ISSN: 2306-6091

International Journal of Pharmaceuticals and Health Care Research (IJPHR)

IJPHR |Vol.14 | Issue 2 | Apr - Jun -2026

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v14.iss2.2026.246-257

TARGETING URAT 1 AND GLUT 9 FOR HYPERURICEMIA MANAGEMENT: IMPORTANCE OF PRECLINICAL EVALUATION

Ayshathu Shamseena[1], Anchana K. K[1], Fathima Rasha[1], Laya M.C[1], G. Babu[2], Anson S. Maroky*[1]

[1]Department of Pharmacology, Devaki Amma Memorial College of Pharmacy, Malappuram, Affiliated to Kerala University of Health and Sciences, Kerala.
[2]Department of Pharmaceutical Chemistry, Devaki Amma Memorial College of Pharmacy, Malappuram, Affiliated to Kerala University of Health Sciences, Kerala.

*Corresponding author: Anson S. Maroky
Email id: ansonmarokey@gmail.com

Published on: 06.05.2026
Published by: Futuristic Publications

Abstract: Hyperuricemia is marked by elevated serum uric acid levels. It is the primary risk factor for gout and several related complications. Urate homeostasis involves balancing uric acid production and renal excretion. Urate transporters, such as urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9), play crucial roles. Evidence suggests that dysfunction or genetic variation in these transporters contributes to abnormal urate accumulation and disease progression. This review summarises knowledge of uric acid metabolism, renal urate handling, and the physiological roles of URAT1 and GLUT9 in urate balance. It discusses the involvement of these transporters in hyperuricemia and gout, as well as therapeutic strategies targeting urate transporters, including uricosuric drugs and emerging transporter-specific inhibitors. The importance of preclinical evaluation using animal models and cell-based transporter assays for the discovery and development of novel antihyperuricemic agents is highlighted. Understanding the molecular mechanisms and pharmacological modulation of urate transporters may help develop more effective therapies for hyperuricemia and gout.

Keywords: Hyperuricemia, GOUT, URAT 1, GLUT 9, Xanthine oxidase

INTRODUCTION

Overview of uric acid metabolism

Uric acid is the final product of purine metabolism in humans and plays a key role in maintaining metabolic balance. Purines originate from endogenous nucleotide turnover and dietary sources, and their degradation produces uric acid through enzymatic reactions. Unlike most mammals, humans lack uricase, which converts uric acid into the more soluble allantoin, resulting in relatively high circulating urate levels. Dysregulation of this process leads to hyperuricemia, which occurs when uric acid production exceeds its elimination [1].

Uric acid metabolism involves hepatic production and renal excretion. Approximately two-thirds of uric acid is eliminated through the kidneys, while the remainder is excreted via the intestine. After glomerular filtration, urate undergoes reabsorption and secretion in the renal proximal tubules through transporter-mediated mechanisms. Nearly 90% of filtered urate is reabsorbed, highlighting the importance of transporter regulation in urate homeostasis [2]. Disruption of these processes results in elevated serum urate levels and may lead to monosodium urate (MSU) crystal formation in tissues and joints, causing gout. Molecular and genetic studies have identified urate transporters, particularly URAT1 and GLUT9, as central regulators of serum uric acid and promising therapeutic targets [3].

Global prevalence and clinical significance of hyperuricemia and gout

Hyperuricemia is a common metabolic disorder defined by serum uric acid levels above 6.8 mg/dL. It is the primary risk factor for gout, an inflammatory arthritis caused by MSU crystal deposition. Gout affects

approximately 1- 4% of adults globally, with increasing prevalence due to ageing, dietary habits, obesity, and metabolic syndrome [4].

Hyperuricemia is also associated with chronic kidney disease, hypertension, cardiovascular disease, and metabolic syndrome. Elevated uric acid contributes to oxidative stress, endothelial dysfunction, and inflammation, increasing cardiovascular and renal risk [5]. Current therapies aim to reduce uric acid production or enhance excretion, with growing emphasis on targeting renal urate transporters [6].

Importance of urate transporters in disease management

Renal urate transporters are key determinants of serum uric acid levels and important therapeutic targets. URAT1 (SLC22A12) and GLUT9 (SLC2A9) play central roles in urate reabsorption [7]. URAT1, located on the apical membrane of proximal tubular cells, functions as a urate-anion exchanger, while GLUT9 on the basolateral membrane facilitates urate transport into the bloodstream [2, 3].

Genetic studies, including GWAS, have identified SLC22A12 and SLC2A9 as major regulators of serum urate levels. Variations in these genes can alter transporter function and contribute to hyperuricemia [8]. Consequently, URAT1 and GLUT9 are key targets for urate-lowering therapies [9].

URIC ACID METABOLISM AND URATE HOMEOSTASIS

Purine metabolism and uric acid production

Uric acid is produced from purine degradation, with purines derived from endogenous and dietary sources. Adenine and guanine nucleotides are metabolised into intermediates such as inosine, hypoxanthine, and xanthine, which are converted into uric acid [10].

Humans lack uricase, increasing susceptibility to hyperuricemia. Uric acid is mainly produced in the liver, with contributions from the intestine and vascular endothelium. Increased purine metabolism due to high dietary intake, rapid cell turnover, or metabolic disorders elevates uric acid production and contributes to hyperuricemia [12, 13].

Role of the enzyme xanthine oxidase

Xanthine oxidase (XO), also known as xanthine oxidoreductase (XOR), is a key enzyme in purine metabolism. It catalyses the sequential oxidation of hypoxanthine to xanthine, then to uric acid. XOR exists in two forms: xanthine dehydrogenase (XDH), which uses NAD^+ as an electron acceptor under normal conditions, and xanthine oxidase (XO), which uses molecular oxygen as an electron acceptor under pathological conditions like oxidative stress or inflammation. XO activity produces reactive oxygen species (ROS), including superoxide and hydrogen peroxide. ROS contribute to oxidative stress and tissue injury, connecting uric acid metabolism with metabolic and cardiovascular disorders. Elevated XOR activity is linked to obesity, insulin resistance, liver dysfunction, and hyperuricemia. This highlights its role in urate synthesis and the progression of metabolic diseases [14].

Due to its central role in uric acid production, xanthine oxidase is an important pharmacological target in the treatment of hyperuricemia and gout. Drugs such as allopurinol and febuxostat inhibit xanthine oxidase activity, thereby reducing uric acid synthesis and preventing urate crystal formation [15].

Balance between urate production and excretion

Urate homeostasis depends on the balance between production and elimination. Approximately 750 mg of uric acid is produced and excreted daily [16]. The kidneys account for about 70% of excretion, while the intestine handles the remaining 30% [11].

Hyperuricemia develops when production exceeds excretion, most commonly due to impaired renal clearance. Factors such as kidney disease, genetic mutations, medications, and metabolic disorders disrupt this balance [16]. Maintaining this equilibrium is essential for preventing gout and related complications [17].

RENAL HANDLING OF URATE

The kidney regulates urate homeostasis through filtration, reabsorption, secretion, and post-secretory reabsorption. Although urate is freely filtered at the glomerulus, only about 10% is excreted due to extensive tubular reabsorption [18].

Filtration of urate in the glomerulus

Uric acid present in the bloodstream is freely filtered across the glomerular capillary membrane into the renal tubular lumen because it is a small, water-soluble molecule that does not significantly bind to plasma proteins. As a result, the concentration of urate in the glomerular filtrate is similar to that in plasma [19].

Following filtration, urate enters the proximal tubule, where its transport is tightly controlled by several membrane transport proteins. Although the entire filtered urate load initially enters the nephron, only a small proportion is ultimately excreted in the urine because most of the filtered urate undergoes reabsorption during

passage through the renal tubules. Physiologically, the fractional excretion of urate is typically 8-12% in healthy individuals, indicating that nearly 90% of filtered urate is reabsorbed. This reabsorption is essential for maintaining appropriate serum uric acid concentrations but can also contribute to hyperuricemia if transporter activity becomes dysregulated [18].

Reabsorption and secretion in renal proximal tubules

The proximal tubule is the primary site of urate transport in the kidney, where urate undergoes both reabsorption from the tubular lumen into epithelial cells and secretion from the blood into the tubular fluid, with these bidirectional processes ultimately determining the amount of urate excreted in urine. Reabsorption occurs mainly in the early proximal tubule via transporters on the apical and basolateral membranes, where urate is first taken up from the tubular lumen into epithelial cells and then returned to the bloodstream, allowing efficient conservation of urate. In contrast, urate secretion involves transporters that move urate from the peritubular capillaries into the tubular lumen for elimination. The balance between these reabsorptive and secretory mechanisms governs the net renal clearance of uric acid; disturbances in this balance, such as enhanced reabsorption or reduced secretion, can lead to hyperuricemia, whereas increased secretion may result in excessive urate excretion (hyperuricosuria) [18].

Transporter systems involved in urate regulation

Multiple membrane transport proteins participate in renal urate transport. These transporters belong primarily to the solute carrier (SLC) family and ATP-binding cassette (ABC) transporter family, which regulate the movement of urate across renal tubular epithelial cells [20].

Reabsorption transporters

The major urate reabsorption transporters include URAT1 (SLC22A12), located on the apical membrane of proximal tubular cells and functioning as the primary urate–anion exchanger that reabsorbs urate from the tubular lumen [18]. GLUT9 (SLC2A9) is primarily located on the basolateral membrane and facilitates urate transport from epithelial cells back into the bloodstream [21]. In addition, OAT4 (SLC22A11) and OAT10 (SLC22A13) are additional transporters involved in urate reabsorption in the proximal tubule [20].

Secretion transporters

Several transporters mediate urate secretion into the tubular lumen, including OAT1 (SLC22A6) and OAT3 (SLC22A8), which are basolateral transporters responsible for moving urate from the blood into tubular epithelial cells. ABCG2 (BCRP) functions as an ATP-dependent efflux transporter that secretes urate into the tubular lumen. In addition, NPT1 (SLC17A1) and NPT4 (SLC17A3) are sodium-dependent phosphate transporters that also contribute to urate secretion [18].

Among these transporters, URAT1 and GLUT9 are considered the most important regulators of urate reabsorption, and dysfunction or genetic mutations affecting these proteins can significantly alter serum uric acid levels. Loss-of-function mutations in either URAT1 or GLUT9 have been associated with renal hypouricemia, whereas increased transporter activity can contribute to hyperuricemia and gout [22].

Understanding the coordinated activity of these transporter systems is essential for developing targeted therapies to regulate urate excretion. Many modern uricosuric drugs specifically inhibit URAT1 or modulate transporter activity to increase urinary urate excretion and reduce serum uric acid levels [19].

URATE TRANSPORTERS IN THE KIDNEY

URAT1 and GLUT9 are the key transporters regulating renal urate reabsorption and serum urate levels [22].

URAT 1

Structure and localization

URAT1 is encoded by the SLC22A12 gene and belongs to the organic anion transporter (OAT) family. Structurally, URAT1 is a membrane protein composed of 12 transmembrane domains, which enable it to function as a transporter across renal epithelial cell membranes [22].

This transporter is predominantly expressed on the apical membrane of proximal tubular epithelial cells in the kidney, where it mediates the uptake of urate from the tubular lumen into epithelial cells. The molecular identification of URAT1 clarified the mechanism underlying renal urate reabsorption and provided important insights into urate homeostasis in humans [23].

URAT1 plays a key role in determining serum urate levels, as most of the filtered urate is reabsorbed via transporter-mediated processes. Mutations in the SLC22A12 gene can impair urate reabsorption and lead to renal hypouricemia, characterised by reduced serum uric acid levels and increased urinary urate excretion [24].

Mechanism of urate reabsorption

URAT1 functions as a urate - anion exchanger, transporting urate from the tubular lumen into proximal tubular epithelial cells in exchange for organic anions such as lactate, nicotinate, and pyrazinoate. This exchange mechanism allows efficient reabsorption of urate across the apical membrane [25].

After urate enters epithelial cells via URAT1, it is transported across the basolateral membrane into the bloodstream through other transporters such as GLUT9. Studies have demonstrated that URAT1 and GLUT9 act cooperatively to mediate the vectorial transport of urate from the renal tubular lumen to the blood [26].

Pharmacological inhibition of URAT1 significantly increases urinary urate excretion and lowers serum urate levels. Consequently, URAT1 is the primary molecular target of several uricosuric drugs used to treat hyperuricemia and gout [27].

Physiological role in urate balance

URAT1 is considered the major transporter responsible for renal urate reabsorption, accounting for a substantial portion of renal urate handling. By regulating the reuptake of urate into the bloodstream, URAT1 maintains serum uric acid concentrations within physiological limits [22].

Alterations in URAT1 activity can significantly affect urate homeostasis. Increased URAT1 activity enhances urate reabsorption and contributes to hyperuricemia, whereas reduced transporter activity results in excessive urinary urate excretion. Genetic studies have confirmed that mutations in URAT1 are associated with hereditary renal hypouricemia and altered urate metabolism [28].

Because of its central role in urate homeostasis, URAT1 has become a major therapeutic target for the management of hyperuricemia.

GLUT 9

Isoforms and tissue distribution

GLUT9, encoded by the SLC2A9 gene, is a member of the facilitative glucose transporter family but functions primarily as a urate transporter rather than a glucose transporter. Two main isoforms of GLUT9 have been identified: GLUT9a (long isoform) and GLUT9b (short isoform) [29].

These isoforms differ mainly in their N-terminal sequences and cellular localisation. GLUT9a is primarily located on the basolateral membrane of proximal tubular epithelial cells, whereas GLUT9b is found on the apical membrane of renal tubular cells. GLUT9 is also expressed in several other tissues, including the liver, intestine, and placenta, suggesting that it plays an important role in systemic urate metabolism beyond the kidney [30].

Role in urate transport and regulation

GLUT9 functions as a high-capacity urate transporter that facilitates urate transport across cell membranes. Studies have demonstrated that SLC2A9-mediated urate transport occurs at rates significantly higher than glucose transport, highlighting its specialised role in urate handling [31].

In renal physiology, GLUT9 primarily mediates the transport of urate from proximal tubular epithelial cells into the bloodstream following apical uptake through URAT1. This coordinated action between URAT1 and GLUT9 ensures efficient urate reabsorption and maintenance of serum urate homeostasis [26].

Genetic studies have shown that mutations in the SLC2A9 gene significantly influence serum uric acid levels. Loss-of-function mutations reduce urate reabsorption and cause renal hypouricemia, whereas increased transporter activity has been associated with hyperuricemia and gout [32]. Therefore, GLUT9 is considered a crucial regulator of urate transport and a potential therapeutic target for the development of novel urate-lowering agents.

ROLE OF URAT1 AND GLUT9 IN HYPERURICEMIA AND GOUT

Urate transporters play a fundamental role in maintaining serum uric acid homeostasis. Among the various renal transport proteins involved in urate handling, urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) are considered the most important mediators of urate reabsorption in the kidney. Dysfunction or altered regulation of these transporters can significantly affect urate levels, leading to hyperuricemia and gout. Genome-wide association studies (GWAS) and molecular analyses have consistently demonstrated that genetic variations in the genes encoding these transporters - SLC22A12 for URAT1 and SLC2A9 for GLUT9 - strongly influence serum urate concentrations and susceptibility to gout [33].

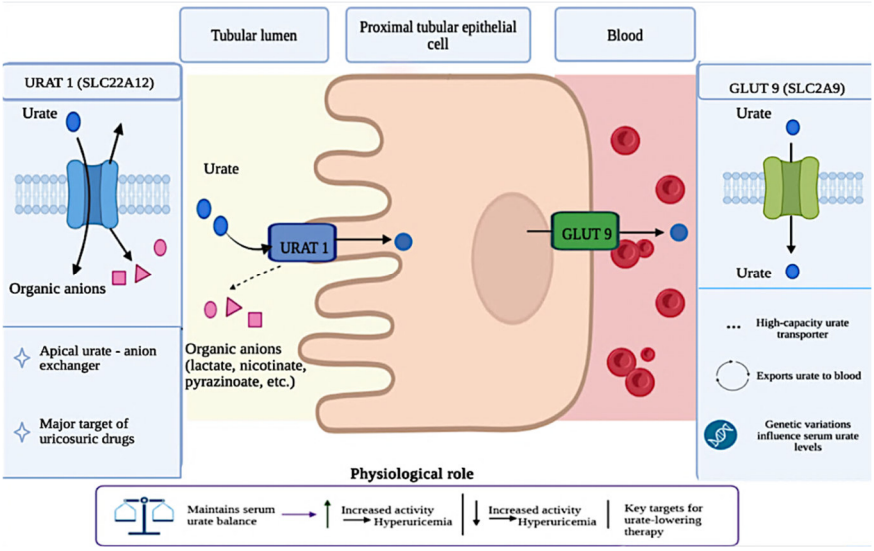

Fig 1: Mechanism of renal urate reabsorption in the proximal tubule. (Created with BioRender.com)

Transporter dysfunction and urate accumulation

URAT1 and GLUT9 regulate the reabsorption of urate from the renal tubular lumen back into the bloodstream. URAT1, located on the apical membrane of proximal tubular cells, facilitates urate uptake from the tubular lumen into epithelial cells, while GLUT9 on the basolateral membrane transports urate from epithelial cells into the circulation. Together, these transporters mediate the majority of renal urate reabsorption [33].

When the function or expression of these transporters becomes dysregulated, excessive urate reabsorption may occur, leading to elevated serum urate levels. Increased reabsorption reduces urinary urate excretion, contributing to urate accumulation in the blood. Chronic hyperuricemia can result in supersaturation of urate and formation of monosodium urate crystals, which deposit in joints and tissues and initiate inflammatory responses characteristic of gout [34].

Experimental and clinical studies have also shown that metabolic factors such as insulin resistance can increase URAT1 activity, further enhancing urate reabsorption and aggravating hyperuricemia. Increased phosphorylation and surface expression of URAT1 have been observed under hyperinsulinemic conditions, suggesting that metabolic signalling pathways regulate transporter activity and influence urate levels [35].

Genetic variations affecting transporter activity

Genetic polymorphisms in SLC22A12 and SLC2A9 significantly influence urate transporter activity and serum uric acid concentrations. Numerous genetic studies have identified variants in these genes that alter transporter function and modify susceptibility to hyperuricemia and gout [33].

For example, several single-nucleotide polymorphisms (SNPs) in the SLC2A9 gene, which encodes GLUT9, have been strongly associated with serum urate levels. Variants such as rs16890979 and rs3733591 have been linked to altered urate transport activity and differences in gout risk across populations [36].

Similarly, mutations in SLC22A12, which encode URAT1, can significantly affect urate transport. Functional studies have demonstrated that some variants reduce URAT1-mediated urate uptake, while others may enhance urate reabsorption. Rare variants causing loss of transporter function can lead to renal hypouricemia, a condition characterised by low serum urate levels and increased urate excretion [28].

Population-based genetic analyses have further revealed that combinations of polymorphisms in urate transporter genes contribute to the variability in serum urate levels among individuals. In some cases, certain variants may even provide protective effects against gout by reducing urate reabsorption [33].

Contribution to disease pathogenesis

The dysfunction of URAT1 and GLUT9 plays a critical role in the pathogenesis of hyperuricemia and gout. Increased transporter activity enhances urate reabsorption and reduces renal excretion, resulting in persistent elevation of serum uric acid levels. Over time, excessive urate accumulation leads to crystal formation in synovial fluid and tissues, triggering inflammatory responses mediated by immune cells and inflammatory cytokines [34].

Genetic predisposition also contributes significantly to disease development. Variations in urate transporter genes can interact with environmental and lifestyle factors such as diet, alcohol consumption, and metabolic disorders to influence disease susceptibility. Studies have shown that individuals carrying specific risk

alleles in SLC2A9 or SLC22A12 may be at higher risk of developing hyperuricemia and gout, especially when combined with metabolic risk factors such as obesity or insulin resistance [35].

Furthermore, research has suggested that rare variants in URAT1 account for a substantial portion of the genetic contribution to serum urate regulation. Functional analyses indicate that several nonsynonymous variants significantly alter URAT1 transport activity and explain part of the "missing heritability" of urate levels observed in population studies [37].

Overall, the combined effects of transporter dysfunction, genetic variability, and environmental influences determine the risk of developing hyperuricemia and gout. Understanding these mechanisms is essential for identifying high-risk individuals and developing targeted therapies to modulate urate transporter activity.

THERAPEUTIC TARGETING OF URATE TRANSPORTERS

Targeting renal urate transporters has emerged as an important therapeutic strategy for the treatment of hyperuricemia and gout. Since the majority of uric acid is reabsorbed in the renal proximal tubules through transporter-mediated mechanisms, pharmacological inhibition of these transporters can significantly enhance urate excretion and reduce serum uric acid levels. Among the various transport proteins involved in urate handling, urate transporter 1 (URAT1) is considered the primary pharmacological target for uricosuric drugs. Recent advances in medicinal chemistry and molecular pharmacology have also led to the development of novel transporter-targeted therapies to improve efficacy and safety in the management of hyperuricemia [38].

Uricosuric drugs targeting URAT1

Uricosuric drugs lower serum urate concentrations by inhibiting renal urate reabsorption, thereby increasing urinary uric acid excretion. The main molecular target of most uricosuric agents is URAT1, which mediates the uptake of urate from the tubular lumen into renal epithelial cells. Inhibition of URAT1 prevents urate reabsorption and promotes urate elimination through urine [39].

Historically, several uricosuric agents such as benzbromarone, sulfinpyrazone, and probenecid have been used to enhance urate excretion. These drugs interact with URAT1 and related organic anion transporters, thereby reducing serum urate levels. However, earlier uricosuric agents often lacked selectivity and were associated with drug - drug interactions and adverse effects [38].

The identification of URAT1 as a key transporter in urate homeostasis has enabled the development of more selective inhibitors. Structural and pharmacological studies have demonstrated that URAT1 inhibitors bind to specific transmembrane regions of the transporter and block urate exchange activity, thereby reducing urate reabsorption [40].

Probenecid

Probenecid is one of the earliest uricosuric drugs used for the treatment of gout. It lowers serum urate levels primarily by inhibiting URAT1 and other organic anion transporters involved in urate reabsorption. Clinically, probenecid is typically initiated at 500 mg once or twice daily and can be titrated to 2 g per day to achieve target urate levels. Although probenecid is effective in increasing urate excretion, it is considered a second-line therapy because of limitations such as potential drug - drug interactions and the risk of uric acid kidney stones (urolithiasis). These effects occur because probenecid can influence the renal excretion of several drugs, including penicillin, methotrexate, and diuretics [38].

Lesinurad

Lesinurad is a more selective URAT1 inhibitor developed specifically for the treatment of hyperuricemia associated with gout. It acts by inhibiting URAT1 and OAT4 in the renal proximal tubule, thereby increasing the fractional excretion of uric acid and reducing serum urate levels. Clinical studies have demonstrated that a single 200 mg dose of lesinurad can significantly increase uric acid excretion and reduce serum urate levels by approximately 33% within several hours [41].

Lesinurad was approved in 2015 as an adjunct therapy to xanthine oxidase inhibitors such as allopurinol or febuxostat for patients who do not achieve adequate urate control with monotherapy. However, due to limited clinical use and market considerations, the drug was later discontinued by its manufacturer, although not because of safety concerns [38].

Emerging transporter-targeted therapies

Recent research has focused on developing next-generation urate transporter inhibitors with improved potency, selectivity, and safety. Verinurad is a highly potent and selective URAT1 inhibitor that significantly lowers serum urate levels and increases urinary urate excretion, with reductions of up to 60% reported in clinical studies [42]. Dotinurad is another selective urate reabsorption inhibitor (SURI) that effectively targets URAT1 and has shown strong urate-lowering effects in both experimental and clinical studies [43].

In addition, novel small-molecule compounds targeting both URAT1 and GLUT9 are being developed. These dual inhibitors may enhance therapeutic efficacy by blocking multiple pathways of urate reabsorption and have shown promising results in preclinical models [44].

Overall, transporter-targeted therapies represent a promising strategy for improving the treatment of hyperuricemia and gout, with ongoing research aimed at developing safer and more effective uricosuric agents.

PRECLINICAL EVALUATION OF ANTIHYPERURICEMIC AGENTS

Preclinical evaluation is a crucial step in developing new therapies for hyperuricemia and gout. Before clinical trials, compounds are tested to assess efficacy, mechanism of action, and safety. Studies focus on targeting key pathways such as xanthine oxidase (XO) and urate transporters, including URAT1 and GLUT9. These evaluations combine in vitro assays, cell-based models, and animal studies to analyse drug-target interactions, pharmacodynamics, and toxicity [45].

Importance of preclinical testing in drug development

Preclinical testing validates drug candidates by evaluating their ability to reduce serum uric acid through inhibition of production or enhancement of excretion. Cell-based assays expressing urate transporters are commonly used to assess inhibition of URAT1 and GLUT9, allowing measurement of potency and selectivity. These systems have identified several effective URAT1 inhibitors with favourable pharmacokinetic properties [46].

Animal studies are essential for assessing safety, including potential hepatotoxicity, nephrotoxicity, and metabolic effects. Pharmacokinetic studies further evaluate drug absorption, distribution, metabolism, and excretion, guiding dosage selection and clinical trial design.

Screening of natural products

Natural products are important sources of antihyperuricemic agents, often acting by inhibiting XO or modulating urate transporters. Compounds such as flavonoids, alkaloids, terpenoids, coumarins, and stilbenes have demonstrated URAT1 inhibitory activity. Flavonoids, in particular, show strong potential due to structural features that enhance transporter interaction [47].

Some natural compounds act through multiple mechanisms. For example, piperine from *Piper nigrum* reduces serum uric acid, improves renal function, and inhibits URAT1 and GLUT9 expression in experimental models [48]. Advances in screening technologies have accelerated the identification of such bioactive compounds.

Screening of synthetic compounds

Synthetic compounds are widely studied to develop potent urate-lowering agents. Techniques such as structure-activity relationship (SAR) analysis help optimise drug properties. Recent studies have identified synthetic inhibitors targeting URAT1 and GLUT9, including thienopyrimidine derivatives with strong activity in experimental models [44].

Dual-target inhibitors that block both XO and URAT1 show enhanced efficacy by reducing urate production and reabsorption simultaneously [45]. Computational methods such as molecular docking and virtual screening have further improved the identification of high-affinity inhibitors [49].

Significance of preclinical screening

Preclinical evaluation is essential for identifying safe and effective antihyperuricemic agents. By integrating biochemical assays, cellular models, and animal studies, researchers can determine drug efficacy, safety, and mechanisms. Both natural and synthetic compounds provide valuable leads targeting URAT1, GLUT9, and related pathways. Continued advances in drug discovery are expected to support the development of improved therapies for hyperuricemia and gout.

EXPERIMENTAL MODELS FOR HYPERURICEMIA

Experimental models are essential for studying the pathophysiology of hyperuricemia and gout and for evaluating potential therapies. Since humans lack uricase, leading to higher urate levels, various pharmacological, genetic, and dietary animal models have been developed to mimic human conditions. These models are widely used in preclinical studies to investigate urate metabolism, assess transporter function, and screen antihyperuricemic agents [50].

Table 1: experimental animal model for hyperuricemia

Experimental model	Method	Purpose	Reference
Potassium Oxonate–Induced	Administration of potassium oxonate (uricase	Inhibits conversion of uric acid to allantoin, resulting in elevated serum uric	50

Hyperuricemia Model	inhibitor) in rodents, usually intraperitoneally or orally	acid levels and mimicking human hyperuricemia. Commonly used to evaluate antihyperuricemic drugs due to its rapid and reproducible effect.	
Diet-Induced Hyperuricemia Model	Feeding animals a high-purine diet containing compounds such as yeast extract or hypoxanthine	Increases uric acid production and helps study metabolic regulation of urate and drug responses.	51
Genetic Hyperuricemia Model	Uricase-deficient mice	Closely mimics human urate metabolism because humans naturally lack uricase. Animals often develop severe hyperuricemia, renal dysfunction, and metabolic disturbances.	51
Combined Hyperuricemia Model	Co-administration of potassium oxonate with hypoxanthine or adenine	Simultaneously increases urate production and blocks uric acid metabolism, producing sustained hyperuricemia and renal pathological changes.	52
Monosodium Urate MSU) Crystal-induced Gout Model	Intra-articular injection of MSU crystals into animal joints	Simultaneously increases urate production and blocks uric acid metabolism, producing sustained hyperuricemia and renal pathological changes.	53
Combined Hyperuricemia and Gout Model	Potassium oxonate-induced hyperuricemia combined with MSU crystal injection	Reproduces both metabolic hyperuricemia and inflammatory responses such as joint swelling, immune cell infiltration, and cytokine release.	54
Cell-Based Transporter Assays	Cultured cells expressing urate transporters (URAT1, GLUT9, OAT1, ABCG2)	Used to study urate transport mechanisms and screen potential inhibitors affecting transporter activity.	55
HEK293 Transporter Expression System	Human embryonic kidney (HEK293) cells transfected with urate transporter genes	Allows quantitative measurement of urate transport kinetics and drug–transporter interactions.	56
URAT1 Screening Assays	Cell lines expressing URAT1 transporter	Used to identify compounds that inhibit URAT1 and enhance urate excretion by blocking renal reabsorption.	57

Together, animal models and cell-based assays provide complementary approaches to investigate the mechanisms underlying hyperuricemia and gout and to evaluate novel therapeutic strategies targeting urate metabolism.

SIGNIFICANCE OF PRECLINICAL STUDIES IN DRUG DEVELOPMENT

Preclinical studies are a vital stage in drug development, providing key insights into the pharmacological activity, safety, and translational potential of therapeutic agents. In hyperuricemia and gout research, these studies focus on compounds targeting urate transporters such as URAT1 and GLUT9. Using in vitro assays, animal models, and pharmacokinetic analyses, preclinical testing helps identify promising drug candidates before clinical trials. Advances in urate transporter biology have further highlighted their importance in developing effective urate-lowering therapies [58].

Evaluation of efficacy and safety

A major goal of preclinical research is to assess the efficacy and safety of candidate antihyperuricemic agents. Cell-based assays are used to evaluate inhibition of URAT1 and GLUT9, providing data on potency and selectivity [58]. Animal models further assess pharmacodynamic effects, including reduction in serum uric acid and increased urate excretion. For example, novel URAT1 inhibitors have shown strong urate-lowering effects in hyperuricemic models with favourable safety profiles [46].

Safety evaluation is equally important, as earlier uricosuric drugs were associated with toxicity. Animal studies help identify adverse effects, determine safe dosage ranges, and evaluate metabolic pathways, reducing risks in clinical trials [59].

Translational relevance to clinical trials

Preclinical studies bridge laboratory research and clinical application by clarifying drug mechanisms and predicting therapeutic outcomes. In hyperuricemia, these studies examine how URAT1 and GLUT9 inhibitors influence urate transport and systemic homeostasis, guiding clinical trial design and dosing strategies. Pharmacokinetic and pharmacodynamic analyses provide essential data on drug absorption, distribution, metabolism, and excretion (ADME), supporting clinical development [27].

Preclinical models also aid in identifying biomarkers such as serum urate levels and inflammatory markers, which can be used in clinical trials to monitor treatment response.

Identification of novel urate-lowering therapies

Preclinical research has enabled the discovery of new urate-lowering agents through advanced screening and drug design approaches. Novel small-molecule inhibitors targeting URAT1 and GLUT9 have shown strong activity in experimental models. Dual-target inhibitors that block both urate production and reabsorption may offer improved efficacy [45].

Compounds such as CDER167 have demonstrated potent inhibition of URAT1 and GLUT9 and significant urate reduction in animal studies [60]. Additionally, structural studies of urate transporters have provided insights into drug-binding mechanisms, supporting the rational design of safer and more effective therapies [27].

FUTURE PERSPECTIVES

Advances in molecular pharmacology, genomics, and structural biology have improved understanding of urate transport in hyperuricemia and gout, particularly the roles of URAT1 and GLUT9. This has enabled the development of more selective and effective urate-lowering therapies. Recent studies report novel small-molecule inhibitors with enhanced activity, including modified versions of lesinurad showing improved efficacy [44]. Structural insights from cryo-electron microscopy have further supported the design of targeted inhibitors [61]. Additionally, multi-target compounds and advanced drug delivery systems are being explored [62].

Genetic studies, including GWAS, have identified key genes such as SLC22A12 and SLC2A9 that regulate urate levels, with variants influencing disease risk [32]. Structural and computational analyses of GLUT9 have also revealed targets for drug development [63].

Overall, integrating structural biology, pharmacogenomics, and precision medicine may lead to more effective and personalised treatments for hyperuricemia and its complications.

CONCLUSION

Hyperuricemia is a common metabolic disorder that is most commonly associated with gout. An abundance of other systemic complications have also been linked to hyperuricemia. The renal urate transporters URAT1 and GLUT9 have recently been implicated in urate homeostasis. Impairment or mutation of these urate transporters leads to altered serum uric acid levels and ultimately the development of the associated disorders. Elucidation of the molecular mechanisms mediating urate transport has therefore become an area of interest in the discovery of new hyperuricemia therapies.

Urate transporter inhibitors and transporters are also of great interest for development as urate-lowering drugs. Experimental models as well as urate transporter assays are useful tools for preclinical drug efficacy, safety, and mechanism studies. Further developments in the field of molecular characterization, pharmacogenomics, and drug discovery will allow the design of more selective and stronger transporter-targeted treatments for hyperuricemia and gout, with additional benefits for prevention and treatment.

REFERENCES

1. Xu L, Shi Y, Zhuang S, Liu N. Recent advances on uric acid transporters. Oncotarget [Internet]. 2017. Report No. Available from: www.impactjournals.com/oncotarget/
2. Gustafsson D, Unwin R. The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. BMC Nephrology. 2013. doi: 10.1186/1471-2369-14-164 PubMed PMID: 23895142.
3. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. International Journal of Cardiology. 2016 Jun 15; 213:8–14. doi:10.1016/j.ijcard.2015.08.109 PubMed PMID: 26316329.
4. Dalbeth N, Merriman TR, Stamp LK. Gout. The Lancet. Lancet Publishing Group; 2016. p. 2039–52. doi:10.1016/S0140-6736(16)00346-9 PubMed PMID: 27112094.
5. Feig DI, Kang DH, Johnson RJ. Uric Acid and Cardiovascular Risk. New England Journal of Medicine. 2008 Oct 23; 359(17):1811–21. doi: 10.1056/nejmra0800885 PubMed PMID: 18946066.

6. Lan Q, Zhao Z, Liao H, Zheng F, Chen Y, Wu T, et al. Mutation in Transmembrane Domain 8 of Human Urate Transporter 1 Disrupts Uric Acid Recognition and Transport. ACS Omega. 2022 Sep 27; 7(38):34621–31. doi:10.1021/acsomega.2c04543
7. Mishra, S., Harwansh, R.K. & Mazumder, R. URAT1 and GLUT9 as drug targets in gout: progress in transporter-directed therapies and delivery technologies. *Inflammopharmacol* **33**, 6535–6553 (2025). https://doi.org/10.1007/s10787-025-01997-3
8. Merriman TR. An update on the genetic architecture of hyperuricemia and gout. Arthritis Research and Therapy. 2015 Apr 10; 17(1). doi:10.1186/s13075-015-0609-2 PubMed PMID: 25889045.
9. Dan Kaufmann, Nathorn Chaiyakunapruk, Naomi Schlesinger,Optimizing gout treatment: A comprehensive review of current and emerging uricosurics,Joint Bone Spine,Volume 92, Issue 2,2025,105826,ISSN 1297-319X, https://doi.org/10.1016/j.jbspin.2024.105826
10. King RD, Kelley EE. Urate Biology and Biochemistry: A Year in Review 2022. Gout, Urate, and Crystal Deposition Disease. Multidisciplinary Digital Publishing Institute (MDPI); 2023. p. 115–21. doi:10.3390/gucdd1030011
11. Liu N, Xu H, Sun Q, Yu X, Chen W, Wei H, et al. The role of oxidative stress in hyperuricemia and xanthine oxidoreductase (XOR) inhibitors. Oxidative Medicine and Cellular Longevity. Hindawi Limited; 2021. doi:10.1155/2021/1470380 PubMed PMID: 33854690.
12. Yanai H, Adachi H, Hakoshima M, Katsuyama H. Molecular biological and clinical understanding of the pathophysiology and treatments of hyperuricemia and its association with metabolic syndrome, cardiovascular diseases and chronic kidney disease. International Journal of Molecular Sciences. MDPI; 2021. doi:10.3390/ijms22179221 PubMed PMID: 34502127.
13. 13.Liang N, Yuan X, Zhang L, Shen X, Zhong S, Li L, et al. Fatty acid oxidation-induced HIF-1α activation facilitates hepatic urate synthesis through upregulating NT5C2 and XDH. Life Metabolism. 2024 Oct 1; 3(5). doi:10.1093/lifemeta/loae018
14. Furuhashi M. New insights into purine metabolism in metabolic diseases: Role of xanthine oxidoreductase activity. American Journal of Physiology - Endocrinology and Metabolism. American Physiological Society; 2020. p. E827–34. doi:10.1152/ajpendo.00378.2020 PubMed PMID: 32893671.
15. Harrison D, Richardson E. Uric acid metabolism, purine degradation pathways, and their pathophysiological role in the development and progression of gout. International Journal of Advanced Biochemistry Research. 2025 May 1; 9(5):66–9. doi:10.33545/26174693.2025.v9.i5a.7529
16. Zhang T, Liu W, Gao S. Exercise and hyperuricemia: an opinion article. Annals of Medicine. Taylor and Francis Ltd.; 2024. doi:10.1080/07853890.2024.2396075 PubMed PMID: 39183708.
17. Yang S, Liu H, Fang XM, Yan F, Zhang Y. Signaling pathways in uric acid homeostasis and gout: From pathogenesis to therapeutic interventions. International Immunopharmacology. Elsevier B.V.; 2024. doi:10.1016/j.intimp.2024.111932 PubMed PMID: 38560961.
18. Chung S, Kim GH. Urate transporters in the kidney: What clinicians need to know. Electrolyte and Blood Pressure. Korean Society of Electrolyte and Blood Pressure Research; 2021. p. 1–9. doi:10.5049/EBP.2021.19.1.1
19. Łapczuk-Romańska J, Droździk M, Oswald S, Droździk M. Kidney Drug Transporters in Pharmacotherapy. International Journal of Molecular Sciences. MDPI; 2023. doi: 10.3390/ijms24032856 PubMed PMID: 36769175.
20. Yang B, Xin M, Liang S, Xu X, Cai T, Dong L, et al. New insight into the management of renal excretion and hyperuricemia: Potential therapeutic strategies with natural bioactive compounds. Frontiers in Pharmacology. Frontiers Media S.A.; 2022. doi:10.3389/fphar.2022.1026246
21. Du L, Zong Y, Li H, Wang Q, Xie L, Yang B, et al. Hyperuricemia and its related diseases: mechanisms and advances in therapy. Signal Transduction and Targeted Therapy. Springer Nature; 2024. doi: 10.1038/s41392-024-01916-y PubMed PMID: 39191722.
22. Otani N, Ouchi M, Misawa K, Hisatome I, Anzai N. Hypouricemia and Urate Transporters. Biomedicines. MDPI; 2022. doi:10.3390/biomedicines10030652
23. Enomoto, A., Kimura, H., Chairoungdua, A. *et al.* Molecular identification of a renal urate–anion exchanger that regulates blood urate levels. *Nature* 417, 447–452 (2002). https://doi.org/10.1038/nature742
24. Bibert S et al. SLC2A9 is a high-capacity urate transporter in humans. *PLoS Genetics*. https://pubmed.ncbi.nlm.nih.gov/18842065/
25. Kanai Y. [Molecular mechanisms of urate transport in renal tubules: localization and function of urate transporters]. Nihon Rinsho. 2008 Apr; 66(4):659-66. Japanese. PMID: 18409511.

26. Takeo Nakanishi, Kouhei Ohya, Sho Shimada, Naohiko Anzai, Ikumi Tamai, Functional cooperation of URAT1 (*SLC22A12*) and URATv1 (*SLC2A9*) in renal reabsorption of urate, *Nephrology Dialysis Transplantation*, Volume 28, Issue 3, March 2013, Pages 603–611, https://doi.org/10.1093/ndt/gfs574
27. Fan J, Xie W, Ke H, Zhang J, Wang J, Wang H, et al. Structural Basis for Inhibition of Urate Reabsorption in URAT1. JACS Au. 2025 Mar 24; 5(3):1308–19. doi:10.1021/jacsau.4c01188
28. Perdomo-Ramírez A, Ramos-Trujillo E, Claverie-Martín F. New SLC22A12 (URAT1) Variant Associated with Renal Hypouricemia Identified by Whole-Exome Sequencing Analysis and Bioinformatics Predictions. Genes. 2023 Sep 1; 14(9). doi: 10.3390/genes14091823 PubMed PMID: 37761963.
29. Takada T, Miyata H, Toyoda Y, Nakayama A, Ichida K, Matsuo H. Regulation of Urate Homeostasis by Membrane Transporters. Gout, Urate, and Crystal Deposition Disease. Multidisciplinary Digital Publishing Institute (MDPI); 2024. p. 206–19. doi:10.3390/gucdd2020016
30. Szablewski L. Distribution of glucose transporters in renal diseases. Journal of Biomedical Science. BioMed Central Ltd.; 2017. doi:10.1186/s12929-017-0371-7 PubMed PMID: 28854935.
31. Caulfield MJ, Munroe PB, O'Neill D, Witkowska K, Charchar FJ, Doblado M, et al. SLC2A9 is a high-capacity urate transporter in humans. PLoS Medicine. 2008 Oct; 5(10):1509–23. doi:10.1371/journal.pmed.0050197 PubMed PMID: 18842065.
32. Matsuo H, Chiba T, Nagamori S, Nakayama A, Domoto H, Phetdee K, et al. Mutations in Glucose Transporter 9 Gene SLC2A9 Cause Renal Hypouricemia. American Journal of Human Genetics. 2008 Dec 12; 83(6):744–51. doi:10.1016/j.ajhg.2008.11.001 PubMed PMID: 19026395.
33. Pavelcova K, Bohata J, Pavlikova M, Bubenikova E, Pavelka K, Stiburkova B. Evaluation of the influence of genetic variants of slc2a9 (Glut9) and slc22a12 (urat1) on the development of hyperuricemia and gout. Journal of Clinical Medicine. 2020 Aug 1; 9(8):1–21. doi:10.3390/jcm9082510
34. MedlinePlus Genetics. SLC2A9 gene [Internet]. Bethesda (MD): National Library of Medicine (US); [cited 2026 Mar 10]. Available from: https://medlineplus.gov/genetics/gene/slc2a9
35. Fujii W, Yamazaki O, Hirohama D, Kaseda K, Kuribayashi-Okuma E, Tsuji M, et al. Gene-environment interaction modifies the association between hyperinsulinemia and serum urate levels through SLC22A12. Journal of Clinical Investigation. 2025 May 15; 135(10). doi:10.1172/JCI186633 PubMed PMID: 40100301.
36. Lukkunaprasit T, Rattanasiri S, Turongkaravee S, Suvannang N, Ingsathit A, Attia J, et al. The association between genetic polymorphisms in ABCG2 and SLC2A9 and urate: an updated systematic review and meta-analysis. BMC Medical Genetics. 2020 Dec 1; 21(1). doi: 10.1186/s12881-020-01147-2 PubMed PMID: 33087043.
37. Misawa K, Hasegawa T, Mishima E, Jutabha P, Ouchi M, Kojima K, et al. Contribution of rare variants of the SLC22A12 gene to the missing heritability of serum urate levels. Genetics. 2020 Apr 1; 214(4):1079–90. doi:10.1534/GENETICS.119.303006 PubMed PMID: 32005656.
38. Jenkins C, Hwang JH, Kopp JB, Winkler CA, Cho SK. Review of Urate-Lowering Therapeutics: From the Past to the Future. Frontiers in Pharmacology. Frontiers Media S.A.; 2022. doi:10.3389/fphar.2022.925219
39. Dai Y, Lee CH. Transport mechanism and structural pharmacology of human urate transporter URAT1. Cell Research. 2024 Nov 1; 34(11):776–87. doi: 10.1038/s41422-024-01023-1 PubMed PMID: 39245778.
40. Tan PK, Ostertag TM, Miner JN. Mechanism of high affinity inhibition of the human urate transporter URAT1. Scientific Reports. 2016 Oct 7; 6. doi: 10.1038/srep34995 PubMed PMID: 27713539.
41. Miner J, Tan PK, Hyndman D, Liu S, Iverson C, Nanavati P, et al. Lesinurad, a novel, oral compound for gout, acts to decrease serum uric acid through inhibition of urate transporters in the kidney. Arthritis Research and Therapy. 2016 Oct 3; 18(1). doi:10.1186/s13075-016-1107-x PubMed PMID: 27716403.
42. Tan PK, Liu S, Gunic E, Miner JN. Discovery and characterization of verinurad, a potent and specific inhibitor of URAT1 for the treatment of hyperuricemia and gout. Scientific Reports. 2017 Dec 1; 7(1). doi:10.1038/s41598-017-00706-7 PubMed PMID: 28386072.
43. Taniguchi T, Ashizawa N, Matsumoto K, Saito R, Motoki K, Sakai M, et al. Pharmacological evaluation of dotinurad, a selective urate reabsorption inhibitor. Journal of Pharmacology and Experimental Therapeutics. 2019; 371(1):162–70. doi:10.1124/jpet.119.259341 PubMed PMID: 31371478.
44. J. Shi X, Zhao T, Wang S, Xu S, Liao H, Gao S, et al. Discovery of a novel thienopyrimidine compound as a urate transporter 1 and glucose transporter 9 dual inhibitor with improved efficacy and favorable druggability. J Med Chem. 2024 Mar 14; 67(6):5032-5052. doi:10.1021/acs.jmedchem.4c00136.
45. Yang X, Li Y, Pan S, Ma F, Chen H, Deng J, Yue J, Gong Q, Zheng M, Zeng Y, Li J, Zhang Y, Wang X, Zhang X. Discovery of a potent and orally bioavailable xanthine oxidase/urate transporter 1 dual inhibitor as a

potential treatment for hyperuricemia and gout. J Med Chem. 2024 Aug 6; 67(16):14668-14691. doi:10.1021/acs.jmedchem.4c01480.

46. Zhao T, Meng Q, Sun Z, Chen Y, Ai W, Zhao Z, Kang D, Dong Y, Liang R, Wu T, Pang J, Liu X, Zhan P. Novel human urate transporter 1 inhibitors as hypouricemic drug candidates with favorable druggability. J Med Chem. 2020 Sep 8; 63(19):10829–10854. doi:10.1021/acs.jmedchem.0c00223.
47. Du, C., Yin, H., Xie, A., Yu, J., Wang, Y., Yao, F., Zhang, S., Zhang, Y., Liu, L., Wang, P., Dong, J., & Xu, X. (2025). Virtual screening and biological evaluation of natural products as urate transporter 1 (URAT1) inhibitors. *Journal of biomolecular structure & dynamics*, *43*(17), 10008–10021. https://doi.org/10.1080/07391102.2024.2331101
48. Lu L, Zhao K, Luo J, Tian J, Zheng F, Lin X, Xie Z, Jiang H, Li Y, Zhao Z, Wu T, Pang J. Piperine improves hyperuricemic nephropathy by inhibiting URAT1/GLUT9 and the AKT-mTOR pathway. J Agric Food Chem. 2024 Mar 18; 72(12):6565–6574. doi:10.1021/acs.jafc.3c07655.
49. Yang Y, Hu Y, Yao F, Yang J, Ge L, Wang P, et al. Virtual screening and activity evaluation of human uric acid transporter 1 (hURAT1) inhibitors. RSC Advances. 2023 Jan 24; 13(6):3474–86. doi:10.1039/d2ra07193b
50. Patil T, Soni A, Acharya S. A brief review on in vivo models for Gouty Arthritis. Metabolism Open. 2021 Sep; 11:100100. doi:10.1016/j.metop.2021.100100
51. Zhenzhen Xu, Wanqian Sha, Chuanli Hou, William Kwame Amakye, Maojin Yao, Jiaoyan Ren,Comparison of 3 hyperuricemia mouse models and evaluation of food-derived antihyperuricemia compound with spontaneous hyperuricemia mouse model,Biochemical and Biophysical Research Communications,Volume 630,2022,Pages 41-49,ISSN 0006-291X,https://doi.org/10.1016/j.bbrc.2022.09.043.
52. Zhang S, Li K, Zhang H, Fu T, Ma Y, Zhang S, et al. Progress in animal models for studying hyperuricemia. Frontiers in Pharmacology. Frontiers Media SA; 2025. doi:10.3389/fphar.2025.1636205
53. Xu Y, Wang Y, Gao F, Lu C, Liu S, Chen S, et al. Innovative modeling: a diet-induced quail model for progressive pathological changes in uric acid metabolism disorders. Frontiers in Nutrition. 2025; 12. doi:10.3389/fnut.2025.1612479
54. Tian J, Wang B, Xie B, Liu X, Zhou D, Hou X, et al. Pyroptosis inhibition alleviates potassium oxonate- and monosodium urate-induced gouty arthritis in mice. Modern Rheumatology. 2022 Jan 1; 32(1):221–30. doi:10.1080/14397595.2021.1899569 PubMed PMID: 33705241.
55. Nigam SK, Bush KT, Martovetsky G, Ahn SY, Liu HC, Richard E, et al. The Organic Anion Transporter (OAT) Family: A Systems Biology Perspective. Physiol Rev. 2015; 95:83–123. doi:10.1152/physrev.00025.2013.
56. Enomoto, A., Kimura, H., Chairoungdua, A. *et al.* Molecular identification of a renal urate–anion exchanger that regulates blood urate levels. *Nature* 417, 447–452 (2002). https://doi.org/10.1038/nature742
57. Vitart, V., Rudan, I., Hayward, C. *et al.* SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 40, 437–442 (2008). https://doi.org/10.1038/ng.106
58. Tátrai P, Erdő F, Dörnyei G, Krajcsi P. Modulation of urate transport by drugs. Pharmaceutics. MDPI; 2021. doi:10.3390/pharmaceutics13060899
59. Kumagai Y, Sakaki M, Furihata K, Ito T, Inoue K, Yoshida T, et al. Dotinurad: a clinical pharmacokinetic study of a novel, selective urate reabsorption inhibitor in subjects with hepatic impairment. Clinical and Experimental Nephrology. 2020 Mar 1; 24:25–35. doi: 10.1007/s10157-019-01816-4 PubMed PMID: 31760530.
60. Zhao, Za., Jiang, Y., Chen, Yy. *et al.* CDER167, a dual inhibitor of URAT1 and GLUT9, is a novel and potent uricosuric candidate for the treatment of hyperuricemia. *Acta Pharmacol Sin* 43, 121–132 (2022). https://doi.org/10.1038/s41401-021-00640-5
61. Suo Y, Fedor JG, Zhang H, Tsolova K, Shi X, Sharma K, et al. Molecular basis of the urate transporter URAT1 inhibition by gout drugs. Nature Communications. 2025 Dec 1; 16(1). doi: 10.1038/s41467-025-60480-3 PubMed PMID: 40467597.
62. Mishra, S., Harwansh, R. K., & Mazumder, R. (2025). URAT1 and GLUT9 as drug targets in gout: progress in transporter-directed therapies and delivery technologies. *Inflammopharmacology*, *33*(11), 6535–6553. https://doi.org/10.1007/s10787-025-01997-3
63. Raul Cachau, Shahin Shahsavari, Sung Kweon Cho, The in-silico evaluation of important GLUT9 residue for uric acid transport based on renal hypouricemia type 2, Chemico-Biological Interactions, Volume 373,2023,110378, ISSN 0009-2797, https://doi.org/10.1016/j.cbi.2023.110378.