Research Advances in Uric Acid Excretion and Related Transporters in Hyperuricemia: Post-print

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Abstract

Hyperuricemia is a heterogeneous disease resulting from the disruption of homeostasis between urate production and excretion in the human body, leading to elevated serum uric acid levels beyond the normal range. Urate is primarily synthesized in the liver, with the kidneys representing the principal organs for urate excretion, followed by the intestine. In the kidneys, urate first undergoes glomerular filtration, followed by a series of complex reabsorption and secretion mechanisms in the proximal tubules, thereby achieving dynamic equilibrium of urate. To identify the transport mechanisms of urate in the kidneys, intestine, and liver, numerous studies have investigated many urate-related genes, significantly expanding human knowledge of urate transporters. Research has demonstrated that three common genes—ABCG2, SLC2A9, and SLC22A12—exert the greatest influence on human serum uric acid levels (~5%). Other urate-related transporter genes, such as SLC16A9, SLC22A6, SLC22A7, SLC22A8, SLC22A9, SLC22A11, SLC22A13, and ABCC4, also play crucial roles in regulating urate levels. Therefore, genome-wide association studies (GWAS) have shown that urate transporters play a central role in regulating serum uric acid concentrations and maintaining homeostasis of the urate microenvironment. This article will review currently identified urate transporters associated with the occurrence and development of hyperuricemia, providing theoretical and data support for future clinical treatment.

Full Text

Preamble

Uric Acid Excretion and Its Related Transporters in Hyperuricemia: Research Advances

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Abstract: Hyperuricemia is a heterogeneous disease resulting from dysregulation of urate production and excretion homeostasis, leading to elevated serum uric acid levels beyond the normal range. Urate is primarily produced in the liver, with the kidney serving as the main excretory organ, followed by the intestine. In the kidney, urate undergoes glomerular filtration, followed by complex reabsorption and secretion mechanisms in the proximal tubules to maintain dynamic equilibrium. Extensive research on urate-related genes has significantly expanded our understanding of urate transporters in the kidney, intestine, and liver. Three common genes—ABCG2, SLC2A9, and SLC22A12—exert the greatest influence on human serum uric acid levels (~5%). Other urate transporter genes, including SLC16A9, SLC22A6, SLC22A7, SLC22A8, SLC22A9, SLC22A11, SLC22A13, and ABCC4, also play crucial roles in regulating urate levels. Genome-wide association studies (GWAS) demonstrate that uric acid transporters serve a central function in regulating serum uric acid concentration and maintaining uric acid microenvironment homeostasis. This review summarizes currently identified urate transporters involved in the pathogenesis and progression of hyperuricemia to provide theoretical and data support for future clinical treatments.

Keywords: Hyperuricemia; Uric acid transporter; Protein/gene expression; Review

Uric acid is an important hydrophilic antioxidant that plays a significant role in regulating human microenvironment homeostasis. As a natural product of purine metabolism in humans, approximately two-thirds originates from endogenous sources (typically DNA and RNA), while the remaining one-third derives from dietary purine-rich foods [1]. However, due to the evolutionary loss of uricase in humans, we cannot further metabolize uric acid into the more water-soluble allantoin [2], resulting in serum uric acid levels that are 5–6 times higher than those in other mammals. This makes humans susceptible to gout, kidney stones, and hypertension when uric acid synthesis is excessive and/or excretion is impaired. Clinically, hyperuricemia (HUA) is generally defined as serum uric acid (SU) levels exceeding 6.0 mg/dL (357 mol/L) in women and 7.0 mg/dL (416 mol/L) in men [3]. The prevalence of HUA has increased significantly

compared with previous decades. In the United States, an estimated 47.2 million individuals (20%) have hyperuricemia, with 27.9 million (11.9%) suffering from severe hyperuricemia. The prevalence in men (20.2%) is approximately five times higher than in women (4.2%) [4]. However, HUA management remains suboptimal in many countries, with only one-third to one-half of patients receiving urate-lowering therapy, underscoring the need for continued medical research [5]. Chronic hyperuricemia leads to urate crystal deposition, triggering inflammation and tissue damage—the pathological basis of gout [6]. Furthermore, studies indicate that HUA is closely associated with kidney disease, hypertension, and cardiovascular disease [7], all of which involve disrupted homeostasis between urate production and excretion. The causes of hyperuricemia can be summarized as either excessive uric acid production and/or reduced excretion, with impaired excretion being the dominant factor. The kidney accounts for approximately 70% of uric acid excretion, while extrarenal organs handle the remaining 30% [8]. Multiple GWAS have demonstrated that the pathogenesis of hyperuricemia is closely linked to polymorphisms in genes encoding uric acid transporters. These molecules are primarily categorized as urate reabsorption transporters, such as glucose transporter 9 (GLUT9) and urate transporter 1 (URAT1), and urate secretion transporters, including organic anion transporters 1 and 3 (OAT1, OAT3), ATP-binding cassette transporter G2 (ABCG2), sodium-dependent phosphate transporters 1 and 4 (NPT1, NPT4), and multidrug resistance protein 4 (MRP4) [9]. This review will elaborate on the relevant urate transporters in the major organs responsible for uric acid excretion.

1. Renal Urate Transporters

As the primary organ for uric acid excretion, most urate transport in the kidney occurs in the proximal tubules, where approximately 90% of filtered urate is reabsorbed into the bloodstream, with the remaining 10% excreted [10]. This process represents a dynamic balance between reabsorption and secretion, with the efficiency of urate reabsorption influenced by reabsorptive transporters and secretion efficiency significantly controlled by these same proteins [11]. Consequently, research on renal urate transporters is particularly important for understanding the pathophysiology of hyperuricemia and broadening therapeutic approaches.

1.1.1 URAT1

In 2002, Enomoto et al. first identified abundant URAT1 expression on the luminal membrane of renal cortical proximal tubular epithelial cells [12] and demonstrated that URAT1 reabsorbs approximately 50% of urate in the proximal tubules, establishing it as a primary mechanism for regulating urate levels. Encoded by the SLC22A12 gene, URAT1 belongs to the organic anion transporter (OAT/SLC22) family and interacts with the multivalent PDZ domain protein PDZK1 via its -COOH terminal PDZ motif to regulate urate transport

activity. Through URAT1-mediated exchange, anions in proximal tubular epithelial cells can exchange with urate via electrochemical concentration gradients across the luminal membrane. URAT1' s low affinity and high capacity characteristics make it crucial for regulating serum uric acid concentration [13,14]. URAT1 is also recognized as a key target in hyperuricemia pathogenesis, as urate reabsorption is substantially influenced by amino acid variations [15]. Studies have shown that mutations rs121907896 and rs121907892 in the SLC22A12 gene reduce urate reabsorption, thereby lowering serum uric acid levels and decreasing hyperuricemia risk [16]. Clinically, uricosuric agents such as probenecid, benzbromarone, and losartan promote uric acid excretion by acting on URAT1 to reduce reabsorption [17,18].

1.1.2 GLUT9

Research indicates that GLUT9 plays a significant, potentially more prominent role than URAT1 in proximal tubular urate reabsorption [19]. Also known as URATv1 and regulated by the SLC2A9 gene, GLUT9 transports urate in a voltage-dependent manner independent of sodium or chloride ions [20]. GLUT9 exists as two N-terminal variants: GLUT9S (short isoform) and GLUT9L (long isoform), differing only in the first 29 residues of the N-terminal domain. These unique N-termini determine differential localization: GLUT9S localizes to the apical membrane of renal proximal tubular cells, while GLUT9L resides on the basolateral membrane. GLUT9L primarily facilitates urate excretion, whereas GLUT9S exhibits stronger urate transport capacity, reabsorbing urate from the tubular lumen [21]. GLUT9 mutations can reduce serum urate levels, leading to type 2 renal hypouricemia [22]. Studies show that a 36 kb deletion in the SLC2A9 gene causing truncation of 231 amino acids impairs GLUT9 function, resulting in clinical manifestations of hyperuricemia, spontaneous hypertension, and elevated lipids [23].

1.1.3 OAT4/10

Both OAT4 and OAT10 are located on the apical membrane of renal proximal tubular cells and mediate urate exchange with OH- ions [24,25]. OAT4, encoded by the SLC22A11 gene, mediates urate/dicarboxylate exchange. Hyperuricemic patients with OAT4 variants exhibit impaired renal excretion efficiency, highlighting OAT4' s role in renal urate homeostasis [26], though its affinity for urate is lower than that of URAT1 [24]. OAT10, regulated by SLC22A13, is expressed at the mRNA level rather than protein level in human kidneys. Its function as a urate/monocarboxylate transporter has only been confirmed in vitro, and no studies have linked OAT10 to hyperuricemia. Like OAT4, OAT10 is a low-affinity urate transporter [27].

1.2.1 ABCG2

ABCG2, also known as BCRP, is a low-affinity, high-capacity urate transporter [28] that transports diverse substrates. Initially discovered in placental tissue

for its role in drug resistance in breast cancer patients, it is also called breast cancer resistance protein (BCRP) [29]. ABCG2 is expressed in both kidney and intestine, with relatively weak expression in the kidney [30]. GWAS have identified ABCG2 as playing a critical role in serum urate homeostasis. Regulated by genes at the gout susceptibility locus on chromosome 4q21-q22 (MIM 138900), ABCG2 is expressed in liver, kidney, and intestine, mediating both renal and extrarenal (intestinal) uric acid excretion. Functional abnormalities can lead to deficient renal urate secretion and renal underexcretion hyperuricemia [31,32]. Komori et al. demonstrated in vitro that oxidative stress in hyperuricemic environments inhibits Akt phosphorylation, downregulating ABCG2 expression and causing cellular damage while explaining the progression from HUA to gout [34]. Studies show that 88.2% of early-onset gout patients have mild to severe ABCG2 dysfunction, with severe dysfunction significantly increasing early gout attack risk [33]. Two ABCG2 variants are commonly associated with hyperuricemia: Q126X and Q141K. The Q126X variant, with substantial protein loss, lacks urate transport function, while the Q141K variant retains only 50% activity compared to wild-type [34]. The Q141K mutation is carried by 11% of individuals of European ancestry [35]. Although less common than Q141K, the Q126X variant is also associated with increased hyperuricemia and gout risk.

1.2.2 OAT1/3

Organic anion transporters (OATs), encoded by SLC22A genes, are widely distributed in human tissues including kidney, liver, and small intestine [36]. Among them, OAT1, OAT3, OAT4, and OAT10 are associated with urate transport, with OAT1 and OAT3 being the primary proteins responsible for urate secretion [37]. Both are highly expressed on the basolateral membrane of renal proximal tubular cells. OAT1, first identified in 1996 as a novel kidney transporter (NKT) [38], is regulated by the SLC22A6 gene on chromosome 11q12.3 and comprises 12 transmembrane domains. OAT1 maintains urate homeostasis; reduced expression or dysfunction significantly increases the risk of hyperuricemia and gout, potentially progressing to gouty nephropathy [39]. Conversely, high OAT1 expression increases urinary uric acid concentration and reduces serum levels, suggesting it promotes urate excretion [40]. OAT3, encoded by SLC22A8, is expressed in liver, kidney, and brain, with particularly high expression on the basolateral membrane of renal proximal tubules [41]. Its sequence shares high similarity with OAT1 [42], though OAT3 also functions in distal tubules [43]. Wu et al. found that OAT3 knockout mice exhibited serum uric acid concentrations 1.4 times higher than controls, confirming OAT3' s role in urate transport [44]. Studies indicate that OAT1 and OAT3 participate in renal urate transport through exchange of organic ions with dicarboxylates, particularly excelling in urate secretory excretion [45]. Therefore, targeting OAT1/OAT3 for drug development could increase urinary uric acid excretion and reduce serum concentrations, providing data support for novel therapeutics [46].

1.2.3 MRP4

Multidrug resistance protein 4 (MRP4), a member of the ATP-binding cassette transporter family located on chromosome 13q32 and regulated by the ABCC4 gene, is an important drug transporter that handles endogenous metabolites [47,48]. MRP4 is a lipophilic anion efflux pump with multiple allosteric substrate binding sites that performs ATP-dependent urate transport through positive cooperative mechanisms. Located on the apical membrane of renal proximal tubular cells, MRP4 transports urate from epithelial cells into the tubular lumen for excretion. Studies in Polynesian and New Zealand Māori populations show that the MRP4 single nucleotide polymorphism rs4148500 is associated with hyperuricemia and gout, reducing uric acid excretion in males [49]. This rare allele encodes the P1036L mutation, which reduces urate transport by 30% when expressed in Xenopus oocytes [50]. Interestingly, an animal study found that chickens' renal and intestinal uric acid excretion capacities correlate positively with BCRP and MRP4 expression. When renal function was impaired by sulfonamides, ileal MRP4 and BCRP levels increased significantly, while renal levels increased only modestly, suggesting that MRP4 and BCRP are not only primary regulators of renal uric acid excretion but also play a greater role in extrarenal elimination [51]. Thus, MRP4 represents a potential target for drugs maintaining urate balance, though further animal and clinical studies are needed for evaluation.

1.2.4 NPT1/4

NPTs belong to the SLC17 protein family, initially characterized as phosphate carriers mediating organic anion transport. GWAS have identified two SLC17 family members associated with serum uric acid concentration in the kidney: NPT1 (SLC17A1) and NPT4 (SLC17A3). NPT1, the first discovered member of solute carrier family 17, is encoded by the SLC17A1 gene on chromosome 6p22.2 and expressed primarily on the apical membrane of renal proximal tubules, where it mediates voltage-sensitive urate transport [52]. GWAS show that SNPs in SLC17A1/NPT1 are closely related to serum urate levels. A Japanese study of hyperuricemic and gout patients found that the NPT1 1269T mutant exhibited stronger urate transport capacity than wild-type, reducing gout risk [47]. Another study identified an NPT1 mutation (rs3799352) with anti-gout effects that decreases gout risk (OR $<$ 1) [53]. NPT4, encoded by SLC17A3 on chromosome 6p21.3, is expressed in liver, kidney, and brain. Similar to NPT1 in immunolocalization, NPT4 is highly expressed on the apical membrane of renal proximal tubular epithelial cells, where both proteins cooperate to secrete urate into the tubular lumen, thereby reducing serum urate concentration [54]. Additionally, as a voltage-driven urate efflux transporter, NPT4' s transport capacity increases with elevated extracellular potassium levels but is inhibited in a dose-dependent manner by loop diuretics, leading to hyperuricemia [55,56]. This suggests that secondary gout induced by loop diuretics in clinical practice may be related to NPT4 inhibition. Therefore, careful

consideration of drug selection is necessary when using diuretics to treat hyperuricemia or primary gout.

[Figure 1: see original paper] Renal urate transporters. Urate transporters are primarily distributed on either the apical or basolateral membrane. On the apical membrane, transporters mediating urate reabsorption include URAT1, OAT10, OAT4, and GLUT9-S; those mediating urate secretion include MPR4, ABCG2, NPT1, and NPT4, with MPR4 and ABCG2 consuming ATP during transport. On the basolateral membrane, urate secretory transporters such as GLUT9-L, OAT1, and OAT3 are predominantly distributed. Arrows indicate the direction of urate movement.

Classification, distribution, and function of renal urate transporters

Urate Transporter Classification	Gene	Primary Distribution and Function
URAT1	SLC22A12	Mediates urate reabsorption on the luminal membrane of proximal tubular epithelial cells
GLUT9	SLC2A9	Mediates urate reabsorption on the basolateral membrane of proximal tubular epithelial cells
OAT10	SLC22A13	Mediates urate reabsorption on the apical membrane of proximal tubular epithelial cells, regulating urate/OH- exchange
OAT4	SLC22A11	Mediates urate reabsorption on the apical membrane by exchanging with lactate and other anions
ABCG2/BCRP	ABCG2	Expressed on the apical membrane of proximal tubular epithelial cells and intestinal epithelial cells, participating in renal and intestinal urate excretion
OAT1	SLC22A6	Mediates urate secretion into the tubular lumen on the basolateral membrane of proximal tubular epithelial cells
OAT3	SLC22A8	Mediates urate secretion into the tubular lumen on the basolateral membrane of proximal tubular epithelial cells

Urate Transporter Classification	Gene	Primary Distribution and Function
MRP4	ABCC4	Mediates urate secretion into the tubular lumen on the apical membrane of proximal tubular cells
NPT1	SLC17A1	Mediates urate transport on the apical and luminal membranes of renal proximal tubular cells
NPT4	SLC17A3	Mediates urate transport on the apical and luminal membranes of renal proximal tubular cells

2. Intestinal Urate Transporters

Approximately 65% of daily urate excretion occurs through the kidneys in healthy individuals, with the remainder primarily eliminated via the intestine. As the main absorption site for ingested compounds, the intestine metabolizes large amounts of dietary purines into urate through xanthine oxidase, making it an important site of urate production [57]. Intestinal urate excretion has become a significant focus, with studies showing that some gout patients excrete only about 40% of urate through the kidneys, suggesting that extrarenal excretion may play a relatively larger role in patients with renal failure. Similar to the kidney, urate transporters participate in intestinal urate handling [27], and gut microbiota also contributes to this process [58]. For example, *Lactobacillus gasseri* in the human intestine can directly utilize dietary purines, reducing the total amount of purines degraded by the intestine [59], and lactobacilli also have urate-lowering effects in the gut [60].

Intestinal urate handling is more complex than renal processing. The intestine serves as a site for exogenous urate generation while harboring microbial communities capable of urate degradation, and also undergoes urate reabsorption and secretion. Research on intestinal urate transporters may provide data support for potential therapeutic targets to modulate hyperuricemia and its complications, particularly in patients with insufficient renal excretion.

2.1 GLUT9

In addition to high renal expression, GLUT9 is also expressed in the intestine, primarily on the basolateral membrane of mouse intestinal cells, where it transports urate and mediates secretion from enterocytes into the intestinal lumen. However, due to insufficient intestinal expression, its role in intestinal urate handling is less pronounced than that of ABCG2. Experiments show that mice with specific GLUT9 deletion exhibit significantly elevated blood uric acid and develop early-onset hyperuricemia metabolic syndrome [61,62]. The mechanism of

GLUT9 action in the intestine remains unclear, and current research is limited, likely due to the complex intestinal environment. Further studies are needed to elucidate its specific mechanisms in hyperuricemia [63] and provide important theoretical foundations for gut-targeted drugs [64].

2.2 ABCG2

ABCG2 is the most abundantly expressed urate transporter in the intestine, located on the apical membrane of enterocytes, where it excretes approximately 30% of uric acid, making it the primary transporter responsible for intestinal urate elimination. Consequently, low ABCG2 activity reduces intestinal urate excretion and correlates with more severe hyperuricemia [65]. PDZK1 plays an important regulatory role in ABCG2 function; PDZK1 knockdown significantly inhibits ABCG2 expression and transport activity, suggesting that PDZK1 and ABCG2 interact to enhance intestinal urate transport efficiency [66]. Patients with end-stage renal disease and severely reduced renal uric acid excretion are highly dependent on ABCG2-mediated intestinal urate secretion [67]. ABCG2-deficient mice show significantly reduced intestinal urate excretion and elevated plasma uric acid levels [68]. Yano et al. found that ABCG2 expression increased markedly in the ileum of 5/6 nephrectomized mice, and the absence of elevated serum uric acid despite reduced urate excretion suggests that the intestine may serve a compensatory extrarenal role [69]. GWAS also indicate that ABCG2-mediated intestinal urate transport can compensate for metabolic deficiencies when renal uric acid excretion is impaired in chronic kidney disease [70]. Patients with mild to moderate ABCG2 dysfunction account for 88.2% of early-onset gout cases, while severe dysfunction significantly increases early-onset gout risk [71]. These findings suggest that reduced intestinal urate excretion due to ABCG2 dysfunction may be a common mechanism in HUA pathogenesis and a potential therapeutic target.

2.3 NPT5

NPT5, encoded by the SLC17A4 gene on chromosome 6p21.3-p22, belongs to the SLC17 (NPT) family and is the only family member expressed in the small intestine, where it resides on the apical membrane of intestinal cells and transports various organic anions. NPT5 shares 48% amino acid sequence similarity with NPT1, which is responsible for renal urate excretion, suggesting NPT5 may participate in intestinal urate transport [72,73]. Zheng Dong et al. found that NPT5 is indeed closely related to serum uric acid concentration and the progression from hyperuricemia to gout [47].

[Figure 2: see original paper] Intestinal urate transporters. Urate enters enterocytes via GLUT9 on the basolateral membrane, then is secreted from enterocytes into the intestinal lumen primarily through ABCG2, with NPT5 also contributing to urate secretion. Arrows indicate the direction of urate movement.

Classification, distribution, and function of intestinal urate transporters

Urate Transporter Classification	Gene	Primary Distribution and Function
GLUT9	SLC2A9	Expressed on the basolateral membrane of intestinal cells, mediating urate secretion from enterocytes into the intestinal lumen
ABCG2	ABCG2	Expressed on the apical membrane of intestinal epithelial cells, mediating urate secretion from enterocytes into the intestinal lumen
NPT5	SLC17A4	Expressed on the apical membrane of intestinal epithelial cells, mediating urate secretion from enterocytes into the intestinal lumen

Conclusion and Future Directions

With the global hyperuricemic population continuing to grow, deeper understanding of urate transport mechanisms will inevitably lead to more comprehensive treatment options and more efficient drugs with fewer side effects for maintaining urate homeostasis. However, current research on human urate transporters has several limitations. As discussed in this review, some urate transporters are expressed in both kidney and intestine, yet whether their transport mechanisms are similar in these distinct organs remains unclear. Unlike the kidney, which primarily excretes urate, the intestine also participates in exogenous urate generation. Moreover, the intestinal space is vast with complex and diverse bacterial populations, making intestinal urate transport mechanisms seemingly more complicated than renal processes. The liver, as the primary site of endogenous urate production, is another important focus. Limited research precluded a dedicated section, but human hepatocytes express several urate transporters, including ABCG2 and GLUT9 [74], though their mechanisms in the liver remain unknown. Experiments show that liver-specific GLUT9 knockout mice (LG9KO) have higher SU levels than whole-body GLUT9 knockout mice (G9KO), suggesting GLUT9 may be essential for hepatic urate uptake in mice [75]. ABCG2 is primarily distributed on the canalicular membrane of hepatocytes and may participate in hepatic urate secretion into bile. Measurements in PO-induced hyperuricemic mice revealed only 0.68% of carbon-14-labeled uric acid in bile, compared with 42.58% in urine and 8.9% in the intestinal lumen, suggesting minimal hepatic urate excretion [76] and leaving hepatic urate transport mechanisms poorly understood. Thus, urate transporter research faces numerous challenges. Only through continued exploration and deeper investigation into the precise mechanisms of urate transport can we provide more effective

and comprehensive treatment options for hyperuricemia and gout patients.

[1] Feng S, Wu S, Xie F, et al. Natural compounds lower uric acid levels and hyperuricemia: Molecular mechanisms and prospective[J]. Trends in Food Science and Technology, 2022, 123: 87-102. [2] Petreski T, Ekart R, Hojs R, et al. Hyperuricemia, the heart, and the kidneys - to treat or not to treat? Ren Fail. 2020 Nov;42(1):978-986. [3] Tátrai P, Erdő F, Dörnyei G, et al. Modulation of urate transport by drugs[J]. Pharmaceutics, 2021, 13(6): 899. [4] Chen-Xu M, Yokose C, Rai S K, et al. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the National Health and Nutrition Examination Survey, 2007-2016 [J]. Arthritis & rheumatology, 2019, 71(6): 991-999. [5] Soltani Z, Rasheed K, Kapusta DR,et al. Potential role of uric acid in metabolic syndrome, hypertension, kidney injury, and cardiovascular diseases: is it time for reappraisal? Curr Hypertens Rep. 2013 Jun;15(3):175-81. [6] Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun. 2012 Apr 3;3:764. [7] Johnson RJ, Nakagawa T, Sanchez-Lozada LG,et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes. 2013 Oct;62(10):3307-15. [8] Burns CM, Wortmann RL. Gout therapeutics: new drugs for an old disease. Lancet. 2011 Jan 8;377(9760):165-77. [9] Becker MA, Kisicki J, Khosravan R, et al. Febuxostat (TMX-67), a novel, non-purine, selective inhibitor of xanthine oxidase, is safe and decreases serum urate in healthy volunteers. Nucleosides Nucleotides Nucleic Acids. 2004 Oct;23(8-9):1111-6. [10] Ruiz A, Gautschi I, Schild L, et al. Human mutations in SLC2A9 (Glut9) affect transport capacity for urate[J]. Frontiers in physiology, 2018, 9: 476. [11] Mandal A K, Mercado A, Foster A, et al. Uricosuric targets of tranilast[J]. Pharmacology Research & Perspectives, 2017, 5(2): e00291. [12] Enomoto, Atsushi, Hiroaki Kimura, Arthit Chairoungdua, Yasuhiro Shigeta, Promsuk Jutabha, Seok Ho Cha, Makoto Hosoyamada et al. "Molecular identification of a renal urate–anion exchanger that regulates blood urate levels." Nature 417, no. 6887 (2002): 447-452. [13] Tan PK, Liu S, Gunic E, et al. Discovery and characterization of verinurad, a potent and specific inhibitor of URAT1 for the treatment of hyperuricemia and gout. Sci Rep. 2017 Apr 6;7(1):665. [14] Misawa K, Hasegawa T, Mishima E,et al. Contribution of Rare Variants of the SLC22A12 the Missing Heritability of Serum Urate Levels. Genetics. 2020 Apr;214(4):1079-1090. [15] Sakiyama M, Matsuo H, Shimizu S, et al. The effects of URAT1/SLC22A12 nonfunctional variants, R90H and W258X, on serum uric acid levels and gout/hyperuricemia progression. Sci Rep. 2016 Jan 29;6:20148. [16] Shin HJ, Takeda M, Enomoto A, et al. Interactions of urate transporter URAT1 in human kidney with uricosuric drugs. Nephrology (Carlton). 2011 Feb;16(2):156-62. [17] Novikov A, Fu Y, Huang W, et al. SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. Am J Physiol Renal Physiol. 2019 Jan 1;316(1):F173-F185. [18] Xu L, Lu L L, Gao J D. Traditional Chinese Herbal Medicine Plays a Role in the Liver, Kidney, and Intestine to Ameliorate Hyperuricemia according to Experimental Studies[J]. Evidence-based Complementary and Alternative Medicine: Ecam, 2021, 2021: [19] Clémençon B, Lüscher

BP, Fine M, et al. Expression, purification, and structural insights for the human uric acid transporter, GLUT9, using the Xenopus laevis oocytes system. PLoS One. 2014 Oct 6;9(10):e108852. [20] Dinour D, Gray NK, Campbell S, et al Homozygous SLC2A9 mutations cause severe renal hypouricemia. J Am Soc Nephrol. 2010 Jan;21(1):64-72. [21] DeBosch BJ, Kluth O, Fujiwara H, et al. Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. Nat Commun. 2014 Aug 7;5:4642. [22] Xu X, Li C, Zhou P, et al. Uric acid transporters hiding in the intestine. Pharm Biol. 2016 Dec;54(12):3151-3155. [23] Chung S, Kim G H. Urate Transporters in the Kidney: What Clinicians Need to Know[J]. Electrolytes & Blood Pressure: E & BP, 2021, 19(1): 1. [24] Hagos Y, Stein D, Ugele B, et al. Human renal organic anion transporter 4 operates as an asymmetric urate transporter[J]. Journal of the American Society of Nephrology, 2007, 18(2): [25] Bahn A, Hagos Y, Reuter S, et al. Identification of a new urate and high affinity nicotinate transporter, hOAT10 (SLC22A13)[J]. Journal of Biological Chemistry, 2008, 283(24): [26] Sakiyama M, Matsuo H, Shimizu S, et al. A common variant of organic anion transporter 4 (OAT4/SLC22A11) gene is associated with renal underexcretion type gout[J]. Drug metabolism and pharmacokinetics, 2013: DMPK-13-NT-070.. [27] Hyndman D, Liu S, Miner J N. Urate handling in the human body[J]. Current rheumatology reports, 2016, 18(6): 1-9. [28] Matsuo H, Takada T, Ichida K, et al. Common defects of ABCG2, a high-capacity urate exporter, cause gout: a function-based genetic analysis in a Japanese population[J]. Science translational medicine, 2009, 1(5): 5ra11-5ra11. [29] Toyoda Y, Mančíková A, Krylov V, et al. Functional Characterization of Clinically-Relevant Rare Variants in ABCG2 Identified in a Gout and Hyperuricemia Cohort. Cells. 2019 Apr 18;8(4):363. [30] Fujita K, Yamada H, Iijima M, et al. Electrochemical analysis of uric acid excretion to the intestinal lumen: Effect of serum uric acid-lowering drugs and 5/6 nephrectomy on intestinal uric acid levels. PLoS One. 2019 Dec 31;14(12):e0226918. [31] Komori H, Yamada K, Tamai I. Hyperuricemia enhances intracellular urate accumulation via down-regulation of cell-surface BCRP/ABCG2 expression in vascular endothelial cells. Biochim Biophys Acta Biomembr. 2018 May;1860(5):973-980. [32] Uhlén M, Fagerberg L, Hallström B M, et al. Tissue-based map of the human proteome[J]. Science, 2015, 347(6220): 1260419. [33] Matsuo H, Tsunoda T, Ooyama K, et al. Hyperuricemia in acute gastroenteritis is caused by decreased urate excretion via ABCG2. Sci Rep. 2016 Aug 30;6:31003. [34] Woodward O M, Köttgen A, Coresh J, et al. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout[J]. Proceedings of the National Academy of Sciences, 2009, 106(25): 10338-10342. [35] Ishikawa T, Aw W, Kaneko K. Metabolic interactions of purine derivatives with human ABC transporter ABCG2: genetic testing to assess gout risk[J]. Pharmaceuticals, 2013, 6(11): [36] Liu HC, Jamshidi N, Chen Y, et al. An Organic Anion Transporter 1 (OAT1)-centered Metabolic Network. J Biol Chem. 2016 Sep 9;291(37):19474-86. [37] 王传旭, 周嘉宝, 吴志远, 吴燕升, 郭亚芳, 高建东. 基于 IL-1β 探讨矢志方对高尿酸血症小鼠肾组织 OAT1/3 表达的影响 [J/OL]. 中国中医药信息杂志:1-6. [38] Nigam S K, Bush K T, Martovetsky G, et al. The organic anion transporter (OAT) family: a systems biology perspec-

tive[J]. Physiological reviews, 2015, 95(1): 83-123. [39] Yong T, Chen S, Xie Y, et al. Hypouricemic Effects of Armillaria mellea on Hyperuricemic Mice Regulated through OAT1 and CNT2. Am J Chin Med. 2018;46(3):585-599. [40] Fan Y, Liang Z, Zhang J, et al. Oral Proteasomal Inhibitors Ixazomib, Oprozomib, and Delanzomib Upregulate the Function of Organic Anion Transporter 3 (OAT3): Implications in OAT3-Mediated Drug-Drug Interactions. Pharmaceutics. 2021 Feb 28;13(3):314. [41] Dragojević J, Mihaljević I, Popović M, et al. Zebrafish (Danio rerio) Oat1 and Oat3 transporters and their interaction with physiological compounds. Comp Biochem Physiol B Biochem Mol Biol. 2019 Oct;236:110309. [42] Wu W, Bush KT, Nigam SK. Key Role for the Organic Anion Transporters, OAT1 and OAT3, in the in vivo Handling of Uremic Toxins and Solutes. Sci Rep. 2017 Jul 10;7(1):4939. [43] Truong D M, Kaler G, Khandelwal A, et al. Multi-level analysis of organic anion transporters 1, 3, and 6 reveals major differences in structural determinants of antiviral discrimination[J]. Journal of Biological Chemistry, 2008, 283(13): 8654-8663. [44] Otani N, Ouchi M, Hayashi K, et al. Roles of organic anion transporters (OATs) in renal proximal tubules and their localization. Anat Sci Int. 2017 Mar;92(2):200-206. [45] Sun HL, Wu YW, Bian HG, et al. Function of Uric Acid Transporters and Their Inhibitors in Hyperuricaemia. Front Pharmacol. 2021 Jul 14;12:667753. [46] van Aubel RAMH, Smeets PHE, Peters JGP, er al. The MRP4/ABCC4 gene encodes a novel apical organic anion transporter in human kidney proximal tubules: putative efflux pump for urinary cAMP and cGMP. J Am Soc Nephrol. 2002 Mar;13(3):595-603. [47] Dong Z, Zhou J, Jiang S,et al. Effects of multiple genetic loci on the pathogenesis from serum urate to gout. Sci Rep. 2017 Mar 2;7:43614. [48] Slot AJ, Molinski SV, Cole SP. Mammalian multidrug-resistance proteins (MRPs). Essays Biochem. 2011 Sep 7;50(1):179-207. [49] Ding X, Li M, Peng C, et al. Uric acid transporters BCRP and MRP4 involved in chickens uric acid excretion. BMC Vet Res. 2019 May 30;15(1):180. [50] Tanner C, Boocock J, Stahl E A, et al. Population-specific resequencing associates the ATP-binding cassette subfamily C member 4 gene with gout in New Zealand Māori and Pacific men[J]. Arthritis & Rheumatology, 2017, 69(7): 1461-1469. [51] Chiba T, Matsuo H, Kawamura Y, et al. NPT1/SLC17A1 is a renal urate exporter in humans and its common gain-of-function variant decreases the risk of renal underexcretion gout. Arthritis Rheumatol. 2015 Jan;67(1):281-7. [52] Wright A F, Rudan I, Hastie N D, et al. A 'complexity' of urate transporters[J]. Kidney international, 2010, 78(5): 446-452. [53] Jutabha P, Anzai N, Wempe MF, et al. Apical voltage-driven urate efflux transporter NPT4 in renal proximal tubule. Nucleosides Nucleotides Nucleic Acids. 2011 Dec;30(12):1302-11. [54] Sun HL, Wu YW, Bian HG, et al. Function of Uric Acid Transporters and Their Inhibitors in Hyperuricaemia. Front Pharmacol. 2021 Jul 14;12:667753. [55] Jutabha P, Anzai N, Kitamura K, et al. Human sodium phosphate transporter 4 (hNPT4/SLC17A3) as a common renal secretory pathway for drugs and urate. J Biol Chem. 2010 Nov 5;285(45):35123-32. [56] Li Q, Huang Z, Liu D, et al. Effect of berberine on hyperuricemia and kidney injury: A network pharmacology analysis and experimental validation in a mouse model[J]. Drug Design, Development and Therapy, 2021, 15: 3241. [57] Ristic B, Sikder

M O F, Bhutia Y D, et al. Pharmacologic inducers of the uric acid exporter ABCG2 as potential drugs for treatment of gouty arthritis[J]. Asian journal of pharmaceutical sciences, 2020, 15(2): 173-180. [58] Yun Y, Yin H, Gao Z, et al. Intestinal tract is an important organ for lowering serum uric acid in rats[J]. PloS one, 2017, 12(12): e0190194. [59] Yamada N, Iwamoto C, Kano H, et al. Evaluation of purine utilization by Lactobacillus gasseri strains with potential to decrease the absorption of food-derived purines in the human intestine[J]. Nucleosides, Nucleotides and Nucleic Acids, 2016, 35(10-12): 670-676. [60] Wu J, Wei Z, Cheng P, et al. Rhein modulates host purine metabolism in intestine through gut microbiota and ameliorates experimental colitis[J]. Theranostics, 2020, 10(23): 10665. [61] DeBosch B J, Kluth O, Fujiwara H, et al. Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9[J]. Nature communications, 2014, 5(1): 1-7. [62] Li Q, Lin H, Niu Y, et al. Mangiferin promotes intestinal elimination of uric acid by modulating intestinal transporters[J]. European Journal of Pharmacology, 2020, 888: 173490. [63] Kuhns V L H, Woodward O M. Urate transport in health and disease[J]. Best Practice & Research Clinical Rheumatology, 2021, 35(4): 101717. [64] 李秋睿, 李玲, 林华. 肠道尿酸排泄及相关转运体的研究进展 [J]. 国际药学研究杂志,2019,46(04):261-265. [65] Sarkadi B, Özvegy-Laczka C, Német K, et al. ABCG2–a transporter for all seasons[J]. FEBS letters, 2004, 567(1): 116-120. [66] Chen M, Lu X, Lu C, et al. Soluble uric acid increases PDZK1 and ABCG2 expression in human intestinal cell lines via the TLR4-NLRP3 inflammasome and PI3K/Akt signaling pathway[J]. Arthritis research & therapy, 2018, 20(1): 1-12. [67] Matsuo H, Tsunoda T, Ooyama K, et al. Hyperuricemia in acute gastroenteritis is caused by decreased urate excretion via ABCG2[J]. Scientific reports, 2016, 6(1): 1-6. [68] Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia[J]. Nature communications, 2012, 3(1): 1-7. [69] Bhatnagar V, Richard EL, Wu W, et al. Analysis of ABCG2 and other urate transporters in uric acid homeostasis in chronic kidney disease: potential role of remote sensing and signaling. Clin Kidney J. 2016 Jun;9(3):444-53 [70] Nigam SK. The SLC22 Transporter Family: A Paradigm for the Impact of Drug Transporters on Metabolic Pathways, Signaling, and Disease. Annu Rev Pharmacol Toxicol. 2018 Jan 6;58:663-687. [71] Matsuo H, Ichida K, Takada T, et al. “Common dysfunctional variants in ABCG2 are a major cause of early-onset gout.” Scientific Reports 3 (2013): 2014-2014. [72] Shibui A, Tsunoda T, Seki N, et al. Isolation and chromosomal mapping of a novel human gene showing homology to Na+/PO4 cotransporter[J]. Journal of human genetics, 1999, 44(3): [73] Togawa, Natsuko, et al. “A Na+-phosphate cotransporter homologue (SLC17A4 protein) is an intestinal organic anion exporter.” American Journal of Physiology-Cell Physiology 302.11 (2012): C1652-C1660. [74] Hilgendorf C, Ahlin G, Seithel A, et al. Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines[J]. Drug Metabolism and Disposition, 2007, 35(8): 1333-1340. [75] Preitner F, Bonny O, Laverrière A, et al. Glut9 is a major regulator of urate homeostasis and its genetic inactivation induces hyperuricosuria and urate nephropathy[J]. Proceedings of the National Academy of Sciences, 2009, 106(36): 15501-15506. [76] Hosomi A,

Nakanishi T, Fujita T, et al. Extra-renal elimination of uric acid via intestinal efflux transporter BCRP/ABCG2[J]. PloS one, 2012, 7(2): e30456.

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