Review Article

Effects and Mechanisms of Traditional Chinese Medicine and Related Active Constituents Treating Gout

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Abstract

Gout is an inherited metabolic disorder resulting from abnormalities in purine metabolism manifesting as episodes of acute inflammatory arthritis. The incidence of gout shows an increasing tendency each year, due to the complicated pathogenesis, the currently available drugs have poor treatment effects on it. Therefore, the development of effective drugs for gout treatment is urgently needed. Because of its high biological activity and safety, Traditional Chinese medicine (TCM) has significant advantages in the prevention and treatment of gout. This paper systematically reviewed the related research on TCM's treatment of gout in the previous five years, and summarized the actions and mechanisms of 25 Chinese herbal extracts, 38 Chinese medicinal monomers, and 19 Chinese medicinal compounds in the treatment of gout, including serum uric acid levels reduction, anti-inflammation, and anti-oxidative stress. These primarily involve the signaling pathways NLRP3/ASC/caspase, TLRs/MYD88/NF-κB, ATP/P2X7R, and others. Furthermore, the limitations and shortcomings of the experimental study on the treatment of gout with TCM are discussed and appropriate measures are proposed. To summarize, TCM is likely to be a potential candidate for gout treatment, but more clinical research is needed to fully understand its role in the treatment of gout.

Interleukin-18; IL-6- Interleukin-6; TGF-β- Transforming growth factor beta; MAPK- Mitogen-activated protein kinase; SDF-1: Stromal cell-derived factor 1; MCP-1: Monocyte chemoattractant protein-1; IL-10- Interleukin-10; OCT- Organic cation; PTGS2- Prostaglandin-endoperoxide synthasetransporter; UA- Uric acid.

Introduction

Gout is a common inherited metabolic disorder resulting from abnormalities in purine metabolism or reduced uric acid excretion and is characterized by hyperuricemia-associated inflammatory arthritis, belonging to the category of metabolic rheumatism [1-3]. Acute gouty arthritis, the main form of gout [4], occurs due to the deposition of sodium urate crystals in the joints and other tissues because of the high level of uric acid persisting in the body for a long time [5]. The common clinical manifestations of gout are redness and swelling of the affected joints accompanied by severe pain [6]. The first gouty attack episode involves a single joint, with the unilateral first metatarsophalangeal joint being the most common one [7]. Notably, when gout repeatedly recurs for a long period, tophi formation occurs in the joints and soft tissues, and with disease progression, joint deformity, urinary calculi, and renal impairment can occur, which confers a great effect on the health and quality of life of the affected patients [8,9]. Current epidemiology worldwide indicates an increasing trend in morbidity and prevalence in both developed and developing countries [10,11]. Therefore, identifying an effective treatment for gout has attracted increasing attention and has become a top priority.

Because of the complexity of the pathogenesis of gout, no drugs available so far can completely cure gout. In western medicine, nonsteroidal anti-inflammatory drugs, glucocorticoids, and colchicine are mainly used for treating acute gouty attacks owing to their excellent analgesic and anti-inflammatory effects in rapidly relieving acute gouty attacks [12]. Febuxostat and allopurinol are mainly used for the treatment of gout in the chronic phase to reduce uric acid levels [13]. These first-line anti-gout drugs exert not only a significant therapeutic effect but also significant side effects, and these drugs cannot fundamentally eliminate the disease [14]. Hence, there is an urgent need to develop new anti-gout drugs. TCM has a long history of therapeutic effect on gout and has demonstrated good clinical effects. Thus far, a large number of experimental studies have focused on the anti-gout effect of TCM. It is believed that TCM exerts the anti-gout effect mainly by reducing uric acid levels, inflammation, and oxidative stress. Currently, there is a lack of a comprehensive review on gout treatment with TCM. We, therefore, present a review on the pathophysiological mechanism of gout and mechanisms of effective of TCM and related effective constituents for treating gout to provide novel ideas and directions for the prevention and treatment of gout in the future.

Pathogenesis of Gout

Hyperuricemia, which is the most important factor for gout development, is characterized by elevated level of uric acid in the body, with a subsequent increase in the risk of gout [15]. Hyperuricemia is mainly caused by two factors: increased uric acid production and reduced uric acid excretion. Uric acid is the end product of purine nucleotide degradation in the body, and the dietary source is attributed to the absorption of purine from purine-rich foods by the small intestine. Xanthine oxidase (XOD) catalyzes the oxidation reactions of hypoxanthine to xanthine and finally to uric acid, which directly affects uric acid formation [16]. Additionally, uric acid excretion is regulated by the kidneys and intestines, particularly through glomerular filtration, as well as active and passive reabsorption at the beginning and straight segments of the proximal tubule. Many transporters are involved in the filtration and reabsorption processes, namely, URAT1; GLUT9; OAT1, OAT2, and OAT3; and secretion transporter ABCG2 [17-22]. The expression and dysfunction of these transporters affect uric acid excretion.

Uric acid mostly exists as soluble urate in the body [23]. When the uric acid concentration in the body exceeds the solubility threshold of 7.0 mg/dL [24], MSU crystals are deposited in the joints, soft tissues, cartilage, and kidneys. The MSU crystal is an injury-related pathogen that activates not only the innate immune response but also the macrophages and monocytes, leading to the activation of NLRP3 inflammasomes. NLRP3 inflammasomes are closely associated with gout episodes [25]. The activation of NLRP3 inflammasomes depends on two steps, namely, initiation and activation [26]. The initiation step affects the assembly and activation of the NLRP3 inflammasomes and is related to the TLR signaling pathway. TLR2 and TLR4 play a vital role in the production of inflammatory factors [27]. The complex formed by the binding of MSU crystals to CD14 receptors located on the cell surface is recognized by the TLRs; IL-1R–related kinase (I-RAK) is activated by the recruitment of myeloid differentiation factor (MYD88) through IL-1R and binds to tumor necrosis factor (TNF) receptor–related factor 6 (TRAF6), which then activates IκB kinase to allow free NF-κB to enter the nucleus. Subsequently, the transcription of chemokines and proinflammatory mediators, including pro-interleukin (pro-IL)-1β, pro-IL-18, and TNF-α [28-30]. It is worth noting that the MSU crystals activate TLRs only by binding with the TLR ligand (fatty acid/ LPS) [31]. Additionally, the activation step of the NLRP3 inflammasomes is influenced by the MSU crystals. The NLRP3 inflammasome comprises three parts: nucleotide oligomerization domain (NOD)–like receptors (NLRs), apoptosis-associated dot-like protein (apoptosis-

associated speck-like protein containing a caspase recruitment domain [ASC]), and pro-cysteine–dependent aspartate-directed protease-*1* (pro-caspase-1). NLRs are cytoplasmic pattern recognition receptors that sense a danger signal from the MSU crystals, connect with the ASC and pro-caspase-1, and assemble into an inflammasome, thereby leading to Caspase-1 cleavage and activation, which cleaves pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, respectively [32-34]. The MSU crystal can also induce the monocytes to secrete COX-2, which first transforms arachidonic acid into PGE2 and then stimulates the inflammatory reaction [35,36].

Excessive extracellular ATP concentration can also promote the activation of NLRP3 inflammasomes and thus produce more inflammatory factors. Particularly, the abnormally high ATP level activates the P2X7R receptor on the cell surface and induces the formation of cation channels, which promote the influx of extracellular Na ions and Ca ions and the efflux of K ions simultaneously [37]. K ion outflow promotes the activation of the NLRP3 inflammasome [38]. Additionally, the engulfment of the MSU crystals by the macrophages punctures the mitochondria, leading to the production of ROS [39], further activation of the NLRP3 inflammasome, and increased production of the inflammatory factor IL-1β [40].

To summarize, MSU crystals can upregulate the expression of many inflammatory factors, including TNF-α, IL-1β, and IL-18, among others, and IL-1β is the main inflammatory factor causing gout. IL-1β stimulates an inflammatory response that generates the recruitment of monocytes and neutrophils at the site of MSU crystal deposition, and the resulting inflammatory response causes gout [41]. Notably, continuous accumulation of IL-1β activates matrix-degrading enzymes, causing cartilage damage and bone destruction [42] (Figure 1).
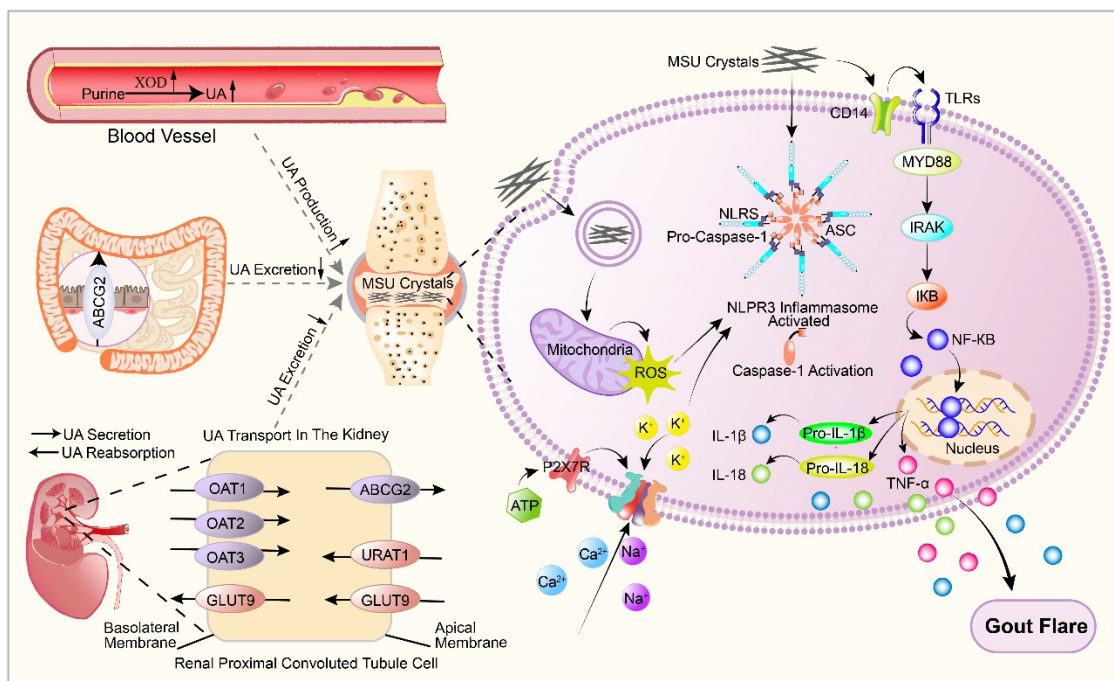
Figure 1: Schematic diagram of the pathology of gout. Gout is characterized by high serum uric acid levels, MSU crystal deposition, inflammation, and oxidative stress. Increased uric acid production and decreased uric acid excretion can result in increased serum uric acid levels, and persistently high serum uric acid levels can result in the deposition of MSU crystals, which trigger inflammatory reactions that lead to gout. Oxidative stress promotes the formation and activation of inflammasomes, as well as the production of more inflammatory factors, aggravating the inflammatory response.

Therapeutic Effects of Herbal Medicines

Herbal Medicines Originated from Asteraceae

Atractylodis rhizome, a dry rhizome from *Atractylodes lancea* (Thunb.) DC., is a common Chinese herbal medicine with anti-inflammatory, anticancer, antibacterial, and other pharmacological effects [43]. Li et al. identified the effective components and the mechanism of atractylodis rhizome extract in the treatment of gouty arthritis through network pharmacology and verified their results through experiments. Atractylodes macrocephala could lower the levels of TGF-β1, PGE2, UA, IL-1β, IL-6, and TNF-α and XOD activity and can regulate apoptosis-related pathways, which may be the mechanism of atractylodes macrocephala for gout treatment [44]. The atractylodes macrocephala extract can inhibit XOD activity, reduce uric acid level, and decrease inflammation in gouty arthritis rats by hindering the formation of inflammatory factors such as IL-1β and TNF-α [45]. The chicory extract regulates the NF-κB and NLRP3 signaling pathways and exerts a therapeutic effect on gouty arthritis. In vivo studies have shown that the chicory extract significantly reduced the degree of joint swelling in mice and blocked the NF-κB/NLRP3 signaling pathways, thereby inhibiting the release of IL-1β. Similar results were obtained under in vitro conditions. Chicory and chicoric acid inhibited IL-1β expression [46]. *Siegesbeckia orientalis* L. reduces serum uric acid concentration by inhibiting XOD activity. It can also reduce carrageenan-induced foot swelling and synovitis *in vivo* [47]. The sunflower (*Helianthus annuus*) head extract (SHE) can significantly inhibit MSU crystal–induced ankle joint swelling in rats by reducing the serum IL-10 level and inhibiting MCP-1 protein expression. The SHE extract can also decrease the uric acid level in hyperuricemic mice by inhibiting XOD activity *in vivo* [48] (Table 1).

Herbal Medicines Originated from Dioscoreaceae

Dioscorea collettii extract (DCE) exerts a therapeutic effect on gouty arthritis. DCE reduces the expression of NALP3 and ASC proteins in vivo, decreases the expression of the NALP3 protein, and inhibits the activation of Caspase-1 protein in THP-1 macrophages *in vitro* [49]. Lu et al. reported that the Rhizoma Dioscoreae Nipponicae(*Dioscoreaceae*) extract may exert a pharmacological effect in gouty arthritis by regulating the p38 MAPK and SDF-1/CXCR-4 signaling pathways. In addition, its action mechanism is also closely related to the metabolism of glycerophospholipids, inositol phosphate and galactose [50,51] (Table 1).

Herbal Medicines Originated from Liliaceae

The extract of *Smilax glabra* Roxb. can stimulate uric acid excretion and confer protection against uric acid nephropathy. The mechanism of *Smilax glabra* Roxb. in lowering uric acid levels is related to the upregulated expression of ABCG2, OAT1, organic cation transporter 2 (OCT2), and organic cation/carnitine transporter 2 (OCTN2). *Smilax glabra* Roxb. may thus exert a therapeutic effect on gout by reducing uric acid levels. *Smilax glabra* Roxb. can also improve renal damage caused by urate [52]. Interestingly, *Smilax glabra* Roxb. can also reduce serum uric acid levels by inhibiting XOD activity. *In vivo* experiments have confirmed that *Smilax glabra* Roxb. can treat gouty arthritis by reducing the expression of the inflammasome [53,54]. Wu et al. demonstrated that *Smilax riparia* can stimulate uric acid excretion by inhibiting mURAT1 expression, suggesting that it may exert a therapeutic impact on gout by reducing uric acid levels [55]. The extract of *Smilax china* L. can decrease uric acid levels, and its mechanism of action may be associated with the inhibition of XOD activity, suggesting its possible therapeutic impact on gout [56] (Table 1).

Herbal Medicines Originated from Other Families

Some Chinese herbal extracts can reduce serum uric acid levels by inhibiting the formation of uric acid, including corni fructus, which is the dry and mature pulp of *Cornus officinalis* Sieb. et Zucc (Cornaceae), *Salvia plebeia* R. Br. (Lamiaceae), *Alocasia longiloba* Miq. (Araceae), *Olea europaea* L. (Oleaceae) and *Camellia japonica* L.*(Theaceae)*. The extracts of Chinese herbal medicines can reduce uric acid production by inhibiting XOD activity, which reduces serum uric acid levels, thus contributing to the prevention and treatment of gout [57-61].

Some Chinese herbal extracts reduce uric acid levels by promoting uric acid excretion. The ethanolic extract of the barks of *Liriodendron chinense* (Hemsl.) Sarg (Magnoliaceae) (EELC) can promote uric acid excretion, reduce uric acid accumulation in the kidneys, and decrease blood uric acid levels. The uric acid–lowering effect occurs through the upregulated expression of ABCG2, OAT1, and OTA3 proteins in the kidney. EELC can also inhibit the JAK2/STAT3 and NF-κB pathways. The enhancement of the ASK1/c-jun signaling pathway reduces the release of inflammatory factors and alleviates the symptoms of hyperuricemic nephropathy [62]. The extract of *Polygonum capitatum* Buch. Ham. ex D. Don (Polygonaceae)can downregulate the expression of GLUT9 and URAT1 to promote uric acid excretion. It is worth noting that the extract can also reduce uric acid production by hindering XOD activity [63]. Another study reported a similar result. The *Mori Ramulus* (Moraceae) extract can promote uric acid excretion by inhibiting the mRNA and protein expression of URAT1, GLUT9, and OAT1 and upregulating the mRNA and protein expression of OCT1/2 and OCTN1/2, respectively [64]. Han et al. reported that the extract of *Urtica hyperborea* Jacq. ex (Urticaceae) can significantly reduce uric acid levels in a hyperuricemia mouse model. In vitro studies have shown that

the extract acts by upregulating OAT1 expression in HK2 cells and downregulating URAT1 expression [65]. The aforementioned herbals have therapeutic effects on gout, mainly by lowering uric acid levels (Table 1).

However, some herbals can treat gouty arthritis through their anti-inflammatory effect. For example, relative to the control group, the model group, and the treatment group, the *Phyllanthus emblica* (Phyllanthaceae) extract significantly reduced the inflammatory response in the ankle joint of rats with gout; it significantly inhibited the expression of NLRP3 and Caspase-1 in the synovial cells of the ankle joints of rats and decreased the levels of inflammatory factors such as IL-10, and TNF-α [66]. The seed extract of *Apium graveolens* L. (Apiaceae) can reduce the levels of IL-1β and TNF-α. [67]. The *Aconitum carmichaelii* Debeaux (Ranunculaceae) extract can evidently downregulate the mRNA expression of Caspase-1, PTGS2, spleen tyrosine kinase, MAPK14, matrix metalloproteinase (MMP) 9, and COX-2 in

MSU-treated THP-1 cells in vitro. In vivo studies have shown that the extract can significantly inhibit the expression of serum IL-1β and IL-18 in gouty arthritis rats induced by MSU crystals [68]. Similarly, the extract of *Cinnamomum cassia* (Lauraceae) can reduce the secretion of the inflammatory factor IL-1β by activating AIM2, NLRP3 inflammasome [69]. Interestingly, the extract of *Ginkgo biloba* L. (Ginkgoaceae) leaves can also inhibit the production of serum IL-1β [70]. Liu et al. confirmed that the *Eurycoma longifolia* (Simaroubaceae) extract can effectively inhibit joint swelling in rats with gouty arthritis induced by MSU crystals. Network pharmacology, molecular docking, and the enrichment method of KEGG demonstrated that the *Eurycoma longifolia* extract might have a therapeutic effect on gouty arthritis by synergistically regulating TLRs, NLRs, and MAPK signaling pathway [71]. Similarly, Hua et al. speculated that the extract of *Stauntonia brachyanthera Hand*-Mazz (Lardizabalaceae) plays an anti-gout role by regulating MAPK, TLRs, NLRs, and PI3K-Akt signaling pathway [72] (Table 1).

Plant family	herbals	Model	Functions	Mechanisms	Ref.
Asteraceae	*Atractylodes Lancea* (Thunb.) DC.	SPF SD rats RAW264.7 macrophages	Anti-inflammatory	IL-1β↓; IL-6↓; TNF-α↓; PTGS2↓	[44]
	Atractylodes macrocephala Koidz.	Male SD rats	Anti-inflammatory Anti-hyperuricemia Improve renal injury	IL-1β↓; TNF-a↓; XOD↓	[45]
	Cichorium intybus L.	Male SD rats macrophages	Anti-inflammatory	NLRP3↓;IL-1β↓; NF-κB p65↓	[46]
	Siegesbeckia orientalis L.	Male Wistar rats	Anti-inflammatory Anti-hyperuricemia Inhibit uric acid production	XOD↓	[47]
	Helianthus annuus Head	Male BALB/c mice	Anti-inflammatory Anti-hyperuricemia	IL-10↓; MCP-1↓;XOD↓	[48]
Dioscoreaceae	*Dioscorea collettii*	THP-1 cell	Anti-inflammatory	NLRP3↓;IL-1β↓; IL-18↓; TNF-α↓;	[49]
	Discorea nipponica Makino	Male SD rats	Anti-inflammatory	glutathione metabolism, glycerol phospholipid metabolism, inositol phosphate metabolism, galactose metabolism p38 MAPK, SDF-1/CXCR-4	[50,51]

Liliaceae	*Smilax glabra Roxb*	Male SD rats Male BALB/c mice	Anti-inflammatory Anti-hyperuricemia Promote uric acid excretion Improve kidney injury Inhibit uric acid production	IL-1β↓; IL-6↓; IL-12↓; TNF-α↓; TGF-β1↓; ABCG2↑; OAT1↑; OCT2↑; OCTN2↑ mURAT1↓; XOD↓	[52-55]
	Smilax china L.	Male ICR mice	Anti-hyperuricemia	XOD↓	[56]
Cornaceae	*Cornus officinalis Sieb.*	Male ICR mice	Anti-hyperuricemia	XOD↓	[57]
Lamiaceae	*Saluia plebeia* R. Br.	Male ICR mice	Anti-hyperuricemia	XOD↓	[58]
Araceae	*Alocasia longiloba Miq.*	Male SD rats	Anti-hyperuricemia	XOD↓	[59]
Oleaceae	*Olea europaea L.* leaf	Male SD rats	Anti-hyperuricemia	XOD↓	[60]
Theaceae	*Camellia japonica* L.	Male SD rats	Anti-hyperuricemia	XOD↓	[61]
Magnoliaceae	*Liriodendron chinense (Hemsl.) Sarg.*	Male C57BL/6 mice	Anti-inflammatory Anti-hyperuricemia Improve kidney injury Promote uric acid excretion	TNF-α↓; NF-κB p65↓ OAT1↓; OAT3↓; ABCG2↓	[62]
Polygonaceae	*Polygonum capitatum* Buch. Ham. ex D. Don	Male Kunming mice	Anti-inflammatory Anti-hyperuricemia Promote uric acid excretion Improve kidney injury Inhibit uric acid production	IL-1β↓; IL-6↓; TNF-α↓; GLUT9↓; URAT1↓; OAT1↓; XOD↓	[63]
Moraceae	*Mori Ramulus*	Male Kunming mice	Anti-hyperuricemia Promote uric acid excretion	GLUT9↓; URAT1↓; OAT1↓; mOCT1↑; mOCT2↑; mOCTN1↑; mOCTN2↑	[64]
Urticaceae	*Urtica hyperborea* Jacq.	Human renal tubular epithelial HK2 cells Male Kunming mice	Anti-hyperuricemia Promote uric acid excretion Inhibit uric acid production	URAT1↓; OAT1↓; XOD↓	[65]
Phyllanthaeae	*Phyllanthus emblica* L.	SPF Male SD rats	Anti-inflammatory	NLRP3↓; caspase-1↓; MMP13↓; IL-1β↓; IL-10↓; TNF-α↓;	[66]
Apiaceae	*Apium graveolens* L. seed	Male BalB/c mice	Anti-inflammatory Antioxidant stress	IL-1β↓; IL-10↓; ROS↓	[67]
Ranunculaceae	*Aconitum carmichaelii* Debeaux	Male SD rats THP-1 cells	Anti-inflammatory	IL-1β↓; IL-18↓; TNF-α↓; MAPK14↓; MMP9↓; PTGS2↓;	[68]
Lauraceae	*Cinnamomum cassia* Presl	Bone marrow-derived macrophages Male C57BL/6 mice	Anti-inflammatory	NLRP3↓; IL-1β↓	[69]
Ginkgoaceae	*Ginkgo biloba* L. leaves	Male SD rats	Anti-inflammatory	L-1β↓	[70]

Simaroubaceae	*Eurycoma longifolia* Jack.	Adult Wistar albino rats	Anti-inflammatory	Toll-like receptor, MAPK, chemokine, NOD-like receptor, T cell receptor signaling pathway	[71]
Lardizabalaceae	*Stauntonia brachyantherand*-Mazz		Anti-inflammatory	MAPK, PI3K-Akt, Toll-like Receptor, NOD-like receptor signaling pathway	[72]

Table 1: Summary of Single herbs for gout

Therapeutic Effects of Natural Compounds from TCM for Gout

Polysaccharides

Polysaccharides isolated from herbal medicines have important pharmacological properties, including anti-inflammatory, anticancer, antioxidant, antidiabetic, antiviral, hypolipidemic, and immune regulation properties [73,74]. *Isatidis Radix* is a biennial herb of the Brassicaceae family. In TCM, *Isatidis Radix* plays an important role in heat clearance and detoxification [75]. As reported in modern pharmacological research, *Isatidis Radix* contains many important components, including polysaccharides, alkaloids, and organic acids [76].

Isatidis Radix polysaccharide (IRP) extracted from *Isatidis Radix* could inhibit the activation of multiple inflammasomes and alleviate gouty arthritis, as seen both in vivo and in vitro experiments. Under in vitro conditions, IRP can inhibit caspase-1 cleavage and IL-1β secretion by blocking NLRP3 inflammasome activation. Under in vivo conditions, IRP can alleviate joint swelling caused by MSU crystals in mice and reduce the secretion of MPO, IL-6, IL-18, and IL-1β in the swollen joints [77].

Plantaginis semen polysaccharide (PSP) can alleviate gout and renal damage. *O*ral administration of PSP (0.27 g/kg body weight, daily for 20 days) can significantly reduce serum uric acid and urine protein levels. PSP can also inhibit the expression of TNF-α, TGF-β, and IL-6 and downregulate the expression of caspase-1, ASC, and NLRP3 proteins. *To sum up, PSP* can alleviate gout by reducing uric acid levels, and PSP can alleviate gout nephropathy by reducing urinary protein levels and inhibiting the release of inflammatory factors by reducing the expression of caspase-1, ASC, and NLRP3 proteins [78].

Lonicera japonica polysaccharide (i.p., 0.1, 0.2, and 0.3 g/kg body weight) exerted anti-hyperuricemic effects in rats by inhibiting XOD activity. It also decreased the flares of gouty arthritis and alleviated ankle swelling in mice by downregulating the expression of IL-1β, IL-6, TNF-α, and COX-2–related inflammatory factors in murine serum [79]. (Table 2).

Monomers	Sources	Model	Functions	Mechanisms	Ref.
Isatidis Radix Polysaccharide	*Isatis tinctoria* Linnaeus (*Brassicaceae*)	male C57BL/6 mice THP-1 cells BMDMs cells	Anti-inflammatory	NLRP3↓; IL-1β↓; IL-6↓; IL18↓; TNF-α↓	[77]
Plantaginis Semen Polysaccharides	*Plantago asiatica L.* (*Plantaginaceae*)	Male SD rats	Anti-inflammatory Improve renal function	NLRP3↓; IL-6↓; TNF-α↓; TGF-β↓	[78]
Lonicera japonica Polysaccharide	*Lonicera japonica* Thunb. (*Caprifoliaceae*)	Male SD rats	Anti-inflammatory Anti-hyperuricemia	IL-1β↓; IL-6↓; TNF-α↓; COX-2↓XOD↓	[79]

Table 2: Summary of Polysaccharides for gout

Alkaloids

Alkaloids are an important kind of natural products widely existing in various plant species. Most alkaloids have significant biological potential, such as alleviating gouty arthritis, anti–human immunodeficiency virus activity, lowering blood pressure, and antiparasitic activity. *Phellodendri chinensis cortexis* a TCM for treating gout and hyperuricemia in China, which is mainly used for clearing heat dampness and purging fire detoxification [80]. Berberine is the main component of Phellodendron chinense cortex and has anti-hyperuricemic and anti-gout effects [81]. Berberrubine (BRB) is the biologically active metabolite of berberine in the body. Lin et al. reported that oral administration of BRB (6.25, 12.5, and 25.0 mg/kg body weight) reduced serum uric acid levels in a hyperuricemic mouse model induced by potassium oxazinate, and the mechanism involved reduction of XOD activity in the liver and inhibition of the expression of GLUT9 and URAT1. Additionally, ABCG2 and BRB activate the expression of OAT1/3 [82].

Dihydroberberine (DHB) is a derivative of berberine. Xu et al. investigated the effects of DHB on the reduction of uric acid levels and renal protection in hyperuricemic mice. Oral DHB (25 and 50 mg/kg body weight) decreased the uric acid level triggered by potassium oxazinate and hypoxanthine in a dose-dependent manner. DHB significantly inhibits XOD activity, thereby decreasing uric acid production. DHB can also promote uric acid excretion by downregulating the expression of URAT1 and GLUT9. Additionally, DHB inhibits the mRNA expression of NLRP3, ASC, caspase-1, and IL-1β in the kidney to protect renal function [83].

Palmatine (PAL) is the main active ingredient in *Corydalis yanhusuo*. Juanjuan et al. demonstrated that PAL has the potential as an effective therapeutic candidate for gouty arthritis because of its anti-inflammatory activities. PAL treatment at doses of 20, 40, and 80 μm alleviated MSU-induced gouty arthritis in a rat model. PAL treatment dose-dependently inhibits the mRNA expression of IL-1β, IL-6, IL-18, and TNF-α. Additionally, it can promote the production of superoxide dismutase and glutathione (GSH) and reduce the production of malondialdehyde (MDA). Western blotting has shown that PAL can effectively inhibit the NF-κB/NLRP3 signaling pathway by inhibiting the expression of NLRP3, ASC, IL-1β, and Caspase-1, while enhancing the expression of the antioxidant proteins Nrf2 and HO-1. Moreover, PAL further reduces the infiltration of neutrophils into synovitis [84]. Tetrahydropalmatine (THP), another effective compound from *Corydalis yanhusuo,* can attenuate MSU-induced gouty arthritis. Oral THP (10, 20, and 40 mg/kg body weight) dose-dependently reduced MSU-induced plantar swelling, and when compared with the model group, the levels of inflammatory factors in the treatment group decreased and the infiltration of inflammatory cells weakened, both of which are attributed to the role of THP in inhibiting NLRP3 inflammasome activation and caspase-1 formation. THP also reduces ROS production induced by MSU crystal deposition by increasing the activity of antioxidant enzymes under both in vivo and in vitro conditions. It is worth noting that the impact of a high dose is equivalent to that of a positive drug [85].

Coptisine, the main effective component of *Coptis chinensis*, can significantly inhibit the secretion of mature IL-1β from RAW264.7 macrophages stimulated by LPS together with MSU, ATP, and nigericin, by inhibiting caspase-1 activation. Moreover, it blocks the NF-κB signaling pathway to inhibit NLRP3 expression, thereby preventing the priming of inflammasome. Under in vivo conditions, oral administration of coptisine reduced the degree of foot swelling in mice of the treatment group. The aforementioned findings suggest that coptisine can be used to treat gouty arthritis caused by NLRP3 inflammasomes [86]. (Table 3).

Monomers	Sources	Model	Functions	mechanisms	Ref.
Berberrubine	*phellodendri chinensis cortex* (*Rutaceae*)	male KM mice	Anti-inflammatory Anti-hyperuricemia Improve kidney injury Inhibit uric acid production Promote uric acid excretion	IL-1β↓; IL-6↓; TNF-α↓; URAT1↓; GLUT9↓; OAT1/3↑; ABCG2↑; XOD↓	[82]
Dihydroberberine	*phellodendri chinensis cortex* (*Rutaceae*)	male KM mice	Anti-inflammatory Anti-hyperuricemia Improve kidney injury Inhibit uric acid production Promote uric acid excretion	NLRP3↓; IL-1β↓; IL-6↓; IL18↓; TNF-α↓; URAT1↓; GLUT9↓; XOD↓	[83]
Palmatine	*Corydalis yanhusuo* (*Papaveraceae*)	male KM mice THP-1 cells	Anti-inflammatory	IL-1β↓; IL-6↓; IL18↓; TNF-α↓; MDA↓; Nrf2↓; HO-1↓	[84]
Tetrahydropalmatine	*Corydalis yanhusuo* (*Papaveraceae*)	Male C57BL/6 mice RAW264.7 macrophage	Anti-inflammatory Antioxidant stress reaction	NLRP3↓;IL-1β↓; IL-6↓; IL18↓; TNF-α↓; ROS↓	[85]
Coptisine	*Coptis chinensis Franch.* (*Ranunculaceae*)	Male Kun Ming mice RAW 264.7 cell macrophage	Anti-inflammatory	NLRP3↓; IL-1β↓; TNF-α↓	[87]

Table 3: Summary of Alkaloids for gout

Phenolic Compounds

Phenolic compounds exert a wide range of pharmacological activities, including antioxidation, anti-gout, mprovement of vascular endothelial function, anti-atherosclerosis, and inhibition of platelet aggregation [87].

Caffeic acid can effectively reduce serum uric acid levels in hyperuricemic mice triggered by potassium oxazinate, and it acts by inhibiting XOD activity in the liver [88,89].

Chlorogenic acid alleviates mouse foot swelling induced by MSU crystals by blocking the expression of IL-6, IL-1β, and TNF-α. Moreover, chlorogenic acid alleviates gouty arthritis [90]. With regard to the mechanism of chlorogenic acid in relieving gouty arthritis, its action may show an association with the regulation of mitogen-activated protein kinase (MAPK), PI3K-Akt, and NF-κB signaling pathways and the intervention of TLRs, affecting the release of cellular inflammatory factors [91].

Vanillin, a phenolic compound, is an effective component in *Amomum villosum* Lour. Under *in vitro* conditions, vanillic acid inhibits XOD activity [92], but its effect on uric acid has not been investigated. Based on previous experimental results, we speculate that vanillic acid may have a beneficial effect on gouty arthritis by reducing serum uric acid levels.

Paeonol is an effective component of *Moutan Cortex*. Chen et al. reported that paeonol can attenuate gouty arthritis induced by MSU crystals. Specifically, oral paeonol reduced foot swelling induced by MSU crystals in rats; reduced the expression of TNF-α, IL-1β, and IL-6; upregulated the protein expression of P65 in the nucleus; and significantly inhibited NF-κB DNA binding activity. The aforementioned results indicate that paeonol may play an anti-inflammatory role and hinder the expression of proinflammatory cytokines and NF-κB [93].

6-Shogaol is an active ingredient extracted from *Zingiber officinale Roscoe*. that can effectively reduce serum uric acid levels by inhibiting XOD activity. Moreover, *6-shogaol* can also reduce the production of inflammatory cytokines such as IL-1β and TNF-α [94] (Table 4).

Monomers	Sources	Model	Functions	Mechanisms	Ref.
Caffeic acid	*Tabebuia roseoalba* (*Bignoniaceae*)	male albino Swiss mice	Anti-inflammatory Anti-hyperuricemia	XOD↓	[88,89]
Chlorogenic acid	*Tabebuia roseoalba* (*Bignoniaceae*) *Porana sinensis* Hemsl. (*Convolvulaceae*) *Smilax china* L. (*Liliaceae*)	male albino Swiss mice male Kun-Ming strain of mice	Anti-inflammatory Anti-hyperuricemia Inhibit uric acid production	IL-1β↓; IL-4↓; IL-6↓; TNF-α↓; TGF-β↓; XOD↓	[90,91]
Vanillic acid	*Amomum villosum* Lour. (*Zingiberaceae*)		Anti-hyperuricemia Inhibit uric acid production	XOD↓	[92]
Paeonol	Paeonia suffruticosa Andr. (Ranunculaceae)	Male SD rats	Anti-inflammatory	IL-1β↓; IL-6↓; TNF-α↓	[93]
6-shogaol	*Zingiber officinale* Roscoe (*Zingiberaceae*)	Male SD rats	Anti-inflammatory Anti-hyperuricemia	IL-1β↓; TNF-α↓; XOD↓	[94]

Table 4: Summary of Phenolic compounds for gout

Flavonoids

Most Chinese herbal medicines contain flavonoids. They have a wide range of pharmacological activities, including anti-inflammatory, antioxidant, immune enhancement, anticancer, and other effects [95].

Kaempferol, the main effective component of Cudrania tricuspidata leaf ,can decrease serum uric acid levels in hyperuricemic mice by hindering XOD activity, the therapeutic effect of kaempferol is equivalent to that of allopurinol [96], it is a promising drug as an alternative to allopurinol in the treatment of hyperuricemia and gout.

Icariin is the main active ingredient in Epimedium. Cao et al. confirmed the therapeutic effect of icariin against gouty arthritis and reported that icariin (20, 40, and 80 mg/kg body weight) inhibits the expression of IL-1β, IL-6, PGE_2, and TNF-α in the synovial tissue, alleviates the infiltration of inflammatory factors, and weakens ankle joint swelling in rats. Moreover, icariin can reduce the expression of the NALP3 inflammasome by inhibiting the nuclear transcription of proteins participating in the NF-κB pathway. In vitro studies showed that icariin reduced the activity of chondrocytes and inhibited the levels of the inflammasome and glycosaminogly [97].

Luteolin and luteolin-4′-O-glucoside, effective components extracted from *Gnaphalium affine* D. Don., can inhibit the protein expression of URAT1 and the activity of XOD to reduce uric acid production and increase uric acid excretion, thereby alleviating hyperuricemia symptoms. It can also reduce foot swelling induced by MSU crystals and the production of inflammatory cytokines such as IL-1, IL-β, and TNF-α [98]. Other studies have obtained consistent results, that is, luteolin-4′-O-glucoside and luteolin-4′-

O-glucoside can alleviate hyperuricemia and gouty arthritis [99].

Chrysin, a flavonoid compound extracted from *Oroxylum indicum* (L.) (*Bignoniaceae*) has the effect of anti-inflammation, anti-oxidation and anti-hyperuricemia. Chang et al. reported that oral administration of chrysin (50, 100, and 150 mg/kg body weight, daily for 28 days) lowered serum uric acid levels in hyperuricemia induced by high-fructose syrup in a dose-dependent manner. Moreover, chrysin can inhibit XOD activity; western blotting analysis demonstrated that the protein expression of URAT1 and GLUT9 showed an evident decrease, whereas that of OAT1 and human ABCG2 protein was increased. Chrysin can significantly reduce IL-1β levels in the kidney and serum of rats and MDA levels, suggesting that chrysin has significant antioxidant and anti-inflammatory activities. It is worth noting whether such a high dose (*50 mg/kg* body weight) will produce toxic and side effects in experimental animals [100].

Quercetin, a flavonoid compound widely dispersed throughout the plant kingdom has the effect of anticancer, antioxidant and anti-gouty arthritis. Feng et al. predicted 72 potential targets of quercetin for gout using network pharmacology analysis and constructed an interaction network between quercetin and gout. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis showed that the IL-17, TNF-α, MAPK, and PI3K signaling pathways were the main involved pathways. Quercetin administration to mice with MSU-induced gouty arthritis, relative to the model group and the control group, significantly reduced ankle joint swelling, hindered the expression of IL-6/17A/F in the IL-17 signaling pathway, and reduced the expression of retinoic acid–related orphan receptor, TNF-α, and TGF-β, all of which are in line with those obtained previously [101].

(-)-Epicatechin (EC) is the main active component in some medicinal plants and food, with anti-inflammatory and anti-oxidant effects. Chen et al. conducted in-depth research on its role and mechanism in gouty arthritis treatment. First, in vitro experiments showed that EC could increase the activity of THP-1 cells treated with MSU; reduce the levels of IL-6, IL-18, IL-1β, and TNF-α in the supernatant of THP-1 cells; and significantly increase the expression of ASC, NLRP3, and caspace-1 induced by MSU administration. Nuclear P65 expression was found to be reduced, suggesting that EC restricted P65 from entering the nucleus. The same results were obtained during the in vivo experiments either [102].

Baeckein E (BF-2) is an active compound isolated from Baeckea frutescens L. BF-2 evidently blocks IL-1β secretion, inhibits the thermophilicity of macrophages, and alleviates ankle swelling. BF-2 also alleviates oxidative stress by inhibiting the combination of pre-Caspase 1 and ASC, thereby inhibiting the assembly of the NLRP3 inflammasome. More interestingly, BF-2 can block the activation of the NLRP3 inflammasome by inhibiting the MAPK/NF-κB signaling pathway [103] (Table 5).

Monomers	Sources	Model	Functions	Mechanisms	Ref.
Kaempferol	*Cudrania tricuspidata* Leaf (*Moraceae*)	male ICR mice	Anti-hyperuricemia	XOD↓	[96]
Icariin	*Epimedium brevicornu Maxim* (*Berberidaceae*)	Male SD rats chondrocytes	Anti-inflammatory	NLRP3↓;IL-1β↓; IL-6↓; TNF-α↓; PGE2↓;	[97]
Luteolin Luteolin-4′-O-glucoside	*Gnaphalium affine* D. Don. (*Asteracea*e)	male Kun-Ming mice male ICR mice	Anti-inflammatory Anti-hyperuricemia Improve kidney injury Inhibit uric acid production Promote uric acid excretion	IL-1β↓; TNF-α↓; URAT1↓; GLUT9↓; XOD↓	[98,99]
Chrysin	Many plants	Male SD rats	Anti-inflammatory Anti-hyperuricemia Antioxidant stress reaction Inhibit uric acid production Promote uric acid excretion	IL-1β↓; ROS↓; URAT1↓; GLUT9↓; OAT1↑; ABCG2↑	[100]
Quercetin	Many plants	Male SD rats	Anti-inflammatory	IL-1β↓; IL-6↓; IL-17A↓; IL-17F↓; TNF-α↓	[101]
(-)-Epicatechin (EC)	Many plants	Male C57BL/6 mice THP-1 cells	Anti-inflammatory	NLRP3↓;IL-1β↓; IL-6↓; IL-18↓; TNF-α↓;	[102]
Baeckein E	*Baeckea frutescens* L. (*Myrtaceae*)	J774A.1 macrophages male C57BL/6 mice	Anti-inflammatory Antioxidant stress reaction	NLRP3↓;IL-1β↓; ROS↓	[103]

Table 5: Summary of Flavonoids for gout

Quinones

Rhein, a active components of *Rheum tanguticum* Maxim. ex Regel, can significantly inhibit the production of IL-1β and TNF-α by macrophages and caspase-1 protein. The rate of inhibition of IL-1β by rhein at a concentration of 2.5 µg/mL is 47%, and rhein (5 µg/mL) can significantly reduce ASC content and inhibit NLRP3 expression. To sum up, rhein alleviates gouty arthritis by inhibiting the activation of the NLRP3 inflammasome and macrophages [104].

Polydatin , a quinone compound isolated from *Reynoutria japonica* Houtt., has a wide range of pharmacological effects, including its efficacy in preventing and treating diabetes, atherosclerosis, hyperlipidemia, and gout [105]. Oral administration of polydatin (20 and 50 mg/kg body weight) to hyperuricemic rats induced by potassium oxazinate reduced the levels of uric acid and creatinine in blood and urine respectively and achieved the same effect as that of the positive drug allopurinol. It can also restore TNF-α, IL-1, IL-β, and IL-6 levels in the serum and kidney of the rats in the model group to the original level. Polydatin blocked NF-κB protein expression and significantly lowered IκBα phosphorylation. Additionally, western blotting showed that the expression of ASC, Caspase-1, and NLRP3 was inhibited. Furthermore, polydatin upregulated the expression of p-AMPK and SIRT1 proteins in the kidney. It is speculated that polydatin may inhibit the production of NF-κB and NLRP3 inflammasome in the kidney by regulating the AMPK/SIRT1 signaling pathway in gout treatment [106] (Table 6).

Monomers	Sources	Model	Functions	Mechanisms	Ref.
Rhein	*Rheum tanguticum* Maxim. ex Regel (*Polygonaceae*)	THP-1 cells	Anti-inflammatory	IL-1β↓; TNF-α↓; caspase-1↓	[104]
Polydatin	*Reynoutria japonica* Houtt. (*Polygonaceae*)	Male SD rats	Anti-inflammatory Anti-hyperuricemia Improve kidney injury	IL-1β↓; IL-6↓; TNF-α↓; NF-κB p65↓	[106]

Table 6: Summary of Quinones for gout

Saponins

Saponin is an effective active component of many Chinese herbal medicines. Modern pharmacology has demonstrated that saponin has diverse biological activities, including anti-inflammatory, anticancer, hypoglycemic, and other effects [107].

Smilaxchinoside A and Smilaxchinoside C are steroidal saponins isolated from the ethanolic extract of *Smilax riparia*. Wu et al. reported that these two compounds inhibit uric acid production and stimulate uric acid excretion by inhibiting mURAT1 expression in the kidney and XOD activity. Smilaxchinoside A and Smilaxchinoside C are, therefore, potential clinical drugs for gout treatment [108]. Riparoside B and timosaponin J, which are also extracted from *Smilax riparia*, have the same effect as that of Smilaxchinoside A and Smilaxchinoside C and promote uric acid excretion by inhibiting URAT1 expression [109] (Table 7).

Monomers	Sources	Model	Functions	Mechanisms	Ref.
Smilaxchinoside A	*Smilax riparia*. (*Liliaceae*)	Male Kunming mice	Anti-hyperuricemia Inhibit uric acid production Promote uric acid excretion	mURAT1↓; mGLUT9↓; XOD↓; OAT1↑	[108]
Smilaxchinoside C					
Riparoside B	*Smilax riparia* (*Liliaceae*)	Male Kunming mice	Anti-hyperuricemia Inhibit uric acid production Promote uric acid excretion	mURAT1↓; XOD↓	[109]
Timosaponin J					

Table 7: Summary of Saponins for gout

Terpenoids

Terpenoids are widely present in many plants and have extensive pharmacological and biological activities [110].

Andrographolide (AND), the main component of *Andrographis paniculata* (*Burm. f.*) Nees, can inhibit IL-1β production by bone marrow macrophages in mice with gout induced by MSU crystals and infiltration of monocytes. AND interacts with the IKK/NF-κB signaling pathway and inhibits the activation of the NLRP3 inflammasome (endotoxin induced), leading to the downregulation of NLRP3 and Pro-IL-1β protein expression. AND also inhibits HO-1 protein expression and reduces ROS production. It is worth noting that AND reduces the combination of ASC and NLRP3. AND alleviates gouty arthritis by inhibiting ROS-induced NLRP3 inflammasome assembly and IL-1β release by increasing HO-1 expression [111].

Cucurbitacin B (CUB) is a terpenoid compound isolated from plants belonging to Cucurbitaceae. Xue et al. confirmed that CUB could significantly reduce IL-1β secretion by blocking the formation of NLRP3 inflammasome and inhibiting the key enzymes of macrophage glycolysis. Through histopathological analysis, the authors also showed that CUB improved foot swelling and inflammatory cell infiltration in gouty arthritis mice [112].

Tanshinones is a class of effective biological components in *Salvia miltiorrhiza* Bge. Yue et al. identified 15 tanshinones that can inhibit NLRP3 inflammasome activation, among which tanshinone IIA, isocryptotanshinone, and dihydrotanshinone I can reduce the production of oxygen free radicals in macrophages. Tanshinone protects mitochondria by promoting autophagic protein kinase and AMP-activated protein kinase, suggesting that tanshinone is effective for treating gouty arthritis [113].

Budlein A is a metabolite in the biosynthesis of sesquiterpene lactones in Asteraceae plants. Budlein A can alleviate knee joint swelling, reduce neutrophil aggregation, inhibit neutrophil phagocytosis due to the deposition of MSU crystals, and block the mRNA expression of IL-1β and TNF-α in the knee joint tissue homogenate. It is worth noting that inhibition of NF-κB activation may reduce TNF-α production. The aforementioned results suggest that Budlein A alleviates gouty arthritis by activating NF-κB and promoting the assembly of inflammatory factors [114].

Tripterine pentacyclic triterpene compound isolated from *Tripterygium wilfordii* Hook., can alleviate gouty arthritis. Specifically, it can reduce the swelling degree in MSU-induced joint swelling in mice. A high dose of tripterine (1 mg/kg body weight) can reduce the swelling degree by 83.9%, and a low dose can reduce the swelling degree by 72.4%. Hematoxylin-eosin staining analysis has shown that tripterine can reduce the infiltration of inflammatory cells. Additionally, enzyme-linked immunosorbent assay has demonstrated that tripterine inhibited the secretion of IL-1β. The protein expression of Caspase-1 was also downregulated [115] (Table 8).

Monomers	Sources	Model	Functions	Mechanisms	Ref.
Andrographolide	*Andrographis paniculata* (*Burm. f.*) Nees (*Acanthaceae*)	male C57BL/6J mice Bone marrow-derived macrophages	Anti-inflammatory Antioxidant stress	NLRP3↓;IL-1β↓; caspase-1↓; HO-1↓; ROS↓	[111]
Cucurbitacin B	Cucurbitaceae plants	Male C57BL/6 mice Bone marrow-derived macrophages	Anti-inflammatory	IL-1β↓; IL-18↓; HK1↓; HK2↓; PKM2↓; LDHA↓; PDH↓;	[112]
Tanshinone IIA	*Salvia miltiorrhiza Bge.* (*Lamiaceae*)	Male C57BL/6 mice J774A.1 macrophages	Anti-inflammatory Antioxidant stress	IL-1β↓; ROS↓	[113]
Isocryptotanshinone					
Dihydrotanshinone I					

Budlein A	Asteraceae plants	Male C57BL/6 mice Bone marrow-derived macrophages	Anti-inflammatory	IL-1β↓; TNF-α↓; NF-κB p65↓	[114]
Tripterine	*Tripterygium wilfordii* Hook. f. (*Celastraceae*)	male WT C57BL/6J mice HEK293T cells THP-1 cells Bone marrow-derived macrophages	Anti-inflammatory Improve liver injury	NLRP3↓; IL-1β↓;	[115]

Table 8: Summary of Terpenoids for gout

Glycosides

Gentiopicroside (GPS) is an iridoid glycoside isolated from *Gentiana Macrophylla* Pall. GPS can reduce foot swelling caused by MSU crystals; block the secretion of inflammatory factors, namely, IL-1β, IL-6, IL-18, and TNF-α; and significantly inhibit neutrophil infiltration. Immunosuppression analysis has demonstrated that GPS significantly restored the expression of NLRP3, ASC, and Caspase-1 proteins in the model group. GPS can inhibit the activation of NLRP3 inflammasomes in macrophages under in vitro conditions. GPS can be used to treat gouty arthritis by hindering the activation of the NLRP3 inflammasome [116].

Kinsenoside is the main effective ingredient in Anoectochilus roxburghii (Wall.) Lindl. in the treatment of gouty joints. Kinsenoside can negatively regulate the NF-κB/MAPK signaling pathway, thereby reducing the expression of inflammatory cytokines present downstream of NF-κB and inhibiting the biological activity of vascular endothelial cells. Kinsenoside can also inhibit the expression of NALP3 and TLR2 and the uptake of CD14 mediated by MSU crystals in macrophages. Under in vivo conditions, kinsenoside can significantly reduce inflammatory cell infiltration and endothelial damage and alleviate ankle swelling [117].

Total glucosides of paeony囗the main components of Paeoniae Radix Alba, regulates the interaction among MALAT1, MIMR876-5p, and NLRP3 proteins, blocks the TLR4/MYD88/NF-κB signaling pathway, and inhibits the THP-1 macrophage inflammation induced by MSU crystals, thus producing a therapeutic effect on gouty arthritis [118] (Table 9).

Monomers	**Sources**	**Model**	**Functions**	**Mechanisms**	**Ref.**
Gentiopicroside	*Gentiana Macrophylla* Pall. (*Gentianacea*e)	Male C57BL/6 mice RAW264.7 macrophage cell	Anti-inflammatory	NLRP3↓; IL-1β↓; IL-6↓; IL18↓;	[116]
Kinsenoside	*Anoectochilus roxburghii (Wall.) Lindl.* (*Orchidacea*e)	human umbilical vein endothelial cell Male SD rats	Anti-inflammatory	IL-1β↓; IL-6↓; TNF-α↓; COX-2↓; NF-κB p65↓; PGE2↓;	[117]
Total glucosides of paeony	*Paeonia lactiflora* Pall. (*Paeoniaceae*)	THP-1 cells	Anti-inflammatory	NLRP3↓; Caspase-1↓; IL-1β↓; MALAT1/miR-876-5p/NLRP3 axis TLR4/MyD88/NF-κB	[118]

Table 9: Summary of Glycosides for gout

TCM Prescription for Gout

Ermiao Pill is made up of *phellodendron chinense* Schneid. (*Rutaceae*) and *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*), and it was introduced in "Dan Xi Xin Fa" by Zhu Danxi during the Yuan Dynasty in China. Used in the treatment of gouty arthritis, rheumatoid arthritis, and arthralgia [119,120]. The mechanism of the uric acid lowering effect of Ermiao Pill was linked to the regulation of purine metabolism, taurine metabolism, hypotaurine metabolism, glyceride metabolism, amino acid metabolism, and primary bile acid metabolism [121]. By inhibiting the expression of the proinflammatory factor IL-6, it can also reduce ankle swelling in gouty arthritis

rats. Ermiao Wan can be used to treat gouty arthritis by lowering uric acid levels and inhibiting inflammatory reactions; however, its effective components and mechanism need to be investigated further [122].

Sanmiao Pill is a Chinese medicinal compound derived from the Ming Dynasty medical book "Yi Xue Zheng Zhuan", which consists of three components, *Phellodendron chinense* Schneid. (*Rutaceae*), *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*), and *Achyranthes bidentata* Blume (*Amaranthaceae*). Due to damp-heat in the lower energizer, it is primarily used in the clinical treatment of gout [123]. Zhu et al. demonstrated that Sanmiao Pill could treat gout by inhibiting cartilage matrix degradation. The cartilage matrix is primarily made up of proteoglycan and collagen. In particular, when compared to the model group, the treatment group's oral administration of Sanmiao Pill significantly reduced glycosaminoglycan expression while increasing proteoglycan levels. Notably, Sanmiao Pill significantly inhibited MMP-3 and aggrecanase-4 expression while increasing TIMP-1 and TIMP-3 expression [124]. Furthermore, Sanmiao pill reduced joint swelling in a gouty arthritis mouse model induced by MSU crystals and inhibited the production of IL-1β, TNF-α, and MPO. Surprisingly, the alcoholic extract of Sanmiao pill has a stronger anti-inflammatory effect than the aqueous extract [125].

Simiao Pill was derived from China's "Cheng Fang Bian Du" in the Qing Dynasty, which comprises four individual herbs, namely *Phellodendron chinense* Schneid. (*Rutaceae*), *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*), *Achyranthes bidentata* Blume (*Amaranthaceae*), *Coix lacryma-jobi L.var.mayuen*(*Roman.*) *Stapf* (*Poaceae*). It is clinically used to treat damp-heat pouring downward gout [126]. Cao et al. found that by promoting PI3K/Akt activation and M2 polarization in macrophages, Simiao Pill (1 and 10 mg/kg body weight) could significantly inhibit IL-6 and IL-1β levels and alleviate the inflammatory response caused by MSU crystals [127]. Simiao Pill can also reduce serum inflammatory factors like MIP-1α, MIP-1β, interferon-γ, and IL-9, downregulate NLRP3 expression, reduce intestinal cell apoptosis, and improve intestinal microflora to treat gouty arthritis [128]. Network pharmacology has discovered that Simiao Pill can also inhibit IL-17 and TNF-α [129]. Simiao Pill has been shown to lower serum uric acid levels in other studies. Simiao Pill, in particular, inhibited XOD activity and promoted uric acid excretion by inhibiting the expression of OAT1, URAT1, and GLUT9 transporters in the kidney [130,131]. Furthermore, modified Simiao pill can reduce joint swelling in rats with gouty arthritis caused by MSU crystals and can inhibit the expression of inflammatory factors like IL-6, IL-1β, and TNF-α. The p-STAT3 and MMP3 proteins were upregulated in C28/I2 cells in cartilage tissue, but the tissue inhibitor of metalloproteinase (TIMP)-3 protein was downregulated [132-134].

The Quzhuo-Tongbi decoction (QTD) is a TCM empirical prescription used clinically to treat acute gouty arthritis that consists of nine different Chinese herbal medicines (Table 10). Oral administration of QTD (0.5 g/kg body weight) inhibited the expression of NLRP3, reduced the production of IL-1β and TNF-α, and alleviated ankle swelling in rats with gouty arthritis caused by MSU crystals [135]. Other research has found that QTD can treat gout by regulating intestinal flora. QTD specifically improves intestinal barrier function by increasing the abundance of butyrate-producing bacteria and encouraging the production of SCFAs. Notably, a lack of SCFAs was linked to increased glycolysis. Furthermore, QTD can lower serum uric acid levels, and its mechanism may be linked to increased ABCG2 expression [136,137].

Zisheng-Shenqi decoction (ZSD), derived from "the Golden mirror of medicine" in China's Qing dynasty, is made up of ten Chinese herbal medicines (Table 10) and has the function of tonifying the kidneys and removing dampness. It is used to treat gout in clinical settings. According to network pharmacology, ZSD can inhibit inflammatory reactions, resist oxidative stress, and relieve pain by regulating the ATP-P2X7R and NLR signaling pathways, thereby treating gout [138]. Another study found comparable results. ZSD can effectively treat gouty arthritis in vivo due to its anti-inflammatory and antioxidant properties. Oral ZSD (400 mg/10 g body weight) administration could inhibit the expression of inflammatory factors TNF-α and IL-1β, as well as the activation of NF-κB. Furthermore, glutathione peroxidase and superoxide dismutase activated the antioxidant stress effects. This study's findings provided sufficient evidence for its use in gout treatment [139].

Guizhi-Shaoyao-Zhimu decoction (GSZD) is a classical prescription in China, which is derived from "Outline of the Golden Chamber". It is a combination of nine Chinese herbal medicines (Table 10) that is clinically used to treat gout and osteoarthritis [140]. By blocking the NLRP3/NF-κB signaling pathway, Zhou et al. demonstrated that GSZD could inhibit the expression of IL-1β, IL-6 inflammatory factor, and MCP-1 levels. Therefore, an anti-inflammatory effect is produced. Furthermore, GSZD can lower serum uric acid levels [141,142].

The Shuang-Qi gout capsule (SQGC) is made up of six different herbs: *Phragmites australis* (Cav.) Trin. ex Steud. (*Poaceae*), *Berchemia floribunda* (Wall.) Brongn. (*Rhamnaceae*), *Mallotus apelta* (Lour.) Muell. Arg. (*Euphorbiaceae*), *Schefflera arboricola* Hay. (*Araliaceae*), *Cinnamomum camphora* (L.) presl (*Lauraceae*), *Panax notoginseng* (Burkill) F. H. Chen (*Araliaceae*). It is used in the treatment of gouty arthritis. SQGC (57, 113, and 225 mg/kg body weight) reduced ankle joint swelling in a dose-dependent manner while also significantly inhibiting the expression of IL-1β and TNF-α. It is worth noting that the high-dose Shuang-qi gout capsule followed the same pattern as

the positive drug [143]. Furthermore, SQGC can increase uric acid excretion. The mechanism is to inhibit URAT1 and GLUT9 expression while increasing the expression of OCT1, OCT2, and OAT1 [144].

Huzhen-Tongfeng formula (HTF) is an empirical prescription developed by Jinan University based on clinical experience with gouty arthritis. *polygonum cuspidatum* Sieb. et Zucc. (Polygonaceae), *ligustri Lucidi* Fructus (*Oleaceae*), *plantago asiatica L.* (Plantaginaceae), and *polistes olivaceus* (DeGeer) (*Vespidae*) are included in the prescription. Deng et al. revealed the mechanism of HTF for the first time in the treatment of gouty arthritis. Network pharmacology analysis predicted that the arachidonic acid metabolic pathway was most closely related to its anti-inflammatory action. In vivo studies revealed that oral administration of HTF reduced ankle swelling and inflammatory cell infiltration in rabbits with gouty arthritis. In vitro, HTF inhibited the expression of COX-1, COX-2, and 5-lipoxygenase [145]. Furthermore, HTF can be used to treat gouty arthritis by inhibiting the release of proinflammatory factors such as IL-1, IL-6, TNF-α, and ASC oligomerization [146].

Jiangsuan-Chubi formula (JCF) was a traditional Chinese medicine prescription obtained through clustering analysis and frequency of use, consisting of 12 Chinese herbal medicines (Table 10) and used clinically to treat gouty arthritis. JCF has been shown in studies to inhibit the secretion of the inflammatory factor IL-1β by inhibiting the expression of the NRLP3 protein, resulting in an anti-gouty arthritis effect [147]. Qingre-Lishi decoction (QLD) is made up of 12 Chinese herbal medicines (Table 10) and is used to promote blood circulation, remove blood stasis, and relieve pain. It is used in the treatment of gout. Yu et al. confirmed that QLD could treat gouty arthritis by inhibiting NRLP3 protein expression and inflammatory factor IL-1β secretion [148]. Huzhang-Guizhi formula (HGF) is a traditional Chinese medicine derived from "Taiping Shenghui Fang," which contains *polygonum cuspidatum* Sieb.et Zucc. (*Polygonaceae*) and *ca*ssia Twig (*Lauraceae*). HGF, according to research, can inhibit the production of TNF-α and IL-1β in synovial fluid and the expression of the NF-KB p65 protein in synovial tissue, resulting in anti-gouty arthritis effects [149]. The ingredients in Shaoyao-Gancao decoction (SGD) are *Paeonia lactiflora* Pall. (*Paeoniaceae*) and *Glycyrrhiza uralensis*

Fisch. (*Fabaceae*). SGD significantly reduced PGE2 production in vitro by inhibiting the release of inflammatory factors COX-2, IL-1β, and IL-6, thereby exerting an anti-gouty arthritis effect [150]. Tongfengding capsule is a traditional prescription that has been approved by the China Pharmacopoeia Committee (2020). It contains eight Chinese herbal medicines (Table 10). The medication is clinically used to treat gout and rheumatoid arthritis. Tongfengding capsule has been shown in studies to have an anti-gouty arthritis effect by inhibiting the secretion of the inflammatory factors TNF-α and IL-6. Furthermore, its mechanism may be linked to the inhibition of the arachidonic acid signaling pathway [151]. Xiaofeng granule is made from a new formula that has been improved from modified simiaowan and has heat-clearing and dampness-drying properties. Shi et al. discovered that Xiaofeng granules can help with gout by inhibiting cartilage matrix degradation [152].

Shenling-Baizhu San (SBS) is a well-known prescription that is derived from "Prescriptions of the Bureau of Taiping People's Welfare" and contains ten Chinese herbal medicines. Used in the treatment of gout and hyperuricemia. According to studies, SBS lowers serum uric acid levels by increasing uric acid excretion. Furthermore, it has been shown to inhibit the expression of p-PPARγSer273 in renal tubular epithelial cells [153]. Erding Formula (EF) is a traditional Chinese medicine prescription included in the China Pharmacopoeia, and it consists of *viola philippica* (*Violaceae*), *taraxacum mongolicum* Hand.-Mazz. (*Asteraceae*), *lobelia chinensis* Lour. (*Campanulaceae*) and *isatis indigotica* Fortune (*Brassicaceae*). According to pharmacological studies, EF can promote uric acid excretion by inhibiting URAT1 expression and increasing OAT3 expression [154]. Tongbixiao Pills (TBX) were a Chinese medicinal prescription developed by the Gout TCM Research Cooperation Group of Jingzhou Hospital of Traditional Chinese Medicine for the clinical treatment of gout. TBX has been shown in studies to have anti-gouty arthritis properties. Furthermore, it can lower serum uric acid levels by increasing uric acid excretion [155]. Tongfengtai granules (TFT) are a combination of seven Chinese herbal medicines that are clinically used to treat gouty nephropathy and rheumatism. Studies have shown that TFT can reduce serum uric acid levels by inhibiting XOD activity [156]. (Table 10).

Prescription	Composition of prescription	Model	Effect	Action mechanism	Ref
Er Miao pill	*Phellodendron chinense* Schneid. (*Rutaceae*) *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*)	Male SD rats	Anti-inflammation Anti-hyperuricemia Promote uric acid excretion	IL-6↓	[121,122]
Sanmiao pill	*Phellodendron chinense* Schneid. (*Rutaceae*) *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*) *Achyranthes bidentata* Blume (*Amaranthaceae*)	Male SD rats chondrocyte	Anti-inflammation Lowering uric acid level Inhibit cartilage matrix degradation	IL-1β↓; TNF-α↓; IL-6↓ MMPs-3↓; ADAMTS-4↓ TIMPs-1↑; TIMPs -3↑	[124,125]
Simiao pill	*Phellodendron chinense* Schneid. (*Rutaceae*) *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*) *Achyranthes bidentata* Blume (*Amaranthaceae*) *Coix lacryma-jobi L.var.mayuen*(*Roman.*)*Stapf*（*Poaceae*）	THP-1 cells; Male C57BL/6 mice Male Kun-Ming strain of mice	Anti-inflammation Anti-hyperuricemia Regulating intestinal flora Lowering uric acid level Promote uric acid excretion	NLRP3↓; IL-6↓; IL-1β↓; TNF-α↓; p-Akt↑; MPO↓; XOD↓; ADA↓; mURAT1↓; mGLUT9↓; mOAT1↑; mOCT2↑	[127-131]
Modified Simiao pill	*Phellodendron chinense* Schneid. (*Rutaceae*) *Atractylodes lancea* (*Thunb.*) *DC.* (*Asteraceae*) *Achyranthes bidentata* Blume (*Amaranthaceae*) *Coix lacryma-jobi L.var.mayuen* (*Roman.*)*Stapf*（*Poaceae*） *Smilax glabra* Roxb. (*Liliaceae*) *Lonicerajaponica* Thunb (*Caprifoliaceae*)	Male SD rats C28/I2 cell THP-1 cell	Anti-inflammation Anti-hyperuricemia	IL-1β↓; TNF-α↓; IL-6↓; MMP-3↓; TIMP-3↑	[132-134]
Quzhuo-tongbi decoction	*Smilax glabra* Roxb. (*Liliaceae*) *Dioscorea septemloba* Thunb (*Dioscoreaceae*) *Zea mays L.* (*Poaceae*) *Coix lacryma-jobi L.var.mayuen*(*Roman.*)*Stapf*（*Poaceae*） *Siegesbeckia orientalis L.* (*Asteraceae*) *Curcuma longa L.* (*Zingiberaceae*) *Taxillus sutchuenensis (Lecomte) Danser* (*Loranthaceae*) *CorydalisyanhusuoW.T.Wang* (*Papaveraceae*) *CitrusmedicaLvar.sarcodac-tylis* Swingle (*Rutaceae*)	Male SD rats male C57BL/6 mice	Anti-inflammation Anti-hyperuricemia Regulating intestinal flora	NLRP3↓; IL-1β↓; TNF-α↓; ABCG2↑; SCFAs↑	[135-137]

Zisheng-shenqi decoction	*Rehmannia glutinosa* (Gaert.) Libosch. (*Scrophulariaceae*) *Cornus officinalis* Sieb. (*Cornaceae*) *Poria cocos(Schw.)Wolf* (*Polyporaceae*) *Cortex moutan (Paeoniaceae)* *Dioscorea polystachya* Turczaninow (*Dioscoreaceae*) *Alisma orientalis* (*Sam.*) *Juzep.* (*Alismataceae*) *Amomum villosum* Lour. (*Zingiberaceae*)	male Wistar rats	Anti-inflammation Antioxidant stress	IL-1β↓; TNF-α↓; NF-κB↓ SOD↓; GSH-Px↓	[138,139]
Guizhi-Shaoyao-Zhimu decoction	*Cinnamomum cassia* Presl (*Lauraceae*) *Atractylodes macrocephala* Koidz. (*Asteraceae*) *Glycyrrhiza uralensis* Fisch. (*Fabaceae*) *Ephedra sinica* Stapf (*Ephedraceae*) *Zingiber officinale* Roscoe (*Zingiberaceae*) *Atractylodes macrocephala* Koidz. (*Asteraceae*) *Anemarrhena asphodeloides* Bunge (*Liliaceae*) *Saposhnikovia divaricata* (Trucz.*)* Schischk. (*Apiaceae*) *Aconitum carmichaelii* Debx (*Ranunculaceae*)	Male C57BL/6J mice	Anti-inflammation Anti-hyperuricemia	NLRP3↓; IL-1β↓; IL-6↓; MCP-1↓; IKKβ↓; p65↓	[140-142]
Shuang-Qi gout capsule	*Phragmites australis* (*Cav.*) Trin. ex Steud. (*Poaceae*) *Berchemia floribunda* (Wall.) Brongn. (*Rhamnaceae*) *Mallotus apelta* (Lour.) Muell. Arg. (*Euphorbiaceae*) *Schefflera arboricola* Hay. (*Araliaceae*) *Cinnamomum camphora* (L.) presl (*Lauraceae*) *Panax notoginseng*(Burkill) F. H. Chen (*Araliaceae*)	Male ICR mice Male SD rats HUVE cells	Anti-inflammation Anti-hyperuricemia Promote uric acid excretion	IL-1β↓; TNF-α↓; mURAT1↓; mABCG2↑ mOAT1↑; mOCT1↑; mOCT2↑ mGLUT9↓	[143,144]
Huzhen-Tongfeng formula	*Polygonum cuspidatum* Sieb.et Zucc. (*Polygonaceae*) *Ligustri Lucidi* Fructus (*Oleaceae*) *Plantago asiatica* L. (*Plantaginaceae*) *Polistes olivaceus* (DeGeer) (*Vespidae*)	Male SD rats RAW264.7 cells THP-1 cell Male Japanese big ear white rabbits	Anti-inflammation Antioxidant stress	IL-1β↓; IL-6↓; TNF-α↓; PGES2↓; COX-1↓; COX-2↓;	[145,146]
Jiang-Suan-Chu-Bi formula	*Smilax glabra* Roxb. (*Liliaceae*) *Paeonia lactiflora* Pall. (*Paeoniaceae*) *Polygonum cuspidatum* Sieb.et Zucc. (*Polygonaceae*) *Iphigenia indica* Kunth (*Liliaceae*) *Rheum officinale* Baill. (*Polygonaceae*) *Clematis chinensis* Osbeck (*Ranunculaceae*) *Heracleum hemsleyanum* Diels (*Apiaceae*) *Phellodendron chinense* Schneid. (*Rutaceae*) *Atractylodes lancea(Thunb.)*DC. (*Asteraceae*) *Glycyrrhiza uralensis* Fisch. (*Fabaceae*) *Salvia miltiorrhiza* Bge. (*Labiatae*) *Angelica sinensis* (Oliv.) Diels (*Apiaceae*)	THP-1 cells	Anti-inflammation	NLRP3↓; IL-1β↓; ACS↓; caspase-1↓	[147]

heat-clearing and diuresis-promoting prescription	*Tulipa gesneriana* L. (*Liliaceae*) *Lysimachia christiniae* Hance (*Primulaceae*) *Atractylodes Lancea* (Thunb.) DC. (*Asteraceae*) *Clematis chinensis* Osbeck (*Ranunculaceae*) *Smilax glabra* Roxb. (*Liliaceae*) *Achyranthes bidentata* Bl. (*Amaranthaceae*) *Coix lacryma-jobi L.var.mayuen(Roman.)Stapf* (*Poaceae*) *Phellodendron chinense* Schneid. (*Rutaceae*) *Lycopus* lucidus Turcz.vat.hirtus Regel (*Labiatae*) *Anemarrhena asphodeloides* Bunge (*Liliaceae*) *Dioscorea polystachya* Turczaninow (*Dioscoreaceae*) *Polygonum cuspidatum* Sieb.et Zucc. (*Polygonaceae*)	Clinical patient	Anti-inflammation Anti-hyperuricemia	NLRP3↓; IL-1β↓	[148]
Huzhang-Guizhi herb pair	*Polygonum cuspidatum* Sieb.et Zucc. (*Polygonaceae*) *CassiaTwig* (*Lauraceae*)	male SD rats	Anti-inflammation	IL-1β↓; TNF-α↓ p65↓	[149]
Shaoyao-gancao decoction	*Paeonia lactiflora* Pall. (*Paeoniaceae*) *Glycyrrhiza uralensis* Fisch. (*Fabaceae*)	Male ICR mice RAW264.7 cells	Anti-inflammation	IL-1β↓**;** IL-6↓; TNF-α↓; COX-2↓; PGES2↓	[150]
Tongfengding capsule	*Gentiana macrophμlla Pall.* (*Gentianaceae*) *Phellodendron chinense* Schneid. (*Rutaceae*) *Corydalis yanhusuo* W. T. Wang (*Papaveraceae*) *Paeonia lactiflora* Pall. (*Paeoniaceae*) *Cyathula officinalis* Kuan (*Amaranthaceae*) *Alisma plantago-aquatica* Linn. (*Alismataceae*) *Plantago asiatica* L. (*Plantaginaceae*) *Smilax glabra* Roxb. (*Liliaceae*)	Male SD rats THP-1 cells	Anti-inflammation	TNF-α↓; IL-6↓**;** PGES2↓	[151]
Xiaofeng Granules	*Atractylodes lancea(Thunb.)DC.* (*Asteraceae*) *Phellodendron chinense* Schneid. (*Rutaceae*) *Coix lacryma-jobi L.var.mayuen(Roman.)Stapf* (*Poaceae*) *Achyranthes bidentata* Bl. (*Amaranthaceae*) *Smilax glabra* Roxb. (*Liliaceae*) *Lonicera japonica* Thunb. (*Caprifoliaceae*)	Male SD rats chondrocyte	Anti-inflammation Inhibit cartilage matrix degradation	L-1β↓; IL-6↓; TNF-α↓ MMPs/TIMP-1↓; ADAMTS-4/ TIMP-3↓	[152]
Shenling Baizhu San	*Panax ginseng C.A.Mey. (Araliaceae)* *Poria cocos (Schw.) Wolf (Polyporaceae)* *Atractylodes macrocephala Koidz. (Compositae)* *Dioscorea opposita Thunb. (Dioscoreaceae)* *Dolichos lablab L. (Leguminosae)* *Nelumbo nucifera Gaertn. (Nelumbonaceae)* *Coix lacryma-jobi. var. ma-yuen.* *(Rom.Caill.) Stapf (Poaceae)* *Amomum villosum Lour. (Zingiberaceae)* *Platycodon grandiflorus (Jacq.) A. DC.* *(Campanulaceae)* *Glycyrrhiza uralensis Fisch.* *(Leguminosae)*	male quails	Anti-hyperuricemia	p-PPARγ↓	[153]

Erding Formula	*Viola philippica* (*Violaceae*) *Taraxacum mongolicum* Hand.-Mazz. (*Asteraceae*) *Lobelia chinensis* Lour. (*Campanulaceae*) *Isatis indigotica* Fortune (*Brassicaceae*)	Male Kunming mice	Anti-hyperuricemia Anti-inflammation relieve pain	mOAT3↑; mURAT1↓	[154]
Tongbixiao Pills	*Rehmannia glutinosa* (Gaetn.) Libosch. (*Scrophulariaceae*) *Cynanchum otophyllum* Schneid. (*Asclepiadaceae*) *Gentiana macrophylla* (*Gentianaceae*) *Achyranthes bidentata* Blume (*Amaranthaceae*) *Homalomena occulta* (*Araceae*) *Cervus nippon* Temminck (*Cervidae*) *Carica papaya* L. (*Caricaceae*) *Coix lacryma-jobi L.var.mayuen(Roman.)Stapf* (*Poaceae*) *Poria cocos(Schw.)Wolf* (*Polyporaceae*) *Citrus reticulata Blanco* (*Rutaceae*) *Cynanchum atratum* Bunge. (*Asclepiadaceae*) *Phellodendron chinense* Schneid. (*Rutaceae*) *Atractylodes lancea (Thunb.) DC.* (*Asteraceae*) *Lonicera japonica* Thunb. (*Caprifoliaceae*) *Tetrapanax papyrifer* (Hook.) K. Koch (*Araliaceae*) *Plantago depressa* Willd. (*Plantaginaceae*) *Taraxacum mongolicum* Hand.-Mazz. (*Asteraceae*) *Clematis chinensis Osbeck* (*Ranunculaceae*) *Aristolochia mollissima* Hance (*Aristolochiaceae*) *Caulis Sinomenii* (*Menispermaceae*) *Dioscorea septemloba Thunbt* (*Dioscoreaceae*) *Areca catechu* L. (*Arecaceae*)	Male SD rats	Anti-hyperuricemia Anti-inflammation	serum creatinine levels↓; serum urea nitrogen levels↓	[155]
TongFengTangSan	*Tinospora sagittata* (Oliv.) Gagnep. (*Menispermaceae*) *Terminalia chebula* Retz. (*Combretaceae*) *Faeces Trogopterpri*	Male SD rats	Anti-hyperuricemia	XOD↓	[156]

Table 10: Summary of antigout TCM prescriptions

Conclusions and Future Perspectives

The prevalence of gout is increasing year by year worldwide, which severely influences the work and life of patients. Because of the large number of affected people, complicated pathogenesis, and few effective clinical treatment strategies, gout has become a research hotspot. Herein, we present a literature review of gout treatment with TCM in recent years and conclude that TCM exerts an anti-gout effect through various pathways, mainly including reduction in uric acid levels (inhibition of uric acid production and promotion of uric acid excretion), anti-inflammation, and prevention of oxidative stress, among others. Additionally, a few studies have also reported the regulation of apoptosis, bone metabolism, and intestinal flora. The findings reflect the fact that TCM has multiple effects, multiple targets, multiple signaling pathways, and other advantages in gout treatment.

However, at present, TCM exerts the therapeutic effect for gout mainly by regulating the NLRP3/ASC/Caspase, TLRs/MyD88/NF-κB, and ATP/P2X7R signaling pathways, while reports of regulating the JAK/STAT, MAPK, and Nrf2/HO-1 signaling pathways are rare. Research on the mechanism of the signaling pathways involved in gout treatment is of great significance, and discovering more signaling pathways is conducive to finding more therapeutic targets. Most research methods currently remain at the gene and protein expression levels as well as metabolomics and protein omics; hence, newer technologies need to be explored, to gain an in-depth understanding of the pharmacodynamic material basis and mechanism of action of TCM against gout. Additionally, the syndrome types of animal models used in some studies are single, and the stability of the model is poor.

On the basis of the long-term development of TCM in treating gout, we have put forward the following suggestions. First, we should explore the ancient books of TCM to gain an in-depth understanding of more Chinese herbal medicines or Chinese herbal compounds with the potential to treat gout. Second, because gout treatment requires long-term medication, it is necessary to conduct more toxicology studies to ensure the safety of the medication. In-depth research on the components of Chinese herbal medicine and Chinese herbal compounds is needed to establish quality control standards for Chinese medicine to ensure the effectiveness of the drugs. Finally, combined with the treatment strategies in different stages of gout, the compatibility and dose of Chinese medicine compounds should be appropriately adjusted.

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