Review Article

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The development from hyperuricemia to gout: key mechanisms and natural products for treatment

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Abstract

Gout is a common of inflammatory arthritis and is caused by the deposition of monosodium urate (MSU) crystals as a result of hyperuricemia (HUA). Although HUA is considered to be the main risk factor for gout, only approximately 10% of the individuals with HUA will eventually experience a gout attack. In this review, we first briefly introduce the development of gout and then summarize several possible reasons for its development. Genetic factors play a more prominent role in gout than in other diseases; functional mutations related to urate control and innate immunity components have been found to be associated with gout. Here, we list some of the most prominent genes involved in the pathogenesis of gout. In joints with MSU deposition, mature macrophages may uptake MSU crystals without causing inflammation, and this helps to maintain joints in an asymptomatic state. As an auxiliary inflammation pathway, the ATP-P2X7R-NLRP3 axis may contribute to the amplification of MSU-induced inflammation to affect the development of gout. Finally, this review summarizes the research progress on natural products that can be used in the treatment of HUA and gout.

Keywords: ATP-P2X7R-NLRP3 axis, Gout, Hyperuricemia, MSU-related inflammation, Natural products

Introduction

Gout is a common chronic disease caused by the deposition of monosodium urate (MSU) crystals due to elevated serum uric acid levels. Clinical studies and surveys have shown that the prevalence of gout varies according to sex, race, countries, and some other factors[1]. In a nutrition and health survey conducted in Taiwan province of China, experts determined its prevalence to be 8.2% in men and 2.3% in women between 2005 and 2008[2]. According to the USA National Health and Nutrition Examination Survey conducted in 2007–2008, the prevalence of gout in the American adult population (age, ≥20 years) was 3.9%, 5.9% in men and 2.0% in women, which is significantly increased compared to the estimates from 1988 to 1994[3]. The global burden of gout is substantial and seems to have increased in many parts of the world over the last 50 years[1]. The increasing prevalence of gout reflects the increase in risk factors for gout. Among these, hyperuricemia (HUA) is undoubtedly a major risk factor for gout development and is the initial stage in the pathogenesis of this disease. Based on the *in vivo* saturation point of urate, HUA is commonly defined as a serum urate (SUA) concentration >6.8 mg/dL[4]. However, clinical studies have suggested that the majority of individuals with HUA show no disease-related clinical manifestations, and merely approximately 10% of them eventually develop gout[5]. Accordingly, there must exist a complex pathological process that underlies the development from HUA to gout. While HUA is indispensable for gout development, it is not a determining factor. Pathological, imaging, and intervention studies have shown that the clinical manifestations of gout are caused by a host inflammatory response to deposited MSU crystals. Recurrent gout flares and chronic gouty arthritis and tophaceous are two main manifestations of clinical gout. Physiologically, gout flares and tophi represent acute and chronic inflammatory granulomatous responses to deposited MSU crystals, respectively[6]. Thus, the appearance of MSU deposits and the resulting inflammation is crucial to a gout attack.

On the one hand, in a certain percentage of individuals with HUA, long-term high concentrations of SUA may not necessarily lead to MSU deposition. On the other hand, in asymptomatic individuals with HUA and MSU deposition, it may be the insufficient inflammation responses to MSU that block gout attack. To treat clinical HUA and gout in a more efficient way, it is urgent to explore the unknown pathogenic mechanisms of HUA and gout and to design and develop new drugs. Several studies have identified active ingredients or extracts of various natural plant species that act effectively on HUA and gout both *in vitro* and *in vivo*. This review aims to explain the main procedures from HUA to gout, provide several possible mechanisms which hinder this pathological process and summarize some natural products' potential for HUA and/or gout treatments. This

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review was conducted to find the most published systematic reviews on MSU deposition, inflammation, and genetic factors about HUA and/or gout in PubMed and Web of Science from 2002 to 2022.

Differences in genetic features between HUA and gout

Although both non-genetic and genetic factors contribute to HUA and gout, gout is more prominently determined by genetic factors than other diseases[7–8]. It is commonly believed that the development of normouricemia to gout occurs in at least two steps. In the first step, normouricemia develops into asymptomatic (A) HUA through an increase in SUA levels, and in the second step, MSU crystal-induced inflammation is experienced as a gout attack. SUA is considered to be a strong nonlinear concentration-dependent predictor of clinically evident gout[9]. Hence, SUA-associated genetic variants seem to be dominant genetic factors contributing to the first step. Elevated SUA levels occur as a consequence of either hepatic overproduction or renal and intestinal underexcretion, or both. Underexcretion is thought to be the dominant pathogenic mechanism for HUA development in patients with gout[10]. Various genes related to SUA have been identified in genome-wide association studies (GWASs) of SUA[11–12]. Among 28 identified SUA-related genetic loci, loci in SLC2A9 and ABCG2, encoding renal, and gut urate transporters, have been shown to be the most prominent[13]. SLC2A9 encodes GLUT9, a member of the GLUT family of hexose transporters distributed at the basolateral membrane of the proximal tubule, where it acts as the main urate exit vehicle. ABCG2, an ATP-driven efflux pump, has a significant role in urate secretion in the proximal tubule and intestine. In addition to SLC2A9 and ABCG2, GWASs of patients with gout have identified a few other gout risk loci, which were consistent with those found in GWASs of HUA[14–16] (Table 1).

Given the prevalence of gout in HUA individuals, it seems that genetic factors involved in the second step weigh more in the pathogenesis of gout than those involved in the first step. Toll-like receptors (TLRs), the NLRP3 inflammasome, and IL1R pathways are strongly involved in the development of gouty inflammation, and innate immunity components, including TLR2, TLR4, CD14, NLRP3, ASC, caspase-1, and CARD8, are critical to MSU-induced inflammation[17]. Variants rs2043211 (CARD8), rs1143623 (IL1B), and rs2569190 (CD14) and multiplicative interaction between IL1B and CARD8 have been determined to be associated with gout[18]. Other innate immunity-associated genes contributing to an increased risk of gout include TLR4, PPARGC1B, and APOAl[19–22]. Given that most gout-associated GWASs included subjects with normouricemia as the control group, one team of researchers for the first time performed a gout GWAS based on clinically defined gout cases and AHUA controls to identify risk loci that aggravates AHUA development to gout[23]. They identified two novel loci (CNTN5 and miR-302f) that have a strong effect in the second step and suggested that single-nucleotide polymorphisms in CNTN5 participate in this stage and may simultaneously cause inflammation at MSU-deposited joints, while miR-302f may contribute to the inflammation observed in gouty arthritis by modulating gene expression.

As indicated above, HUA shares most SUA-associated genetic mutations with gout; therefore, among HUA individuals, the rate of gout may depend on genetic susceptibility to MSU-induced inflammation.

The complexity of gout caused by MSU-induced inflammation

Deposition of MSU crystals

The second stage of gout development involves the deposition of MSU monohydrate crystals due to HUA. MSU monohydrate, one of the predominant crystalline forms of urate, is microscopically observed as negatively birefringent, needle-shaped crystals[24]. Owing to their needle shape, these crystals are thought to be embedded in cartilage and other similar structures[25]. At the molecular level, the three-dimensional structure of MSU crystals is

Table 1

Major genes associated with HUA and gout

Gene	Protein	Functional area	Main function
ABCG2	ABCG2	Intestinal epithelial cells and apical membrane cells of the renal proximal tubule	Mediates intestinal uric acid secretion
SLC2A9	GLUT9L	Apical membrane cells of proximal renal tubule	Mediates the reabsorption of uric acid into the circulation
	GLUT9S	Apical membrane cells of the proximal renal tubule (exclusively)	
SLC22A12	URAT1	Apical membrane cells of the proximal renal tubule	Mediates the reabsorption of uric acid
ABCC4	MRP4	Basolateral membrane of the liver and apical membrane of the renal proximal tubule	Mediates dominant apical membrane uric acid efflux
SLC22A11	OAT4	Apical membrane of the renal proximal tubule	Mediates the reabsorption of uric acid
SLC17A1	NPT1	Apical membrane of the renal proximal tubule	Mediates uric acid efflux
SLC17A3	NPT4	Apical membrane of the renal proximal tubule	Mediates uric acid efflux
GCKR	Glucokinase	Hepatic cells	Catalyzes the phosphorylation of glucose into glucose-6-phosphate (a precursor of de novo purine synthesis)
PDZK1	PDZ domain-containing scaffold protein	Proximal renal tubule cells	Binds uric acid transporters and presumably arranges their cell-surface localization for optimal uric acid transport

HUA: hyperuricemia.

comprised of one-dimensional stacked sheets of closely spaced purine rings[26]. The narrow end faces of MSU crystals are highly hydrophobic, whereas the sides are polar and ionic, which facilitates their nucleation on hydrophobic or polar surfaces, respectively[27].

As in the physicochemical formation of other crystals, reduced solubility (leading to supersaturation), nucleation, and crystal growth are thought to be three crucial steps in MSU crystal formation[28]. Practically, factors influencing the crystallization of circulating urate are consistent with those acting on these three steps, among which the SUA concentration is an absolute key effector as it contributes to all three steps. A systematic review of the factors influencing MSU crystallization demonstrated that temperature, pH, and the concentration of ions, antibodies, proteins, and various connective tissue factors all affected MSU crystallization[14]. Colder temperatures and slightly basic conditions are thought to be conducive to the occurrence of MSU crystals. At the nucleation stage, uric acid-binding antibodies, globulins, collagen, lead, and human serum or synovial fluid play dominant roles in MSU crystallization. An increased urate concentration was the only factor identified as a specific promoter of MSU crystal growth[29]. However, clinical data has shown that in asymptomatic individuals with SUA concentrations >9 mg/dL, only 24% (6/25) had MSU deposits[30]. In contrast, in an extensive study of acute gouty arthritis, 14% of patients had a normal SUA level (<6 mg/dL) during gout attacks[29]. Therefore, the relationship between SUA concentrations and MSU formation seems intricate, and there must exist other equally important factors that contribute to MSU formation and explain the clinical observation that most individuals with HUA do not develop gout.

MSU-induced inflammatory response

Clinical manifestations of gout occur due to the inflammatory response to MSU crystals. During the inflammation processes, both the innate and adaptive immune systems play significant roles, with the former being dominant. Once the deposited MSU crystals make contact with the host cells, MSU induces a series of membrane events that trigger Syk and PI3K activation, phagocytosis, and the production of cytokines such as IL-1β, TNF-α, IL-6, and IL-8. Once inside the cell, MSU further triggers NLRP3 inflammasome activation and induces IL-1 production, triggering the inflammatory response associated with gout[31]. Here, we mainly focus on the possible factors contributing to the insufficient inflammatory response to MSU crystals.

Noninflammatory uptake of MSU crystals by mature macrophages

The noninflammatory removal of MSU by mature macrophages may explain why most individuals with AHUA and MSU deposition will not develop gout eventually. Resident tissue macrophages activated by MSU crystals through phagocytosis and other recognition patterns secrete inflammatory cytokines such as TNF-α and IL-1β, leading to the neutrophil influx, which is the pathophysiologic feature of acute gout[32]. In uninflamed joints of patients with calcium pyrophosphate dihydrate, cells containing intracellular calcium pyrophosphate dihydrate crystals have been found in all synovial fluid samples, suggesting the significance of phagocytosis in non-inflamed joints[33]. In the response of mononuclear phagocytes to MSU, phagocytosis, and TNF-α production are determined by the level of macrophage differentiation[34]. Peak TNF-α levels are synthesized by cells in an intermediate state of differentiation (3.2–14.1ng/mL), whereas mature macrophages only exert an efficient crystal-phagocytizing function, without secreting TNF-α[34]. Using a *in vitro* model of acute gout, Landis et al. demonstrated that human macrophages derived from peripheral blood monocytes differentiated for a minimum of 3–5 d did not secrete TNF-α, IL-1β, IL-6, or any other factors capable of inducing endothelial cell E-selectin expression or promoting secondary neutrophil recruitment under hydrodynamic shear flow, whereas freshly isolated monocytes from the same donor did[35]. Together, these findings suggest that the differentiation level of macrophages determines the inflammatory responses to MSU crystals, and the noninflammatory removal of MSU crystals by mature macrophages seems to inhibit the amplification of inflammation resulting from deposited MSU crystals. Further study revealed that macrophage-derived platelet-activating factor (PAF) is involved in the non-inflammatory phagocytosis of MSU crystals by human blood monocyte-derived differentiated macrophages[36]. PAF is regarded as a potent mediator of immune responses that regulates various processes, including cytokine release and phagocytosis[1,15–16]. When stimulated with MSU crystals, *in vitro* differentiated macrophages were found to secrete PAF, whereas this secretion was absent in immature monocytes under the same stimulation. In addition, when these monocytes were pretreated with recombinant human PAF-acetylhydrolase, the stimulation of MSU crystal production resulted in the suppression of TNF-a secretion[36]. Synovial resident macrophages from normal joints of humans and mice are in a mature state of differentiation[35]. Thus, as MSU crystals precipitate in the synovial fluid, the noninflammatory uptake of crystals by synovial resident macrophages may be a crucial mechanism for joints to maintain a non-inflammatory state.

Auxiliary inflammatory pathways: the ATP-P2X7R-NLRP3-IL-1β inflammation pathway

Clinical studies have revealed that some individuals with AHUA and MSU deposition have tophi and increased vascularity as a sign of inflammation[37], which indicates that AHUA individuals also undergo MSU-induced inflammation. Accordingly, compared to normouricemic individuals, serum inflammatory cytokine levels are significantly increased in individuals with AHUA and MSU deposition[38]. It is known that gout is a result of an inflammatory response to MSU crystals. Insufficient inflammation may be reasonable speculation that hinders the development from HUA to gout. We suggest that in addition to MSU-induced inflammation, there may exist other auxiliary inflammatory pathways required for the amplification of MSU-induced inflammation. Strenuous exercise, cold, alcoholism, and overeating, which all share a common feature: the presence of dramatic changes in ATP levels in the body, have been predicted to be major susceptibility factors for the development of acute gouty arthritis[39]. Extracellular ATP is an endogenous danger signal that activates inflammatory responses in immune cells. As an ATP receptor, P2X7 receptor (P2X7R) has an essential role in inflammation and immunity by modulating IL-1 processing and release through activation of the

NLRP3 inflammasome. Recent studies have provided evidence of the significant role of P2X7R in the pathogenesis of acute gout arthritis. P2X7R polymorphisms have been found to significantly contribute to acute gouty arthritis by influencing the secretion of IL-1b, which is a critical cytokine in gout pathogenesis[40]. A Korean clinical study of gout revealed that the P2X7R rs3751142 polymorphisms may be partially associated with susceptibility to gout[41]. Based on genetic and pharmacological criteria, especially affinities with agonists, purinergic receptors (PRs) are categorized into P1Rs (selective adenosine receptors) and P2Rs (inclined to bind ATP and ADP)[42]. P2X7R is a member of the P2X receptor subfamily of P2 receptors. It is an extracellular ATP-gated ion channel that is mainly expressed in immune cells and has special permeability to macromolecular inorganic substances (up to 900 Da) and organic molecules. Under sustained extracellular ATP stimulation, P2X7R is activated, leading to the opening of a large conductance pore on the cell and massive K^+ efflux. It remains unclear how the nonselective pore forms and what its physiologic significance is, although pannexin-1 (Panx-1) has been suggested to be involved[40]. K^+ efflux is widely accepted as the predominant trigger of NLRP3 inflammasome activation, and P2X7R is the main effector capable of mediating fast and massive K^+ efflux[43]. In addition, researchers have demonstrated that in response to extracellular ATP, human and murine neutrophils express functional P2X7R on their surfaces, inducing K^+ efflux, which leads to NLRP3-dependent IL-1β secretion[44]. Similarly, in various immune cells, the NLRP3 inflammasome is triggered by ATP, the downstream regulator of P2X7R, which further induces IL-1β and IL-18 secretion[45–47]. Researchers have observed a close correlation between P2X7R and NLRP3 expression at both the gene and protein levels in mouse N13 microglial cells using confocal microscopy and immunoprecipitation techniques. Moreover, P2X7R can localize NLRP3 exactly where the K^+ drop occurs to maximize NLRP3 stimulation and minimize adverse effects caused by unlimited loss of cytoplasmic K^+[47]. Thus, while MSU initiates inflammation, the ATP-P2X7R-NLRP3 pathway (Figure 1), which is initiated with extracellular ATP changes, may cause inflammation amplification.

Other factors suppressing the amplification of MSU- induced inflammation

MSU-induced inflammation is an intrinsic characteristic of gout. The ultimate goal of urate-lowering therapies (ULT) for gout is to dissolve MSU crystals by reducing serum uric acid levels, which indicates that a reduction of the MSU deposit burden can effectively block gout attack. In reality, the link between MSU burden and the risk of gout flare is unclear. A recent dual-energy computed tomography-based study suggested a positive correlation between them, and the risk of gout flares seemed to be predictable based on detection of the extent of MSU burden detected with dual-energy computed tomography; using the MSU volume as an indicator, the critical volume best differentiating patients with and without flare was 0.81 cm^3[48]. An MSU burden below the threshold seems to be another possibility for insufficient inflammation. In addition to MSU burden, a recent study suggested that soluble uric acid (sUA) is an intrinsic negative regulator of

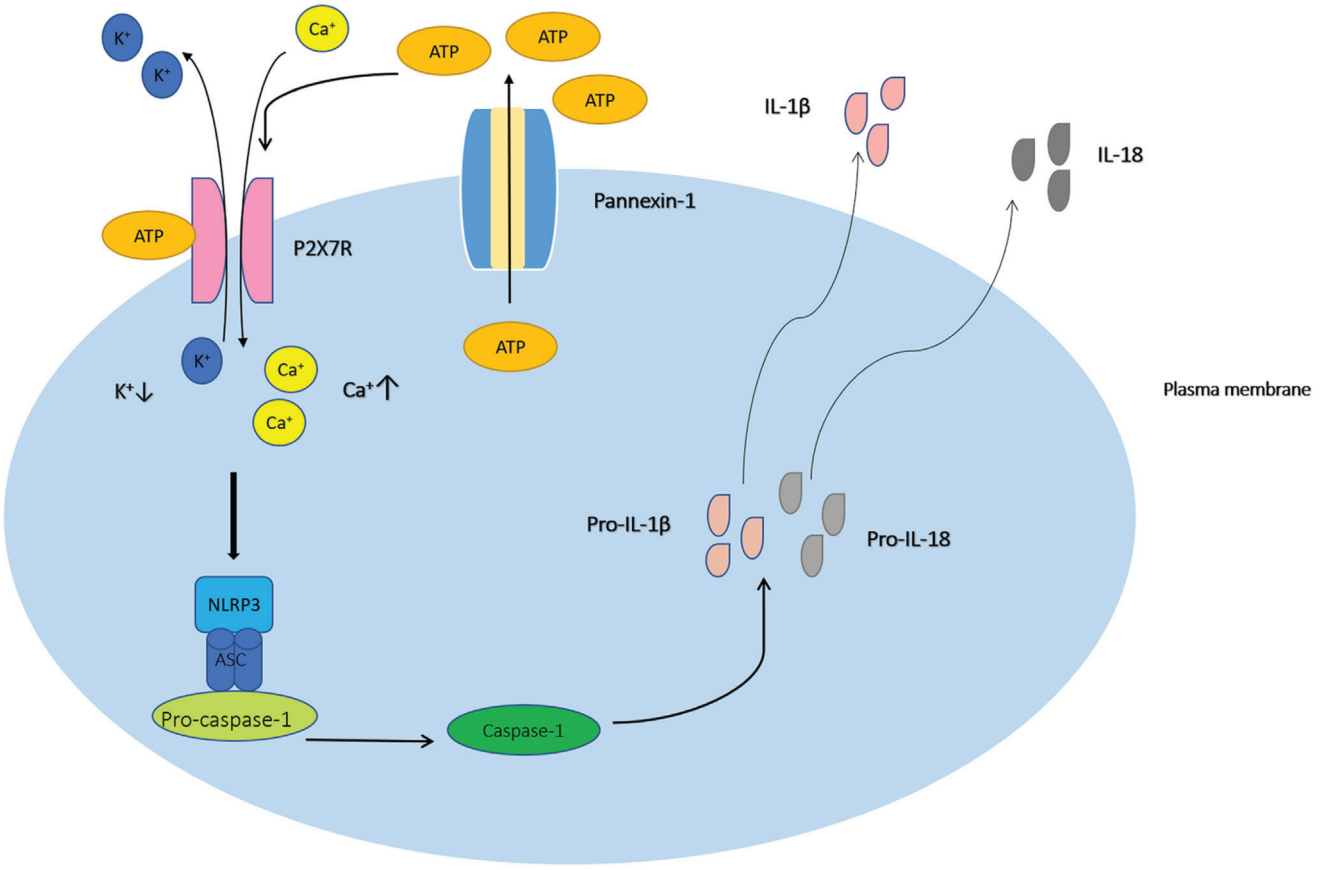

Figure 1. The ATP-P2X7R-NLRP3 inflammatory pathway.

monocyte activation in MSU-induced inflammation[49]. The authors believed that in previous studies, the reason that sUA was regarded as a pro-inflammatory substance is that common preparation methods may cause the appearance of microcrystalline contaminants. After eliminating the interference of microcrystals, they found that sUA suppressed MSU crystal-induced monocyte activation *in vitro*, and that compared with monocytes from normouricemic individuals, $CD14^+$ monocytes isolated from individuals with HUA showed a weaker response to inflammatory stimuli. *In vivo* experiments demonstrated HUA attenuates MSU crystal-induced tissue inflammation by suppressing leukocyte recruitment and activation.

Natural products have a potential role in HUA and gout treatments

Natural products are regarded as an indispensable resource for drug development and design. Numerous studies have demonstrated that various active ingredients and extracts from various natural plants, including polyphenols and saponins, act effectively on HUA and gout both *in vitro* and *in vivo*. Traditional Chinese medicinal herbs have long been used to treat HUA and gout. Pharmaceutical studies are gradually revealing the mechanisms underlying the clinical effectiveness of such natural products. Here, we focus on two types of natural products that have the potential for use in HUA and gout treatments.

Flavonoids are the main type of polyphenols that widely exist in plants. Most flavonoids can reduce the generation of uric acid through a strong xanthine oxidase (XOD) inhibitory effect, which is owing to their unique structures[50]. Quercetin is a major flavonoid in fruits and vegetables, such as apples, berries, and broccoli. The anti-hyperuricemic effect of quercetin is mediated *via* organic ion transporters such as OAT1, URAT1, and GLUT9[51]. Quercetin reversibly inhibits XOD catalysis *via* a ping-pong mechanism which contains three steps, namely inhibiting, reducing XOD, and scavenging the superoxide anion[52]. In MSU-induced mouse models of gout arthritis, quercetin exhibited an anti-inflammatory effect by inhibiting leukocyte recruitment, TNF-α and IL-1β production, NF-κB/ inflammasome activation, and other inflammatory events triggered by MSU crystals[53]. Astilbin, another flavonoid compound, is derived from the rhizomes of *Smilax china* L. Its anti-hyperuricemic function is related to the downregulation of GLUT9 and URAT1 expression and the upregulation of ABCG2 and OAT1/3, and it may alleviate renal inflammation through NLRP3/ NF-κB signaling[54]. Other polyphenols have also shown certain effectiveness in the treatment of HUA and gout. Resveratrol, a polyphenol phytoalexin with excellent antioxidant and anti-inflammatory properties, can lower SUA levels by downregulating GLUT9 while upregulating OAT1[55], and it attenuates the MSU crystal-induced inflammatory response by inhibiting TAK1 activity[56].

In addition to polyphenols, plant saponins have anti-hyperuricemic and anti-inflammatory potentials. Pallidifloside D, a saponin glycoside isolated from the total saponins of *Smilax riparia*, has been found to effectively decrease SUA in a hyperuricemic mouse model by down-regulating renal URAT1 and GLUT9[57]. Moreover, it enhances the urate-lowering effect of allopurinol, a first-line ULT drug[58]. *Dioscorea nipponica* Makino rhizome, a traditional Chinese medicinal herb, is widely used in the clinic for gouty arthritis treatment. Total saponins from D. *nipponica* may effectively treat gouty arthritis by modulating lysosomal enzymes, antioxidant capacities, and the NLRP3 inflammasome[59]. Dioscin, a spirostane glycoside isolated from the total saponins of *Dioscorea septemloba*, lowered serum uric acid levels and promoted urate excretion in HUA animal models, and its metabolite, tigogenin, showed anti-hyperuricemic activity *in vivo* by inhibiting URAT1 and promoting ABCG2 expression[60].

Thus, the mechanisms underlying the effectiveness of natural compounds, including, but certainly not limited to polyphenols and saponins, in the treatment of HUA and gout are quite well established (Table 2, Figure 2). In view of their multitarget actions and safety, natural plant compounds have promising potential for HUA and gout treatments as novel drugs or for co-administration with existing drugs.

Conclusions

HUA is considered the main risk factor for gout, and chronic HUA has also been found to be a potential cause of urolithiasis, hyperuricemic nephropathy, cardiovascular disease, and chronic kidney disease[61]. Compared with AHUA without MSU crystals, AHUA with MSU deposition is associated with more severe coronary artery calcification. As a representative chronic disease caused by MSU deposition resulting from HUA, the pathogenesis of gout has model significance concerning other HUA-related diseases. However, not all individuals with HUA and high SUA concentrations will eventually develop gout. The mechanism underlying this phenomenon is worth exploring. As genetic factors have a larger contribution to gout than in other diseases, we suggest that there may exist genes that critically regulate MSU deposition and subsequent inflammation; however, this hypothesis requires further study. Furthermore, even people with MSU deposition do not necessarily have gout. This may be related to an insufficient amplification of MSU inflammation. In the development of therapies for gout treatment, ULT is thought to be the most promising

Table 2

Natural products with potential for use in HUA and gout treatments and their mechanisms of action

Categories	XOD inhibitor	Regulation of urate transporters	Anti-inflammation target	Reference(s)
Quercetin	√	URAT1↓, GLUT9↑, OAT1↑	NF-κB, NLRP3	[51–53]
Astilbin	×	URAT1↓, GLUT9↓, ABCG2↑, OAT1/3T↑	NF-κB, NLRP3	[54]
Resveratrol	×	GLUT9↓, OAT1↑	TAK1, NF-κB, NLRP3	[55–56]
Pallidifloside D	×	URAT1↓, GLUT9↓	Not mentioned	[57]
Total saponins from Dioscorea nipponica	Not mentioned	Not mentioned	NLRP3	[59]

HUA: hyperuricemia; XOD: xanthine oxidase.

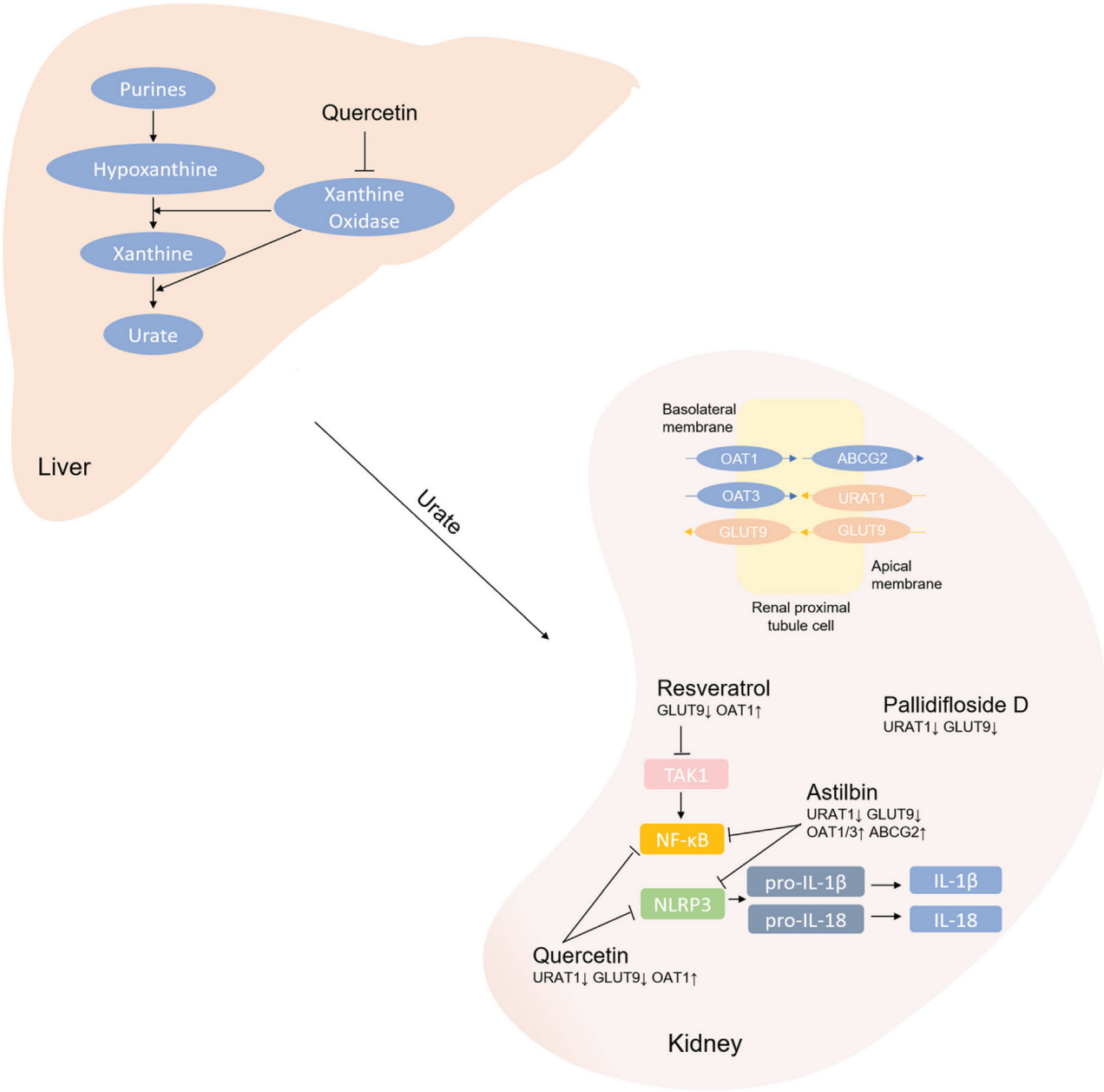

Figure 2. Mechanisms of action of natural products for HUA and gout treatments. HUA: hyperuricemia.

approach. However, due to prolonged therapy and the fact that patients may neglect the significance of long-term ULT, treatment adherence is poor, which explains why it is frequently unsuccessful. Thus, elucidating the reasons why HUA does not necessarily develop into gout may provide us with better insights into the pathogenic mechanisms and even with new therapeutic targets for HUA and gout treatments. Natural products are an indispensable resource for drug development and design, and an increasing number of effective natural compounds for HUA and gout treatments are being identified and their mechanisms are being unraveled. Owing to their multitarget actions and general safety, natural products are definitely promising targets for HUA and gout treatments.

Conflict of interest statement

Tao Wang is the editorial board member of this journal and other authors declare no conflicts of interest.

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Author contributions

Lin Liu, Dan Wang, Yi Zhang, and Tao Wang contributed to the idea for the article. Ruixia Bao, Mengyang Liu, Haiyang Yu, and Qian Chen contributed to performing the literature search and data analysis. Lin Liu, Dan Wang, and Yuzheng Wu drafted the work. Yi Zhang and Tao Wang obtained the funding.

Ethical approval of studies and informed consent

Not applicable.

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