoche, I., Senejoux, F., Cholet, J., Decombat, C., Delort, L., Berthon, J.-Y., Saunier, E., Caldefie Chezet, F., Chalard, P., 2021. Xanthine oxidase inhibitors from *Filipendula ulmaria* (L.) Maxim. and their efficient detections by HPTLC and HPLC analyses. Molecules. 26 (7), 1939. https://doi.org/10.3390/molecules26071939.
Gao, W., Xiong, Y.e., Li, Q., Yang, H., 2017. Inhibition of Toll-like receptor signaling as a promising therapy for inflammatory diseases: a journey from molecular to nano therapeutics. Front. Physiol. 8. https://doi.org/10.3389/fphys.2017.00508.
Haidari, F., Keshavarz, S.A., Mohammad Shahi, M., et al., 2011. Effects of parsley (*Petroselinum crispum*) and its flavonol constituents, kaempferol and quercetin, on serum uric acid levels, biomarkers of oxidative stress and liver xanthine oxidoreductase activity in oxonate-induced hyperuricemic rats. Iran. J. Pharm. Res. 10, 811–819.
Harwood, M., Danielewska-Nikiel, B., Borzelleca, J.F., Flamm, G.W., Williams, G.M., Lines, T.C., 2007. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. Food Chem. Toxicol. 45 (11), 2179–2205.
Heim, K.E., Tagliaferro, A.R., Bobilya, D.J., 2002. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. J. Nutr. Biochem. 13, 572–584. https://doi.org/10.1016/S0955-2863(02)00208-5.
Hosseini, A., Razavi, B.M., Banach, M., Hosseinzadeh, H., 2021. Quercetin and metabolic syndrome: A review. Phytother. Res. 35 (10), 5352–5364.
Hu, Q.-H., Wang, C., Li, J.-M., Zhang, D.-M., Kong, L.-D., 2009. Allopurinol, rutin, and quercetin attenuate hyperuricemia and renal dysfunction in rats induced by fructose intake: renal organic ion transporter involvement. Am. J. Physiol. Renal Physiol. 297 (4), F1080–F1091. https://doi.org/10.1152/ajprenal.90767.2008.
Hu, Q.-H., Zhang, X., Pan, Y., Li, Y.-C., Kong, L.-D., 2012a. Allopurinol, quercetin and rutin ameliorate renal NLRP3 inflammasome activation and lipid accumulation in fructose-fed rats. Biochem. Pharmacol. 84 (1), 113–125. https://doi.org/10.1016/j.bcp.2012.03.005.
Hu, Q.-H., Zhang, X., Wang, X., Jiao, R.-Q., Kong, L.-D., 2012b. Quercetin regulates organic ion transporter and uromodulin expression and improves renal function in hyperuricemic mice. Eur. J. Nutr. 51 (5), 593–606. https://doi.org/10.1007/s00394-011-0243-y.
Huang, J., Wang, S., Zhu, M., Chen, J., Zhu, X., 2011. Effects of genistein, apigenin, quercetin, rutin and astilbin on serum uric acid levels and xanthine oxidase activities in normal and hyperuricemic mice. Food Chem. Toxicol. 49 (9), 1943–1947.
Huang, J., Zhu, M., Tao, Y.e., Wang, S., Chen, J., Sun, W., Li, S., 2012. Therapeutic properties of quercetin on monosodium urate crystal-induced inflammation in rat. J. Pharm. Pharmacol. 64 (8), 1119–1127. https://doi.org/10.1111/j.2042-7158.2012.01504.x.
Ishimoto, T., Lanaspa, M.A., Rivard, C.J., Roncal-Jimenez, C.A., Orlicky, D.J., Cicerchi, C., McMahan, R.H., Abdelmalek, M.F., Rosen, H.R., Jackman, M.R., MacLean, P.S., Diggle, C.P., Asipu, A., Inaba, S., Kosugi, T., Sato, W., Maruyama, S., Sánchez-Lozada, L.G., Sautin, Y.Y., Hill, J.O., Bonthron, D.T., Johnson, R.J., 2013. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. Hepatology. 58 (5), 1632–1643.
Javadi, F., Ahmadzadeh, A., Eghtesadi, S., Aryaeian, N., Zabihiyeganeh, M., Rahimi Foroushani, A., Jazayeri, S., 2017. The effect of quercetin on inflammatory factors and clinical symptoms in women with rheumatoid arthritis: a double-blind, randomized controlled trial. J. Am. Coll. Nutr. 36 (1), 9–15. https://doi.org/10.1080/07315724.2016.1140093.
Javadi, F., Eghtesadi, S., Ahmadzadeh, A., et al., 2014. The effect of quercetin on plasma oxidative status, C-reactive protein and blood pressure in women with rheumatoid arthritis. Int. J. Prev. Med. 5, 293–301.
Jiang, L.-L., Gong, X., Ji, M.-Y., Wang, C.-C., Wang, J.-H., Li, M.-H., 2020. Bioactive compounds from plant-based functional foods: a promising choice for the prevention and management of hyperuricemia. Foods. 9 (8), 973. https://doi.org/10.3390/foods9080973.
Jiang, W., Huang, Y., Han, N., He, F., Li, M., Bian, Z., Liu, J., Sun, T., Zhu, L., 2016. Quercetin suppresses NLRP3 inflammasome activation and attenuates histopathology in a rat model of spinal cord injury. Spinal Cord. 54 (8), 592–596. https://doi.org/10.1038/sc.2015.227.
Kazierad, D.J., Chidsey, K., Somayaji, V.R., Bergman, A.J., Birnbaum, M.J., Calle, R.A., 2021. Inhibition of ketohexokinase in adults with NAFLD reduces liver fat and inflammatory markers: A randomized phase 2 trial. Med. 2 (7), 800–813.e3.
Kebapci, N., Uslu, S., Ozcelik, E., 2013. Metabolic syndrome is a risk factor for the development of chronic renal disease. Ren. Fail. 35 (4), 460–465. https://doi.org/10.3109/0886022X.2013.774680.
Kelly, G.S., 2011. Quercetin. Monograph. Altern. Med. Rev. 16, 172–194.
Kondratiuk, V.E., Synytsia, Y.P., 2018. Effect of quercetin on the echocardiographic parameters of left ventricular diastolic function in patients with gout and essential hypertension. Wiad Lek. 71, 1554–1559.
Kuo, C.-F., Grainge, M.J., Mallen, C., Zhang, W., Doherty, M., 2016. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann. Rheum. Dis. 75 (1), 210–217. https://doi.org/10.1136/annrheumdis-2014-206410.
Kutryb-Zajac, B., Mierzejewska, P., Slominska, E.M., Smolenski, R.T., 2020. Therapeutic perspectives of adenosine deaminase inhibition in cardiovascular diseases. Molecules. 25 (20), 4652. https://doi.org/10.3390/molecules25204652.
Li, L., Zhang, Y., Zeng, C., 2020. Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. Am. J. Transl. Res. 12, 3167–3181.
Li, R., Yu, K., Li, C., 2018. Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. Asia Pac. J. Clin. Nutr. 27, 1344–1356. https://doi.org/10.6133/apjcn.201811_27(6).0022.
Li, X., Zhai, Y., Zhao, J., He, H., Li, Y., Liu, Y., Feng, A., Li, L.i., Huang, T., Xu, A., Lyu, J., 2021. Impact of metabolic syndrome and it's components on prognosis in patients With cardiovascular diseases: a meta-analysis. Front. Cardiovasc. Med. 8. https://doi.org/10.3389/fcvm.2021.704145.
Maiuolo, J., Oppedisano, F., Gratteri, S., Muscoli, C., Mollace, V., 2016. Regulation of uric acid metabolism and excretion. Int. J. Cardiol. 213, 8–14.
Martillo, M.A., Nazzal, L., Crittenden, D.B., 2014. The crystallization of monosodium urate. Curr. Rheumatol. Rep. 16, 400. https://doi.org/10.1007/s11926-013-0400-9.
Mazloom, Z., Abdollahzadeh, S.M., Dabbaghmanesh, M.H., et al., 2014. The effect of quercetin supplementation on oxidative stress, glycemic control, lipid profile and insulin resistance in type 2 diabetes: a randomized clinical trial. J. Health Sci. Surveill. Syst. 2, 8–14.
Melzig, M., 1996. Inhibition of adenosine deaminase activity of aortic endothelial cells by selected flavonoids. Planta. Med. 62 (01), 20–21. https://doi.org/10.1055/s-2006-957788.
Miron, A., Aprotosoaie, A.C., Trifan, A., et al., 2017. Flavonoids as modulators of metabolic enzymes and drug transporters. Ann. N. York Acad. Sc. 1398, 152–167. https://doi.org/10.1111/nyas.13384.
Mirsafaei, L., Reiner, Ž., Shafabakhsh, R., Asemi, Z., 2020. Molecular and biological functions of quercetin as a natural solution for cardiovascular disease prevention and treatment. Plant Foods Hum. Nutr. 75 (3), 307–315. https://doi.org/10.1007/s11130-020-00832-0.
Mo, S.-F., Zhou, F., Lv, Y.-Z., Hu, Q.-H., Zhang, D.-M., Kong, L.-D., 2007. Hypouricemic action of selected flavonoids in mice: structure-activity relationships. Biol. Pharm. Bull. 30 (8), 1551–1556. https://doi.org/10.1248/bpb.30.1551.
Mzhel'skaya, K.V., Trusov, N.V., Guseva, G.N., Aksenov, I.V., Kravchenko, L.V., Tutelyan, V.A., 2019. Effects of quercetin on expression of genes of carbohydrate and lipid metabolism enzymes in the liver of rats receiving high-fructose ration. Bull. Exp. Biol. Med. 167 (2), 263–266. https://doi.org/10.1007/s10517-019-04505-0.
Nagao, A., Seki, M., Kobayashi, H., 1999. Inhibition of xanthine oxidase by flavonoids. Biosci. Biotechnol. Biochem. 63 (10), 1787–1790. https://doi.org/10.1271/bbb.63.1787.
Nile, S.H., Nile, A.S., Keum, Y.S., et al., 2017. Utilization of quercetin and quercetin glycosides from onion (*Allium cepa* L.) solid waste as an antioxidant, urease and xanthine oxidase inhibitors. Food Chem. 235, 119–126. https://doi.org/10.1016/j.foodchem.2017.05.043.
Nimse, S.B., Pal, D., 2015. Free radicals, natural antioxidants, and their reaction mechanisms. RSC Adv. 5 (35), 27986–28006. https://doi.org/10.1039/C4RA13315C.
Ozyel, B., Le Gall, G., Needs, P.W., Kroon, P.A., 2021. Anti-inflammatory effects of quercetin on high-glucose and pro-inflammatory cytokine challenged vascular endothelial cell metabolism. Mol. Nutr. Food Res. 65 (6), 2000777. https://doi.org/10.1002/mnfr.202000777.
Pillinger, M.H., Mandell, B.F., 2020. Therapeutic approaches in the treatment of gout. Semin. Arthritis Rheum. 50, S24–S30. https://doi.org/10.1016/j.semarthrit.2020.04.010.
Rastogi, H., Jana, S., 2014. Evaluation of inhibitory effects of caffeic acid and quercetin on human liver cytochrome P450 activities. Phytother. Res. 28, 1873–1878. https://doi.org/10.1002/ptr.5220.
Ruiz-Miyazawa, K.W., Staurengo-Ferrari, L., Mizokami, S.S., Domiciano, T.P., Vicentini, F.T.M.C., Camilios-Neto, D., Pavanelli, W.R., Pinge-Filho, P., Amaral, F.A., Teixeira, M.M., Casagrande, R., Verri, W.A., 2017. Quercetin inhibits gout arthritis in mice: induction of an opioid-dependent regulation of inflammasome. Inflammopharmacology. 25 (5), 555–570. https://doi.org/10.1007/s10787-017-0356-x.
Sampson, LAURA, Rimm, ERIC, Hollman, P.C.H., de VRIES, J.H.M., Katan, M.B., 2002. Flavonol and flavone intakes in US health professionals. J. Am. Diet. Assoc. 102 (10), 1414–1420.
Santos-Sierra, S., 2021. Targeting Toll-like Receptor (TLR) pathways in inflammatory arthritis: two better than one? Biomolecules. 11 (9), 1291. https://doi.org/10.3390/biom11091291.
Shatylo, V., Antoniuk-Shcheglova, I., Naskalova, S., Bondarenko, O., Havalko, A., Krasnienkov, D., Zabuga, O., Kukharskyy, V., Guryanov, V., Vaiserman, A., 2021. Cardio-metabolic benefits of quercetin in elderly patients with metabolic syndrome. PharmaNutrition. 15, 100250. https://doi.org/10.1016/j.phanu.2020.100250.

Shi, Y., Williamson, G., 2016. Quercetin lowers plasma uric acid in pre-hyperuricaemic males: a randomised, double-blinded, placebo-controlled, cross-over trial. Br. J. Nutr. 115 (5), 800–806. https://doi.org/10.1017/S0007114515005310.

Shibata, T., Nakashima, F., Honda, K., Lu, Y.-J., Kondo, T., Ushida, Y., Aizawa, K., Suganuma, H., Oe, S., Tanaka, H., Takahashi, T., Uchida, K., 2014. Toll-like receptors as a target of food-derived anti-inflammatory compounds. J. Biol. Chem. 289 (47), 32757–32772. https://doi.org/10.1074/jbc.M114.585901.

Singh, J.A., Gaffo, A., 2020. Gout epidemiology and comorbidities. Semin. Arthritis Rheum. 50, S11–S16. https://doi.org/10.1016/j.semarthrit.2020.04.008.

So, A.K., Martinon, F., 2017. Inflammation in gout: mechanisms and therapeutic targets. Nat. Rev. Rheumatol. 13 (11), 639–647. https://doi.org/10.1038/nrrheum.2017.155.

Sun, H.-l., Wu, Y.-W., Bian, H.-g., Yang, H., Wang, H., Meng, X.-M., Jin, J., 2021. Function of uric acid transporters and their inhibitors in hyperuricaemia. Front. Pharmacol. 12. https://doi.org/10.3389/fphar.2021.667753.

Szekanecz, Z., Szamosi, S., Kovács, G.E., Kocsis, E., Benkő, S., 2019. The NLRP3 inflammasome - interleukin 1 pathway as a therapeutic target in gout. Arch. Biochem. Biophys. 670, 82–93.

Tumova, S., Shi, Y., Carr, I.M., et al., 2021. Effects of quercetin and metabolites on uric acid biosynthesis and consequences for gene expression in the endothelium. Free Radic. Biol. Med. 162, 191–201. https://doi.org/10.1016/j.freeradbiomed.2020.10.017.

Ventura-Martínez, R., Déciga-Campos, M., Bustamante-Marquina, A., Ángeles-López, G.E., Aviles-Herrera, J., González-Trujano, M.E., Navarrete-Vázquez, G., 2021. Quercetin decreases the antinociceptive effect of diclofenac in an arthritic gout-pain model in rats. J. Pharm. Pharmacol. 73 (10), 1310–1318. https://doi.org/10.1093/jpp/rgab093.

Wang, C., Pan, Y., Zhang, Q.-Y., Wang, F.-M., Kong, L.-D., Jeyaseelan, S., 2012. Quercetin and allopurinol ameliorate kidney injury in STZ-treated rats with regulation of renal NLRP3 inflammasome activation and lipid accumulation. PloS one. 7 (6), e38285. https://doi.org/10.1371/journal.pone.0038285.

Wang, H., Zhang, H., Sun, L., et al., 2018. Roles of hyperuricemia in metabolic syndrome and cardiac-kidney-vascular system diseases. Am. J. Transl. Res. 10, 2749–2763.

Wang, W., Sun, C., Mao, L., Ma, P., Liu, F., Yang, J., Gao, Y., 2016. The biological activities, chemical stability, metabolism and delivery systems of quercetin: A review. Trends Food Sci. Technol. 56, 21–38.

Xiao, JING, Zhang, XIAO.-LI., Fu, CHENSHENG, Han, RUI, Chen, WEIJUN, Lu, YIJUN, Ye, ZHIBIN, 2015. Soluble uric acid increases NALP3 inflammasome and interleukin-1β expression in human primary renal proximal tubule epithelial cells through the Toll-like receptor 4-mediated pathway. Int. J. Molec. Med. 35 (5), 1347–1354. https://doi.org/10.3892/ijmm.2015.2148.

Xie, P.-J., Huang, L.-X., Zhang, C.-H., et al., 2015. Phenolic compositions, and antioxidant performance of olive leaf and fruit (*Olea europaea* L.) extracts and their structure–activity relationships. J. Funct. Foods. 16, 460–471. https://doi.org/10.1016/j.jff.2015.05.005.

Yi, H., Peng, H., Wu, X., Xu, X., Kuang, T., Zhang, J., Du, L., Fan, G., Nieman, D., 2021. The therapeutic effects and mechanisms of quercetin on metabolic diseases: pharmacological data and clinical evidence. Oxid. Med. Cell. Longev. 2021, 1–16. https://doi.org/10.1155/2021/6678662.

Zamudio-Cuevas, Y., Hernández-Díaz, C., Pineda, C., Reginato, A.M., Cerna-Cortés, J. F., Ventura-Ríos, L., López-Reyes, A., 2015. Molecular basis of oxidative stress in gouty arthropathy. Clin. Rheumatol. 34 (10), 1667–1672. https://doi.org/10.1007/s10067-015-2933-y.

Zamudio-Cuevas, Y., Martínez-Flores, K., Fernández-Torres, J., Loissell-Baltazar, Y.A., Medina-Luna, D., López-Macay, A., Camacho-Galindo, J., Hernández-Díaz, C., Santamaría-Olmedo, M.G., López-Villegas, E.O., Oliviero, F., Scanu, A., Cerna-Cortés, J.F., Gutierrez, M., Pineda, C., López-Reyes, A., 2016. Monosodium urate crystals induce oxidative stress in human synoviocytes. Arthritis Res. Ther. 18 (1). https://doi.org/10.1186/s13075-016-1012-3.

Zeng, Y., Song, J., Zhang, M., Wang, H., Zhang, Y.u., Suo, H., 2020. Comparison of *in vitro* and *in vivo* antioxidant activities of six flavonoids with similar structures. Antioxidants (Basel). 9 (8), 732. https://doi.org/10.3390/antiox9080732.

Zhang, C., Li, L., Zhang, Y., Zeng, C., 2020. Recent advances in fructose intake and risk of hyperuricemia. Biomed. Pharmacother. 131, 110795. https://doi.org/10.1016/j.biopha.2020.110795.

Zhang, C., Wang, R., Zhang, G., et al., 2018. Mechanistic insights into the inhibition of quercetin on xanthine oxidase. Int. J. Biol. Macromol. 112, 405–412. https://doi.org/10.1016/j.ijbiomac.2018.01.190.

Zhu, J.X., Wang, Y., Kong, L.D., Yang, C., Zhang, X., 2004. Effects of *Biota orientalis* extract and its flavonoid constituents, quercetin and rutin on serum uric acid levels in oxonate-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver. J. Ethnopharmacol. 93 (1), 133–140.