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REVIEW ARTICLE

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Management of hypertension addressing hyperuricaemia: introduction of nano-based approaches

Koyeli Girigoswami[a], Radhakrishnan Arunkumar[b] and Agnishwar Girigoswami[a]

[a]Medical Bionanotechnology, Faculty of Allied Health Sciences, Chettinad Hospital & Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai, India; [b]Department of Pharmacology, Chettinad Hospital & Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Chennai, India

ABSTRACT

Uric acid (UA) levels in blood serum have been associated with hypertension, indicating a potential causal relationship between high serum UA levels and the progression of hypertension. Therefore, the reduction of serum UA level is considered a potential strategy for lowering and mitigating blood pressure. If an individual is at risk of developing or already manifesting elevated blood pressure, this intervention could be an integral part of a comprehensive treatment plan. By addressing hyperuricaemia, practitioners may subsidize the optimization of blood pressure regulation, which illustrates the importance of addressing UA levels as a valuable strategy within the broader context of hypertension management. In this analysis, we outlined the operational principles of effective xanthine oxidase inhibitors for the treatment of hyperuricaemia and hypertension, along with an exploration of the contribution of nanotechnology to this field.

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1. Introduction

Since the kidneys perform vital functions, such as urine production and maintaining homeostasis, drug targeting to the kidneys remains a major research focus. A range of severe complications can result from kidney dysfunction [1]. The most common of these are elevated blood pressure (hypertension), inflammatory responses, susceptibility to urinary tract infections, formation of renal calculi (kidney stones) and a variety of other related issues [2,3]. Maintaining overall health requires understanding and addressing these potential complications owing to the intricate nature of renal health. Recent decades have seen a significant increase in research directed towards nephrolithiasis, a particularly serious condition [4]. In addition, this disease is associated with increased serum uric acid (UA) levels, enhanced urinary UA excretion and persistently low urine pH levels (<5.5). All of these factors contribute to the accumulation of UA calculi in the kidney pelvis, collecting ducts and ureters and cause pathological alterations in the kidneys [5–7].

UA is the ultimate by-product of the breakdown of purine. An imbalance involving excessive UA production, diminished excretion or amalgamation of both factors can lead to hyperuricaemia, which is distinguished by elevated UA levels [8,9]. Gout is caused by excessive UA production, diminished excretion or a combination of both. In addition to its association with gout, hyperuricaemia has been conclusively linked to a variety of other medical conditions, including hypertension and renal disease [10,11]. In addition to highlighting the systemic implications of elevated UA levels, this intricate interplay also indicates their relevance to broader health disorders beyond the confines of gout.

A frequently employed therapeutic approach for the supervision of hyperuricaemia in individuals suffering from gout involves the administration of allopurinol and febuxostat, which function as xanthine oxidase

CONTACT Agnishwar Girigoswami agnishwarg@gmail.com Medical Bionanotechnology, Faculty of Allied Health Sciences, Chettinad Hospital & Research Institute (CHRI), Chettinad Academy of Research and Education (CARE), Kelambakkam, Chennai, TN 603103, India.

(XO) inhibitors [12,13]. By interfering with the conversion of hypoxanthine (HPX) and xanthine (XAN) to UA, they are effective in reducing urate synthesis, which is the basis for this therapeutic choice. Febuxostat is believed to exhibit a more robust hypouricemic effect than allopurinol, and a reduced risk of hypersensitivity syndrome [14]. Moreover, febuxostat has been demonstrated to maintain its safety and efficacy profile without requiring dose adjustments in patients with mild-to-moderate renal impairment. In patients with gout requiring careful consideration of renal function during treatment, this attribute enhances the therapeutic utility of febuxostat, providing clinicians with a valuable option for managing hyperuricaemia [15]. Both allopurinol and febuxostat have demonstrated effectiveness in reducing blood pressure and decelerating the progression of chronic kidney disease, as indicated by several studies. These medications exhibit dual benefits, extending beyond their primary roles in hyperuricaemia and gout management. It is believed that the mechanism of action of these drugs is a combination of lowering serum levels of UA, enhancing endothelial function, mitigating oxidative stress, preventing the development of glomerular hypertension, thickening of afferent arterioles and histological changes indicative of ischemic renal damage [16,17].

The lower solubility and reduced half-life of a drug via the oral route result in reduced bioavailability, underscoring the significance of developing sustained-release formulations, particularly for XO inhibitors such as allopurinol [18]. The use of colloidal drug carriers for enhancing bioavailability is becoming increasingly popular, and nanoparticles are emerging as promising candidates [19–21]. In nanotechnology, therapeutic agents are encapsulated, entrapped or adsorbed onto the surfaces of micelles, metal nanoparticles, solid polymeric colloidal particles or vesicular structures [22–26]. A range of natural and synthetic materials can be used to make these nanoparticles, including chitosan, alginate and gelatin, with nanometre size [27,28]. Several factors must be considered when choosing an ideal material for nanoformulation development. The key considerations here are the desired size of the nanoparticles as well as the desired drug release profile of the nanoparticles. The selection of nanomaterials must also consider factors such as biocompatibility, toxicity, biodegradability, inherent physicochemical properties of the drug and surface characteristics of the formulation [29,30]. This review discusses the chemistry and mechanism of XO inhibitors, specifically allopurinol and febuxostat, in the treatment of gout and their potential impact on hypertension. Simultaneously, this review explores research efforts focused on nanoformulated allopurinol and febuxostat to enhance their solubility and bioavailability.

2. Working principle of XO

XO, also known as XAN oxidoreductase, plays a key role in the catabolism or breakdown of purine nucleic acids in many species including humans. Its primary function is to catalyse the conversion of purines such as guanine monophosphate and adenosine monophosphate (AMP) into HPX or XAN [31]. HPX and XAN are further broken down into UA by XO. Uricase transforms UA into allantoin, a water-soluble molecule excreted in the urine [32]. The significance of XO lies in its essential role in mammalian cells, where constant cell turnover results in continuous degradation and renewal of endogenous or ingested purines. The alternative form of XO is xanthine dehydrogenase (XD), which is interchangeable with XO and catalyses the same reactions [33]. Although they utilize different cofactors to perform the same reaction, they differ in the way oxygen is utilized as a substrate in XO, while reduced form of Nicotinamide Adenine Dinucleotide (NADH) is utilized in XD [34]. XO is a homodimer with a reported molecular weight (MW) of 283–290 kDa and consists of two catalytically independent subunits, each of which has a mass of 150–155 kDa [35]. Monomers contain three subunits, each of which has a mass of 20, 40 or 85 kDa. The separation of these subunits is possible only under robust denaturing conditions. Within each monomer, distinct components contribute to the enzyme structure and function. Specifically, the 20 kDa subunit accommodates two iron–sulphur clusters (Fe2–S2), adding a crucial element to its composition [36]. In the 40 kDa subunit, a flavin adenine dinucleotide (FAD) molecule plays a significant role in enzymatic processes. Furthermore, the 85 kDa subunit hosts the molybdenum cofactor (Mo-co), which is intricately bound to the enzyme as molybdopterin [37]. This multicomponent structure highlights the complexity and precision involved in the functioning of the enzyme, with each constituent playing a distinct and essential role in its overall activity. Although each complete monomer with a MW of 150 kDa, demonstrated catalytic activity, the smaller fragments lacked the capability to catalyse the XO reaction. This deficiency arises from the indispensability of all cofactors in catalytic processes. In other words, the absence of any cofactors in the smaller

fragments prevents them from exhibiting the enzymatic activity required for the XO reaction [38].

From a structural standpoint, the XO homodimer enzyme has a subunit comprising 1333 amino acid residues [39]. XO serves as a molybdenum (Mo)-dependent enzyme responsible for catalysing two pivotal steps that limit the breakdown rate of purine nucleotides [40]. XO is a key enzyme in biochemical processes, specifically in the conversion of HPX to XAN [41]. Following this initial step, XO continues its catalytic function by further transforming XAN into UA. Notably, the successful conversion of XAN to UA by XO relies on the presence of a Mo-co, emphasizing the essential role of this cofactor in the enzymatic activity of XO [42]. The intricate enzymatic pathway involving XO is significant in the metabolism of purine compounds, ultimately contributing to the production of UA in biological systems. This intricate biochemical process unfolds through a series of four distinct reaction steps. Initially, a proton was transferred from the hydroxyl group of the Mo-co to Glu1261, a key event that activates the hydroxyl group [43]. The activated hydroxyl group then participates in a nucleophilic attack on XAN, marking the commencement of the catalytic process. Subsequently, in the second step, a hydride is relocated from the tetrahedral transition compound to the sulphur atom of the Mo cofactor. This transfer leads to the reduction of Mo from its higher oxidation state of Mo(VI) to Mo(IV), a crucial reaction in the enzymatic cycle [38]. In the third step, UA is generated through the protonation of an intermediate by Arg880. This step represents a pivotal transformation in the pathway and contributes to the ultimate formation of UA. As illustrated in Figure 1, the completion of these steps is associated with the reduction of FAD to FADH2. Simultaneously, this process oxidized Mo back to the initial oxidation state of Mo(VI). This coordinated redox activity highlights the intricate interplay between various cofactors and substrates within the XO enzymatic mechanism. It is noteworthy that, despite the recognition of XO as a source of superoxide, it has traditionally not been considered the primary contributor to reactive oxygen species (ROS) in cellular processes [44]. XO has been extensively implicated in many diseases including gout, UA stone formation and xanthinuria. As a result of the heightened activity of XO, the UA level increases, causing conditions such as gout and hyperuricaemia. Correspondingly, UA precipitates in joints, skin and blood capillaries, forming needle-like crystals that cause pain. The formation of kidney stones is also related to UA, which can form sodium urate crystals [45]. In contrast, xanthinuria is a unique genetic disorder that is associated with low XO activity. Consequently, elevated levels of circulating XAN can occur as a result of this disorder, which is associated with several diseases, including renal failure.

3. Health hazards related to UA level

Males have a higher serum UA level than females in the general population. The hypothesis is that oestrogen and progesterone, which are produced by females, may lower UA levels, contributing to this sex

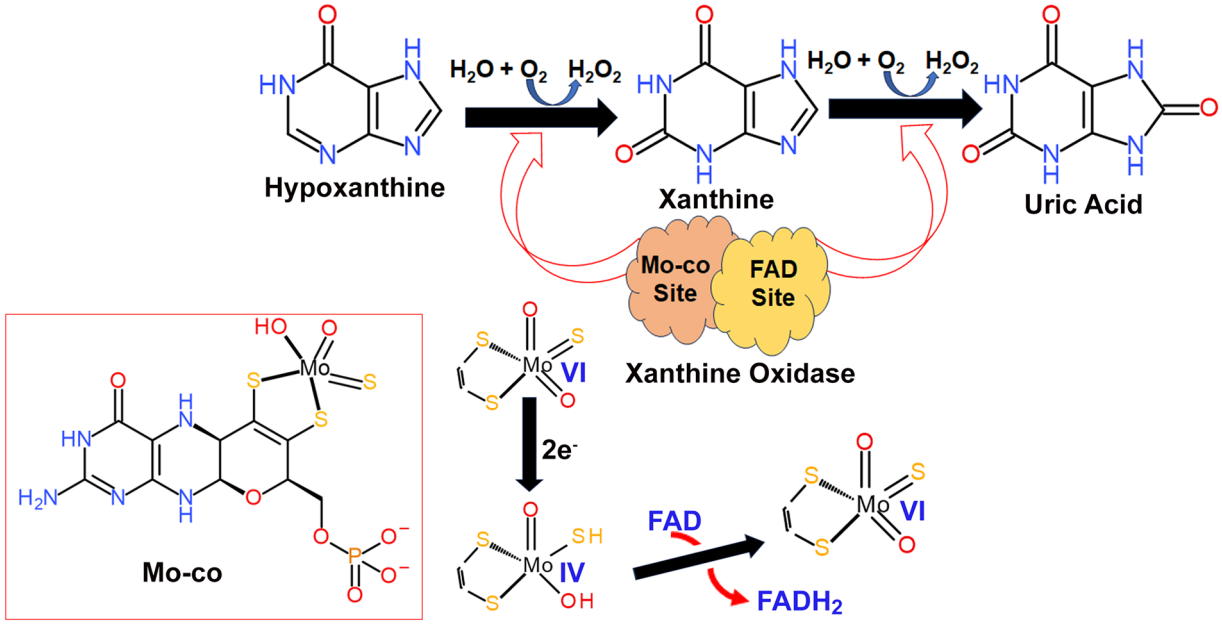

Figure 1. Role and mechanism of XO to convert HPX to UA.

difference. Additionally, studies have reported that the impact of genetic variants on hyperuricaemia is more significant than that of dietary exposure in the common population. Overproduction of UA along the purine breakdown pathway, which primarily occurs in the liver, is one of the causes of hyperuricaemia. An additional factor in the development of hyperuricaemia is insufficient elimination of UA by the kidneys, involving disruptions in reuptake carriers [46]. Key players in this process include urate transporter 1 (URAT1), glucose transporter 9 (GLUT9) and secretory transporter ATP-binding cassette subfamily G member 2 (ABCG2) [47]. The malfunction of URAT1 and GLUT9, responsible for the reuptake of UA, can lead to a breakdown in the regulation of UA levels within the kidneys. Similarly, impairment of the secretory transporter ABCG2 can result in inadequate removal of UA from renal tubules, contributing to the accumulation of UA in the bloodstream. Generally speaking, hyperuricaemia is defined as a blood UA level exceeding 7 mg/dL, as the formation of UA crystals starts when the blood UA level reaches 6.8 mg/dL at 37 °C, and therefore, hyperuricaemia is considered a significant risk factor for conditions like gout and urolithiasis [48]. Metabolic imbalances in obesity, insulin resistance, dyslipidaemia and hypertension are intimately linked to hyperuricaemia, gout and urolithiasis. As a result, elevated UA levels are often considered as surrogate markers of metabolic syndrome. According to the homeostasis model assessment of insulin resistance, UA levels are linearly correlated with fasting insulin levels, and a linear increase in UA levels correlates with a linear increase in insulin resistance measured using the homeostasis model assessment of insulin resistance [49]. It is interesting to note that fasting glucose and haemoglobin A1c levels are related to UA levels in a bell-shaped manner. In addition, in patients with type-1 diabetes mellitus, glycosuria has been identified as an important mechanism by which urinary UA is excreted, and it has been found that sodium-glucose cotransporter 2 (SGLT2) inhibitors can facilitate glycosuria and urate excretion [50]. A mechanism or procedure for the reduction of UA levels in hyperglycaemia involves glycosuria-induced UA secretion through GLUT9 isoform 2 or similar transporters at the proximal tubule, as well as GLUT9 isoform 2 inhibiting the uptake of UA from the collecting duct of the renal tubule, causing a reduction in UA levels. However, evidence suggests that gout can protect against diseases related to the central nervous system. In addition to Alzheimer's disease, Parkinson's disease, vascular dementia and non-vascular dementia, this protective effect extends to these conditions.

4. Treatment for higher UA level: XO inhibitors

4.1. Allopurinol

Allopurinol, a drug that resembles HPX, has been used for over 50 years as a treatment for gout and has been widely used to reduce UA levels in the bloodstream [51]. Allopurinol hinders the activity of XAN oxidoreductase, the enzyme responsible for overseeing the last two phases of purine breakdown: the oxidative conversion of HPX to XAN, and the consecutive transformation of XAN into UA. XO transforms allopurinol into its primary metabolite, oxypurinol. Allopurinol and oxypurinol share structural similarities with the purine bases HPX and XAN, respectively (Figure 2). They competitively attach to XO, consequently

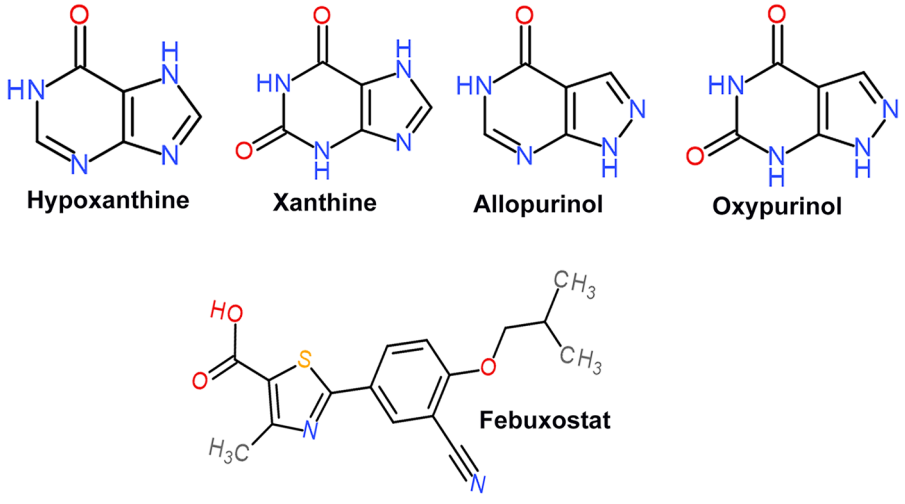

Figure 2. Chemical structures of HPX, XAN, allopurinol, oxypurinol and febuxostat.

impeding the enzyme's role in converting HPX to XAN and subsequently XAN to UA. The administration of allopurinol therapy results in elevated levels of HPX and XAN in both the urine and plasma, accompanied by a reduction in UA concentrations in the plasma [52]. Allopurinol also acts by reducing de novo purine biosynthesis, a process believed to result from the feedback inhibition of amidophosphoribosyl transferase, an enzyme that governs the rate-limiting step in purine biosynthesis. At low concentrations, allopurinol serves as both a substrate for the enzyme and a competitive inhibitor. Conversely, at higher concentrations, it assumes the role of a non-competitive inhibitor. Oxypurinol is a non-competitive inhibitor of this enzyme [53]. The creation of this compound, coupled with its prolonged retention in tissues, accounts for a significant portion of the pharmacological activity associated with allopurinol.

In pharmacokinetics, allopurinol exhibits swift absorption, with peak plasma concentrations achieved within a relatively short timeframe of 30–60 min following oral administration [54]. This rapid absorption highlights the efficiency of drug uptake into the bloodstream, influencing its onset of action and therapeutic effects. Oxypurinol is characterized by lower oral bioavailability than allopurinol. Allopurinol has a relatively short half-life in the plasma, ranging from 2 to 3 h. In contrast, the half-life of oxypurinol is significantly prolonged, ranging from 14 to 30 h [55]. This extended half-life is attributed to renal reabsorption, which contributes to the sustained presence of oxypurinol in the blood stream. Allopurinol hinders XAN oxidoreductase activity via two distinct mechanisms. Initially, the primary drug allopurinol served as a substrate for XAN oxidoreductase. However, the resulting complex between the reduced and oxidized products, oxypurinol, is exceptionally stable. The breakdown of the complex occurs at a notably slow rate, although it occurs somewhat more rapidly in the presence of XAN, resulting in the formation of oxypurinol [56]. The interaction between allopurinol and XAN oxidoreductase is pseudo-irreversible. Another method of inhibiting XAN oxidoreductase involves oxypurinol, even in the absence of allopurinol. Oxypurinol, which is potentially generated through the action of aldehyde oxidoreductase, demonstrates a strong affinity for the reduced form of XAN oxidoreductase, effectively inhibiting the enzyme. This pathway is the second-most acceptable mechanism of inhibition.

The metabolic breakdown of allopurinol is a multifaceted process characterized by extensive transformation. This complicated series of metabolic reactions involves two primary pathways. Firstly, allopurinol undergoes XO-mediated conversion, leading to the formation of its active counterpart, oxypurinol, which serves as an inhibitor of the enzyme [57]. Secondly, the compound undergoes further modification through the action of phosphoribosyltransferases, specifically hypoxanthine-guanine phosphoribosyltransferase and orotate phosphoribosyltransferase. At this stage, allopurinol gives rise to nucleotide analogs, adding another layer of complexity to its metabolic fate [58]. Predictably, owing to their structural resemblance to natural purines and pyrimidines, not only do allopurinol and its derivative oxypurinol exhibit inhibitory effects on XO; however, they also extend their influence to other enzymes within the purine and pyrimidine metabolic pathways. This includes the inhibition of purine nucleoside phosphorylase and orotidine-5′-monophosphate decarboxylase [59]. Although allopurinol is generally recognized for its satisfactory efficacy and safety profile, it is essential to acknowledge the occurrence of exceedingly rare and severe adverse reactions associated with its administration. These adverse effects include interstitial nephritis, kidney or renal failure, liver impairment, vasculitis and a spectrum of skin rashes ranging from mild to highly severe, potentially leading to life-threatening conditions. The higher incidence of severe adverse reactions to allopurinol in patients with renal insufficiency may be due to the accumulation and metabolic effects of allopurinol, oxypurinol and their derivatives beyond XO inhibition [60]. This is underscored by their primary renal excretion.

Evidence from both randomized controlled trials (RCTs) and observational studies by van der Pol et al. suggested that allopurinol treatment can lower cardiovascular risk in individuals with hyperuricaemia [61]. However, the quality of evidence from RCTs is currently assessed as being low to moderate. Gois and Souza highlighted that existing RCT data are insufficient to ascertain whether UA-lowering therapy effectively reduces blood pressure, and they emphasized the necessity for additional studies to address this question definitively [62]. To conclusively determine whether allopurinol effectively reduces the risk of cardiovascular events, a meticulously designed and sufficiently powered randomized placebo-controlled trial is essential, particularly in high-risk patients with hyperuricaemia. In their clinical trial, Badve et al. did not observe greater effectiveness of allopurinol compared to placebo in decelerating the decline in estimated glomerular filtration rate over a 104-week period among patients with stage 3 or 4 chronic kidney disease and an increased risk of disease progression [63]. A study by Mackenzie et al. revealed that the use of

allopurinol at a daily dosage of 600 mg did not show any enhancement in cardiovascular outcomes when compared with standard care among patients with ischemic heart disease [64]. Consequently, based on the ALL-HEART study results, it is not advisable to recommend allopurinol for secondary prevention of cardiovascular events in individuals with ischaemic heart disease.

4.2. Febuxostat

Febuxostat serves as a non-purine inhibitor of XO and plays a role in purine catabolism. Febuxostat differs structurally from allopurinol because it lacks a purine ring (Figure 2). Febuxostat belongs to the category of thiazole-carboxylic acid derivatives and exhibits distinctive selectivity in its mechanism of action [65]. It effectively inhibits both the oxidized and reduced forms of XO, which is a crucial enzyme involved in purine metabolism. It is a more selective and potent XO inhibitor than allopurinol. The structural dissimilarity between febuxostat and purine or pyrimidine compounds makes it a unique pharmaceutical agent in its class. This specific design contributes to targeted and effective modulation of XO activity, highlighting its significance in the treatment of conditions associated with abnormal purine metabolism, such as gout. Febuxostat demonstrates remarkable specificity in its effect on enzymes related to purine or pyrimidine metabolism [66]. Although it effectively inhibits XO, its influence on other crucial enzymes in this metabolic pathway, such as purine nucleoside phosphorylase, adenosine deaminase and pyrimidine nucleoside phosphorylase, is minimal. This targeted action is significant, as it allows for the selective modulation of XO without interfering with the activities of other enzymes associated with purine or pyrimidine metabolism. Notably, the pharmacological profile of febuxostat underscores its ability to address specific targets, providing a nuanced and tailored approach for the treatment of conditions related to aberrant purine metabolism, such as gout.

Upon oral administration, febuxostat exhibits high absorption, with approximately 85% of the administered dose readily absorbed [67]. Interestingly, doses exceeding 120 mg/day resulted in a greater than dose-proportional increase in the area under the curve (AUC). This phenomenon is attributed to a reduction in renal clearance of the conjugated form, coupled with an elevation in biliary excretion and enterohepatic recirculation. The presence of food, particularly high-fat meals, impedes the absorption of febuxostat, leading to a decrease in the AUC by 16–19%. At steady state, Febuxostat demonstrated a volume of distribution of 0.7 L/kg. It is worth noting that the drug exhibits high binding affinity, with 99.2% binding to circulating plasma proteins such as albumin [68]. Febuxostat undergoes hepatic metabolism within the cytochrome P450 enzyme system, which results in the formation of acylglucuronide metabolites. This metabolic process predominantly involves conjugation facilitated by uridine diphosphate-glucuronosyltransferase. The elimination of febuxostat occurs predominantly through the renal pathways, with a mean half-life ($t_{1/2}$) of 9.1 h observed for a 120-mg dose [69]. This comprehensive understanding of the pharmacokinetic profile of febuxostat provides valuable insights into its absorption, distribution, metabolism and elimination dynamics, aiding its effective clinical application. *In vitro* studies showed a minimal impact of febuxostat on various isoenzymes, with a weak inhibitory effect on CYP2D6. No significant interactions were observed between colchicine and indomethacin. Coadministration with antacids slightly reduced the C_{max} of febuxostat by 32%, but the AUC was unaffected [69]. Although no formal studies have been conducted, caution is advised when using febuxostat with theophylline, mercaptopurine or azathioprine because of the potential risks of increased drug levels and toxicity. Febuxostat offers flexibility of administration without the need to consider food intake or the concurrent use of antacids. Patients with mild or moderate renal impairment, as well as those with mild to moderate hepatic impairment, do not require dosage adjustments when using febuxostat. However, it is important to note that febuxostat is contraindicated in patients undergoing treatment with azathioprine, mercaptopurine or theophylline. This caution arises from the potential of concurrent administration of febuxostat to elevate the plasma levels of these specific drugs [70]. To prevent any adverse interactions, the concomitant use of febuxostat with azathioprine, mercaptopurine or theophylline should be avoided. This precautionary measure ensures the optimal and safe use of febuxostat in clinical settings.

O'Dell et al. conducted a trial indicating that allopurinol is as effective as febuxostat in reducing flares in individuals with gout [71]. This study emphasizes that both urate-lowering therapies, when applied in a titrate-to-target approach, are highly effective in achieving uniform serum urate goals. This efficacy extends to participants with stage 3 chronic kidney disease, a prevalent comorbidity in gout. Importantly, the study found no indications that febuxostat elevates cardiovascular morbidity or overall mortality when compared to allopurinol. The investigation

conducted by Zhang et al. did not achieve the primary objective of establishing the non-inferiority of febuxostat at a dose of 40 mg/day in comparison to allopurinol at a dosage of 300 mg/day, as determined by the proportion of participants with serum UA levels equal to or below 6.0 mg/dL at the 24-week mark [72]. Nevertheless, febuxostat at 60 and 80 mg/day showed superiority when compared to allopurinol at 300 mg per day, as evidenced by the percentage of participants with serum UA levels equal to or below 6.0 mg/dL at the 16-week and 24-week intervals, respectively. Peng et al. indicated that febuxostat demonstrated superiority over allopurinol in maintaining a sustained reduction in serum UA levels among patients with chronic kidney disease [73]. However, there were no discernible differences in renal function changes between patients who received either febuxostat or allopurinol in a typical clinical setting. It is crucial to closely monitor serum creatinine and UA levels in patients undergoing XO inhibitor therapy to promptly identify acute kidney injury and prevent the deterioration of renal function. To establish cost-effective practices, they suggested that further long-term follow-up studies are essential to assess variances in renal outcomes between febuxostat and allopurinol in patients with chronic kidney disease and hyperuricaemia. The study conducted by Pawar et al. provided reassurance for patients intolerant to allopurinol requiring febuxostat treatment, as it did not detect elevated cardiovascular or all-cause mortality, even in individuals with a history of cardiovascular disease [74]. The strengths of the study include its incident new-user and active-comparator design, employing propensity score matching to minimize confounding factors. These findings are applicable to a broad population of elderly patients with gout. The primary as-treated approach addresses non-adherence bias, which is a limitation of the CARES trial. However, residual confounding remains a possibility, and misclassification bias may arise from reliance on diagnostic codes for participant eligibility, covariates and outcome identification. Several other studies on febuxostat are presented in Table 1.

5. UA production on hypertension

The correlation between serum UA levels and elevated blood pressure or hypertension in humans has been established. An illustrative case comes from a cross-sectional study, where it was found that each incremental increase of 1 mg/dL in serum UA was associated with an approximately 20% greater prevalence of hypertension within a general population that was not undergoing treatment for hyperuricaemia and hypertension [84,85]. Furthermore, when examining data from longitudinal cohort studies, it becomes apparent that individuals with asymptomatic hyperuricaemia, devoid of any accompanying health issues, are more likely to develop hypertension over time. This finding suggests a significant link between elevated UA levels and the subsequent onset of high blood pressure. Moreover, the influence of hyperuricaemia extends beyond merely predicting hypertension. It also

Table 1. Use of febuxostat against several other complications with a specific mechanism of action.

Specific functions	Chemical agent used	Mode of action	References
Febuxostat suppresses endoplasmic (ER) stress	Tunicamycin	Through upregulation of SIRT1-AMPK-HO-1/TRX expression	[75]
Reduces NLRP3-dependant inflammations	Nigericin, MSU	MitoROS independent activation of purine salvage pathways and restoration of cellular ATP/ bioenergetics	[76]
Protective effect against ulcerative colitis	Acetic acid	Inhibiting inflammatory mediators (NF-κB) and oxidative stress moderators	[77]
Prevent necrosis of the skin flap	–	Reduced expression of interleukin-1β inhibits oxidative stress and inflammation due to ischemia-reperfusion.	[78]
Prevent ROS-dependant osteoclastic bone loss	RNKL, Dox	ROS scavenging	[79]
Therapeutic potential against allergic rhinitis	Histamine	Inhibit inflammation regulating transcriptional factor KLF6	[79]
Suppress adipogenesis	Hydrogen peroxide	Controlling ROS production and Nrf2 activation	[80]
Relieves renal injury	Arsenic trioxide	Inhibiting the expression of TLR4, caspase-1, ASC and NLRP3	[81]
Protects brain post intracerebral haemorrhage	–	Regulating LncRNA	[82]
Therapeutic efficacy for Parkinson's disease	1-Methyl-4-phenyl-pyridine	Suppress the JNK/NF-κB signalling pathways	[83]

Abbreviations: SIRT1, silent mating type information regulation 2 homology 1; AMPK, AMP activated protein kinase; HO-1, [heme oxygenase-1; TRX, thioredoxin; NLRP3, nucleotide-binding oligomerization domain (NOD), Leucine-rich repeat (LRR), Pyrin domain-containing protein 3; MSU, monosodium urate; MitoROS, mitochondrial ROS; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; RNKL, receptor activator of NF-κB ligand; Dox, doxorubicin; KLF6, Kruppel-like-factor-6; Nrf2, nuclear factor erythroid-2-related factor 2; TLR4, toll-like receptor 4; ASC, apoptosis-associated speck-like protein containing a CARD (caspase recruitment domain); LncRNA, long non-coding RNA; JNK, c-Jun NH_2-terminal kinase.

contributes to the transition from prehypertension, a precursor stage, to fully manifest hypertension [86]. This highlights the progressive role of UA in the continuum of blood pressure elevation. In light of these comprehensive observations, the reduction of serum UA levels has emerged as a particularly intriguing and promising therapeutic approach in the realm of hypertension management. By addressing the role of UA in predicting and contributing to hypertension, interventions aimed at lowering UA levels may have substantial potential in mitigating the risk and progression of high blood pressure. Research has shown that increased serum UA levels can activate the renin-angiotensin system (RAS) [87]. This activation occurs either through the direct inhibition of nitric oxide (NO) synthesis in the juxtaglomerular apparatus or indirectly by stimulating the proliferation of smooth muscle cells in the wall of the afferent arteriola (Figure 3). These processes ultimately lead to a reduction in renal perfusion, highlighting the intricate mechanisms through which elevated serum UA levels may affect the regulatory systems involved in blood pressure and renal function.

Hyperuricaemia contributes to arterial stiffness via two primary mechanisms. In the first scenario, elevated levels of serum UA directly induce arteriosclerosis. This occurs as macrophages engulf urate crystals, triggering activation of the NOD-like receptor NLRP3 inflammasome [88]. Consequently, the NLRP3 inflammasome pathway plays a crucial role in interleukin-1β secretion from MSU-stimulated human macrophages. This secretion, which occurs in a post-translational modification-related manner, leads to inflammation and heightened collagen production, ultimately fostering the progression of arteriosclerosis. Atherosclerosis is strongly correlated with arterial stiffness at various locations in the vascular network. In the second mechanism, UA induces oxidative stress within the cells and mitochondria, diminishing the bioavailability of endothelial NO. This process also stimulates the intracellular RAS [89]. The combined effects of intracellular and mitochondrial oxidative stress reduced NO availability and activated RAS, collectively contributing to the development of arterial stiffness (Figure 3). Hyperuricaemia is widely recognized as a biomarker for XO activation, a process that releases oxidants during UA generation. The increased production of oxidants, particularly superoxide, contributes to endothelial dysfunction. Human blood vessels express the urate transporter GLUT9, which is a key player in the absorption of UA into the bloodstream. This absorption triggers inflammation, dephosphorylation of endothelial nitric oxide synthase (eNOS) in the vasculature and oxidative stress [90]. NO plays a crucial role in regulating vascular tone and arterial stiffness. Any reduction in NO bioavailability or disproportion in its reduced production can lead to endothelial dysfunction, subsequently resulting in elevated blood pressure. UA within the blood vessels sets in motion a cascade of events, including inflammation, which ultimately leads to arteriosclerosis and arterial stiffness. In this intricate pathway, the interplay between UA, oxidative stress and NO availability is a critical determinant of vascular health and the development of cardiovascular complications [91].

Based on both *in vitro* and *in vivo* data collected by Lee et al. dysregulation of the asymmetric dimethylarginine (ADMA)/DDAH-2 (dimethyl arginine dimethylaminotransferases-2) axis plays a crucial role in the activation of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase/ROS signalling,

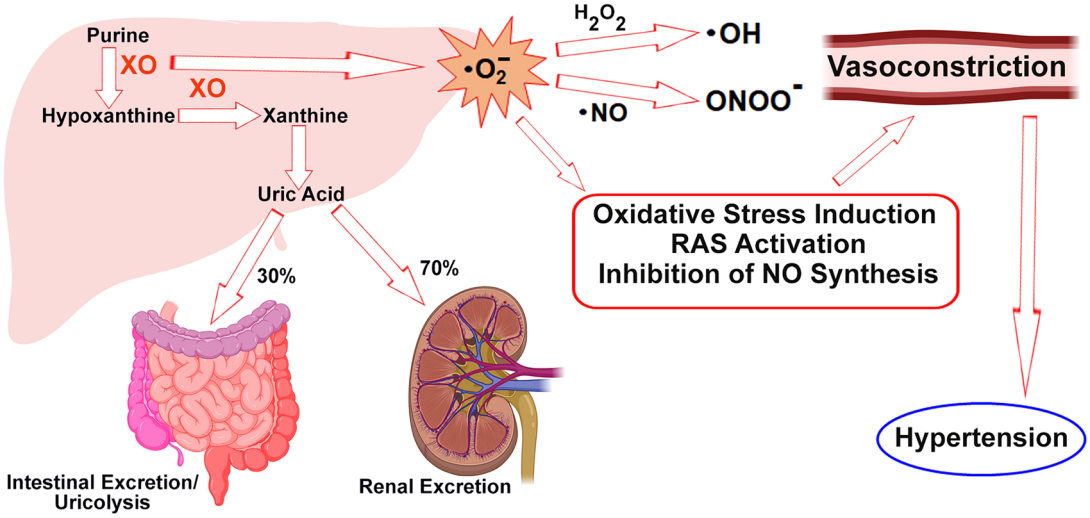

Figure 3. Important metabolic pathways that relate hypertension and serum UA level.

endothelial cell dysfunction, inflammation and the hastening of atherosclerosis induced by hyperuricaemia [92]. These findings reveal a novel molecular mechanism that underscores the adverse effects of hyperuricaemia on atherosclerosis development. Furthermore, they proposed a connection between UA metabolism and the ADMA/DDAH-2-component related to the cardiovascular system. Wang et al. found a link between a higher serum UA level and serum creatinine ratio and an increased risk of hypertension [93]. Their analyses suggested that blood lipid concentration, body mass index, blood pressure, high-sensitivity C-reactive protein and blood glucose concentration may act as possible mediators of this association. This highlights the possible role of these factors in the observed association between serum UA and serum creatinine levels and cardiovascular disease risk. The research carried out by Tian et al. revealed that an elevated risk of myocardial infarction is specifically linked to consistently high levels of serum UA [94]. Additionally, the study confirmed that hypertension plays a mediating role in the association between variations in serum UA levels and the occurrence of myocardial infarction.

It is crucial for health care professionals and public health practitioners to recognize that monitoring the longitudinal trends of both serum UA and hypertension could contribute to reducing the risk of myocardial infarction. Cardio-nephro-metabolic disorders must be evaluated in a diverse sample that is representative of the general population in order to clarify the relationship between UA levels and these disorders. Clarification of serum UA threshold values is crucial for identifying elevated UA levels associated with heightened risk. In order to address this need, the Uric Acid Right for Heart Health (URRAH) project has been specifically designed [95–97]. An essential aim of this study is to determine the level of uricaemia that, in a general Italian population, is associated with a significant increase in the independent risk of cardiovascular disease. There is a direct relationship between serum UA and serum creatinine levels (SUA/sCr), and this ratio provides a more comprehensive assessment than serum UA alone when it comes to predicting cardiovascular risk since it considers the influence of renal function, which is closely related to serum UA levels. In the URRAH population, a threshold indicating cardiovascular risk has recently been established. An SUA/sCr ratio greater than 5.35 units has been shown to be an independent predictor of mortality from cardiovascular disease among men and women [98]. Table 2 summarizes a few additional studies on the mechanism underlying the relationship between hypertension and uricaemia.

Table 2. Proposed mechanism related to the connection between UA level elevation and hypertension.

Model/method used	Mechanism involved	References
Genotyped-based studies on 2769 European populations	Hypertension is associated with the SNPs in XAN oxidoreductase genes	[99]
312 participants from Bangladeshi adults	XO affects the pathophysiology of hypertension, generating ROS	[100]
Unilaterally nephrectomized Sprague-Dawley male rats	Endothelin-1 activated XO functions and mitochondrial oxidative phosphorylation to promote vascular ROS generation and hypertension	[101]
Patients with hypertension and renal dysfunction	XO-based ROS generation to the progression of hypertension	[102]
Neonatal rats	XO-derived superoxide	[103]
Population-based cohort studies on nondiabetic 271 subjects	XOR activity and ROS generation are the key factors for hypertension in nondiabetics	[104]
192 volunteers not taking medication to treat hyperuricaemia	ROS-based oxidative stress due to UA without XOR involvement	[105]
Sprague-Dawley rats	Hyperuricaemia induces oxidative stress, and the RAS is involved	[106]
1548 participants with preeclampsia	UA and superoxide dismutase are responsible for hypertension	[107]
123 participants	Higher levels of UA lower nitrite concentrations	[108]
17 pregnant women having preeclampsia and 14 normal pregnant women	Higher serum UA concentrations elevate serum hydrogen peroxide levels and oxidative stress	[109]

6. Elevated UA on atrial fibrillation

The prevalence and incidence of atrial fibrillation (Afib) are increasing worldwide, making it one of the most common cardiac arrhythmias in the elderly. Numerous investigations have identified a link between heightened serum UA levels and a higher likelihood of AFib [91]. However, it remains uncertain whether UA actively contributes to the mechanisms underlying the onset and persistence of AFib. The association between UA and AFib can be attributed to features such as oxidative stress, related inflammation, activation of the renin–angiotensin–aldosterone system and endothelial dysfunction [110]. The association between elevated UA levels and the progression or development of AFib may be explained by the fact that each of these elements has been demonstrated to contribute to atrial remodelling. In a cross-sectional study of a large Japanese general population conducted by Kawasoe et al. a significant association was found between

serum UA levels and AFib in both sexes [111]. Ding et al. found that elevated levels of UA were associated with an increased risk of serious health problems after AFib diagnosis in middle adulthood [112]. It may also be possible, as they concluded, to link high levels of UA directly to the development of AFib via mechanisms other than CVD or cardiovascular risk factors, which may increase the risk of AFib. Based on clinical and experimental evidence, hyperuricaemia has been associated with an elevated incidence of AFib, as shown by Deng et al. [113]. They also demonstrated in a number of small *in vitro* and *in vivo* studies that hyperuricaemia, both at low and high UA concentrations, may play a crucial role in the pathogenesis of AFib by activating oxidative stress, stimulating inflammation, triggering fibrosis and immune responses.

7. Disease-associated with UA in the kidneys

Whether lowering a patient's serum UA level in the case of gout will have an effect on kidney damage or cardiovascular events has been controversial. It is believed that urate crystals accumulate not only in the joints but also in several tissues [114]. The collecting ducts of the kidneys are one of the most common locations of urate crystals. The concentration of UA in urine increases its acidity, facilitating the crystallization of urate as the urine becomes more acidic. The adhesion of some crystals of urate to the tubular epithelium can lead to local inflammation and rupture of the tubular wall, which allows the crystals to escape into the interstitial space. The process of inflammation may trigger localized macrophage infiltration as a result of this process. Individuals with gout often excrete substantially less UA than normal, especially after consuming meals high in purines and fructose. In addition to preventing recurrent gout attacks, emerging evidence suggests that urate crystals play a direct role in atherosclerosis. Urate crystals are found in the bloodstream of a substantial percentage of individuals with gout, ranging from 75% to 86% [115]. Additionally, almost 30% of subjects diagnosed with gout exhibit the presence of these crystals, specifically in their coronary arteries, with atherosclerotic plaques appearing to be the primary location. These lesions seem to be at risk of expanding or rupturing because urate crystals activate inflammasomes, similar to cholesterol crystals. The link between hyperuricaemia, gout and cardiovascular mortality may be explained by these findings. In addition, crystal deposits of urate can trigger both local and systemic inflammation, which contribute to kidney disease and cardiovascular events, in addition to local inflammation.

8. XO inhibitors on hypertension

Febuxostat and allopurinol, inhibitors of XO, showed comparable efficacy in averting gout attacks in individuals with gout. However, febuxostat has a strong potential to lower blood UA levels [116]. Allopurinol competes with XAN to bind to XO as a XAN analog, and the active metabolite of this compound competes with HPX, consequently impeding the production of UA. In contrast, febuxostat selectively blocked XO activity without further involvement of metabolites. Moreover, UA triggers the growth of vascular smooth muscle cells and plays a significant role as an inflammatory agent. The activity of XO produces ROS, such as superoxide, H_2O_2 and hydroxyl radicals [117]. These ROS contribute to tissue damage and impairment of NO function, ultimately leading to endothelial dysfunction, an initial stage of atherosclerosis, and vascular damage. Allopurinol inhibits XO activity, thereby decreasing ROS levels and increasing the availability of NO for vascular smooth muscle relaxation.

NO synthesis by the vascular endothelium is vital for the maintenance of vasodilator tone. Aside from its role in vasodilation, endothelium-derived NO has profound physiological effects that influence cardiovascular homeostasis in profound ways. The ability of endothelium-derived NO to inhibit smooth muscle cell proliferation is crucial for preventing arterial wall thickening, which is a process associated with atherosclerosis. Additionally, NO plays a key role in preventing leukocyte adhesion to the vascular surface, contributing to an overall anti-inflammatory environment within the blood vessels by reducing platelet aggregability, thereby diminishing the risk of blood clot formation [118]. Various aspects of cardiovascular health are regulated by endothelium-derived NO through multifaceted actions. The impaired bioavailability of NO originating from the endothelium may contribute to atherosclerosis. Decreased NO activity has been identified as an indicator of endothelial dysfunction in individuals with established atherosclerosis risk factors, such as hypercholesterolemia and arterial hypertension [119]. This highlights the intricate relationship between NO synthesis, endothelial function and cardiovascular diseases, emphasizing the importance of maintaining healthy endothelium. Endothelial dysfunction and increased degradation of NO are linked in numerous animal models of hypercholesterolemia and hypertension, according to numerous studies. As scavengers of endothelium-derived NO, superoxide anions are integral to this degradation process. It is generated by a variety of pathways involving enzymes and nonenzymes. In addition to the activation of circulating

neutrophils, the XO system plays a major role in the production of superoxide anions within the vascular endothelium. Endothelial cells were exposed to superoxide anions using the XO system. XO can be inhibited with inhibitors such as febuxostat, allopurinol and oxypurinol, which are structurally similar to XAN [120]. These XO inhibitors bind to XO and prevent radical formation and UA production. This suggests that superoxide anions, primarily derived from the XO system, may be responsible for the reduced bioavailability of NO in patients with hypercholesterolemia and essential hypertension (Figure 4). Hypercholesterolemia and hypertension are cardiovascular conditions associated with endothelial dysfunction, which can be addressed through therapeutic interventions targeting superoxide anions and NO.

9. XO inhibitor-based nanomedicine

In an effort to bridge the gap between biological and physical sciences, nanotechnology has proven to be extremely successful in utilizing nanostructures and nanophases across a wide range of scientific fields [121–123]. This is particularly evident in areas such as nanomedicine and nano-based drug delivery systems, where the focus is on the significant potential that can be derived from such nanoparticles. Significant advancements have been made in nanomedicine through the use of therapeutic agents on the nanoscale, including drug delivery, biosensing and a wide variety of applications in tissue engineering [124,125]. Nanoparticles are composed of molecules or atoms engineered at the atomic level. Nanoscale particles exhibit distinct structural, chemical, mechanical, magnetic, electrical and biological properties [25,126]. This allows them to manoeuvre within the human body more freely than bulk materials do. By addressing issues ranging from biodistribution to intracellular trafficking, nanotechnology can address some of the drawbacks of traditional delivery methods. Specific cell targeting, molecular transport to diseased cells or specific organelles, and other innovative approaches can be used to accomplish this goal. As a result of nanoparticles, enclosed payloads are more stable and solubilized, membranes are more easily crossed, and circulation times are extended, thus enhancing safety and efficacy (Figure 5) [24,127].

Fuxostat is classified as class 2 by the biopharmaceutical classification system because of its low solubility in water and weak acidity in nature, with a pKa of approximately 3.08. Therefore, Bhatt et al. encapsulated febuxostat in a nano-based lipid carrier composed of oleic acid and stearic acid [128]. The optimized formulations were engineered using a combination of the homogenization process and bath sonication techniques and showed an encapsulation efficiency of more than 80 ± 2.3%. The size of the formulated nanostructures was restricted to less than 229 nm, demonstrating the release of febuxostat with zero-ordered kinetics, making it ideal for oral delivery for the treatment of chronic gout. Gurumukhi et al. reported febuxostat-loaded nanoemulsions to improve bioavailability and membrane permeability [129]. Febuxostat loaded in the microemulsion showed increased permeability in the artificial membrane model and everted-gut sac system. An approximately 2.5-fold increase in bioavailability was observed in Wistar rat models, and the formulation was stable for more than 90 days at room temperature (25 °C) and 4 °C. To overcome the poor gastrointestinal absorption and bioavailability of febuxostat, Al-Amodi et al. incorporated this XO inhibitor into a self-emulsifying nano-drug delivery system composed of several essential oils, surfactants and lipids [130]. The group established the efficacy of these formulations in the management of gout using several *in vitro* and *in vivo* studies.

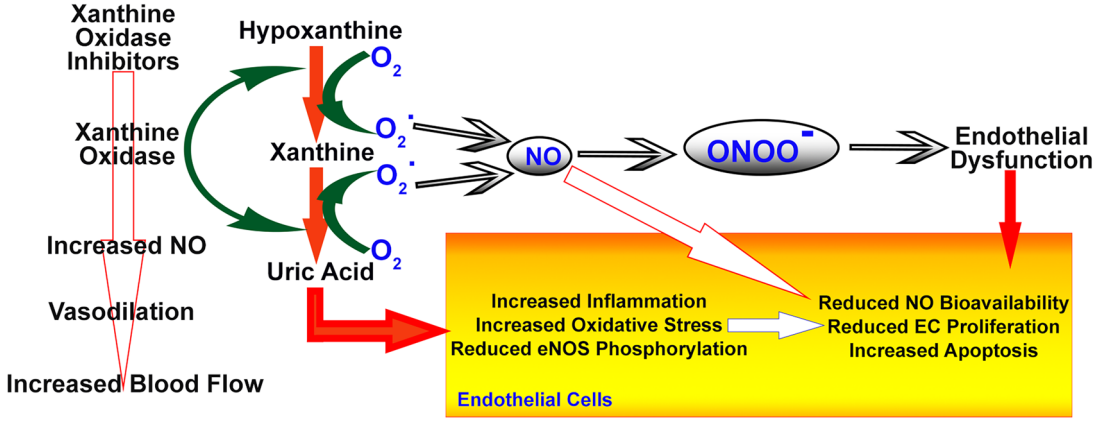

Figure 4. The way XO inhibitors affect hypertension.

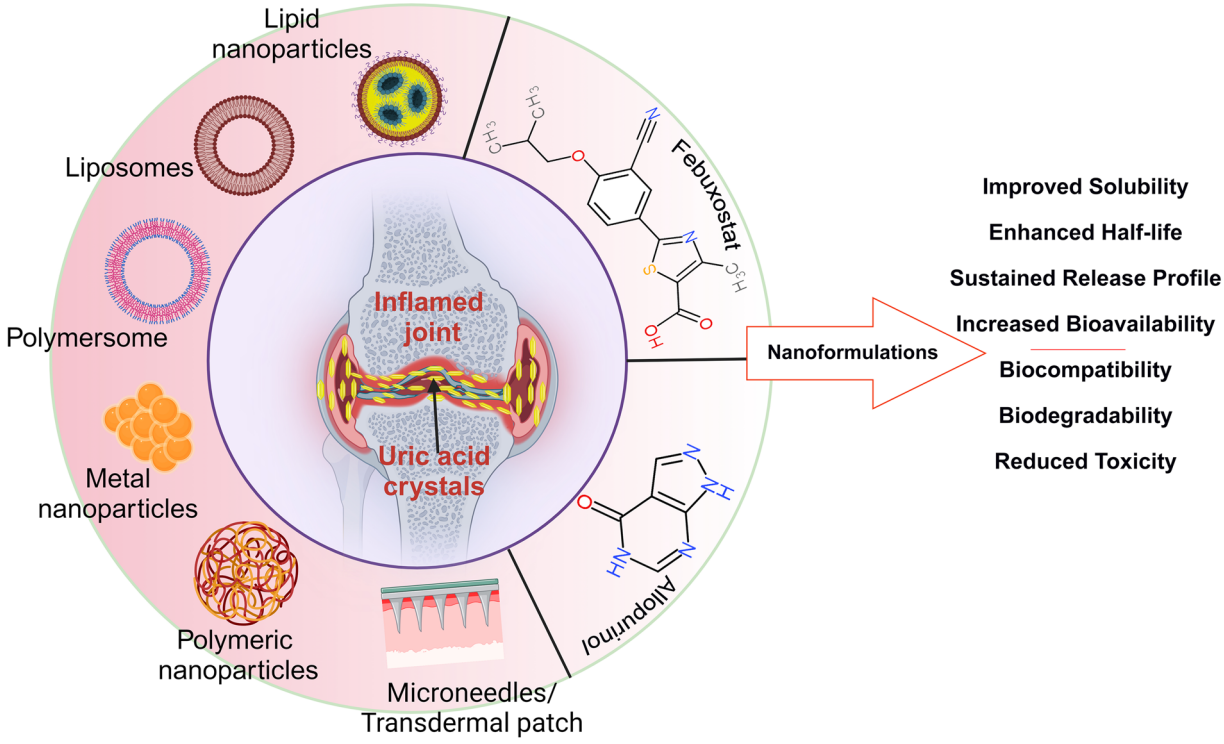

Figure 5. Nanostructures involved in the formulations of allopurinol and febuxostat.

The limited solubility in aqueous media and susceptibility to enzymatic breakdown in the liver or intestine limit the oral delivery of febuxostat. Simultaneously, the plasma concentration of febuxostat was affected by food intake. Therefore, Singh et al. proposed transdermal delivery of febuxostat using niosomal gel formulations [131]. The formulations were prepared using thin-film hydration techniques, and Span-60 and Tween-20 were used as essential components. They demonstrated an extended drug permeation of approximately 80.4% in *in vitro* and *in vivo* studies using rabbit models. A transdermal drug delivery system for febuxostat was developed by Patel et al. to improve patient compliance and bioavailability [132]. Using a bottom-up approach and micromoulding, febuxostat cubosomes were incorporated into a microneedle to improve skin penetration. In this process, lipids and polyvinyl alcohol are used along with specific organic and aqueous phases. They concluded that the nano-patch loaded with febuxostat in cubosomes maintained UA levels better than other reported formulations in rats. As a member of the Biopharmaceutics Classification System class-2 drugs, allopurinol encounters solubility issues, impacting its bioavailability and reducing its plasma half-life. Ali et al. used lipid-based nanocarriers in their study to increase bioavailability and improve efficacy and safety for the *in vivo* use of formulated allopurinol [133]. Drug-loaded emulsions were prepared using oleic acid, stearic acid and Tween-20 surfactants. The formulations showed a sustained-release profile with reduced toxicity and better anti-gout activity than the conventional allopurinol treatment. A few more nanoformulated applications of allopurinol and febuxostat are given in Table 3.

10. Coadministration of hyperuricemic and hypertensive drugs

An increased concentration of UA in blood serum is closely associated with the inception and progression of hypertension. Therefore, treatment to lower serum UA levels causes a reduction in blood pressure or hypertension. XO inhibitors constitute the primary category of hyperuricemic medications and have the potential to reduce hypertension. Elevated UA levels mainly affect hypertension in two phases [145]. Initially, UA can prompt acute vasoconstriction through the activation of the renin–angiotensin–aldosterone system. Second, the absorption of serum UA into vascular smooth muscle cells results in cellular proliferation and subsequent arteriolosclerosis, compromising the compliance of resistant vessels and impeding blood pressure-induced natriuresis. Hence, hypertension is a common comorbidity in individuals with gout. This considerable comorbidity burden may arise from either

Table 3. Applications of nanoformulated XO inhibitors.

Drugs used	Specific nanoformulations	Treatment/purpose	References
Allopurinol	Low MW chitosan nanoparticles	Hyperuricemic-connected nephrolithiasis management	[134]
Allopurinol	BSA nanoparticles	Hyperuricemic-linked nephrolithiasis maintenance	[135]
Allopurinol	Thioctic acid-loaded lipid nanocarriers	Gout and nephrotoxicity treatment	[136]
Febuxostat	Hydroxypropyl methylcellulose and α-D-Tocopherol-PEG1000-succinate stabilized nanosuspension	Increased oral bioavailability	[137]
Febuxostat	B-cyclodextrin based nanosponge	Improvement of oral bioavailability	[138]
Febuxostat	Chitosan nanoparticles	Increased encapsulation efficiency and bioavailability to alter the pharmacokinetics with sustained release	[139]
Febuxostat	Chitosan-coated tin dioxide-based nanosphere	Increase intestinal absorption and bioavailability	[140]
Allopurinol	Glutaraldehyde-based polymerized albumin microparticles	Management of ischemic stroke and hypertension	[141]
Allopurinol	Chitosan alginate nanohydrogels	Modulate oxidative stress and decrease inflammation	[142]
Febuxostat	Nanoengineered lipid carrier	Modified release profile, improved dissolution, bioavailability minimizing the side effect	[143]
Febuxostat	Ethosomes made of ethanol and soya lecithin	Better transdermal delivery system for gout management	[144]

Abbreviations: BSA, bovine serum albumin; PEG, polyethylene glycol.

the co-pathogenesis of the two conditions or renal alterations in hypertension, resulting in diminished urate excretion [146]. Research indicates that the occurrence of hypertension is autonomously linked to the likelihood of developing gout, which is primarily attributable to lowered renal blood circulation, heightened renal and systemic vascular resistance and diminished renal excretion of urate.

Certain antihypertensive medications have been shown to elevate serum UA levels, thereby potentially contributing to an elevated risk of gout. Beyond the well-established associations between diuretic-induced hyperuricaemia and related gout, it has been perceived that the use of β-blockers can lead to an increase in serum UA levels. This phenomenon has been documented in short-term trials, suggesting a link between β-blocker use and the modulation of UA concentrations, adding another dimension to the understanding of how certain antihypertensive drugs may influence the risk profile for gout [147]. The co-crystallization of drugs represents an innovative mechanism for facilitating effective pharmaceutical combinations in therapy. Ganesan et al. synthesized a drug-drug co-crystal, focusing on combining a hypertension therapeutic, telmisartan and a hyperuricaemia drug, febuxostat, in a 1:1 molar ratio [148]. This co-crystal was prepared using a solvent evaporation method, as outlined in their research work. This approach represents a noteworthy endeavour in exploring novel formulations through co-crystallization, potentially offering enhanced therapeutic outcomes through the combination of these two pharmacologically relevant drugs. A febuxostat-telmisartan co-crystal (120 mg) was composed of approximately 46 mg of febuxostat and 74 mg of telmisartan [148]. These quantities align with the intended range, mirroring the standard doses of febuxostat used in clinical practice, which is typically 40–80 mg/day, and telmisartan, which is usually prescribed at doses ranging from to 40–80 mg/day. This formulation was designed strategically to optimize the combined pharmacological effects within the established therapeutic ranges for both constituent drugs. This groundbreaking concept holds the potential to provide a significant breakthrough for individuals with both hyperuricaemia and hypertension.

11. Conclusion and future perspective

Considering the involvement of XO in diverse pathological conditions, it becomes apparent that targeted inhibition of XO could lead to a wide-ranging therapeutic approach for ailments such as gout or hyperuricaemia, inflammation and oxidative damage. Therefore, XO inhibitors have emerged as promising agents with substantial potential for the treatment of various medical conditions. Hyperuricaemia and gout primarily manifest as excessive UA production. XO inhibitors have demonstrated exceptional efficacy in reducing UA levels in the bloodstream and specific peripheral tissues. Their role in the management of hypertension-related disorders is also discussed in this review, which can help physicians during prescription. Studies have clearly demonstrated that nanoformulations of allopurinol and febuxostat resolved several challenges regarding the poor solubility and bioavailability of these potent drugs during the management of diseased conditions.

The primary objective of this review was to caution clinicians regarding prescribing medications for hypertension in patients with hyperuricaemia. Instead of approaching these conditions separately, there is a potential benefit of simultaneously addressing hyperuricaemia by using XO inhibitors. These inhibitors can manage both conditions concurrently, providing a more holistic approach to treatment. In the realm of nanotechnology, there is clear potential for reducing the dosage of XO inhibitors through enhancement of bioavailability and circulation half-life. As time advances, more refined formulations are expected to be created, and researchers will continue to develop improved nanoformulations. During the engineering of new nanoformulations, the choice of materials and their biocompatibility are the main focus, along with their cost-effective formulations. Polymer chemistry is growing rapidly, and several biocompatible and biodegradable polymers have been reported to be ideal carriers for transporting medically active components. XO inhibitors can be encapsulated to enhance their circulation half-life and other therapeutic benefits to control serum UA and blood pressure. Another approach to the co-crystal concept was presented in the previous section. More co-crystal synthesis in a balanced way will be the game changer and will help medical practitioners easily generate prescriptions for those who are suffering from both hyperuricaemia and hypertension. These advancements aim to overcome the current challenges faced by allopurinol and febuxostat, promising a more effective and efficient approach to their application.

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Authors contributions

Koyeli Girigoswami collected all data and prepared the initial draft. Arunkumar edited the manuscript and added additional information. Agnishwar was involved in the conception, additional data collection, design, drawings and final manuscript preparation. All listed authors approved the final draft for communication.

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ORCID

Koyeli Girigoswami http://orcid.org/0000-0003-1554-5241
Agnishwar Girigoswami http://orcid.org/0000-0003-0475-2544

Data availability statement

All the data are available in the manuscript.

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