Mechanism of flavonoids in the treatment of gouty arthritis (Review)

FEIFAN LIU[1*], YUANMEI BAI[1*], YAN WAN[1*], JINGLIN HE[1], QIONGCHAO LI[1], YUHUAN XIE[2] and PEIXIN GUO[1]

[1]College of Ethnic Medicine, Yunnan University of Chinese Medicine, Kunming, Yunnan 650500, P.R. China; [2]College of Basic Medical Sciences, Yunnan University of Chinese Medicine, Kunming, Yunnan 650500, P.R. China

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Abstract. The present review expounds the advancements in the application and mechanisms of flavonoids in gouty arthritis, highlighting their significance in managing the disease. Gouty arthritis is among the most common and severe inflammatory diseases, caused by hyperuricemia and the deposition of sodium urate crystals in the joints and surrounding tissues, posing a serious threat to human life and health. Flavonoids, extracted from various herbs, have attracted significant attention due to their efficacy in improving gouty arthritis. The present study systematically reviews the *in vivo* studies and *in vitro* animal studies on flavonoids from herbal medicines for the treatment of gouty arthritis that have been previously published in the PubMed, ScienceDirect, Google Scholar and China National Knowledge Infrastructure databases between 2000 and 2023. The review of the literature indicated that flavonoids can improve gouty arthritis through multiple mechanisms. These include lowering xanthine oxidase activity, inhibiting uric acid (UA) synthesis, regulating UA transporters to promote UA excretion, reducing the inflammatory response and improving oxidative stress. These mechanisms predominantly involve regulating the NOD-like receptor 3 inflammasome, the Toll-like receptor 4/myeloid differentiation factor 88/nuclear factor-κB signaling pathway, and the levels of UA transporter proteins, namely recombinant urate transporter 1, glucose transporter 9, organic anion transporter (OAT)1 and OAT3. Various flavonoids used in traditional Chinese medicine hold therapeutic promise for gouty arthritis and are anticipated to pave the way for novel pharmaceuticals and clinical applications.

Correspondence to: Professor Peixin Guo, College of Ethnic Medicine, Yunnan University of Chinese Medicine, 1076 Yuhua Road, Kunming, Yunnan 650500, P.R. China
E-mail: 718374546@qq.com

Professor Yuhuan Xie, College of Basic Medical Sciences, Yunnan University of Chinese Medicine, 1076 Yuhua Road, Kunming, Yunnan 650500, P.R. China
E-mail: kmkamma@163.com

*Contributed equally

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Contents

1. Introduction

Gouty arthritis is a non-infectious autoinflammatory disease caused by persistently high levels of serum uric acid (UA), leading to the deposition of monosodium urate (MSU) crystals in the joints and surrounding tissues (1). Over recent decades, the incidence and prevalence of gout have steadily increased, driven by lifestyle and dietary changes, as well as an aging population (2). Statistics indicate that the global prevalence of gout ranges between 1 and 4%, with a male to female ratio ranging between 3:1 and 10:1, impacting the quality of life (3). Gouty arthritis commonly affects obese postmenopausal women, older men and individuals of middle age (4). The disease is associated with several factors, including disruptions in purine metabolism (5), decreased UA excretion and excessive UA production (6,7). According to the European League Against Rheumatism, gout can be categorized into the following four stages based on disease progression: Asymptomatic hyperuricemia, acute gouty arthritis attack, intercritical gouty arthritis and chronic gouty arthritis (8). From the second to the fourth stage of gout, the primary treatment strategies include anti-inflammatory measures and serum UA reduction. Common medications include allopurinol (9), febuxostat (10) and non-steroidal anti-inflammatory drugs, such as celecoxib and ibuprofen (11). However, long-term use of these drugs is inevitably accompanied by serious toxic side effects. For example, allopurinol can lead to kidney

damage (12), febuxostat can increase the risk of cardiovascular diseases (13), and ibuprofen is associated with symptoms such as dizziness and drowsiness (14). Addressing gouty arthritis has become a global challenge, and identifying potential effective ingredients for its treatment holds significant promise for overcoming this issue (15).

Flavonoids are significant secondary metabolites in plants, characterized by a basic chemical structure comprising two benzene rings linked by three carbon atoms, forming a C6-C3-C6 structure (Fig. 1) (16). These compounds are known for their pronounced antitumor (17), antioxidant (18) and antibacterial (19) properties, making them widely utilized in clinical research. Notably, flavonoids have been identified to alleviate gouty arthritis. For instance, Morin (2',3',4',5,7-pentahydroxyflavone), found in figs, apples, guava leaves, onions, tea and grains, is recognized for its potential in treating gouty arthritis; it is particularly effective in inhibiting inflammation triggered by MSU crystals (20).

The present study systematically reviewed the *in vivo* and *in vitro* animal studies on flavonoids from herbal medicines for the treatment of gouty arthritis that have been previously published in the PubMed (https://pubmed.ncbi.nlm.nih.gov), ScienceDirect (http://www.sciencedirect.com), Google Scholar (http://scholar. google.cz) and China National Knowledge Infrastructure databases (http://www.cnki.net) between 2000 and 2023. We searched using the keywords 'gouty arthritis', 'flavonoids' and 'mechanism study'. The literature inclusion criteria for this study were that the study was a mechanistic study of flavonoids in the treatment of gouty arthritis; and the study model was a gouty arthritic animal receiving flavonoid treatment. The study excluded repetitive studies, unfinished studies, studies with no available data or incomplete data, literature with too low a quality rating and literature with only abstracts and no access to full text.

Given the extensive variety of flavonoid structural classifications, it is challenging to generalize the structural features of flavonoids that may be effective against gouty arthritis. The representative structural formulae of a number of flavonoids are shown in Fig. 2.

Extensive research has demonstrated that flavonoids derived from natural herbs can markedly decrease UA levels (21-23). More crucially, their therapeutic benefits in managing gouty arthritis are attributed to various mechanisms. These include reducing xanthine oxidase (XOD) activity (24), regulating UA transporters to promote UA excretion (25), alleviating the inflammatory response (25,26) and reducing oxidative stress (27). Such findings are fundamentally important for the screening and identification of medications for gouty arthritis from the natural chemical components found in herbs. Table I outlines the mechanisms of action of these flavonoids.

2. XOD and gouty arthritis

Abnormal XOD activity. XOD serves a crucial role in UA metabolism within the body, promoting the oxidation of hypoxanthine to xanthine and then further catalyzing the oxidation of xanthine to UA. Elevated UA concentrations can lead to hyperuricemia, potentially triggering attacks of gouty arthritis (28).

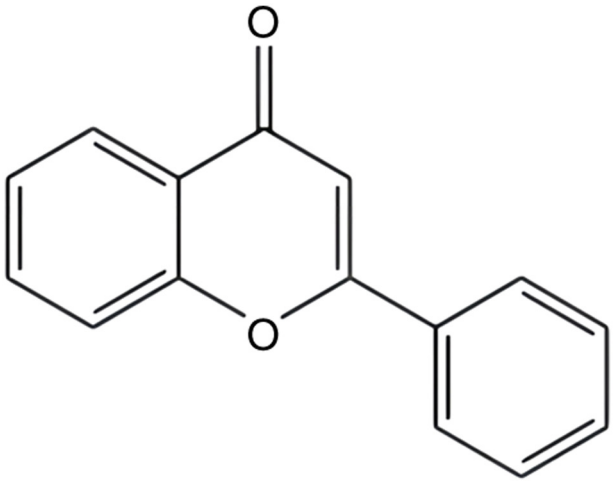

Figure 1. Basic structural formula of flavonoids.

Inhibiting XOD activity reduces UA production. In mouse models treated with intraperitoneal injections of potassium oxonate and oral administration of xanthine, Morin, a principal component of Gouji [*Maclura cochinchinensis* (Lour.) Corner heartwood] extract, can inhibit XOD activity in a non-competitive manner, lowering serum UA levels (29). Sangye (*Morus alba* L.), the leaf of the mulberry tree, contains flavonoids as its main bioactive components (30). A previous study (24) has indicated that the key constituents of Sangye total flavonoids include myricetin, quercetin, rutin, kaempferol and isorhamnetin. Serum UA levels in hyperuricemic mice induced by potassium oxonate decreased after 1 week of administration of Sangye total flavonoids. In the same study, after 3 weeks of administration of Sangye total flavonoids, serum UA approached normal levels in rats, and XOD activity was reduced by 25.01% compared with that in the model group. Furthermore, serum triglyceride and free fatty acid levels were lowered, while total flavonoids of Sangye reduced the abnormal liver and heart coefficient caused by adenine in mice (24). This suggests that Sangye total flavonoids may regulate serum UA levels by inhibiting XOD and managing lipid disorders. A study has also shown that luteolin 4'-O-glucoside and its aglycones, two primary flavonoid compounds in *Pseudognaphalium affine* (D. Don) Anderb., can inhibit the activity of XOD in hyperuricemic mice, thereby preventing UA synthesis, and reducing the swelling and inflammation caused by MSU crystals (31). In animal research, a gouty arthritis rat model induced by MSU crystals revealed reductions in XOD activity and improvements in gouty arthritis symptoms after 5 days of rutin administration (Fig. 3) (25).

Furthermore, XOD generates a vast array of reactive oxygen species (ROS), including H_2O_2 and O_2, through cascade reactions, using molecular oxygen as an electron acceptor. These ROS are intricately linked to cell damage, inflammation, carcinogenesis and aging (32). Thus, inhibiting XOD activity not only potentially prevents gouty arthritis but also blocks inflammatory pathways, reduces pro-inflammatory cytokines, and offers protection against kidney injury, cardiovascular disease, aging and cancer (33).

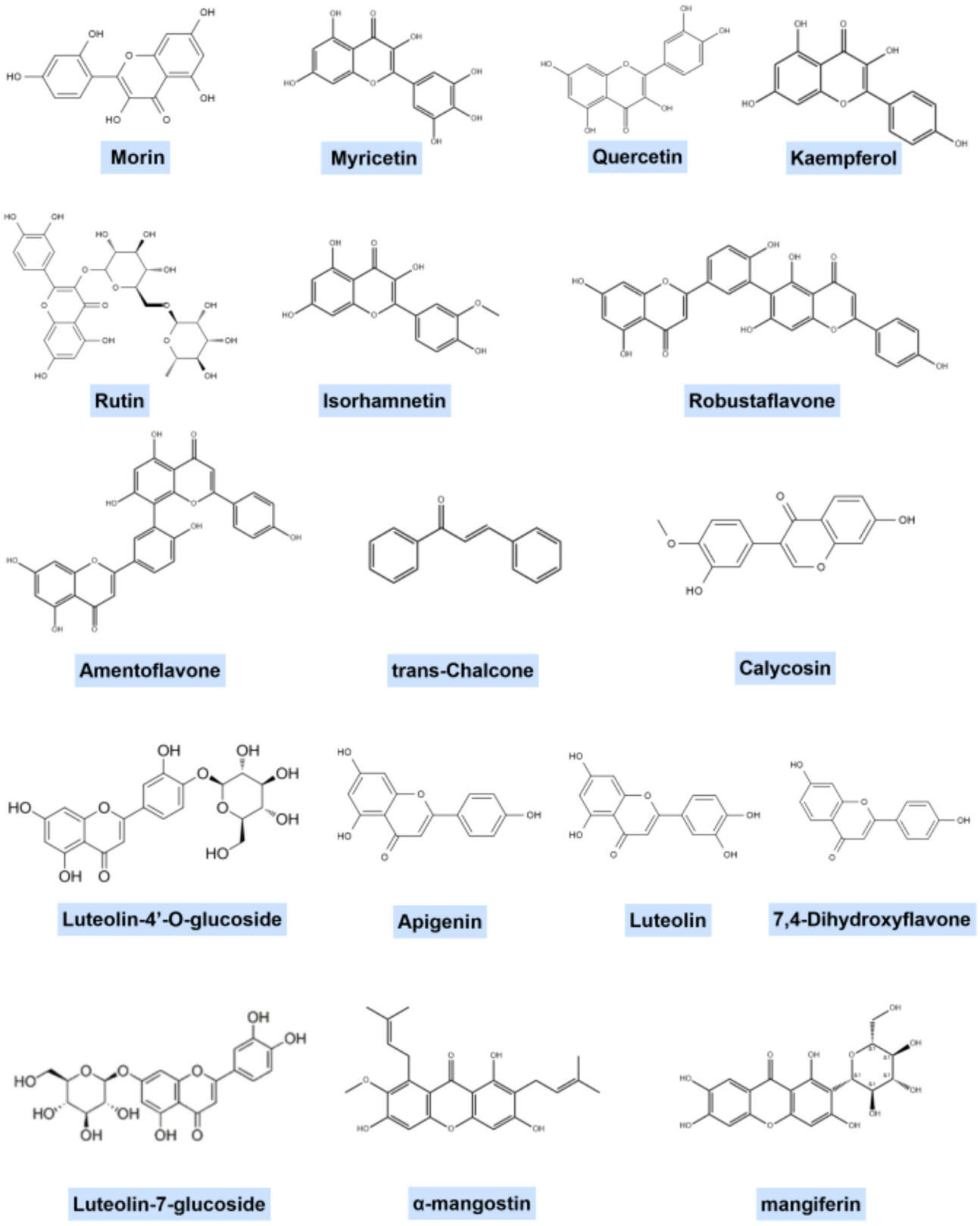

Figure 2. Structural formulae of a few flavonoids that have a protective effect on gouty arthritis.

3. UA transporter and gouty arthritis

UA transporter disorder. The excretion of UA primarily occurs through UA transporters in the kidneys, which are responsible for the reabsorption and secretion of UA. The regulation of recombinant urate transporter 1 (URAT1) and recombinant ATP binding cassette transporter G2 promotes UA excretion and serves a crucial role in the treatment of elevated UA levels (34). The kidney is a key organ in UA excretion, and this process is divided into four stages (35): i) In total, >99% of

Table I. Pathways involved in flavonoid-mediated improvement of gouty arthritis.

Mechanisms	Source	Name	Models	Regulated targets
Inhibition of XOD activity	*Maclura cochinchinensis* (Lour.) Corner heartwood	Morin	Mice, PO	XOD
	Morus alba L.	Myricetin, quercetin, rutin, kaempferol, isorhamnetin	Mice, PO	XOD
	Gnaphalium pensylvanicum Willd.	Luteolin-7-glucoside	Mice, MSU	XOD
	Pseudognaphalium affine (D. Don) Anderb.	Luteolin-4'-O-glucoside	Mice, MSU	XOD
Regulation of the uric acid transporter	*Gnaphalium affine* D. Don	7,4-Dihydroxyflavone	Mice, PO	mURAT1, mGLUT9
	Gnaphalium pensylvanicum Willd.	Luteolin-7-glucoside	Mice, MSU	GLUT9, OAT1, URAT1
	Garcinia mangostana L.	α-Mangostin	Mice, PO	GLUT9
	Anemarrhena asphodeloides Bge.	Mangiferin	Mice, PO	mURAT1, mGLUT9, mOAT1
Inhibition of inflammation				
NLRP3 inflammasome	*Cunninghamia lanceolata* (Lamb.) Hook.	Amentoflavone	Mice, MSU	IL-1β, caspase-1
	Cunninghamia lanceolata (Lamb.) Hook.	Robustaflavone	Mice, MSU	IL-1β, caspase-1, ASC, NLRP3
	Angelica keiskei Koidz.	trans-Chalcone	Mice, MSU	IL-1β, TNF-α, IL-6, TGF-β, NLRP3, ASC, pro-caspase-1, pro-IL-1β, NF-κB
	Ruta graveolens L.	Rutinum	Quail, high purine diet	NLRP3
TLR4/MyD88/ NF-κB	*Astragalus membranaceu*s (Fisch.) Bge.	Calycosin	Mice, MSU	AIM2, Keap1, p-p65, p-IκBα, p62
			PBMCs and THP-1 cells	IL-1β, IL-6, TNF-α, IL-10, AIM2, Keap1, p-p65, p-IκBα, p62
	Lagotis brachystachys Maxim	Luteolin	Rats, MSU	TLR4, MyD88, NF-κB
	Lagotis brachystachys Maxim	Luteolin-4'-O-glucoside	Rats, MSU	TLR4, MyD88, NF-κB
	Lagotis brachystachys Maxim	Apigenin	Rats, MSU	TLR4, MyD88, NF-κB
Improvement of oxidative stress	*Apocynum lancifolium* Rus.	Quercetin	Rats, MSU	MDA
	Ruta graveolens L.	Rutinum	Quail, high purine diet	ROS
			Rats, MSU	MDA, NO, SOD, GSH-PX, CAT

MSU, monosodium urate; XOD, xanthine oxidase; URAT1, recombinant urate transporter 1; OAT, organic anion transporter; GLUT9, glucose transporter 9; NLRP3, NOD-like receptor 3; ASC, apoptosis-associated speck-like protein containing a CARD; ROS, reactive oxygen species; TLR, Toll-like receptor; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κB; AIM2, interferon-inducible protein AIM2; p-, phosphorylated; MDA, malondialdehyde; NO, nitric oxide; SOD, superoxide dismutase; GSH-PX, glutathione peroxidase; CAT, catalase; PBMC, peripheral blood mononuclear cell; Keap1, Kelch-like ECH-associated protein 1; m,murine; PO, oral administration.

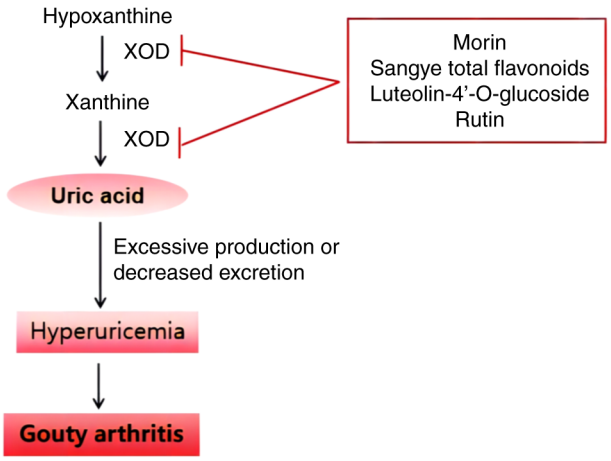

Figure 3. Flavonoids inhibit XOD activity. XOD, xanthine oxidase.

serum UA is filtered by the glomerulus; ii) 98% of the filtered UA is actively reabsorbed in the S1 segment, the initial part of the proximal renal tubules; iii) the active reabsorption of UA gradually decreases in the S2 segment of the curvature of the proximal renal tubules, and 50% of UA is secreted into the renal tubules; and iv) in the straight S3 segment of the proximal renal tubules, the concentration of UA in the renal tubules exceeds that in the surrounding capillaries, resulting in passive reabsorption of UA into the surrounding capillaries. Various transporters are involved in this process. URAT1 is specifically expressed in human kidneys and is located on the luminal side of the proximal tubular epithelial cells in the renal cortex, mainly participating in the reabsorption of urate by the proximal renal tubules (36). Glucose transporter 9 (GLUT9) is primarily expressed in the kidney and liver, with two subtypes (GLUT9L and GLUT9S); GLUT9L is found in the basement membrane of proximal renal tubule cells and GLUT9S is located in the lateral membrane of the proximal renal tubule (37). Studies have indicated that GLUT9 serves a crucial role in the transport of UA from intracellular to extracellular spaces and participates in urate reabsorption at the apical membrane of renal proximal tubules (38,39). Furthermore, organic anion transporter (OAT)1 has been demonstrated to be involved in the transport of UA in a dose- and time-dependent manner, and it has been suggested to serve a role in the first step of urate secretion, specifically, the uptake of urate from the peritubular space into renal tubular cells (40,41). OAT3 is predominantly expressed in proximal curved tubules, thick ascending limbs of medullary loops and collecting ducts, and is involved in urate transport. While the precise mechanism of OAT3 in urate transport remains unclear, based on its expression site, it is speculated that it may participate in the uptake of urate in peripheral tubules, contributing to urate secretion, or in moving urate from the basement membrane side into the peritubular capillaries, thus engaging in urate reabsorption (42-44). The aberrant transport of UA in the kidneys is a significant pathogenic factor in gouty arthritis (45).

Regulation of UA transporters. In a mouse model of hyperuricemia induced by oteracil potassium, the extract of *Gnaphalium affine* D. Don, specifically 7,4-dihydroxyflavone, could regulate murine (m)URAT1 and mGLUT9 to reduce serum UA levels. This also assisted in inhibiting the increase of urea nitrogen and creatinine levels (46). *Gnaphalium pensylvanicum* Willd., a traditional folk medicine used for relieving inflammation, coughs and rheumatoid arthritis, contains a high concentration of luteolin-7-O-glucoside, as identified by ultra-performance liquid chromatography-electrospray tandem mass spectrometry in prior studies (31,47). Extracts from *Gnaphalium pensylvanicum* Willd. have been demonstrated to alleviate foot swelling symptoms induced by MSU crystals and reduce the infiltration of inflammatory cells (48). Furthermore, western blotting results indicated that the extract primarily decreased serum UA by influencing GLUT9, OAT1 and URAT1, and by inhibiting XOD activity in mice (48). Corn silk, the style and stigma of the gramineous plant *Zea mays* L., also known as Yu Shu Li Rui, is both a traditional food and medicine in China, with flavonoids being its most effective components (49). These flavonoids, found in high concentrations in all parts of the corn plant (50), can reduce UA levels in hyperuricemia, effectively treating gout and gouty arthritis (51). In an *in vitro* experiment using HK-2 human renal tubular epithelial cells, the impact of total flavonoids from corn silk on UA absorption and related gene expression in HK-2 cells was assessed. After 48 h of incubation, each concentration of total flavonoids from corn silk inhibited UA absorption in HK-2 cells to varying degrees, with the inhibition rate increasing with increasing concentration. Furthermore, total flavonoids were able to reduce the UA-induced apoptosis rate in HK-2 cells. There was a marked decrease in GLUT9 mRNA expression, and an increase in OAT1 and OAT3 mRNA expression (52). α-Mangostin, the primary active component in mangosteen peel extract, was shown to decrease the serum UA level in hyperuricemic mice in a dose-dependent and time-dependent manner, and increased the UA clearance rate in hyperuricemic rats, indicative of the promotion of UA excretion in the kidney. The study also revealed a reduction in the expression levels of GLUT9 mRNA and protein in the kidneys of hyperuricemic mice, suggesting the involvement of α-mangostin in the downregulation of GLUT9 protein expression (53). Similarly, mangiferin, an active component found in *Anemarrhena asphodeloides* Bge., was capable of downregulating the mRNA and protein expression levels of urate transporters mURAT1 and mGLUT9 in mice with renal hyperuricemia induced by potassium oxonate. Mangiferin also upregulated the expression levels of mOAT1, indicating that it may promote UA excretion in hyperuricemic mice by inhibiting renal UA reabsorption and increasing UA secretion, thus reducing serum UA levels (54). These findings suggest that the regulation of UA transporters is one of the mechanisms through which flavonoids can improve hyperuricemia and gouty arthritis (Fig. 4).

4. Immunoinflammatory disorders and gouty arthritis

Immunoinflammatory disorders. The elevation of body UA levels due to abnormal purine metabolism, surpassing the normal physiological serum UA concentration, leads to a supersaturated state. This results in the precipitation of MSU crystals, which accumulate in the joints and surrounding tissues, causing inflammation (55). Inflammation and damage to the joints and surrounding tissues are driven by the release

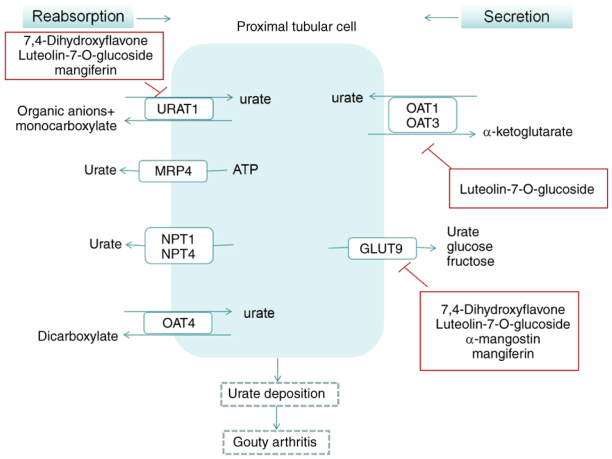

Figure 4. Flavonoids improve gouty arthritis by regulating the expression of URAT1, OAT1, OAT3 and GLUT9 in uric acid transporters. URAT1, recombinant urate transporter 1; OAT, organic anion transporter; MRP4, multidrug resistance protein 4; NPT, sodium-dependent phosphate transport protein; GLUT9, glucose transporter 9.

of inflammatory factors, which are regulated by numerous immune cells and signaling pathways (56). Phagocytes recognize the MSU crystals deposited in the joints through various mechanisms, including the formation of immune antibody complexes with the MSU crystals, promoting phagocytosis through fragment crystallizable (Fc) receptors. MSU crystals can also be directly recognized and phagocytosed by cell surface receptors. Key receptors involved in recognizing MSU crystals include CD16, CD11b, Toll-like receptor (TLR)2, TLR4 and CD14. The interactions between these receptors and MSU crystals activate downstream signaling pathways that mediate inflammation (57-59). It has been suggested that MSU crystals can also directly bind to cell membranes, causing tissue inflammatory damage (60,61). Following phagocytosis and recognition of MSU crystals in the joints, IL-1β expression is induced by signaling pathways such as TLR, NOD-like receptor 3 (NLRP3), P2X purinoceptor 7 and mitogen-activated protein kinase pathways, among others, leading to an inflammatory response. Activation of these signaling pathways results in the release of activated IL-1β into the cell, subsequently attracting and activating inflammatory cells, such as neutrophils, and releasing more inflammatory factors (62-64). This process triggers an inflammatory cascade amplification reaction (Fig. 5) (65).

Anti-inflammatory response. i) NLRP3 inflammasome. The NLRP3 inflammasome comprises the effector protein pro-caspase-1, the receptor protein NLRP3 and the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC). The inflammasome can be activated through various stimuli, including danger-associated molecular patterns and pathogen-associated molecular patterns (66). Upon detection of a specific activator, NLRP3 undergoes a conformational change, which then promotes ASC oligomerization to form ASC 'spots' (67). Serving as a platform for macromolecular signaling, ASC attracts pro-caspase-1 through its CARD domain, enabling pro-caspase-1 to be cleaved and produce active caspase-1. Caspase-1 then processes pro-IL-18 and pro-IL-1β into mature IL-18 and IL-1β, respectively, leading to tissue damage and inflammation (68,69). The abnormal activation of the NLRP3 inflammasome is associated with various diseases, including gouty arthritis, cardiovascular disease and diabetes (70). A recent study (71) has demonstrated that amentoflavone (AM) and its total flavonoid (TF) extract from the Chinese fir [*Cunninghamia lanceolata* (Lamb.) Hook.] exhibited inhibitory effects on foot thickness, lymphocyte infiltration, synovial injury and cartilage destruction in mouse models of gouty arthritis. Further investigation revealed that AM and TF reduced IL-1β secretion and caspase-1 cleavage in a dose-dependent manner, suggesting that they inhibit NLRP3 inflammasome activation. Additionally, TF treatment notably decreased the formation of ASC spots, indicating that TF could prevent the assembly of the NLRP3 inflammasome, characterized by the formation of ASC spots and reduced NLRP3 expression (71,72). trans-Chalcone, a precursor to flavonoids found mainly in herbs such as licorice (*Glycyrrhiza uralensis* Fisch.) (73), exhibits anti-inflammatory and antioxidant biological activities. In an experiment investigating its protective effects in mice with gouty arthritis, trans-Chalcone pre-treatment was administered to mice that were then injected in the joints with MSU. This treatment was observed to inhibit MSU-induced edema, mechanical hyperalgesia, leukocyte recruitment and inflammatory cell recruitment in a dose-dependent manner. Additionally, it reduced the *in vivo* production of IL-1β, TNF-α and IL-6, while increasing the production of TGF-β. Notably, trans-Chalcone also decreased nuclear factor κB (NF-κB) activation and the mRNA expression of inflammasome components such as ASC, NLRP3, pro-IL-1β and pro-caspase-1 (74). Similarly, quail models with endogenous gout induced by a high-purine diet were treated with rutinum for 10 days. The results indicated that rutin could exert an anti-inflammatory effect by inhibiting the activation of the NLRP3 inflammasome (26).

ii) TLR4/myeloid differentiation factor 88 (MyD88)/NF-κB pathway. In models of gouty arthritis, TLR4 in the synovial tissue of rats is notably increased due to disturbances in purine metabolism. Such disturbances lead to elevated UA levels, which in turn activate the TLR4-mediated signaling pathway, promoting the production of inflammatory cytokines and chemokines (75). The TLR4/MyD88/NF-κB signaling pathway involves TLR4, MyD88 and NF-κB, serving a key role in immune and inflammatory responses (76). Activation by lipopolysaccharide leads TLR4 to recruit MyD88, further activating the IL-1 receptor-associated kinase, which associates with TNF receptor-associated factor 6. This sequence activates TGF-activated kinase 1, leading to the phosphorylation of the inhibitor of κB kinase, degradation of IκB, release of NF-κB and its translocation into the nucleus to regulate the expression of various inflammatory responses (77).

NF-κB is a crucial mediator of the inflammatory response, linking extracellular stimuli with intracellular signaling pathways, influencing the progression of gouty arthritis (78). Inhibiting NF-κB activation presents a valid strategy for improving gouty arthritis. Studies (79,80) have demonstrated that calycosin reduces knee joint swelling and neutrophil infiltration in a mouse model of gouty arthritis induced by MSU. Inflammatory markers such as IL-1β, IL-6, IL-10 and TNF-α showed notable decreases in peripheral blood mononuclear cells and THP-1 cells induced by 0.2 mg/ml MSU after a 24-h

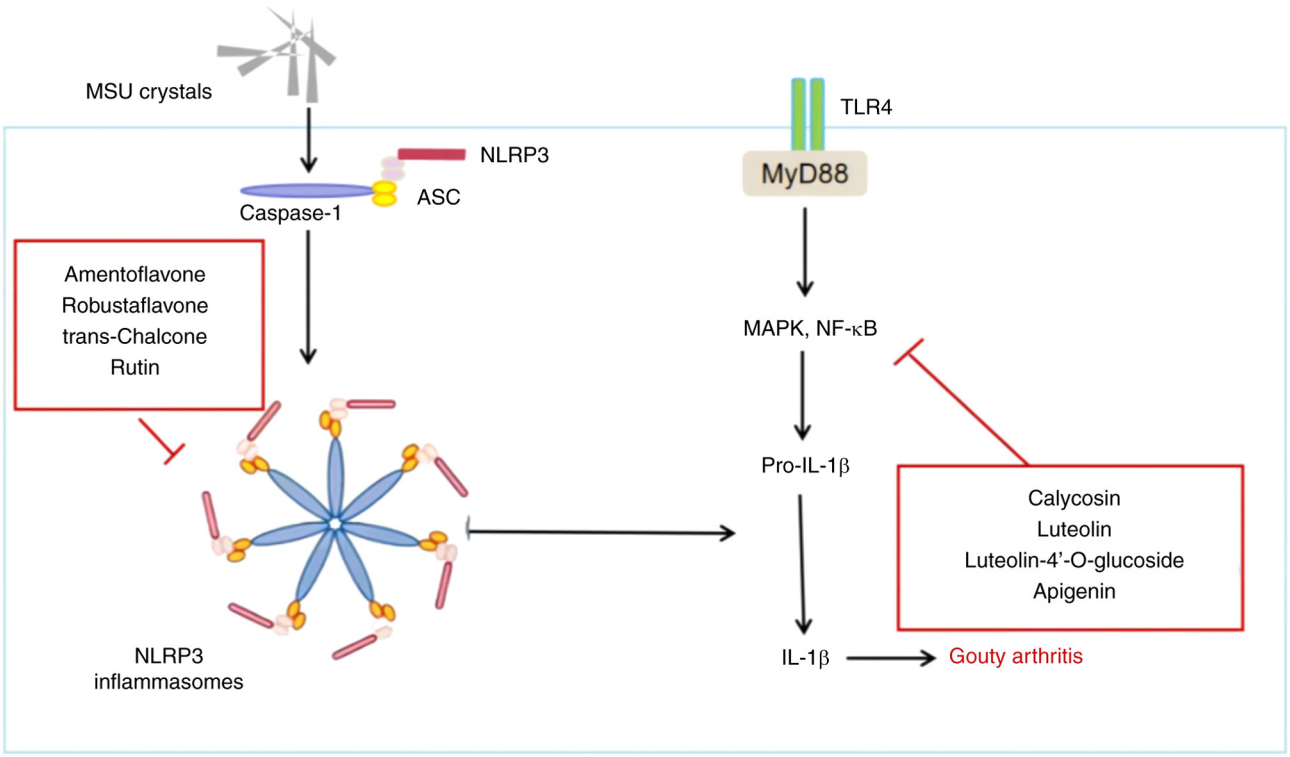

Figure 5. Flavonoids improve gouty arthritis by regulating the NLRP3 inflammasome and TLR4/MyD88/NF-κB pathways to inhibit inflammatory responses. MSU, monosodium urate; NLRP3, NOD-like receptor 3; ASC, apoptosis-associated speck-like protein containing a CARD; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation factor 88; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor κB.

pre-treatment with calycosin. Further investigation revealed that calycosin decreased the levels of interferon-inducible protein AIM2 (AIM2), Kelch-like ECH-associated protein 1 (Keap1), phosphorylated (p-)p65 and p-IκBα proteins in MSU-challenged cells *in vitro*, and increased the protein expression levels of p62 (79). These findings suggest that calycosin may exert a protective role in gouty arthritis by inhibiting the AIM2 inflammasome-mediated inflammatory response via the NF-κB and p62-Keap1 pathways. Similar to the effects of calycosin, silencing of AIM2 also reversed MSU-induced apoptosis in monocytes and macrophages, indicating that calycosin can suppress apoptosis by deactivating the AIM2 inflammasome via certain pathways, thereby impacting MSU-induced gouty arthritis (79). *Lagotis brachystachys* Maxim. is recognized as an essential herb in the clinical treatment of 'Huang-shui' disease, symptoms of which are similar to those of arthritis, as understood in traditional Chinese medicine (81). In Tibet, China, this herb has been traditionally utilized for its anti-inflammatory properties, particularly in conditions such as gouty arthritis and alcoholic liver injury (82,83). Research indicates that its antigout effects are achieved by downregulating the expression levels of TLR4, MyD88 and NF-κB proteins in the synovial tissue of rats. Three active flavonoids, namely luteolin, luteolin-4'-O-glucoside and apigenin, have been isolated from *Lagotis brachystachys* Maxim. (84). These active flavonoids have been shown to exhibit anti-inflammatory activities *in vivo* (85-87). Recent studies have suggested that luteolin can reduce the inflammatory response in acute gouty arthritis by inhibiting the TLR/MyD88/NF-κB pathway, reducing the

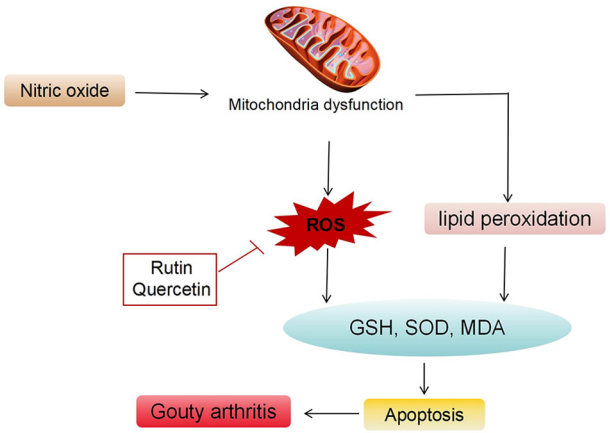

Figure 6. Flavonoids inhibit oxidative stress by regulating MDA, NO, SOD and GSH levels. ROS, reactive oxygen species; GSH, glutathione; SOD, superoxide dismutase; MDA, malonaldehyde.

joint swelling index (88,89). Similarly, luteolin-4'-O-glucoside was demonstrated to reduce foot swelling in rats by lowering serum pro-inflammatory cytokines in MSU crystal-induced gouty arthritis (31). Previous research has also revealed that luteolin (90), luteolin-4'-O-glucoside (91) and apigenin (92) inhibit the TLR4 signaling pathway. Furthermore, a study employing molecular docking techniques to evaluate the binding effects of luteolin, luteolin-4'-O-glucoside and apigenin on TLR4 (93) found that these compounds interact with TLR4 through hydrophobic interactions and hydrogen bonding, with binding energy results less than-7 kcal/mol. This

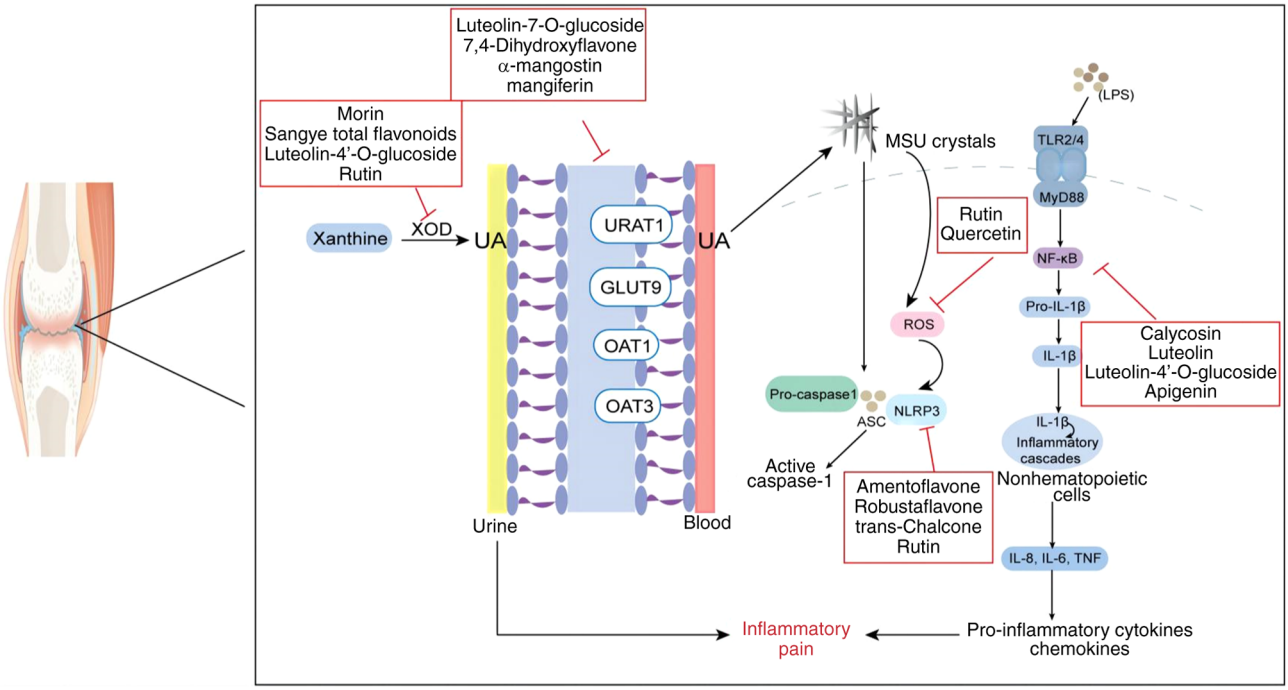

Figure 7. Different targets of flavonoid action in gouty arthritis. XOD, xanthine oxidase; UA, uric acid; URAT1, recombinant urate transporter 1; OAT, organic anion transporter; GLUT9, glucose transporter 9; NLRP3, NOD-like receptor 3; ASC, apoptosis-associated speck-like protein containing a CARD; ROS, reactive oxygen species; TLR, Toll-like receptor; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor κB; LPS, lipopolysaccharide; MSU, monosodium urate.

suggests a high affinity of luteolin, luteolin-4'-O-glucoside and apigenin with TLR4, indicating their potential therapeutic effects in inhibiting inflammation.

5. Oxidative stress and gouty arthritis

Abnormal oxidative stress. Under typical conditions, the body maintains a balanced and gradual oxidation equilibrium. However, certain stimuli can disrupt the antioxidant system of the body, leading to oxidative stress reactions triggered by factors such as ROS, resulting in localized or systemic damage (94). Currently, abnormal number and function of T lymphocyte subpopulations, the activation of inflammatory cytokines and the pathological loss of cell histology in the pathogenesis of gouty arthritis are closely linked to the extensive release of free radicals following oxidative stress. This connection indicates that oxidative stress serves an important role in the development of autoimmune diseases (95). Research has demonstrated that the accumulation and deposition of MSU crystals in the joint cavity can enhance oxidative stress, releasing large quantities of oxidants such as ROS, nitric oxide (NO) and malondialdehyde (MDA), while suppressing the activity of antioxidants such as superoxide dismutase (SOD) and glutathione (GSH). This exacerbates joint damage and causes symptoms such as redness, swelling, warmth, pain and restricted joint mobility (96). Catalase is abundantly found in the synovial cells of patients with gouty arthritis, with the inflammatory response it triggers being a result of oxidative stress. The marked increase in cellular NO^-, Hydroxyl radical (OH^-), Peroxyl Radical (ROO^-) and Alkoxyl group (RO^-) leads to an inflammatory response induced by ROS. In gouty arthritis, UA crystals enter endothelial cells through anion transporters in an exogenous pathogen-associated molecular pattern, becoming pro-oxidants and swiftly inducing oxidative stress. This promotes NO^- production by activating XOD and reduced nicotinamide adenine dinucleotide phosphate oxidase (97,98). The interaction between NO^- and O_2 releases peroxynitrite anion ($ONOO^-$), affecting cell proliferation, leading to the degradation of connective tissue and joint tissue deterioration (Fig. 6) (98).

Anti-oxidative stress. An animal study demonstrated that the administration of quercetin in a rat model of gouty arthritis, induced by injecting MSU crystal suspension into the right hind leg ankle, alleviated edema in a dose-dependent manner and reduced acute inflammatory histological characteristics in the treated animals. Quercetin treatment was found to inhibit leukocyte aggregation, decrease chemokine levels, lower the levels of MDA, a lipid peroxidation end product, and enhance the activity of antioxidant enzymes (27).

In rodents, such as rats and mice, UA resulting from purine metabolism is further degraded by uricase into allantoin, which has a higher solubility compared with UA and is excreted through urine. Quail, similar to humans, lack uricase in their UA synthesis and metabolism processes. The nucleic acids produced from nucleotide proteolytic hydrolysis are degraded into purine substances, which are then converted into UA by XOD and excreted as UA (99,100). An animal experiment in quail, involving a model of endogenous gout induced by a high-purine diet, examined administration of rutin for 10 days. The results indicated that rutin could improve gouty arthritis in quail by reducing XOD activity and UA levels. Rutin restored the oxidative stress balance by inhibiting the production of ROS and served a crucial anti-inflammatory role (26).

Another study on a rat model of gouty arthritis, induced by MSU crystals and followed by a 5-day administration of rutin, found that rutin reduced ankle swelling, and the levels of MDA and NO, and improved the activities of GSH-peroxidase, SOD and catalase in rats (25). These findings suggest that rutin could reduce gouty arthritis induced by MSU crystals in rats, likely through its anti-oxidative stress effects (25).

6. Conclusion and prospects

Flavonoid compounds hold a significant position in the treatment of gout and gouty arthritis, although the pathogenesis of these conditions is multifaceted. The present review delves into the pathogenesis of gouty arthritis and the mechanisms through which flavonoids reduce the condition, primarily by inhibiting UA synthase activity and reducing UA production. Flavonoids regulate the expression of renal UA transporters and promote UA excretion; they also inhibit oxidative stress by suppressing the production of ROS, MDA and other oxidants, while boosting the activity of antioxidants such as SOD and GSH. Furthermore, they regulate the expression of proteins in inflammatory signaling pathways such as the TLR/MyD88/NF-κB and NLRP3 pathways, reducing the release of inflammatory factors, as illustrated in Fig. 7. Thus, flavonoids serve a therapeutic role in managing hyperuricemia and gouty arthritis. Based on evidence-based guidelines for the diagnosis and treatment of gouty arthritis, the present review suggests the use of flavonoids in symptomatic treatment according to the stages of gout: During gouty arthritis attacks, flavonoids manage oxidative stress and inflammatory signaling pathways to exert anti-inflammatory effects, while in stages of asymptomatic hyperuricemia, intermittent gouty arthritis and chronic gouty arthritis, flavonoids inhibit UA synthase activity and regulate UA transporter expression to reduce serum UA levels (101).

Currently, research into the anti-gouty arthritis mechanism of flavonoids is predominantly conducted in animal studies, with relatively few clinical trials. In a randomized controlled clinical study (102), 40 patients were treated with self-compatible Fuling (Smilax glabra Roxb.) total flavone decoction plus conventional treatment regimen, while the control group received a conventional treatment regimen only. Routine treatment includes: i) Preventive treatment of diet and lifestyle; and ii) non-steroidal anti-inflammatory drugs should be used locally, and uricotropin drugs should be used depending on the patient's condition. Clinical symptom self-rating scale was used to evaluate the improvement of curative effect. The results showed that the clinical symptoms of patients in both the experimental group and the control group had improved to a certain extent, but the clinical improvement effect of pain in the experimental group was more significant compared with that in the control group, and the serum uric acid level of patients in the experimental group was prominently lower compared with that of the control group (102). The present review has certain limitations, including an incomplete understanding of the pharmacological effects of flavonoids in treating gouty arthritis. Besides reducing XOD activity, inhibiting UA synthesis, regulating UA transporters, promoting UA excretion, alleviating inflammation and improving oxidative stress, it remains to be seen whether flavonoids alleviate gouty arthritis through additional mechanisms. Furthermore, toxicological studies on flavonoid treatment for gouty arthritis are scarce, with limited reports on adverse reactions, complications, recurrence rates in patients treated with flavonoids and the specific drug metabolism process within the body. Addressing these gaps necessitates further investigation and analysis in future studies.

At present, the clinical treatment of gouty arthritis aims to reduce UA and inhibit inflammation as the main method, and the treatment mechanism is singular, with patients often needing to take multiple drugs at the same time to control the disease (103). In the treatment of gouty arthritis, herbal flavonoids have advantages of multi-target and multi-pathway synergistic actions. In terms of short-term efficacy, they can alleviate the symptoms of acute gouty arthritis through anti-inflammatory effects. In terms of long-term efficacy, they can serve a role in the treatment of gouty arthritis by reducing serum UA levels and good safety (104), which can make up for the shortcomings of modern medicine in the treatment of gouty arthritis. Therefore, the present review can provide theoretical support and direction for the treatment of gouty arthritis using flavonoids from herbs used in traditional Chinese medicine in the future, and provides an improved basis for the clinical development of drugs for the treatment of gouty arthritis.

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Authors' contributions

PG and FL provided the concept of this article. PG, FL, YB, YW, JH, YX and QL wrote, revised and finalized the article. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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