Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 1708-1741 | ISSN:2251-6727

# Inflammopharmacological Perspectives in Gout: Clinical Response Evaluation, Drug Safety, and Emerging Therapeutic Strategies

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*(Received: 16 January 2026 Revised: 25 February 2026 Accepted: 17 March 2026)*

**KEYWORDS**

Gouty arthritis, Hyperuricemia, Urate-lowering agents, Xanthine oxidase inhibitors, Adverse drug reactions, Natural therapy

**ABSTRACT:**

Gout is a persistent inflammatory arthritis resulting from monosodium urate crystals deposition due to hyperuricemia, resulting in recurrent attacks, joint damage and serious systemic comorbidities. This review article offers a thorough review of the molecular and immunological pathophysiology of gout, focusing on purine metabolism, urate transport regulation, inflammasome activation and inflammatory signalling pathways. Although significant progress has been made in the field of arthritis, allowing for a better understanding of the disease mechanisms, the traditional treatment protocols have remained a source of significant challenges in terms of adverse effects and clinical resistance in complex patients. The article also reviews the current diagnostic methods of gout, including synovial fluid analysis, imaging studies and new biomarkers, in the context of evaluating therapeutic response and monitoring disease activity. In addition a comprehensive review of pharmacotherapy for acute and chronic gout attacks is offered, including the safety and efficacy profiles of nonsteroidal anti-inflammatory drugs, corticosteroids, colchicine, urate-lowering agents, biologic agents and recombinant uricases. Special attention is paid to adverse effects, possible drug interactions, and the limitations of treatments that impact long-term disease management. Finally, the review article also examines new approaches to therapy, including new xanthine oxidase inhibitors and plant-derived phytochemicals with anti-inflammatory and uric acid-lowering activities, which may provide safer alternatives or complementary approaches to traditional treatments. Through the integration of clinical outcomes, pharmacological mechanisms and new therapeutic approaches. This article provides a view on gouty arthritis to help promote personalized treatment approaches for gout and hyperuricemia.

## 1. Introduction

Gout is a type of inflammatory arthritis that occurs due to the deposition of monosodium urate crystals within the joints, usually due to hyperuricemia. The prevalence of gout in adults is three to four times higher than that of rheumatoid arthritis. One of the main clinical signs of gout is buildup of monosodium urate (MSU) crystals in and around joints, particularly the fingers, knees, and first metatarsophalangeal joint. The acute attack of gout can lead to severe pain and also impact the lifestyle of the patient resulting in reduced mobility and a decrease in the overall quality of life. Apart from the effects on joint health, gout also affects the healthcare system and can impact work productivity. Moreover, the condition is also associated with metabolic syndrome and has been recognized to increase the risk of various serious health conditions such as cardiovascular disease, type 2 diabetes, chronic kidney disease and early mortality [1]. Prevalence of gout worldwide has been estimated to be 1 to 4%, with an annual incidence of 0.1 to 0.3%. Gout is more common in men than women, with ratios of 3:1 to 10:1. The incidence and prevalence of gout increase

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(2), 1708-1741 | ISSN:2251-6727

steadily with age, and particularly in older people, the prevalence has been found to be 11-13% and the incidence 0.4% in people above 80 years of age [2].

Uric Acid (UA) is a heterocyclic organic compound with the chemical formula $C_5H_4N_4O_3$ (7,9-dihydro-1H-purine-2,6,8(3H)-trione) and a molecular weight of 168 Daltons. It is the final product of purine metabolism in the human body and has antioxidant properties, which can be pro- or anti-oxidant in nature [3]. The main form of uric acid under physiological conditions is the deprotonated urate anion, which readily forms a complex with sodium ions to produce monosodium urate (MSU). MSU is a weak acid, and the characteristic needle shape observed under a microscope is due to the triclinic arrangement of its crystals which consist of purine ring layers. In gout the deposition of monosodium urate (MSU) crystals in joints and surrounding connective tissues triggers extreme yet localized inflammatory reactions. The tendency for crystallization of monosodium urate (MSU) is due to high circulating levels of soluble urate, a metabolic end product of purine catabolism. Hyperuricemia is generally considered to be serum urate levels above the saturation point of MSU, beyond which the likelihood of crystal formation becomes greater. This is generally considered to be above 6.8 mg/dL [4].

Gouty arthritis is conventionally treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, and urate-lowering therapies (ULTs). While these pharmacologic therapies have been proven effective for most patients, they often come with limitations, as will be discussed in this article. Furthermore, despite conventional treatment, some patients with multiple comorbid conditions often fail to achieve optimal serum urate levels or continue to experience recurrent episodes of gout flares [5].

This review article offers a thorough review of the methods used in evaluating clinical response and therapeutic outcomes in the management of gout, with a focus on both laboratory and imaging techniques. The article reviews the efficacy and safety profiles of conventional medications, with a discussion of their mechanisms of action and possible side effects that may contraindicate their use. The article also reviews new treatments as alternative therapies for patients with refractory gout. Moreover it investigates plant-based and phytochemical agents as promising alternative treatments with fewer side effects. In general this review article combines conventional therapeutic approaches with emerging therapies to enhance clinical practice in the management of gout.

## 2. Purine Metabolism

Purine metabolism is a fundamental biochemical process responsible for synthesis, interconversion and degradation of purine nucleotides which are essential components of nucleic acids, energy metabolism and cellular signaling. In humans purine metabolism plays a crucial role in maintaining nucleotide homeostasis, however its dysregulation leads to pathological conditions such as hyperuricemia and gout.

### 2.1. Purine production

Purines including adenine and guanine are essential molecules that support a wide range of cellular activities. They form the basic building blocks of nucleic acids contribute to structure of key coenzymes such as NADH and coenzyme A and play a vital role in regulating energy metabolism as well as intracellular signaling pathways [3].

De novo synthesis pathway and salvage pathway are two processes used to create purines [6] which is shown in Figure 1. Salvage system recycles degraded bases to produce the majority of cellular purine pool under normal physiological circumstances [7]. In the salvage pathway hypoxanthine-guanine phosphoribosyltransferase (HPRT) converts hypoxanthine and guanine into inosine 5′-monophosphate (IMP) and guanosine 5′-monophosphate (GMP) respectively. In addition adenine reacts with phosphoribosyl pyrophosphate (PRPP) to form adenosine 5′-monophosphate (AMP) a reaction catalyzed by adenine phosphoribosyltransferase (APRT) [8].

When cells require increased amounts of purines this demand is fulfilled by activating de novo purine biosynthetic pathway [9, 10]. This conserved and energy-intensive pathway synthesizes inosine monophosphate (IMP) from phosphoribosyl pyrophosphate (PRPP) through a sequence of ten reactions involving six enzymes [11]. Pathway begins with rate-limiting conversion of PRPP to 5-phosphoribosylamine (PRA) by PRPP amidotransferase. PRA is later transformed through a series of intermediates like FGAR, FGAM, AIR, SAICAR and AICAR via the coordinated action of

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JCHR (2026) 16(2), 1708-1741 | ISSN:2251-6727

enzymes such as GART, PFAS, PAICS and ADSL. In the final steps AICAR is converted into IMP by the bifunctional enzyme ATIC. De novo purine biosynthetic pathway requires high amount of energy and depends on several amino acids and one-carbon donors during its ten enzymatic steps includes glutamine, ATP and formate. To produce a single molecule of inosine monophosphate (IMP) pathway consumes five molecules of ATP two molecules each of glutamine, formate and one molecule each of glycine, aspartate and carbon dioxide [8].

### 2.2. Purine catabolism

Purine breakdown mainly takes place in liver, intestine and vascular endothelium[12]. In this process adenosine monophosphate (AMP) is converted to inosine monophosphate (IMP) and subsequently to hypoxanthine through the action of purine nucleoside phosphorylase[6]. The final steps of purine degradation in humans are controlled by the rate-limiting enzyme xanthine oxidoreductase (XOR). This enzyme exists in two interchangeable forms, xanthine dehydrogenase (XDH) and xanthine oxidase (XO) both of which catalyze conversion of hypoxanthine to xanthine and xanthine to uric acid [13, 14]. XDH primarily uses $NAD^+$ as an electron acceptor and generates NADH whereas XO utilizes molecular oxygen and produces reactive oxygen species such as superoxide anion ($O_2^-$) and hydrogen peroxide ($H_2O_2$) during purine catabolism [15].

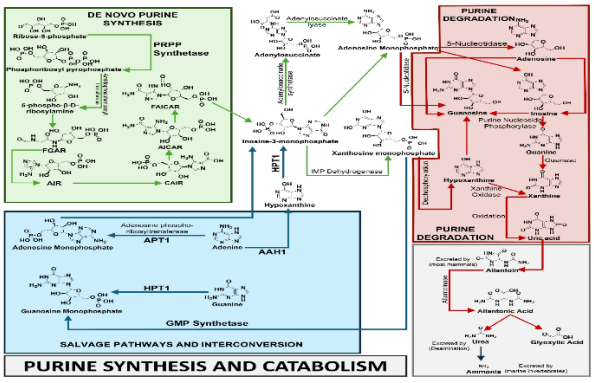


**Figure 1.** Pathway showing the metabolism of the purine and the process of the formation of the uric acid

### 3. Uricase Deficiency

In mammals uricase is key enzyme responsible for converting uric acid into allantoin which is more water soluble compound [16] as shown in Figure 1. In primates serum urate levels are elevated because uricase activity gradually declined during primate evolution and became completely inactivated in the ancestors of humans before the emergence of lesser apes millions of years ago [17]. Specifically this results from nonsense mutation at codon 33 in exon 2 another nonsense mutation at codon 187 and splice-site mutation in exon 3 [18]. In contrast animals that retain functional uricase generally maintain serum uric acid levels between 1 and 2 mg/dL whereas studies in apes lacking uricase show approximately doubled levels reaching about 3 to 4 mg/dL [19]. Additionally rising uric acid levels due to reduced uricase activity may have enhanced impact of fructose on energy metabolism and fat storage leading to increased fat and energy storages [20].

### 4. Hyperuricemia

A blood uric acid level that is abnormally high due to either increased uric acid production or decreased excretion by body is known as hyperuricemia (HUA) [21] as shown in figure 2. It is most frequently seen in postmenopausal women and middle aged and older men [22]. In adults hyperuricemia is generally defined as blood uric acid level above 7.0 mg/dL in men and 6.0 mg/dL in women [23].

### 4.1. Overproduction of uric acid

Nucleic acid metabolism can be accelerated by disease conditions which can break down large amounts of purines into uric acid and ultimately cause hyperuricemia [24]. Overproduction of purines and their increased breakdown into uric acid can result from abnormalities in purine base synthesis such as excessively high glutamine levels or deficiencies in enzymes involved in purine reutilization. Metabolic disorders are closely linked to both increased purine synthesis and enhanced nucleic acid metabolism [25, 26]. Oxidation of xanthine to uric acid is catalyzed by xanthine oxidoreductase (XOR). It primarily displays xanthine dehydrogenase activity under normal physiological conditions but in pathological states it shifts toward increased xanthine oxidase activity which eventually leads to excessive uric acid production [27]. Guanine nucleotides are also converted by xanthine oxidase into xanthine which is subsequently further oxidized to uric acid by the same enzyme [23, 28]. Genetic disorder like HPRT deficiency and PRPP overactivity can also lead uric acid production [29]. Also Hyperuricemia can also be induced by diet including high purine rich food (alcohol, bacon, beef,

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JCHR (2026) 16(2), 1708-1741 | ISSN:2251-6727

shellfish, organ meats, dried beans) [30–33], fructose (generates uric acid through the aldolase reductase route in the liver) [34, 35], vitamin B12 and folate [29].

### 4.2. Reduced renal excretion

In a healthy human body the average uric acid pool is about 1200 mg with approximately 750 mg produced each day and 500-1000 mg excreted daily [36]. Approximately two thirds of the uric acid load is excreted by the kidneys while the remaining third is delivered to the gastrointestinal tract [23]. But in hyperuricemia uric acid is under excreted from both kidney and gut [29]. The majority of uric acid is eliminated by kidneys but about 20% is broken down in the intestine into carbon dioxide and ammonia. Consequently uric acid accumulates and hyperuricemia develops as a result of decreased uric acid elimination caused by kidney dysfunction [37]. Certain transport mechanisms involving several urate transport proteins that regulate serum urate levels tightly control how uric acid is handled by the renal tubules. Among these uric acid secretion is significantly influenced by ATP-binding cassette subfamily G member 2 (ABCG2) [38]. Gout and hyperuricemia can result from mutations in ABCG2 gene [39]. Furthermore a number of drugs can increase uric acid production or impede renal urate excretion which give rise to hyperuricemia and in certain situations causes gout [40].

### 4.3. Genetic factor

Genetic factors play a crucial role in development and progression of gout. Genes includes SLC2A9 (GLUT9), ABCG2 (BCRP), SLC22A12 (URAT1) and others (Table 1) are key regulators of urate homeostasis and significantly influence susceptibility to gout [41] and their dysfunction leads to abnormalities in urate transport [23].

#### 4.3.1. GLUT9 (SLC2A9)

GLUT9 (glucose transporter 9) is member of the SLC2A glucose transporter family is essential for the transport and reabsorption of urate. Urate movement is controlled by the GLUT9 protein which either encourages urate excretion into urine or facilitates its reabsorption into the bloodstream. Hyperuricemia can result from genetic variations of SLC2A9 that decrease urine urate excretion and increase uric acid reabsorption [42]. Notably the rs7442295 polymorphism in SLC2A9 has been used as a marker to investigate connections with blood pressure and cardiovascular disease and is strongly linked to increased serum uric acid levels, gout and altered urate excretion [43, 44]. Urate handling is further hampered by loss of function mutations affecting the urate transport pore which lower GLUT9 expression and transport activity [45].

#### 4.3.2. URAT1 (SLC22A12)

URAT1 (urate transporter 1) controls blood urate levels and is linked to type 1 renal hypouricemia [46, 47]. By downregulating URAT1 expression, glucocorticoids improve renal urate excretion and play a significant role in uric acid balance through glucocorticoid receptor signaling as demonstrated in kidney studies in mice [48]. Meta-analyses have found links between hyperuricemia risk and the rs3825016 polymorphism in the same gene as well as between the rs475688 polymorphism in SLC22A12 and gout susceptibility [49]. Furthermore the rs11726117 polymorphism in ALPK1 suppresses urate reabsorption which lowers the risk of gout through its interaction with SLC22A12 and elevated expression of ALPK1 decreases URAT1 expression [50].

#### 4.3.3. ABCG2 (BCRP)

ABCG2 (ATP-binding cassette subfamily G member 2) is an ATP-dependent efflux pump that aids in the excretion of urate through the intestine and kidney. BCRP promotes urate secretion in the renal proximal tubules and aids in extra-renal urate clearance in the gut. The risk of hyperuricemia and gout is greatly increased when intestinal and extra-renal urate excretion is reduced due to functional impairment or genetic variants of ABCG2 [51–53]. Especially in Polynesian populations the ABCG2 141K (rs2231142) variant is closely linked to increased serum uric acid levels and development of gout from hyperuricemia [54, 55]. Iron overload in hereditary hemochromatosis inhibits ABCG2 expression which results in increased uric acid accumulation, decreased intestinal urate elimination and onset of related arthritis [56].

**Table 1.** Genetic Factors Associated with Hyperuricemia and Uric Acid Regulation

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| S. No. | Gene / Protein | Encoded Protein / Transporter | Primary Function in Uric Acid Regulation | Effect of Dysfunction / Mutation | Associated Conditions | References |
|---|---|---|---|---|---|---|
| 1 | **SLC22A11 (OAT4)** | Organic Anion Transporter 4 | Sodium-independent transport of organic anions; contributes to renal urate handling | Impaired urate transport | Hyperuricemia | [44] |
| 2 | **SLC17A1 (NPT1)** | Sodium-dependent Phosphate Transporter 1 | Urate export and phosphate reabsorption in renal proximal tubules | Altered urate and phosphate transport | Hyperuricemia | [57] |
| 3 | **SLC22A13 (OAT10)** | Organic Anion Transporter 10 | Apical urate reabsorption from urine to blood | Dysfunctional variants reduce serum uric acid | Hypouricemia | [58] |
| 4 | **LDHD** | Lactate Dehydrogenase D | Regulates urate reabsorption via D-lactate exchange | Excess D-lactate production enhances urate reabsorption | Autosomal recessive gout, hyperuricemia | [59] |
| 5 | **UMOD** | Uromodulin | Maintains tubular integrity and supports urate handling | Protein misfolding causes ER stress and impaired urate excretion | FJHN, MCKD2, GCKDHI, hyperuricemia | [60] |
| 6 | **HPRT1** | Hypoxanthine-Guanine Phosphoribosyl transferase | Purine salvage pathway; reduces uric acid formation | Enzyme deficiency increases uric acid production | Lesch–Nyhan syndrome, Kelley–Seegmiller syndrome | [61, 62] |
| 7 | **SARS2** | Mitochondrial Seryl-tRNA Synthetase | Mitochondrial protein synthesis and metabolism | Mutations disrupt systemic metabolism | HUPRAS syndrome | [63] |
| 8 | **G6PC** | Glucose-6-Phosphatase | Regulates gluconeogenesis and glycogenolysis | Metabolic imbalance increases uric acid | Glycogen storage disease type I | [64] |
| 9 | **XDH** | Xanthine Dehydrogenase | Converts hypoxanthine and xanthine to uric acid | Deficiency causes xanthinuria; downregulation reduces urate | Xanthinuria, hyperuricemia | [65, 66] |
| 10 | **INS** | Insulin | Regulates glucose and lipid metabolism; affects renal urate handling | Insulin resistance associated with reduced urate excretion | Metabolic syndrome, hyperuricemia | [67] |
| 11 | **REN** | Renin | Regulates renal hemodynamics and urate excretion | Reduced urate clearance from kidneys | ADTKD-REN | [68, 69] |
| 12 | **GPATCH8** | G-Patch Domain Protein 8 | Putative regulatory role in urate metabolism | Pathogenic variants linked to urate imbalance | Hyperuricemia | [70] |

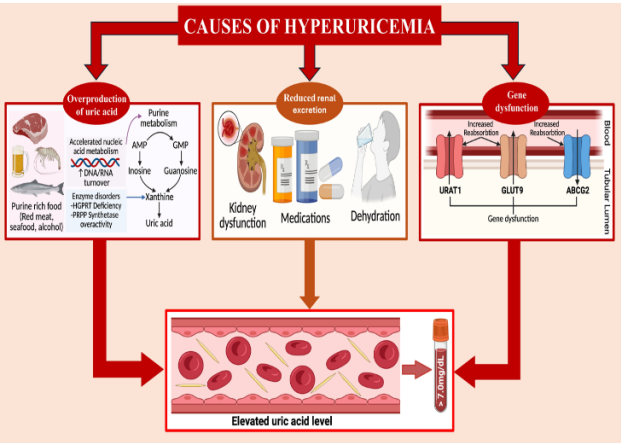


**Figure 2.** Factors that are responsible for the hyperuricemia which ultimately lead to the progression of gout

## 5. Pathophysiology of Gout

### 5.1. Monosodium Urate (MSU) Crystal development

Monosodium urate (MSU) crystal formation and deposition constitute a crucial stage in development of gout. When serum urate levels exceed the physiological solubility limit, monosodium urate (MSU) crystals form in hyperuricemic states. Using compensated polarized light microscopy, MSU crystals can be easily distinguished by their strong negative birefringence and their characteristic needle-shaped appearance with unequal axes [71].

#### 5.1.1. Decreased Urate Solubility

The solubility of urate is mainly affected by high concentrations of urate which is a basic prerequisite for all stages of monosodium urate (MSU) crystal formation

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[72]. In vitro studies show that higher the urate concentration slower the rate of MSU crystal dissolution [73]. Urate solubility is further reduced by high sodium ion concentrations [74]. Another important factor is temperature, at physiological temperature urate solubility is about 0.38 mmol per L (6.8 mg per dL) and slight drop of $2^0$C is enough to reduce solubility to 0.33 mmol per L (6.0 mg per dL) [75]. The preferential deposition of MSU crystals in peripheral tissues where blood flow is lower and heat loss is higher may be explained by this temperature dependent effect. Remarkably higher ambient temperatures have also been linked to recurrent gout flare-ups possibly as a result of mild metabolic acidosis and decreased renal urate excretion brought on by dehydration [76]. Additionally experiments show that pH affects urate solubility with mildly alkaline conditions showing the lowest solubility [74]. Additionally it has been demonstrated that components of connective tissue specifically aggregated proteoglycans and protein polysaccharides derived from cartilage increase urate solubility [77].

#### 5.1.2. Nucleation of MSU Crystals

Monosodium urate (MSU) crystal nucleation requires excess urate and studies have consistently shown a positive association between urate concentration and MSU nucleation [73, 78]. Ex vivo research demonstrates that, independent of baseline synovial urate levels, synovial fluid from gout patients strongly promotes MSU crystal nucleation compared to synovial fluid from healthy controls or patients with other inflammatory arthritides [78]. This implies that gout synovial fluid contains additional pro-nucleating factors. The preferential involvement of joints in gout may be explained by the additional facilitation of MSU crystal nucleation by mechanical stress [79]. Furthermore it has been demonstrated that IgG antibodies extracted from gout patient's synovial fluid stabilize MSU nuclei and encourage crystal formation suggesting that humoral factors also play a role [80].

### 5.2. Immune Cell Activation

An important part of inflammatory reaction to monosodium urate (MSU) crystals in gout is activation of NLRP3 inflammasome priming signal that permits inflammasome assembly is first necessary for this process. In this step toll-like receptors especially TLR2 and TLR4 are crucial because they trigger NF-κB signalling which causes inflammasome components to be expressed [81, 82]. Deletion of TLR2 or TLR4 has been shown to decrease cytokine expression in experimental gout models and the rs2149356 polymorphism which is linked to gout and elevated IL-1β expression in Han Chinese people provides additional genetic evidence for the significance of TLR4 [81–83]. Crucially MSU crystals by themselves cannot cause the release of IL-1β a strong inflammatory response requires an additional co-stimulatory signal such as lipopolysaccharide via TLR4 or free fatty acids via TLR2 [81, 84, 85] which is shown in figure 3.

In hyperuricemic conditions soluble urate itself causes inflammation. When peripheral blood mononuclear cells are exposed to hyperuricemia, they express less of anti-inflammatory IL-1 receptor antagonist and more pro-inflammatory cytokines such as IL-1β, IL-6 and tumour necrosis factor. Histone methyltransferase inhibition eliminates these effects which are mediated by transcriptional regulation and epigenetic histone modifications [86]. These results imply that soluble urate can enhance innate immune responsiveness to subsequent inflammatory stimuli such as MSU crystals by inducing a state of trained immunity. Furthermore it has been demonstrated that soluble urate inhibits autophagy which lessens its initial anti-inflammatory effects [87].

Phagocytosis of MSU crystals provides second signal for NLRP3 inflammasome activation which encourages recruitment of adaptor protein apoptosis associated speck-like protein with caspase recruitment domain and subsequent activation of caspase-1 [81]. Inflammation is caused by activated caspase-1 cleaving pro-IL-1β into its mature active form. In experimental models colchicine a common treatment for acute gout inhibits this process by interfering with tubulin polymerisation which hinders inflammasome assembly and lowers IL-1β production [88]. Additionally gasdermins which create membrane holes and cause pyroptotic cell death are activated by caspase-1. This results in release of intracellular pro-inflammatory mediators includes IL-1β [89]. The inflammatory cascade that characterises gout is further intensified by this process as depicted in figure 4.

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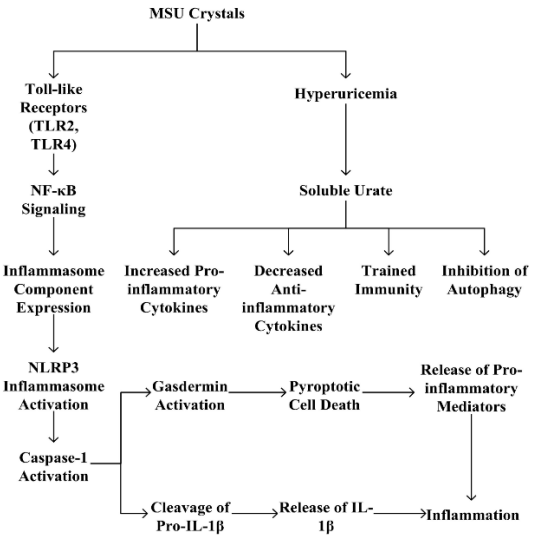


**Figure 3.** Schematic illustration of MSU crystal-induced inflammatory processes in gout involving TLR-mediated priming, NLRP3 inflammasome activation, caspase-1-mediated IL-1β secretion and downstream inflammatory responses promoted by soluble urate.

### 5.3. Amplification of gout inflammation

Pro-inflammatory transcription factors are activated by downstream signalling pathways that are triggered by activated IL-1β binding to its receptor on target cells. This signalling cascade promotes the recruitment of neutrophils and other immune cells to areas of monosodium urate crystal deposition and drives gouty inflammation by inducing the production of cytokines and chemokines [90].

Gasdermin D (GSDMD) is also broken down by active caspase-1 producing amino-terminal fragments that oligomerize to create holes in the plasma membrane [91, 92]. These holes allow cytosolic inflammatory mediators such as IL-1β which in turn causes pyroptosis an inflammatory cell death [93]. By releasing intracellular contents into the extracellular environment this process exacerbates local inflammation. Neutrophil extracellular traps (NETs) are created when recruited neutrophils phagocytose MSU crystals and go through NETosis a process that expels granule proteins and chromatin [94]. Furthermore independent of the inflammasome, neutrophil-derived serine proteases includes proteinase-3, cathepsin G and neutrophil elastase can cleave pro-IL-1β into its active form intensifying the inflammatory response in gout [95].

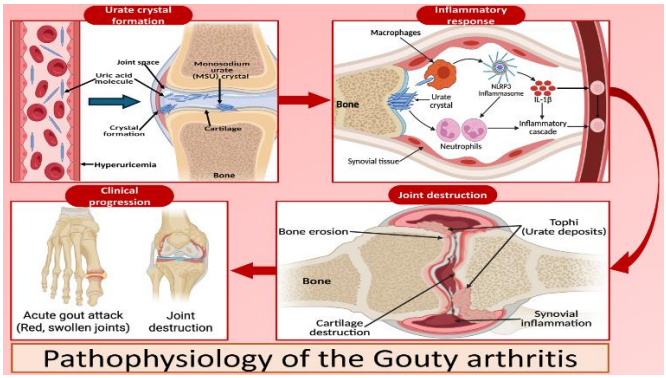


**Figure 4.** Pathophysiology of the gout

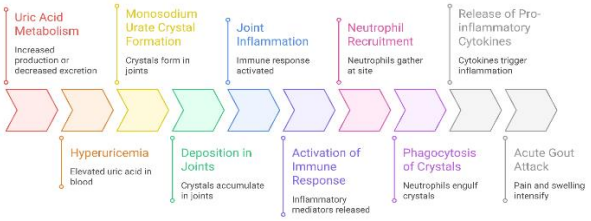


**Figure 5.** Timeline of the gouty arthritis

## 6. Drug response evaluation

By detecting birefringent monosodium urate (MSU) crystals, gout can be definitively diagnosed and checked for drug response. Advances in imaging particularly dual-energy computed tomography (DECT) now allow direct visualization of MSU crystal deposits including those located at extra-articular sites [96].

### 6.1. Gold Standard: Synovial Fluid Analysis

Analysis of synovial fluid using polarized light microscopy is still the gold standard for the diagnosis of gout because it provides direct and definitive evidence of the presence of needle-shaped, negatively birefringent monosodium urate (MSU) crystals. The differentiation of gout from other crystal arthropathies such as calcium pyrophosphate deposition disease can be made by identification of intracellular MSU crystals. The major drawbacks of this technique include its invasive nature, difficulty in obtaining samples from small joints and its dependence on the expertise of the operator with questionable inter-observer reliability. The practical limitations further restrict its use including the need for rapid processing of samples, availability of specialized equipment and its restricted use in some clinical settings. Moreover the crystals can be found in asymptomatic joints or may not be present in the early flare of gout.

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JCHR (2026) 16(2), 1708-1741 | ISSN:2251-6727

Thus underlining the need for other or complementary methods of diagnosis [97, 98].

### 6.2. Serum Uric Acid Measurement

Serum uric acid measurement is a basic part of evaluation of gout but it is not very specific for diagnosis. While hyperuricemia is a prerequisite for the onset of gout high urate does not by itself indicate the presence of gout as many patients with high urate levels never actually develop gout and inflammatory and uricosuric mechanisms can normalize or even decrease levels during an acute attack. Generally therapeutic goals are suggested to be <6.0 mg/dL or <5.0 mg/dL in the presence of tophaceous gout. While levels may increase during attacks inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are not very specific [99]. Chronic hyperuricemia is best considered in a broader sense of complex diagnostic algorithms and it is a very important tool in monitoring and managing urate-lowering therapy [97].

### 6.3. Imaging

#### 6.3.1. Radiographs

Radiography is widely accessible and reasonably priced it is typically the initial imaging test performed on patients who may have gout. Early on in the illness X-rays are frequently unremarkable or only reveal nonspecific soft-tissue swelling and it usually takes years for the disease's distinctive bone changes to manifest. Distinct erosive lesions usually appear only after 5 to 10 years of disease progression [100–103]. In established or chronic gout radiographs commonly reveal well-defined marginal and juxta-articular erosions with sclerotic borders and characteristic "overhanging edges," which may also extend into the joint space. Smaller tophi (less than 5-10 mm) might not show up on an X-ray [104, 105] but they can manifest as dense soft-tissue masses in the bursal or periarticular regions occasionally with amorphous calcifications. These erosions frequently happen next to tophi indicating that they extend into the bone [104]. Until the disease is advanced joint space width and periarticular bone density are typically maintained. For the diagnosis of gout, conventional radiography has high specificity (~93%) but a relatively low sensitivity (~31%) [106, 107].

#### 6.3.2. Ultrasound (US)

High-frequency diagnostic ultrasound (≥12 MHz) is a useful tool for the assessment of patients with suspected gout [108]. It may help in diagnosis, guide joint aspiration or soft tissue biopsy, and assist in monitoring the response to treatment. The advantages of ultrasound include high spatial resolution, multiplanar and dynamic imaging, lack of ionizing radiation, ease of access, portability, and cost-effectiveness. However, it is highly operator-dependent, requiring a great deal of technical skill, and is mainly used for the evaluation of superficial joints. Typical ultrasound features in gout include joint effusion, synovial inflammation, monosodium urate (MSU) crystal deposition, tophi formation and bone erosions [109, 110]. 2018 meta-analysis by Lee *et al.* reported that ultrasound demonstrates high diagnostic specificity (about 89%) with moderate sensitivity (approximately 65.1%) for gout detection [111].

#### 6.3.3. Computed Tomography-Conventional (CT)and Dual Energy (DECT)

When assessing gout both conventional CT and dual-energy CT (DECT) are useful imaging methods. Conventional CT is helpful for identifying erosions and tophi in chronic gout because it provides high spatial resolution, multiplanar imaging and excellent visualization of deep structures [112]. Dense intra-articular deposits can also be observed in acute gout [113] and tophi usually manifest as hyperdense nodules (about 170 Hounsfield units). Despite being more accessible than DECT, CT is constrained by radiation exposure, expense and portability [108].

By directly detecting monosodium urate (MSU) crystal deposition using two energy levels to distinguish urate crystals from other calcifications through color-coded imaging DECT offers a more precise method [104, 105, 114, 115]. 2015 and 2018 ACR/EULAR categorisation criteria for gout include DECT [116] which is independent of serum uric acid levels due to its direct visualization of MSU crystals. It makes it possible to map urate deposits in peripheral tissues, detect subclinical disease and quantify the tophus burden [117, 118]. With reported sensitivity of ~78-100% and specificity of ~89-100% [100, 119], DECT exhibits high diagnostic accuracy. However sensitivity is lower in early or acute gout when crystal burden is low. Early disease detection can be enhanced by combining DECT

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with traditional CT[113]. DECT is especially helpful in difficult cases like axial skeletal gout where tissue diagnosis is challenging, atypical presentations and uncommon sites of involvement [120, 121].

#### 6.3.4. Magnetic Resonance Imaging (MRI)

MRI is high-resolution, non-ionizing imaging methodology that enables detailed assessment of bone marrow, cartilage and periarticular soft tissues making it particularly useful for evaluating gout in deep or inaccessible regions such as the spine [112]. Its clinical use is limited by high cost, long acquisition times, limited availability, lack of portability, patient-related constraints and device incompatibilities. In early disease MRI may show joint effusions, synovitis and bone marrow or soft-tissue edema although direct visualization of MSU crystal deposition is not possible [104, 112]. Erosions appear as cortical defects with overhanging margins with acute lesions showing active synovitis and chronic lesions appearing well-defined and corticated [110]. Bone marrow edema and cartilage damage generally occur only in advanced stages. MRI is effective in defining the extent of tophus involvement including within tendons and bursae. Tophi typically demonstrate low-to-intermediate T1 signal, heterogeneous fluid-sensitive signal and variable post-contrast enhancement while non-enhancing low-signal regions suggest calcification [109, 122].

### 6.4. Emerging Biomarkers and Novel Approaches

New biomarkers and integrated diagnostic techniques have been the focus of recent research to enhance gout diagnosis beyond conventional techniques. Even though serum uric acid is still the most common laboratory marker its drawbacks have led to research into other as of yet unutilized, inflammatory and inflammasome-related biomarkers like interleukin-1β [97, 123]. While they may increase during acute flares conventional inflammatory markers such as CRP and ESR are not disease specific. When compared to single methods studies indicate that combining imaging modalities specifically musculoskeletal ultrasound with serological markers can improve diagnostic accuracy. Although more research is needed before broad clinical adoption, technological advancements in DECT and ultrasound continue to enhance the detection of urate deposits, artificial intelligence and machine learning models have the potential to integrate clinical, laboratory and imaging data [117, 124].

## 7. Treatment and their side effects

### 7.1. Treatment of Acute Gout

#### 7.1.1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a foundation in the management of acute gout flares. Current evidence does not favor one NSAID over another and drug selection should therefore be individualized based on prior patient response, potential adverse effects (such as central nervous system intolerance with indomethacin) and comorbid conditions. COX-2 selective agents like celecoxib may be preferred in patients at higher risk of bleeding including those receiving anticoagulation or with thrombocytopenia [125] as shown in figure 6.

Through inhibition of prostaglandin synthesis all NSAIDs can reduce renal perfusion, cause sodium and water retention, worsen hypertension and increase risk of acute heart failure. Effective treatment of gout flares usually requires relatively high doses of NSAIDs (e.g., naproxen 500 mg twice daily or celecoxib 400 mg twice daily) [126]. Therapy should be continued for the shortest duration necessary to achieve complete symptom control typically 3 to 5 days. In patients with significant comorbidities gradual dose tapering may be considered as premature discontinuation can lead to flare recurrence [127, 128]. An additional benefit of NSAIDs is their inherent analgesic effect which can provide rapid pain relief even before full suppression of inflammation [129].

#### 7.1.2. Corticosteroids

It has been demonstrated that glucocorticoids are just as effective as NSAIDs as anti-inflammatory drugs for treating acute gout flare-ups [130]. An initial oral prednisone dose of roughly 0.5 mg/kg is advised by 2012 American College of Rheumatology (ACR) guidelines. This dose may be continued until symptoms are resolved or followed by a planned tapering schedule [128]. Similar to NSAIDs glucocorticoids should be used for the shortest amount of time possible because tapering off too quickly could cause a flare-up. Even short-term use

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can have negative effects even though the risk of toxicity rises with longer or repeated courses.

Systemic corticosteroids work by reducing proinflammatory cytokines like interleukin-1β, suppressing inflammatory cell activation and migration and preventing prostaglandin synthesis. Comparative research shows that while NSAIDs are linked to a higher incidence of gastrointestinal and related adverse events, systemic corticosteroids and NSAIDs offer comparable pain relief and time to symptom resolution [131, 132]. Acute gout can also be effectively treated with single intramuscular injections of corticosteroids such as methylprednisolone acetate or triamcinolone acetonide especially in severe or polyarticular attacks. Oral prednisone dosages typically vary from 0.5 to 1 mg/kg and are tapered over a period of 7 to 14 days [128, 133].

For severe monoarticular or oligoarticular gout, intra-articular corticosteroid injection is a useful treatment option, particularly in patients with large weight-bearing joints or those for whom colchicine and NSAIDs are not recommended. In one study intra-articular triamcinolone acetonide (10 mg) with dosage modified based on joint size completely relieved pain within 48 hours without rebound flares or notable side effects [134].

**7.1.3. Colchicine**

Colchicine affects leukocyte activation, intracellular transport and cell migration by interfering with microtubule assembly [135]. Colchicine also inhibits NLRP3 inflammasome activation and lowers interleukin-18 production according to in vitro research. However the significance of these effects at clinically achievable concentrations is still unknown [136]. Although a well-conducted study revealed that most patients treated with this dose despite some benefit it needed additional rescue medication for pain control. The current recommended regimen for an acute gout flare is 1.2 mg followed by 0.6 mg an hour later [137]. Patients with chronic kidney disease and those taking concurrent medications metabolized by the CYP3A4 pathway such as some statins (especially atorvastatin), clarithromycin, some antifungal and antiretroviral agents, diltiazem and verapamil should use colchicine cautiously and adjust their dosage [138]. There have been reports of severe adverse reactions with clarithromycin and these pharmacokinetic interactions are more clinically significant when used chronically and when renal impairment is present [139]. Colchicine may be continued as an adjuvant therapy at a lower dose (0.6 mg once or twice daily) following the start of flare treatment in order to prevent recurrence [134].

**7.1.4. Interleukin-1 (IL-1) Inhibitors**

Interleukin-1 targeted biologic therapies used in gout include the monoclonal antibody canakinumab the soluble receptor rilonacept and recombinant receptor antagonist anakinra [140]. Clinical trials have shown that these agents are at least as effective as conventional treatments for both acute and chronic gout with efficacy demonstrated in phase II studies for anakinra [141, 142] and phase III studies for canakinumab and rilonacept [143–145]. In recent randomized, double-blind, active comparator trial involving 88 patients anakinra (100 mg daily for 5 days) was found to be non-inferior to standard therapies such as colchicine, naproxen or prednisone [146].

IL-1 directed therapies are generally well tolerated and are not commonly associated with gastrointestinal, renal or metabolic adverse effects making them particularly suitable for patients with multiple comorbid conditions. Although biologic agents are costly their short treatment duration in acute gout may limit overall expense especially if hospital stays are reduced. While infection risk is a concern with long-term biologic use this has not been observed with short-term therapy. Canakinumab is approved in Europe for acute gout but was not approved by the FDA due to concerns related to its long half-life. In contrast anakinra has a short half-life and is administered for only a few days and despite the lack of FDA approval for gout it is widely used by rheumatologists particularly in hospitalized patients with significant comorbidities [141].

**7.2. Urate-lowering therapies**

Since persistent hyperuricemia is the primary cause of monosodium urate crystal formation and disease progression all rheumatology society guidelines concur that urate-lowering therapy (ULT) is necessary for the effective long-term management of established gout [127, 147, 148]. The American College of Physicians recommendation of a symptom based treatment approach which has drawn harsh criticism from gout specialists [149, 150]. When serum urate levels rise above about 7.0 mg/dL patients who were previously flare free

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experience a recurrence of gout attacks after stopping ULT according to evidence from observational and interventional studies [151]. Higher levels are linked to a quicker relapse. When anti-inflammatory medications are used exclusively to treat flare-ups without addressing hyperuricemia subclinical crystal deposition can continue putting patients at risk for more severe and treatment-resistant illness. Sustained urate lowering lowers the frequency of gout flare-ups according to more recent data.

When to start ULT is still a personal choice that should be made in consultation with the patient. Serum urate concentration, comorbidities, age, flare severity and impact, radiographs showing tophi or joint damage and advanced imaging such as dual-energy CT or ultrasound showing urate deposition or bone involvement are all important factors to take into account. According to current ACR guidelines patients with chronic kidney disease or history of nephrolithiasis should start ULT earlier even after a single flare [147]. Conclusive interventional data are still scarce despite growing evidence that urate lowering may also improve cardiovascular and renal comorbidities [152, 153].

**7.2.1. Xanthine oxidase inhibitors**

The 2012 American College of Rheumatology (ACR) guidelines recommend a xanthine oxidase inhibitor either allopurinol or febuxostat as first-line urate-lowering therapy (ULT) [147]. However concerns regarding potential cardiovascular risk with febuxostat have led FDA to advise using allopurinol as the initial agent reserving febuxostat for patients who do not tolerate or respond adequately to allopurinol. This approach was reaffirmed in the 2020 ACR guidelines [154]. Regardless of whether hyperuricemia is caused by urate overproduction or more frequently impaired renal or gastrointestinal excretion, xanthine oxidase inhibitors effectively lower serum urate. With sustained and appropriately dosed therapy these agents can prevent new urate deposition and promote dissolution of existing crystals and tophi with the rate of crystal clearance corresponding to the extent of urate reduction achieved [155]. Co-administration with azathioprine or 6-mercaptopurine can significantly raise drug levels and cause severe bone marrow suppression because xanthine oxidase inhibitors also prevent the metabolism of purine analog drugs.

**7.2.1.1. Allopurinol**

The most traditional and widely used xanthine oxidase inhibitor for gout is allopurinol. Its active metabolite, oxypurinol, competitively inhibits xanthine oxidase and other purine metabolism-related enzymes, acting as a purine analog. Allopurinol is often underdosed despite its effectiveness and low cost, although 300 mg/day is commonly regarded as standard average doses closer to 400 mg/day are typically needed to achieve serum urate levels below 6.0 mg/dL, and the FDA-approved maximum dose is 800 mg/day. Allopurinol may help maintain kidney function, and there is no evidence to support concerns about renal toxicity. The main safety concern is the rare but potentially fatal allopurinol hypersensitivity syndrome including DRESS with risk increased in patients with chronic kidney disease and those carrying the HLA-B58:01 allele [156]. Therapy should be started at low doses (50–100 mg/day, or 50 mg/day in kidney disease) and gradually titrated until the urate target is reached in order to reduce this risk [147]. In high-risk groups such as Han Chinese, Thai, Korean and African-American patients especially those with kidney disease HLA-B58:01 testing is advised [154, 157]. In known carriers alternative agents should be taken into consideration [125].

**7.2.1.2. Febuxostat**

Unlike allopurinol febuxostat is non-purine, non-competitive xanthine oxidase inhibitor that inhibits both reduced and oxidized forms of enzyme without affecting other metabolic pathways. It is available at doses of 40 to 80 mg in US and 120 mg in Europe for the purpose of lowering urate in gout patients with normal renal function or mild-to-moderate chronic kidney disease (up to stage 3). Although febuxostat is often perceived as more potent than allopurinol, direct comparisons have not consistently used optimally titrated allopurinol doses, and an ongoing Veterans Affairs trial is evaluating both agents when dosed to achieve target serum urate levels [125, 158]. After the phase 4 CARES study showed that patients with preexisting cardiovascular disease treated with febuxostat had greater rates of cardiovascular and all-cause death than those treated with allopurinol FDA issued a black-box warning about the safety of febuxostat [159]. However the results have been contested because of study limitations such as high dropout rates, irregular aspirin use, no increased risk of myocardial infarction

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and lack of an untreated control group which makes it challenging to determine causality [160, 161]. Results from a large European trial are awaited, and subsequent observational studies have not consistently confirmed this risk [162, 163]. When allopurinol is not contraindicated it is typically recommended as first-line therapy until more definitive evidence is available.

#### 7.2.1.3. Topiroxostat

After allopurinol and febuxostat topiroxostat is the third xanthine oxidase inhibitor created however it has only received approval in Japan thus far. Unlike allopurinol mild-to-moderate renal dysfunction has no discernible impact on its pharmacokinetic profile [164, 165]. According to a 2022 study topiroxostat reduced serum urate levels in 66.7% of patients with baseline hyperuricemia to less than 6.0 mg/dL but estimated glomerular filtration rate did not significantly change [166]. Despite these results it is still unclear if topiroxostat will be made available in the US or other foreign markets because of potential side effects. Nasopharyngitis, polyarthritis and increased liver enzyme levels are among the reported adverse effects. Furthermore some patients receiving concurrent warfarin therapy have shown increased anticoagulant effects which may further limit its clinical applicability [167].

#### 7.2.1.4. Tigulixostat

In a phase II study reported in 2021 tigulixostat a novel non-purine selective xanthine oxidase inhibitor, demonstrated promising urate-lowering efficacy in patients in the United States. At 12 weeks medication lowered serum uric acid levels to less than 5 mg/dL and mean maximum reduction in serum urate at the highest evaluated dose of 200 mg was roughly 66.8%. This study also reported that tigulixostat was well tolerated [168].

#### 7.2.1.5. 3,4-Dihydroxy-5-Nitrobenzaldehyde

Although its precise mode of action is still being investigated, 3,4-Dihydroxy-5-nitrobenzaldehyde (DHNB) novel time-dependent xanthine oxidase inhibitor seems to work similarly to allopurinol. Even at low dosages experimental research indicates that DHNB has minimal toxicity and may improve therapeutic efficacy when combined with allopurinol. Furthermore DHNB has direct antioxidant activity that limits cellular damage by lowering production of reactive oxygen species and free radicals at their source. Clinical data in humans are currently unavailable despite the fact that DHNB has demonstrated exceptional safety and efficacy in animal models especially in mice [169].

### 7.2.2. Uricosuric agents

Uricosuric agents increase renal excretion of uric acid which lowers serum urate (SU) levels. Key renal urate transporters especially urate transporter 1 (URAT1) which is responsible for about 90% of urate reabsorption are modulated to produce this effect [170]. ATP-binding cassette transporter ABCG2, glucose transporter GLUT9 and organic anion transporters OAT1, OAT3 and OAT4 are additional transporters involved in urate handling [171].

#### 7.2.2.1. Probenecid

Probenecid introduced in 1951 is a nonspecific uricosuric agent that lowers serum urate (SU) primarily by inhibiting URAT1 as well as OAT1, OAT3 and GLUT9 [172–175]. Its benzoic acid and sulfamoyl functional groups facilitate binding to URAT1 accounting for its uricosuric effect, while inhibition of other transporters contributes to reduced efficacy and clinically relevant drug-drug interactions [174, 175]. Probenecid has a half-life of 4 to 6 hours and is mainly metabolized by liver [176]. Clinical studies show that probenecid significantly reduces SU levels particularly when combined with colchicine or allopurinol with combination therapy being more effective than monotherapy [177]. Although generally contraindicated in patients with chronic kidney disease (CKD) beyond stage 3 limited data suggest comparable urate-lowering effects in patients with reduced versus preserved renal function [178]. Probenecid is typically started at 500 mg once or twice daily and titrated up to 1000 mg twice daily to achieve target SU levels [154]. Owing to its lower efficacy, risk of urolithiasis and significant drug interactions it is considered a second-line option mainly for patients who cannot tolerate xanthine oxidase inhibitors or fail to reach urate targets with them [154, 167, 179]. Evidence regarding cardiovascular effects is mixed however small clinical and epidemiological studies suggest potential cardiovascular benefits or a modestly lower cardiovascular risk compared with allopurinol [180–182]. Overall probenecid remains a second-line urate-lowering therapy with greater efficacy when used in combination with allopurinol and limited use in patients with advanced CKD.

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#### 7.2.2.2. Lesinurad

In certain patients lesinurad a stronger URAT1 inhibitor than probenecid, can significantly lower serum urate levels [183]. Its authorized use is restricted to patients with GFRs of 50 mL/min or greater, despite the possibility that it may be useful at glomerular filtration rates as low as 30 mL/min. Clinical trials revealed a higher incidence of serum creatinine elevations when lesinurad was used alone, most of which were temporary, despite the drug's sufficient potency to be used as monotherapy [184]. Lesinurad was only approved by the FDA as an add-on therapy because these renal side effects were rare when combined with a xanthine oxidase inhibitor. Lesinurad has been demonstrated to be both safe and effective when used in combination [185]. Despite this the drug's high cost, complicated regimen and worries about renal safety hindered its clinical uptake and the manufacturer has since removed it from the market.

#### 7.2.2.3. Benzbromarone

First approved in 1970 benzobromarone is a uricosuric agent that is currently mostly used in Asia and parts of Europe. However due to hepatotoxicity concerns it is not used in the United States [173]. Its chemical makeup makes it possible to strongly inhibit URAT1 and to a lesser degree, GLUT9 which effectively increases renal urate excretion [172, 174]. Similar to other hepatotoxic agents its bis-aryl-ketone structure has been linked to mitochondrial toxicity though the precise mechanism of hepatotoxicity is unknown [178, 186, 187]. By lessening oxidative stress brought on by uric acid benzobromarone also demonstrates antioxidant qualities [188]. With a short half-life of 3 to 5 hours and longer-acting active metabolite 6-hydroxy benzbromarone it is administered at doses of 50-200 mg/day [189]. Particularly in poor metabolisers its inhibition of CYP2C9 and genetic polymorphisms affecting this enzyme may raise plasma levels and the risk of harmful hepatic events [190].

Clinical evidence consistently shows that benzbromarone is very effective at reducing serum urate (SU) frequently outperforming allopurinol and febuxostat especially at standard doses [191, 192]. When compared to monotherapy, combination therapy with either febuxostat or allopurinol further improves treatment success and urate-lowering efficacy [192]. Additionally benzbromarone has demonstrated better tolerability and efficacy than probenecid [193]. While cardiovascular outcomes are still inconsistent across studies observational data point to possible extra advantages such as lower risk of type 2 diabetes and chronic kidney disease when compared to allopurinol [194–197]. Additionally in certain patients small clinical studies have shown improvements in inflammatory markers and insulin resistance without negative cardiac effects. The goal of ongoing research on the structure activity relationship is to create new uricosuric agents with better safety profiles that are based on the scaffold of benzbromarone [174, 175, 187, 198].

#### 7.2.2.4. Dotinurad (FYU-981)

By selectively blocking the URAT1 transporter dotinurad a selective urate reabsorption inhibitor (SURI) reduces serum urate [199]. Dotinurad was approved in 2020 after being developed in Japan through structure activity optimisation of benzbromarone to increase efficacy and decrease toxicity [187, 200]. With a half-life of roughly 10 hours and glucuronidation as the primary metabolic pathway, structural changes enhanced URAT1 inhibition, decreased hepatotoxic potential and produced favourable pharmacokinetics [187, 201]. By inhibiting the NLRP3 inflammasome dotinurad also demonstrates anti-inflammatory activity in vitro [202].

Strong urate-lowering efficacy and good tolerability are shown by clinical studies. Dotinurad (0.5–4 mg/day, usually 2 mg/day) significantly lowered serum urate levels and was as effective as benzbromarone and febuxostat, according to phase II and III trials [203–206]. According to meta-analyses and comparative research, dotinurad has a safer profile than febuxostat and is more effective than benzbromarone [207]. In patients with mild-to-moderate chronic kidney disease (CKD) dotinurad effectively lowers serum urate and may slow or improve renal function according to observational and pooled data [208–210]. Although more research is needed combination therapy with xanthine oxidase inhibitors especially febuxostat may further improve urate lowering in certain CKD patients. Dotinurad monotherapy is safe and effective [173, 211–213].

### 7.2.3. Uricases

Due to the evolutionary loss of the uricase gene some 15-25 million years ago hyperuricemia is mostly specific to

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humans and higher primates. Urate builds up in the body and has the potential to crystallize when uricase is not present. Two recombinant uricase enzymes that can quickly break down urate and significantly lower serum urate levels are available as replacement therapies to address this.

#### 7.2.3.1. Pegloticase

A pegylated recombinant uricase called pegloticase was created for patients with severe treatment resistant gout. For patients who were unable to tolerate intensive oral urate-lowering therapy, continued to experience flare-ups or tophi or failed to reach target serum urate levels it is FDA-approved. In situations where rapid urate depletion is clinically required such as before organ transplantation or in cases of severe functional impairment it might also be regarded as off-label. When given intravenously every two weeks pegloticase causes a significant and quick drop in serum urate frequently in as little as 24 hours. With sustained treatment it can resolve tophi, lessen flares, significantly reduce total body urate stores and enhance quality of life [214].

Up to 40% of patients develop anti-PEG antibodies that neutralize the medication reducing its effectiveness and raising the risk of infusion reactions even though PEGylation is meant to reduce immunogenicity. While true anaphylaxis was uncommon in the trials these reactions including those classified as anaphylaxis were rather common and could be lessened with premedication with corticosteroids and antihistamines. Urate should be measured prior to each infusion and treatment should be stopped after two consecutive values ≥6.0 mg/dL which significantly lowers adverse events because increasing serum urate levels indicate antibody formation and increased infusion risk. Remarkably even after early discontinuation because of partial urate depletion some patients experience long lasting clinical benefit [215]. Emerging data indicates that concurrent immunosuppression with medications like methotrexate or azathioprine may lessen the formation of anti-drug antibodies, improving drug persistence and tolerance. This strategy is presently being researched [216].

#### 7.2.3.2. Rasburicase

Rasburicase is a recombinant fungal uricase that is typically used to quickly lower serum urate levels in patients with tumor lysis syndrome. However due to its high immunogenicity it is typically not used in gout [125]. Uric acid is changed by the enzyme into the more soluble and inactive metabolite allantoin. Rasburicase can reverse hyperuricemia faster than allopurinol but it's unclear if it will be clinically beneficial overall for cancer patients with tumor lysis syndrome, especially if they also have renal failure and high urate levels [217].

**Table 2.** Adverse drug reactions of drugs used in the treatment of the Gout

| S. no. | Drug/Class | Major Adverse Effects / Safety Concerns | Special Concerns / Limitations | Reference No. |
|---|---|---|---|---|
| 1 | **NSAIDs** | Renal perfusion reduction, sodium/water retention, hypertension, heart failure risk; GI toxicity; CNS intolerance (indomethacin) | Avoid in patients with renal disease, cardiovascular disease, or high bleeding risk; require high doses for flares; short-duration use recommended | [125, 126, 131, 132] |
| 2 | **Systemic Corticosteroids** | Systemic metabolic effects; toxicity with repeated use | Rapid tapering may trigger flare recurrence; limit duration due to adverse effects | [128, 130, 133] |
| 3 | **Colchicine** | Drug–drug interactions; increased toxicity in renal impairment | Dose adjustment needed in CKD; caution with CYP3A4 inhibitors (clarithromycin, statins, antifungals); narrow therapeutic window | [138, 139] |
| 4 | **IL-1 Inhibitors** | Infection risk (mainly long-term); biologic-related adverse effects | High cost; limited FDA approval (anakinra off-label); long half-life concerns (canakinumab) | [140, 141, 146] |
| 5 | **Allopurinol** | Hypersensitivity syndrome (AHS), DRESS | Requires slow dose titration; HLA-B58:01 screening in high-risk populations; often underdosed | [154, 156, 157] |

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| | | | | |
|---|---|---|---|---|
| **6** | **Febuxostat** | Possible increased cardiovascular mortality | FDA black-box warning; generally reserved for patients intolerant to allopurinol | [159–161] |
| **7** | **Topiroxostat** | Nasopharyngitis, polyarthritis, elevated liver enzymes | Approved mainly in Japan; potential interaction with warfarin | [167] |
| **8** | **Tigulixostat** | Limited safety data (phase II) | Still investigational; long-term safety unknown | [168] |
| **9** | **3,4-Dihydroxy-5-Nitrobenzaldehyde (DHNB)** | Experimental safety only | Lack of human clinical trials; preclinical stage | [169] |
| **10** | **Probenecid** | Kidney stone risk; drug interactions | Ineffective in advanced CKD; requires adequate renal function; second-line option | [178, 179] |
| **11** | **Lesinurad** | Elevated serum creatinine; renal toxicity risk | Only approved as add-on therapy; withdrawn from market; complex regimen | [184, 185] |
| **12** | **Benzbromarone** | Hepatotoxicity, mitochondrial toxicity | Not approved in USA; CYP2C9 genetic variability affects safety | [186, 190] |
| **13** | **Dotinurad** | Generally well tolerated | Limited global availability; ongoing long-term safety evaluation | [207] |
| **14** | **Pegloticase** | Infusion reactions, anti-PEG antibodies, anaphylaxis risk | Reserved for severe refractory gout; requires IV administration and monitoring of urate levels | [215, 216] |
| **15** | **Rasburicase** | High immunogenicity | Mainly used for tumor lysis syndrome; not routinely used in gout | [125] |

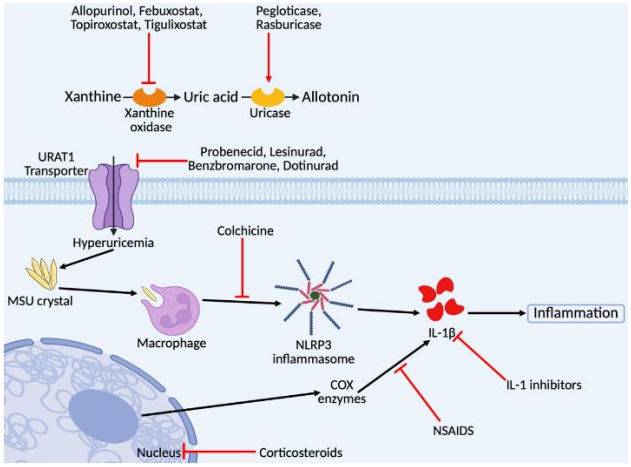


**Figure 6.** Mechanistic overview of drugs used in gouty arthritis showing inhibition of inflammatory pathways, including suppression of NLRP3 inflammasome activation, cytokine release and urate-induced immune responses. The figure illustrates key therapeutic targets that reduce inflammation, prevent crystal-induced signalling and improve clinical outcomes in gout management.

## 8. Natural derived product therapy

In order to effectively treat this difficult condition more potent xanthine oxidase (XOD) inhibitors with better safety profiles are required as the currently available medications are frequently linked to a number of negative side effects. Natural product derived XOD inhibitors have attracted lot of attention lately due to their possible effectiveness and reduced toxicity [218], some natural plants are mentioned in the table 3.

### 8.1. Flavonoids

Through a variety of mechanisms flavonoids show great therapeutic promise in the treatment of hyperuricemia and gout. By blocking the activity of xanthine oxidase (XO), the essential enzyme in uric acid synthesis, these plant-derived compounds successfully reduce serum uric acid levels. Flavonoids interact with XO through hydrogen bonds and hydrophobic interactions, causing structural changes that reduce catalytic activity. Beyond inhibiting enzymes flavonoids control the kidneys uric acid transporters increasing the expression of organic anion transporters (OAT1 and OAT3) and decreasing renal glucose transporter 9 (GLUT9) and urate transporter 1 (URAT1), which increases the excretion of uric acid. Furthermore, by altering the NOD-like receptor 3 inflammasome and Toll-like receptor 4 signaling pathways, flavonoids lessen inflammatory reactions. Many flavonoid types such as kaempferol, luteolin, quercetin and genistein have demonstrated effectiveness

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in animal studies making them viable natural alternatives for the treatment of hyperuricemia[219, 220].

**8.2. Alkaloids**

Elevated serum uric acid levels are a hallmark of hyperuricemia and gout metabolic disorders linked to a number of chronic conditions such as obesity, cardiovascular disease and hypertension. Natural alternatives are being researched because despite their effectiveness conventional treatments like NSAIDs and glucocorticoids have serious side effects. Alkaloids in particular are natural phytochemicals that have shown promise as medicinal substances. Inhibiting uric acid production, decreasing intestinal uric acid secretion and improving renal uric acid elimination are the three main ways in which these bioactive compounds exhibit anti-gout activity. The primary enzyme that catalyzes the conversion of xanthine and hypoxanthine to uric acid, xanthine oxidase (XO) is the target of alkaloids. Since the sixth century AD, colchicine an alkaloid derived from Colchicum autumnale has been used to treat gout. Alkaloids and other phytochemicals have been shown in recent studies to efficiently lower uric acid levels and dissolve monosodium urate crystals providing safer substitutes for prescription drugs [221, 222].

**8.3. Phenolic acids**

Through a variety of mechanisms, phenolic acids are promising natural therapeutic agents for the treatment of gout and hyperuricemia. The main way that these substances work is by blocking xanthine oxidase (XO) which is the essential enzyme that turns xanthine and hypoxanthine into uric acid. According to Wang et al. (2025) certain phenolic acids such as ferulic acid, p-coumaric acid, gallic acid and protocatechuic acid exhibit mixed inhibition patterns against XO mainly influencing the hydrophobic regions and secondary conformation of the enzyme through hydrophobic bonding. Inhibiting uric acid production, decreasing intestinal uric acid secretion and improving renal uric acid elimination are the three primary therapeutic pathways of phenolic acids. XO inhibition depends on hydroxyl groups and their substitutions on benzene rings according to molecular research. These compounds interact through π-π interactions, hydrogen bonds and hydrophobic interactions. With fewer adverse effects these natural substances provide safer substitutes for prescription drugs [221, 223].

**8.4. Glycoside**

Through a variety of mechanisms, natural glycosides show great therapeutic promise in the treatment of gout and hyperuricemia. By downregulating renal glucose transporter 9 (mGLUT9) and urate transporter 1 (mURAT1) and upregulating organic anion and cation transporters, Mulberroside A, a stilbene glycoside derived from Morus alba has strong uricosuric and nephroprotective effects and increases excretion of uric acid. Similarly Gnaphalium affine's luteolin-4'-O-glucoside lowers serum uric acid levels by inhibiting xanthine oxidase activity and mURAT1 expression. It also lessens MSU crystal-induced inflammation by lowering TNF-α and IL-1β levels. By downregulating the mURAT1 and mGLUT9 proteins, pallidifloside D a saponin glycoside derived from Smilax riparia exhibits dose-dependent uricosuric effects [224, 225].

**8.5. Triterpenoids**

In hyperuricemic mice triterpenoid acids from Inonotus obliquus effectively lower uric acid levels and hepatic XO activity due to their potent xanthine oxidase (XO) inhibitory activity which is mixed and reversible. By encouraging PI3K-AKT-mTOR-dependent autophagy and lowering reactive oxygen species and IL-1β production. The compound 3β,23-dihydroxy-12-ene-28-ursolic acid from Cyclocarya paliurus mitigates NLRP3 inflammasome-mediated gout. Hederagenin and oleanolic acid are the primary triterpenoid components of quinoa bran saponins which lower uric acid levels and renal inflammation by controlling uric acid transport genes and blocking PI3K/AKT/NFκB signaling pathways. Targeting both uric acid production and inflammatory processes these natural triterpenoids present promising substitutes for traditional therapies while possibly avoiding the negative side effects of synthetic medications [226, 227].

**8.6. Saponins**

By blocking xanthine oxidase (XOD) activity lowering uric acid production and increasing urinary uric acid excretion, total saponins from Dioscorea species efficiently lower serum uric acid levels. By downregulating urate transporter 1 (URAT1) which reabsorbs uric acid and upregulating organic anion transporters (OAT1 and OAT3) which encourage uric acid excretion these substances also control renal uric

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acid transport. Furthermore saponins have anti-inflammatory qualities by preventing neutrophils stimulated by monosodium urate crystals from releasing inflammatory mediators. By inhibiting the PI3K/AKT/NFκB inflammatory signaling pathway quinoa bran saponins further exhibit renoprotective effects by lowering renal inflammation and damage linked to hyperuricemia. These results imply that saponins provide all-encompassing therapeutic advantages via a combination of renoprotective, anti-inflammatory and uricosuric mechanisms [226, 228].

### 8.7. Tannins

By lowering the production of uric acid and increasing uricosuric action tannins have two effects. Lowering xanthine oxidase activity, preventing uric acid synthesis, controlling uric acid transporters to facilitate excretion and lowering inflammatory responses are some of the mechanisms. The NOD-like receptor 3 inflammasome, Toll-like receptor 4/myeloid differentiation factor 88/nuclear factor-κB signaling and control of urate transporter proteins URAT1, GLUT9, OAT1 and OAT3 are important pathways. Plantains support the multi-target therapeutic approach of natural compounds by targeting multiple pathways, such as MAPK1, RELA, TNF and inflammatory signaling cascades according to network pharmacology analysis [222, 229].

### 8.8. Stilbenoids

Stilbenoids, especially resveratrol, have the potential to be used as treatment for hyperuricemia and gout by inhibiting xanthine oxidase (XO). Although its exact inhibitory mechanisms need more research resveratrol functions as an XO inhibitor targeting the primary enzyme that converts xanthine and hypoxanthine into uric acid. According to structural activity studies hydroxyl (-OH) groups and the substitutions they make on stilbene's benzene rings are essential for XO inhibition. By interacting with XO substrates through π-π interactions, hydrogen bonds and hydrophobic interactions these bioactive compounds inhibit the formation of uric acid as shown by molecular docking studies [230].

**Table 3.** Plants reported for the treatment of gout and hyperuricaemia with their bioactive compounds and pharmacological mechanisms.

| Plant / Source | Major Active Compounds | Main Mechanism / Target | Study Model | Key Findings | Reference |
|---|---|---|---|---|---|
| **Plantago asiatica L.** | Acteoside, isoacteoside, 1H-indolo-3-carbaldehyde | XOD inhibition | In vitro & in vivo | Strong ETSBAS activity; acteoside potent inhibitor | [231] |
| **Tabebuia roseoalba** | Caffeic acid, chlorogenic acid | Hepatic XOD inhibition | Hyperuricaemic mice | Reduced serum urate | [232] |
| **Aster glehni** | Flavonoids, dicaffeoylquinic acids | XOD inhibition + antioxidant | Rat model | Decreased urate level | [233] |
| **Dendropanax morbifera** | Rutin, chlorogenic acid | Antioxidant + XOD inhibition | In vitro | Ethanolic extract most active | [234] |
| **Gnaphalium pensylvanicum** | Caffeoylquinic acids | XOD inhibition + URAT1/GLUT9/OAT1 modulation | Hyperuricaemic mice | Increased urate excretion | [235] |
| **Siegesbeckia orientalis** | Caffeic acid analogues, flavonones | XOD inhibition + anti-inflammatory | Rat model | ~31% urate reduction | [236] |
| **Aristolochia bracteolata** | Phenolics, flavonoids | Uricosuric + antioxidant | Hyperuricaemic rats | Urate reduction similar to allopurinol | [237] |
| **Cudrania tricuspidata** | Chlorogenic acid, rutin, kaempferol | XOD inhibition | In vitro | Flavonoid-rich extract active | [238] |
| **Camellia japonica** | Triterpenes, flavonoids | Hepatic XOD inhibition | Hyperuricaemic mice | Significant urate decrease | [239] |
| **Quercus acuta** | Vitamin E, phenolics | XOD inhibition | Hyperuricaemic mice | Comparable to allopurinol | [240] |

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| | | | | | |
|---|---|---|---|---|---|
| **Salvia plebeia** | Nepetin, scutellarein, luteolin | Strong XOD inhibition | Animal model | IC50 values 1.74–2.35 μM | [241] |
| **Gnaphalium affine** | Phenolics | URAT1 & GLUT9 regulation + XOD inhibition | Hyperuricaemic mice | Enhanced urate excretion | [242] |
| **Selaginella moellendorffii** | Apigenin glycosides | XOD inhibition + anti-inflammatory | Hyperuricaemic mice | Reduced cytokines and urate | [243] |
| **Cordyceps militaris** | Bioactive compounds | URAT1 down-regulation | Hyperuricaemic mice | Lower serum urate | [244] |
| **Mesona procumbens** | Phenolics | XOD suppression | Cell & animal model | Improved transporter expression | [245] |
| **Corylopsis coreana** | Bergenin, quercetin, quercitrin | XOD inhibition | In vitro & in vivo | Reduced hepatic XOD activity | [246] |
| **Tradescantia albiflora** | Bracteanolide A | XOD inhibition | Hyperuricaemic rats | Strong enzymatic inhibition | [247] |
| **Citrus aurantium** | Hesperetin, polymethoxyflavones | XOD inhibition | In vitro | Potent inhibitory flavanones | [248] |
| **Dimocarpus longan** | Proanthocyanidin A2 | XOD inhibition | Hyperuricaemic mice | Flower extract most active | [249] |
| **Rosehip (Rosa canina)** | Vitamin C, flavonoids | XOD inhibition | Hyperuricaemic mice | Functional food potential | [250] |
| **Total saponins of Dioscorea** | Saponins | OATP1A1 upregulation | Rat model | Similar to allopurinol | [251] |
| **Paeonia lactiflora** | Albiflorin, paeoniflorin | XOD inhibition | Enzyme assay | Monoterpene glycosides active | [252] |
| **Dipterocarpus alatus (Vaticaffinol)** | Resveratrol tetramer | XOD/XDH inhibition + transporter regulation | Hyperuricaemic mice | Improved kidney function | [253] |
| **Chatuphalatika (CTPT)** | Gallic acid, ellagic acid | Antioxidant-mediated XOD inhibition | Hyperuricaemic mice | ~40% urate reduction | [254] |
| **RuPeng15 powder** | Multi-herbal phenolics | XOD inhibition | Animal model | Reduced urate synthesis | [255] |
| **Black tea extract** | Polyphenols | XOD + adenosine deaminase inhibition | Hyperuricaemic mice | Dose-dependent reduction | [256] |
| **Green tea extract** | Polyphenols | Adenosine deaminase modulation | Hyperuricaemic mice | Mild urate decrease | [256] |

### 9. Dietary changes

A complex metabolic and inflammatory route underlies the development of gout linked to dietary variables. It starts with abnormalities in purine metabolism and ends with inflammation triggered by monosodium urate (MSU) crystals. Both endogenous and exogenous purines are obtained by diet, and they are then broken down by adenosine monophosphate (AMP), inosine, hypoxanthine and xanthine before being converted to uric acid by xanthine oxidase activity. Consuming too much alcohol, fructose-containing carbohydrates or purine-rich meals speeds up the breakdown of ATP and the synthesis of AMP which increases the synthesis of uric acid and causes hyperuricemia [257]. Diet also affects urate excretion by changing intestinal and renal transport mechanisms. Consuming large amounts of sugar and fat can affect transporters including GLUT9, URAT1 and ABCG2 which lowers uric acid clearance and raises blood urate levels even more. Chronic hyperuricemia causes urate to become supersaturated and MSU crystals to form especially in acidic environments brought on by metabolic diseases or an acidic diet. By activating macrophages NLRP3 inflammasome these crystals cause caspase-1 activation and the production of interleukin-1β which attract neutrophils and intensify inflammatory reactions. By triggering Toll-like receptor signalling and NF-κB pathways, diet-induced metabolic syndrome, gut microbiota dysbiosis and low-grade systemic

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inflammation all contribute to this process and maintain chronic gouty inflammation. As a result nutritional imbalance accelerates the development of gout by a number of interrelated processes including elevated uric acid synthesis, poor excretion, MSU crystal formation and immunological activation mediated by inflammasomes [258].

Studies on metabolic pathways linked to diet have uncovered novel mechanisms and potential treatment approaches in the development of gout as depicted in figure 7. However instead of combining more comprehensive nutritional considerations with systemic metabolic effects the majority of dietary recommendations for gout concentrate primarily on particular food groups. Overall results may be enhanced by a more thorough strategy that incorporates pharmaceutical treatment and targeted dietary management, especially for patients with advanced illness.

**Table 4.** Dietary and Lifestyle Strategies for Gout Management

| Category | Examples | Key Mechanism/Action | Clinical Benefits in Gout | Special Notes / Limitations | Reference No. |
|---|---|---|---|---|---|
| Purine-rich food restriction | Red meat, organ meat (liver, kidney), shellfish, sardines, anchovies, mackerel | Decreases purine metabolism and uric acid production | Lowers serum urate and risk of gout flares | Prefer lean meats, poultry, and plant proteins such as legumes | [259] |
| Alcohol limitation | Beer, spirits; moderate wine intake | Reduces purine intake and improves renal uric acid excretion | Helps reduce serum urate levels | Beer strongly associated with gout risk | [260] |
| Low-fat dairy intake | Skim milk, yogurt | Uricosuric effect; reduces renal urate reabsorption | Decreases serum urate and flare frequency | Evidence stronger for low-fat dairy products | [257] |
| Polyphenol-rich foods | Fruits, vegetables, cherries, berries; quercetin, resveratrol, EGCG | Anti-inflammatory, antioxidant; NF-κB inhibition; xanthine oxidase suppression | May reduce inflammation, oxidative stress, and urate synthesis | Evidence mixed; optimal dosing unclear; more RCTs required | [261, 262] |
| Hydration | Increased water intake (2–3 L/day) | Dilutes urinary urate and enhances renal clearance | Reduces crystal formation and gout attacks | Important during acute flares or dehydration | [263] |
| Vitamin C–rich foods | Oranges, strawberries, bell peppers, broccoli | Uricosuric effect via reduced renal reabsorption | Modest reduction in serum urate levels | Approx. 500 mg/day intake associated with benefit | [264] |
| Fructose restriction | Sugar-sweetened beverages, fruit juices, high-fructose corn syrup | Reduces hepatic uric acid production | Lowers hyperuricemia and gout risk | Prefer whole fruits over juices | [265] |

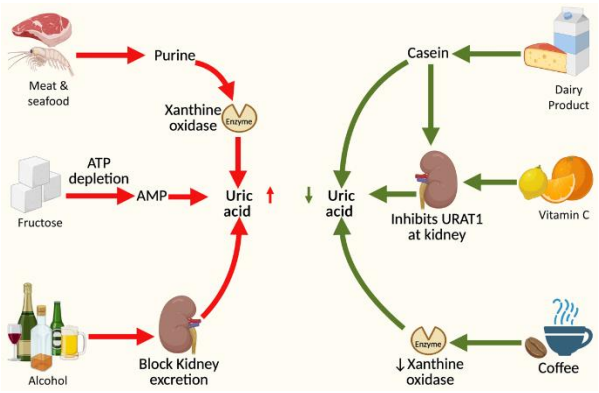


**Figure 7.** Schematic representation of the influence of different dietary factors on serum uric acid levels and the development of gout, highlighting the pro-hyperuricemic factors meat, seafood, fructose, and alcohol, and the protective factors dairy products and vitamin C. This schematic representation illustrates the influence of dietary practices on uric acid metabolism and the inflammatory process in gout.

## 10. Future direction of the treatment

Future directions in the treatment of gout and hyperuricemia include the development of targeted biologics, safer xanthine oxidase inhibitors and precision medicine approaches based on genetic and metabolic profiling.

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### 10.1. Inflammasome and biologics

The inflammasome and downstream pyroptosis pathway has emerged as a prominent target beyond IL-1β with ongoing and proposed therapeutic agents targeting NLRP3, IL-18 and gasdermin D. These strategies focus on mitigating cytokine release and pyroptotic cell death contributing to gout flares and inflammation.

NLRP3 inhibitors have demonstrated clinical efficacy in gout flares with the oral NLRP3 inhibitor dapansutrile decreasing synovial IL-1β levels by ~72% and pain by approximately 50% in a phase II gout flare trial. IL-18 modulation is an active area of development with recombinant IL-18 binding proteins in Phase II trials for related inflammasome disorders, reflecting the translational interest in IL-18 as a target. Gasdermin D inhibition has preclinical validation (e.g., disulfiram, a gasdermin pore inhibitor) and is proposed as a means to suppress pyroptosis, although infection risk and target specificity are concerns [266]. Anti-IL-1 biologics continue to accumulate controlled clinical trial data for flare management. New anti-IL-1β monoclonal antibody, firsekibart demonstrated non-inferiority and superiority to etoricoxib for target joint pain at 72 hours in a Phase II flare trial and biologic development for flares appears justified [267].

### 10.2. Uricosurics and dual inhibitors

Approaches to extend urate-lowering drug classes focus on more potent URAT1 inhibitors and rational dual mechanism drugs, which integrate uricosuric and production-blocking properties. Genetic and transporter biology inform these approaches.

Transporter biology identifies URAT1 and GLUT9 as key drivers of renal urate excretion and thus natural co-targets for dual mechanism drugs. Novel URAT1 drugs have reached the stage of randomized controlled trials for refractory gout with evident urate lowering in Phase IIb trials, suggesting clinical utility for next-generation uricosurics [268]. Dual mechanism approaches (URAT1 + xanthine oxidase inhibition or URAT1 + GLUT9 modulation) are suggested to offer better sUA control and overcome the limitations of single mechanism therapies. However clinical experience with dual mechanism agents in gout as provided in the supplied body of evidence is not presented and thus lacks sufficient evidence for mature clinical outcomes [269].

### 10.3. Innovative modalities

In addition to small molecules and monoclonals, new mechanisms like enzyme therapies, nucleic acid strategies, and AI-assisted discovery are being explored as new approaches for sustained urate lowering and inflammasome modulation. However, the pace of progress is not uniform across these mechanisms in the current literature.

Late-stage clinical testing of enzyme and immunomodulatory biologics has been achieved in treatment-refractory gout, with SEL-212 in Phase III as part of the DISSOLVE I trial and demonstrating safety through 12 months in this specific program context [270]. AI-assisted discovery is rapidly advancing the identification of inflammasome and gasdermin-axes targeting small molecules and nanocarrier formulations [266]. Gene therapy and mRNA-based therapeutics for gout or sustained urate lowering are mechanistically intriguing based on the monogenic transporter but the literature provided does not offer meaningful clinical or advanced preclinical data and thus there is no evidence of meaningful progress in this literature [271].

### Conclusion

In summary, the assessment of clinical response is crucial step in improvement of therapeutic approaches in gout especially with advent of new pharmacologic and plant-based therapies. Validated tools such as serum urate level monitoring, inflammatory biomarkers and advanced imaging modalities such as ultrasound, dual-energy CT scans and MRI offer objective measures of treatment response, disease activity and joint structural changes. The use of these tools in clinical practice will enable a better monitoring of the response to therapy.

Although conventional therapies such as NSAIDs, corticosteroids, colchicine and established urate-lowering therapies are mainstay in the management of gout, long-term use of these therapies is often limited by adverse reactions and risks associated with comorbid conditions. The risks associated with cardiovascular adverse reactions, nephrotoxicity, hypersensitivity, hepatotoxicity and drug interactions highlight the need for a continuous safety assessment in the evaluation of treatment response. This highlights the need for safer and more targeted therapies.

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The new agents like selective urate transport inhibitors, biologic agents for IL-1 pathway, recombinant uricases and phytochemical therapies have shown great potential by targeting both hyperuricemia and inflammation. Natural compounds like flavonoids, phenolic acids, alkaloids and triterpenoids have shown additional benefits due to their antioxidant, uricosuric and anti-inflammatory properties which suggest their use as an adjunct or alternative therapy. However clinical validation on a large scale and standardized approach to measure clinical response are needed to establish their safety and efficacy.

The future of gout management should be focused on the development of precision medicine strategies that integrate genetic testing, biomarker-driven monitoring and advanced imaging data analysis to provide personalized therapy based on specific disease phenotypes. Artificial intelligence and machine learning algorithms may also enhance the early diagnosis of gout and provide predictive models of treatment response to optimize the risk-benefit ratio of both conventional and novel therapies. In addition the future of gout studies should focus on the development of combination therapies that target uric acid metabolism and inflammation as well as the development of phytochemicals with better bioavailability and safety. Through the development of comprehensive response measurement systems and better treatment innovations, the future of gout treatment could be more personalized and effective.

On a general note the integration of effective response measurement systems with the consideration of adverse reactions to drugs is an important step in the optimization of gout treatment. Future studies should aim at improving biomarker-assisted monitoring, optimizing the risk-benefit profile of current drugs, and developing novel multi-target therapies that can improve efficacy with reduced toxicity.

## DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CONSENT FOR PUBLICATION

Not applicable

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financially or otherwise

## ACKNOWLEDGEMENT

The authors would like to express gratitude to management of Noida Institute of Engineering and Technology (Pharmacy Institute), India for their persistent assistance, facilitation, passion and immense expertise and knowledge.

## FUNDING

The author(s) reported that there is no funding associated with the work featured in this article.

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