From crystals to damage: The emerging role of ferroptosis in calcium oxalate nephropathy (Review)

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Abstract. Nephrolithiasis is a major public health concern associated with high morbidity and recurrence rates, placing an immense burden on healthcare systems worldwide. Given that ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death, has emerged as a key pathological mechanism in oxalate-induced renal injury, it has gained increasing attention in nephrolithiasis research. It has been clearly demonstrated that ferroptosis actively promotes calcium oxalate (CaOx) crystal nucleation and adhesion, while CaOx deposition in turn exacerbates ferroptosis, forming a bidirectional positive feedback loop that amplifies renal damage. However, the molecular mechanisms regulating ferroptosis in kidney stone disease, including the roles of gut microbiota metabolites, sex hormone signaling, and epigenetic pathways, have not yet been fully elucidated. The present review presents a comprehensive summary of the existing literature on the mechanisms of ferroptosis in nephrolithiasis, including the SOX4/EZH2/SLC7A11 axis, inflammatory pathways (NF-κB and JAK-STAT3), oxidative/endoplasmic reticulum stress pathways, as well as ferroptosis-targeted therapies (ferrostatin analogs, natural products and repurposed drugs). The present review aimed to advance the current understanding of ferroptosis regulation and its potential therapeutic applications in human kidney stone disease.

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1. Introduction

Kidney stone disease ranks among the most prevalent and painful urological conditions, currently affecting ~11-12% of the adult population globally, with a >50% recurrence rate within 5 years, imposing considerable economic strain on health-care systems (1). Kidney stone disease has an annual incidence ranging from 114 to 720 per 100,000 individuals across different countries. Over the past decades, multiple distinct pathways underlying kidney stone formation have been postulated. Nevertheless, the specific mechanisms responsible for kidney stone formation and the associated renal injury remain incompletely understood. Recent evidence has established ferroptosis as a pivotal driver of oxalate-crystal nephropathy (2-4). The present review provides a comprehensive summary of the bidirectional positive feedback loop between ferroptosis, calcium oxalate crystal deposition and the associated renal injury. In addition, promising agents for ferroptosis-targeted therapy are discussed.

2. Overview of ferroptosis

Ferroptosis is a novel, iron-regulated form of oxidative cell death with potential therapeutic implications for both cancer and neurodegenerative diseases identified in 2012 (5). Ferroptosis is distinct from apoptosis, necrosis, and autophagy in morphology, biochemistry, and genetics. It is characterized by the iron-dependent accumulation of lipid reactive oxygen species (ROS) on the cellular membrane. Mitochondria

appear shrunken with increased membrane density; however, mitochondrial electron transport chain activity is not required (2,4,6-8). Recently, ferroptosis has been intensively studied in various diseases, such as cancer (9,10), kidney injury (11,12), nervous system diseases (13,14) and cardiovascular diseases (15,16), and is suggested to be a valuable therapeutic target for prevention and treatment.

Mechanistically, iron accumulation serves as a pivotal trigger for the induction of ferroptosis. Extracellular ferric iron (Fe^{3+}) binds to transferrin (TF), and is then taken into cells through TFR1, forming the 'TF-Fe^{3+}-TFR1' complex (17). Subsequently, the intracellular Fe^{3+} is converted to ferrous iron (Fe^{2+}) and stored in the cellular iron pool, where excess iron is held in ferritin. Ferritin is responsible for iron storage, consisting of two subunits: Ferritin heavy chain (FTH) and ferritin light chain (FTL). The FTH has ferroxidase activity that converts Fe^{2+} into Fe^{3+}, and FTL can facilitate the iron nuclei formation. The disruption of this balance often results in the excessive accumulation of Fe^{2+} ions. This subsequently triggers the production and accumulation of hydroxyl radicals via the Fenton reaction; these radicals have potent oxidizing capabilities, and ultimately induce cellular ferroptosis.

The execution of ferroptosis is primarily driven by the iron-dependent lipid peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids, a process tightly regulated by key enzymes. Specifically, acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) esterify PUFAs (e.g., arachidonic acid and adrenic acid) into membrane phospholipids, which serve as substrates for peroxidation by lipoxygenases (LOXs) or the Fenton reaction (18).

The glutathione (GSH)- glutathione peroxidase 4 (GPX4) axis is a central regulatory node in the suppression of ferroptosis. GPX4 is a plasma-membrane seleno-enzyme, using GSH as electron donor to reduce membrane lipid hydroperoxides (LOOH → LOH), halting the radical chain reaction that otherwise ruptures membranes. GSH availability therefore sets GPX4 activity: Cystine import via the Xc^- system (SLC7A11/SLC3A2) supplies cysteine for GSH synthesis; Xc^- blockade lowers GSH, inactivates GPX4 and drives ferroptosis. Transcriptional control reinforces this circuit-nNuclear factor erythroid 2-related factor 2 (Nrf2) upregulates both Xc^- subunits and GPX4, whereas p53 represses SLC7A11, sensitizing cells to ferroptosis (19).

Beyond the classical GSH-GPX4 axis, several GPX4-independent antioxidant systems have been identified as critical defense mechanisms against ferroptosis. The ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10)-nicotinamide adenine dinucleotide phosphate [NAD(P)H] axis functions in parallel with GPX4 to suppress lipid peroxidation by reducing CoQ10 to the potent lipophilic antioxidant ubiquinol (20). Similarly, the GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4)-dihydrofolate reductase axis provides another layer of antioxidant defense by generating BH4. Additionally, membrane-bound O-acyltransferase (MBOAT)1/2 functions as another GPX4- and FSP1-independent ferroptosis inhibitor system. MBOAT1/2 belongs to the lysophospholipase family; using monounsaturated fatty acid (MUFA)-CoA as a substrate, this compound catalyzes the acylation of lyso-phosphatidylethanolamine (PE) to generate PE-MUFA, thereby reducing the levels of PE-PUFA, which is prone to lipid peroxidation, in cell membranes, and consequently inhibits ferroptosis at the substrate level (21). Furthermore, within the mitochondria, dihydroorotate dehydrogenase (DHODH) generates mitochondrial $CoQH_2$ to specifically inhibit mitochondrial lipid peroxidation (22-24). These interconnected pathways collectively govern the susceptibility of cells to ferroptosis.

In summary, ferroptosis is orchestrated by iron overload-driven Fenton chemistry and enzymatic lipid peroxidation, with the ACSL4/LPCAT3/LOX axis serving as a key executor. The cellular defense against this death program relies on a multilayered antioxidant network, including the canonical GSH-GPX4 system and GPX4-independent pathways such as FSP1-CoQ10, GCH1-BH4 and DHODH-$CoQH_2$. The balance between these pro-ferroptotic and anti-ferroptotic mechanisms ultimately determines cell fate under various pathological and physiological conditions (Fig. 1).

3. Bidirectional positive feedback loop between ferroptosis and calcium oxalate crystal deposition

Whether ferroptosis serves as either a causative factor or a downstream consequence of crystal formation in kidney stones remains a subject of debate. Nonetheless, it is unequivocal that the induction of ferroptosis actively promotes kidney stone formation (3,25). Conversely, the deposition of calcium oxalate (CaOx) crystals, a hallmark pathological feature of nephrolithiasis, induces substantial renal injury via diverse mechanisms, including ferroptotic cell death (3). Accordingly, a bidirectional positive feedback loop is constituted between ferroptosis and CaOx crystal deposition. In the following section, the upstream triggers, downstream effectors and feedback amplification of this loop are elaborated.

Upstream triggers (microbiota and hormones)

Gut microbiota. Ample evidence have demonstrated that the gut microbiota is involved in the formation of CaOx crystals (26), and the metabolites of gut microbiota represent the most critical mechanism underlying this process.

Specifically, bile acids (BAs), as representative metabolites of gut microbiota, are closely correlated with kidney stone formation by inducing ferroptosis by activating the heat shock protein (HSP)90α/Nrf2/heme oxygenase (HO)-1 signaling pathway (27). Specifically, BAs are metabolized into deoxycholic acid (DCA), which upregulates nuclear Nrf2 and promotes HSP90α expression. On the one hand, Nrf2 transactivates HO-1; sustained high HO-1 expression catalyzes heme degradation, releasing ferrous ions (Fe^{2+}) and carbon monoxide, which drive uncontrolled ROS generation via the Fenton reaction, lipid peroxidation and ferroptosis. On the other hand, HSP90α further enhances Nrf2 expression and directly interacts with GPX4 to promote HSP90α-mediated ubiquitination and degradation of GPX4, thereby promoting ferroptosis (28). Although Nrf2 activation typically plays a protective role (15,29,30), in this DCA-induced context it fails to protect GPX4 due to the following: i) The Nrf2/HO-1 axis amplifies ROS and lipid peroxidation; and ii) HSP90α simultaneously targets GPX4 for ubiquitin-dependent degradation. The paradoxical function of Nrf2 arises from its simultaneous transcriptional regulation of numerous target genes in the

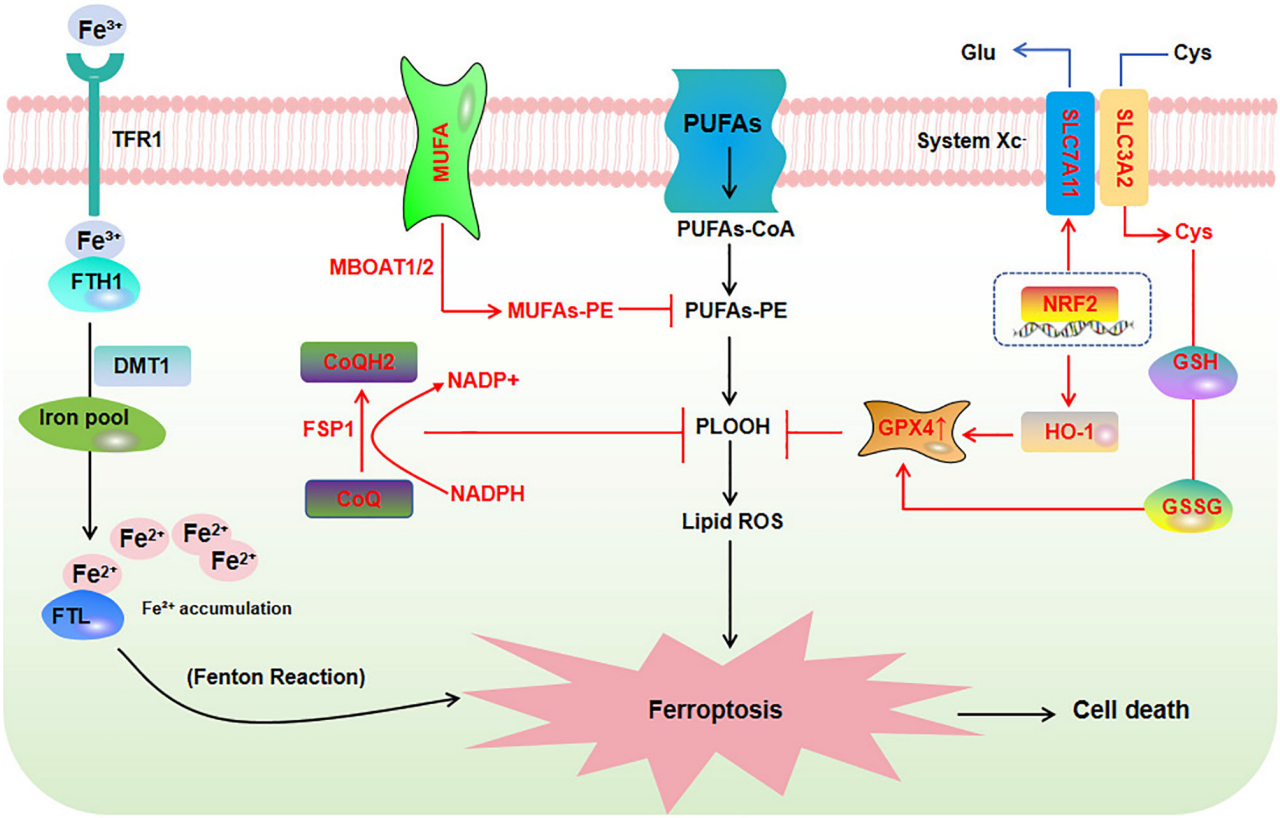


Figure 1. Classical molecular mechanisms of ferroptosis. The schematic diagram depicts the core regulatory pathways governing ferroptosis. On the left panel, the iron metabolism axis drives ferroptosis initiation: Fe^{3+} is imported via TFR1, reduced to Fe^{2+}, and stored in the cellular iron pool. The dysregulation of iron storage proteins (e.g., FTH1 and FTL) leads to excess Fe^{2+} accumulation, which fuels the Fenton reaction to generate ROS. Lipid peroxidation functions as the primary executioner of ferroptosis: PUFAs are incorporated into membrane phospholipids (PUFAs-PE) via ACSL4, generating lipid hydroperoxides (PLOOH). The uncontrolled accumulation of lipid ROS triggers mitochondrial damage and ferroptotic cell death. Anti-ferroptotic defense systems counteract lipid peroxidation: The canonical system Xc^--GSH-GPX4 axis: Cystine import via the System Xc^- complex (SLC7A11/SLC3A2) supports GSH synthesis. GPX4/GSH detoxifies lipid peroxides, and this process is reinforced by Nrf2-mediated transcriptional upregulation of SLC7A11, GPX4 and HO-1. The parallel FSP1-CoQ10 axis: FSP1 reduces ubiquinone (CoQ) to ubiquinol ($CoQH_2$), a lipophilic antioxidant that directly scavenges lipid peroxides independently of GPX4. MBOAT1/2 functions as a GPX4- and FSP1-independent ferroptosis inhibitor system. MBOAT1/2 belongs to the lysophospholipase family, using MUFA-CoA as a substrate, this compound catalyzes the acylation of lyso-PE to generate PE-MUFA, thereby reducing the levels of PE-PUFA, which is prone to lipid peroxidation, in cell membranes, and consequently inhibits ferroptosis at the substrate level. Collectively, the balance between pro-ferroptotic iron overload/lipid peroxidation and anti-ferroptotic antioxidant defenses determines cellular susceptibility to ferroptosis. Activation/promotion is indicated by arrows (↑/→), and inhibition/suppression is indicated by blunt-ended lines (⊣) or down-regulation symbols (↓). Color-coding: Pro-ferroptotic pathways are indicated in black arrows, and anti-ferroptotic pathways are indicated in red arrows. Fe^{3+}, extracellular ferric iron; TFR1, transferrin receptor 1; Fe^{2+}, ferrous iron; FTH, ferritin heavy chain; FTL, ferritin light chain; ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids; GSH, glutathione; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase 1; MBOAT1/2, membrane-bound O-acyltransferase 1/2.

three major ferroptosis pathways, encompassing both ferroptosis-inhibitory factors (GPX4, SLC7A11, FTH1, NQO1 and FSP1) and ferroptosis-promoting factors (HMOX1/HO-1 and MRP1/ABCC1) (30). Therefore, Nrf2 functions as a dynamic regulatory factor, and its functional outcome is jointly determined by the relative expression balance of its target genes, cell type, metabolic and iron status, as well as the intensity and duration of its activation.

Notably, another metabolites of the gut microbiota, the unconjugated bilirubin (UCB) exerts dual effects on kidney stone formation and ferroptosis: It promotes CaOx stone formation by activating caspase-3/PARP-1, upregulating Slc26a6, and reducing crystal zeta potential (31), whereas it inhibit ferroptosis via reducing ROS/lipid peroxidation (32), upregulating Nrf2/HO-1 and GPX4 (32-34), and chelating iron to limit free iron pools (33). The ultimate outcome depends on its free concentration, the specific cell type and the local redox milieu; such context dependency establishes UCB as a sophisticated and key signaling metabolite along the gut-kidney axis.

Moreover, gut microbiota dysbiosis reduces the level of indole-3-acetic acid (IAA), an aryl hydrocarbon receptor (AHR) ligand that upregulates AHR expression and inhibits NF-κB phosphorylation (p-p65/p-IκBα), thereby significantly affecting the oxidative-inflammation-apoptosis network and blocking early stone formation (35).

Based on those molecular pathways, intervention strategies targeting the gut microbiota have shown protective effects (36,37). For instance, healthy human fecal microbiota transplantation (hFMT) can reduce serum creatinine and blood urea nitrogen, alleviate tubular injury and upregulate superoxide dismutase (SOD)/Nrf2 expression, thereby attenuating oxidative stress and renal CaOx crystal deposition (38).

In summary, the gut microbiota metabolites, such as DCA and UCB induce ferroptosis, apoptosis and crystal adhesion, while the loss of protective metabolites such as IAA promotes

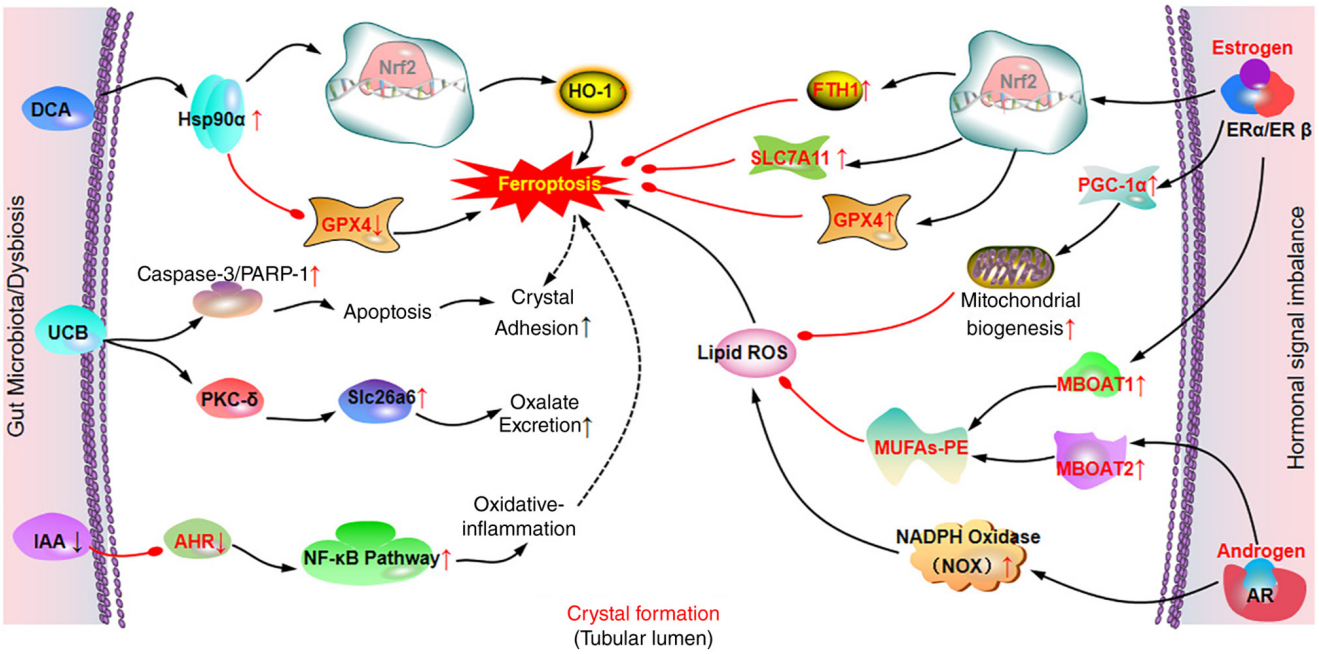


Figure 2. Upstream triggers of ferroptosis contributing to calcium oxalate crystal formation in kidney stone disease. The schematic diagram depicts the dual regulatory functions of gut microbiota-related and hormone-related pathways in ferroptosis and their downstream effects on calcium oxalate crystal formation. The left panel depicts metabolites derived from gut microbiota regulate the fate of renal tubular epithelial cells and the dynamics of crystals. DCA induces ferroptosis by upregulating Hsp90α, activating the Nrf2/HO-1 pathway, and suppressing GPX4, thus resulting in the induction of ferroptosis. UCB demonstrates dual functions. It enhances crystal adhesion, and oxalate excretion via the caspase-3/PARP-1 and Slc26a6 signaling pathways. The reduction of indole-3-acetic acid caused by gut dysbiosis impairs the AHR-mediated inhibition of the NF-κB pathway, aggravating oxidative inflammation and early stone-formation events. The right panel depicts sex hormone signaling modulates the sensitivity to ferroptosis, leading to gender differences in nephrolithiasis. Estrogen (via ERα/ERβ and PGC-1α) exerts anti-ferroptotic effects by activating Nrf2 to upregulate GPX4, SLC7A11 and FTH1, enhancing mitochondrial function, and modulating lipid metabolism. It also transcriptionally upregulates MBOAT1, which suppresses ferroptosis by enriching membrane MUFAs (MUFAs-PE) and reducing polyunsaturated fatty acids. By contrast, androgen signaling plays dual roles in ferroptosis. It can promote ferroptosis by upregulating NOX to increase ROS production; however, it also directly induces MBOAT2 expression to block the progression of ferroptosis. Collectively, ferroptosis functions as a crucial effector in crystal formation by amplifying renal injury, oxidative stress and crystal adhesion. Gut microbiota and sex hormone signaling are the major upstream regulators of this process. Activation/promotion is indicated by arrows (↑/→), and inhibition/suppression is indicated by blunt-ended lines or down-regulation symbols (↓). Color-coding: Pro-ferroptotic pathways are indicated in black arrows, and anti-ferroptotic pathways are indicated in red arrows. DCA, deoxycholic acid; Hsp90α, heat shock protein 90α; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; GPX4, glutathione peroxidase 4; UCB, unconjugated bilirubin; FTH, ferritin heavy chain; MBOAT1, membrane-bound O-acyltransferase 1; MUFA, monounsaturated fatty acid; NOX, NADPH oxidase; ROS, reactive oxygen species.

oxidative stress and inflammation. Conversely, gut microbiota-based interventions, including hFMT, probiotics and recombinant probiotics, hold therapeutic potential by restoring microbial homeostasis, enhancing oxalate degradation, and alleviating renal injury (Fig. 2). These findings highlight the gut-kidney axis as a critical regulatory system and a promising target for the prevention and treatment of nephrolithiasis.

Hormones. Hormones function as critical regulators of ferroptosis, which is involved in the formation of CaOx crystals. Accumulating evidence indicates that female animals and humans exhibit less kidney damage in ischemia-reperfusion injury than males (39,40). Estradiol plays critical roles in this sex-related protective effect via activating estrogen receptor (ER)α to inhibit TGF-βRI, thereby blocking SMAD signaling and reducing inflammation and fibrosis (39). Similarly, epidemiological data reveal that the prevalence of kidney stones is significantly higher among adult men than among women (41). With an advancing age, the risk of developing kidney stones in females continuously rises, while it exhibits an increasing and then decreasing trend in males; this is deemed to be associated with the weakening of androgen signaling (42). These observations highlight the potential significance of hormones in nephropathy and renal injury (43).

Ferroptosis is a key driver in the occurrence and progression of various nephropathies, including acute kidney injury (AKI) and renal fibrosis (11,44). Therefore, it is reasonable to speculate that hormones are closely associated with ferroptosis and may thus contribute to the pathogenesis of renal disorders. Recently, studies have demonstrated that estrogens inhibit ferroptosis through both non-genomic and genomic mechanisms, thereby protecting the kidneys from AKI (45,46). Specifically, 2-hydroxyestradiol functions as a radical-trapping antioxidant, directly inhibiting ferroptosis in renal tubules of male mice (45). Additionally, estrogen receptor 1 exerts anti-ferroptotic effects in female tubular cells by suppressing the ether lipid pathway and enhancing the hydrogen sulfide system (45). These findings provide potential therapeutic targets for AKI by modulating estrogen levels or its receptor activity (47,48).

Beyond AKI, emerging evidence links hormone signaling to ferroptosis in kidney stone disease. Results from *in vitro* and *in vivo* models have demonstrated that ERβ protects against renal CaOx crystal deposition by simultaneously inhibiting hepatic oxalate biosynthesis and renal oxidative stress-induced injury (49,50). This provides a novel molecular mechanism for the sex differences observed in the in incidence of kidney

stones and suggests that ERβ and its downstream pathways (such as NOX2) may serve as potential targets for prevention and treatment (50). These insights provide new perspectives for the management of kidney stone disease mediated by the interplay between hormones and ferroptosis.

Mechanistic studies have demonstrated that estrogen enhances cellular antioxidant defenses by activating Nrf2 and upregulating core anti-ferroptosis genes, such as GPX4, SLC7A11 and FTH1 (51,52). It also promotes mitochondrial biogenesis and function via the peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) signaling axis, reducing ROS production (53,54). Moreover, estrogen regulates lipid metabolism to lower low-density lipoprotein and increase high-density lipoprotein cholesterol, thereby reducing the lipid substrates for ferroptosis (45,55). By contrast, androgens may increase ROS production by upregulating NOX activity, deplete GSH, and weaken the GPX4 system (55,56).

Notably, MBOAT1 and MBOAT2 are transcriptionally upregulated by ER and androgen receptor, respectively. These enzymes function to transfer MUFA to lyso-PE, increasing cellular PE-MUFA, while reducing PE-PUFA, thereby suppressing ferroptosis (21). Thus, the sex hormone signaling pathway affects ferroptosis sensitivity by regulating the expression of MBOAT1 and MBOAT2. Although the involvement of MBOAT1/2 in kidney stone formation via ferroptosis has not yet been directly reported, the sex hormone-MBOAT-ferroptosis signaling axis may provide a novel perspective for the understanding of the molecular mechanisms underlying sex differences in nephrolithiasis (Fig. 2).

In summary, these hormone-mediated ferroptosis regulatory pathways significantly contribute to sex differences in nephrolithiasis. Future research is warranted ts further elucidate the crosstalk between hormone signaling and ferroptosis in kidney stone disease, and evaluate the translational potential of hormone-based interventions for nephrolithiasis.

Downstream effectors [epigenetics, inflammation and endoplasmic reticulum stress (ERS)]

Epigenetics. Epigenetics regulation is a key downstream effector of CaOx crystal initiation and deposition. In the context of CaOx-induced kidney injury, Yan *et al* (57) demonstrated that the SOX4/EZH2/SLC7A11 signaling axis plays a pivotal role in mediating ferroptosis. Specifically, CaOx crystal deposition significantly upregulates the expression of SOX4, a transcription factor known for its involvement in cell fate determination and tissue development. SOX4 functions as a master regulator in this axis by directly binding to the promoter region of EZH2, thereby enhancing its transcription (58). This upregulation of EZH2 is crucial as EZH2, as a core component of the polycomb repressive complex 2, catalyzes the trimethylation of histone H3 lysine 27 (H3K27me3), leading to the epigenetic silencing of downstream genes (59). One of the key downstream targets of EZH2 in this context is SLC7A11, a critical component of the cystine-glutamate antiporter system xc(-) that regulates intracellular GSH levels and maintains cellular antioxidant capacity. EZH2-mediated H3K27me3 enrichment at the SLC7A11 promoter region suppresses its expression, thereby disrupting the antioxidant defense system and promoting ferroptosis (60). This suppression of SLC7A11 expression results in decreased GSH levels and impaired activity of GPX4, which is essential for neutralizing lipid peroxides and maintaining cellular redox balance (61,62). Consequently, the imbalance in antioxidant defenses leads to increased lipid peroxidation [e.g., malondialdehyde (MDA)] and ROS accumulation, and elevated expression of ferroptosis-related proteins, such as ACSL4, hallmarks of ferroptosis. In summary, the SOX4/EZH2/SLC7A11 signaling axis is activated in CaOx-induced kidney injury, driving ferroptosis through epigenetic suppression of SLC7A11 expression (57)

Furthermore, the role of sirtuin1 (Sirt1), an NAD^+-dependent histone deacetylase, has also been investigated in the kidneys of glycolate-treated mice, and the expression of this protein was found to be significantly downregulated in this model (63,64). Sirt1 can effectively reduce ferroptosis via the PGC-1α/NRF2/GPX4 pathway, leading to reduced lipid peroxidation and thus, the alleviation of CaOx-induced renal injury (64,65). Mechanistic studies have demonstrated that Sirt1, mainly through the core epigenetic event of H3K27me3 demethylation, simultaneously activates the miR-34b-5p-Toll-like receptor (TLR)4 anti-inflammatory pathway and the Irg1-itaconate metabolic pathway (63-66). These concerted actions collectively affect CaOx crystal-induced renal injury, inflammation and oxidative stress, and ultimately influence the formation and deposition of kidney stones.

Inflammatory signaling. Inflammation and the aberrant activation of related signaling pathways are the most common causes of kidney injury and crystal deposition (67,68). Among these, the JAK/STAT pathway, particularly STAT3, has been identified as a key regulator of ferroptosis in kidney cells (69). Mechanistically, GPX4 and SLC7A11, the core regulatory nodes of ferroptosis, serve as downstream effectors of STAT3; by modulating their expression, STAT3 suppresses System Xc^- function and thereby promotes ferroptosis (70). Moreover, oxalate induces osteogenic-like differentiation of exacerbate renal tubular epithelial cells (RTECs) via JAK2/STAT3 activation, a recognized initiating step in kidney stone formation (71). Likewise, insulin-like growth factor 1 receptor promotes CaOx crystal-induced epithelial-mesenchymal transition through the JAK2/STAT3 signaling pathway, which in turn facilitates the progression of kidney stones (72,73).

In their study, Wang *et al* (74) demonstrated that the expression of acyl-coenzyme A thioesterase (ACOT)4 and ACOT6 in HK-2 cells was upregulated following CaOx treatment. Further analyses revealed that ACOT4 and ACOT6 may serve as protective factors against CaOx-induced renal tubular cell injury by reducing apoptosis and activating the Akt/mTOR signaling pathway (74). Notably, the overactivation of the PI3K-Akt-mTOR signaling pathway has been shown to protect cancer cells against oxidative stress and ferroptotic cell death (75). These findings suggest that CaOx may upregulate ACOT4 and ACOT6 expression to attenuate renal cell injury, potentially through modulation of Akt/mTOR-related ferroptosis. Similarly, MMP7, a matrix metalloproteinase that can degrade extracellular matrix components, such as collagen and proteoglycans, plays a role in various pathological processes, including inflammation and tissue repair (76,77). The marked upregulation of MMP7 in CaOx kidney stone samples indicates that it may exacerbate renal tubular epithelial cell injury

by promoting inflammatory responses and extracellular matrix degradation, thereby facilitating ferroptosis.

Furthermore, studies have verified that CaOx crystals function as potent activators of the renal NF-κB pathway, which is a core driver of renal tubular injury and inflammatory responses (6,78,79). The activation of the NF-κB pathway suppresses ferritin expression and downregulates the antioxidant system, thereby exacerbating iron overload and lipid peroxidation (80,81). In models such as endothelial injury, NF-κB activation can drive ferroptosis-mediated tissue damage (80).

In summary, an interconnected signaling network exists, which mediates the crosstalk between inflammation and ferroptosis in CaOx crystal-induced renal damage. Therapeutically, targeting these pathways, particularly inhibiting NF-κB or JAK-STAT3, or enhancing the protective PI3K-AKT-mTOR signaling, holds promise for mitigating crystal-induced renal injury.

ROS and ERS. Its well-established that oxalate and CaOx monohydrate (COM) can induce oxidative stress in renal tubular cells (6,82-84). For instance, Chuenwisad *et al* (85) demonstrated that oxalate, COM and urine from patients with kidney stones induced oxidative stress in HK-2 cells by increasing the content of protein carbonyls and decreasing the total antioxidant capacity. As a consequence of this oxidative insult, the proportion of senescent HK-2 cells, as revealed by SA-βgal staining, significantly increases, while the relative telomere length markedly shortens (85-87). Moreover, Sun *et al* (88) suggested that the depletion of GSH directly impairs the activity of GPX4, thereby compromising the cellular capacity to effectively eliminate lipid peroxides. This in turn leads to the accumulation of lipid ROS and the onset of ferroptosis (88).

Further studies have demonstrated that in both oxalate-induced cell models and renal stone mouse models, ERS-related proteins (e.g., GRP78, ATF4 and CHOP) and ferroptosis-related proteins (e.g., GPX4, XCT and FTH1) are significantly upregulated (89-91). The CaOx crystal deposition drives oxidative stress-dependent ferroptosis through a cascade of ERS, glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1)-mediated glutathione depletion, GPX4 inactivation and subsequent lipid peroxidation. CHAC1 serves as the core molecular link between crystal stimulation and ferroptosis, represents a potential interventional target in this process (89,92,93).

To further investigate the kidney stone pathological environment, researchers exposed HK-2 cells to 2 mM CaOx for 24 h. Compared with the controls, CaOx exposure significantly increased the mRNA levels of ACSL4, MMP7, transglutaminase 2, palmitoyl-protein thioesterase 1 and lactotransferrin, while it decreased those of protein tyrosine kinase 2, dual specificity phosphatase 4, secreted protein acidic and rich in cysteine like 1 and pleckstrin homology like domain family B member 2 (94). These key genes associated with ERS in CaOx kidney stones may play a crucial role in the pathogenesis of CaOx kidney stones, with their expression levels closely related to the formation and development of kidney stones (94). Among these, ACSL4 is a long-chain fatty acyl-CoA synthetase that can activate fatty acids into fatty acyl-CoA and is a key initiator of ferroptosis. During ferroptosis, ACSL4 increases the levels of lipid peroxidation within cells, thereby promoting cell death (14,95). The significant upregulation of ACSL4 in CaOx kidney stone samples suggests that it may exacerbate renal tubular epithelial cell damage by promoting ferroptosis during the formation of kidney stones.

In summary, accumulating evidence demonstrates that CaOx crystal deposition triggers oxidative stress-driven ferroptosis in renal tubular cells through multiple interconnected pathways. Key molecules, such as ACSL4 is upregulated in CaOx kidney stones, potentially exacerbating cell injury via ferroptosis. These findings highlight that ferroptosis is a critical pathological process in CaOx-induced kidney injury and may represent a promising therapeutic target for nephrolithiasis-related renal injury (Fig. 3).

Feedback amplification [damage-associated molecular patterns (DAMPs) and NF-κB reactivation]. Accumulating evidence demonstrates that the ferroptosis-kidney stone formation loop is a core pathogenic mechanism driving kidney injury and disease progression. This loop has been proposed as a promising therapeutic target, and disrupting it via various inhibitors may produce protective effects.

First, the lipid peroxidation end-products, MDA and 4-hydroxynonenal (4-HNE), along with DAMPs released from ferroptotic cells, activate NF-κB signaling, which in turn promotes the secretion of pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β). These inflammatory mediators exacerbate RTEC injury, create conditions for crystal deposition and further lower the ferroptosis threshold, completing a positive feedback loop (3,25,96). A number of protective agents, such as lycopene, curcumin and mesenchymal stem cells, exert their anti-inflammatory, antioxidant and renoprotective effects precisely by inhibiting NF-κB activation (97-100). Animal studies have indicated that suppressing the NF-κB signaling pathway represents a potentially effective therapeutic strategy for CaOx nephrolithiasis (101,102).

Second, ferroptotic RTECs release DAMPs [high mobility group box 1 (HMGB1), ATP, DNA, mitochondrial DNA, oxidized phospholipids and MDA] that activate the innate immune response, recruiting and activating macrophages. These macrophages secrete mediators, such as macrophage inhibitory protein-1, monocyte chemoattractant protein-1 and IL-8, leading to interstitial inflammation (3). Critically, inflammatory factors released by macrophages act back on RTECs, upregulating adhesion molecules (CD44, osteopontin and hyaluronic acid) on the surface of ferroptosis-susceptible RTECs, promoting crystal adhesion and disposition. This immune-amplification loop contributes to Randall's plaque formation and the transition to fibrosis.

Third, during ferroptosis the ‘wave of death’ phenomenon amplifies the loop spatially (3,103). When a proximal RTEC undergoes ferroptosis, NADPH diffuses from adjacent cells to the dead cell via gap junctions and tight junctions, reducing the antioxidant capacity of neighboring cells and rendering them more susceptible to ferroptosis. This chain reaction causes large-area tubular damage, releasing more DAMPs and lipid peroxidation products, and further amplifying inflammation (3), in turns promote kidney stone formation. GPX4 serves as a critical negative regulator of the vicious cycle of cellular injury; however, its loss amplifies this feedback loop. GPX4

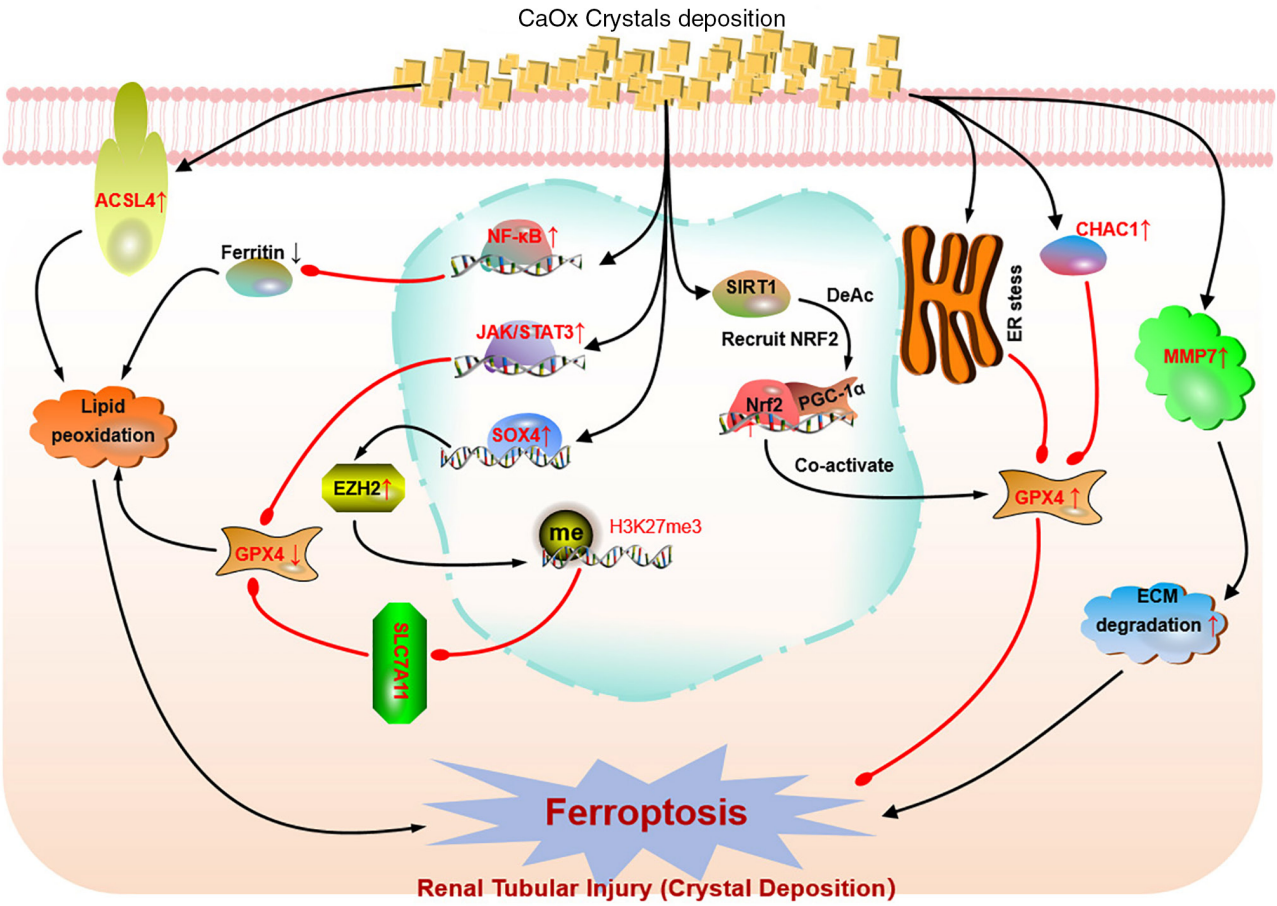


Figure 3. Downstream effectors of the bidirectional positive feedback loop between ferroptosis and calcium oxalate crystal deposition. CaOx crystals trigger three interconnected pathways: i) Epigenetic pathway (top panel): The upregulation of SOX4 enhances EZH2 transcription, leading to the H3K27me3-mediated silencing of SLC7A11. The resulting GSH depletion and GPX4 inactivation promote lipid peroxidation. ii) Inflammatory pathways (middle panel): Activation of NF-κB and JAK-STAT3 suppresses ferritin, GPX4 and SLC7A11, exacerbating iron overload and lipid ROS. DAMPs released from ferroptotic cells further activate NF-κB, forming a positive feedback loop. iii) Oxidative stress/ER stress pathway (bottom panel): ER stress upregulates CHAC1, depleting GSH and inactivating GPX4. Elevated ACSL4 and MMP7 enhance lipid peroxidation and extracellular matrix degradation, while Sirt1 (normally protective via PGC-1α/NRF2/GPX4) is decreased. All pathways converge on ferroptosis (GSH↓, GPX4↓, lipid ROS↑, MDA/4-HNE↑), leading to renal tubular injury and inflammation. Activation/promotion is indicated by arrows (↑/→), and inhibition/suppression is indicated by blunt-ended lines or down-regulation symbols (↓). Color-coding: pro-ferroptotic pathways are indicated in black arrows, and anti-ferroptotic pathways are indicated in red arrows. CaOx, calcium oxalate; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; ER stress, endoplasmic reticulum stress.

deficiency exacerbates TGF-β1 production and fibrosis, while elevated GPX4 attenuates NF-κB activation (3,29,44).

In summary, these findings indicated that the ferroptosis-kidney stone formation loop, driven by lipid peroxidation, inflammatory amplification and intercellular propagation, constitutes a key pathogenic mechanism in renal injury and stone disease, and that targeted disruption of this vicious cycle, particularly by GPX4 restoration or NF-κB inhibition, represents a promising therapeutic strategy for clinical intervention.

4. Ferroptosis-targeted therapy for kidney stone-related injury

Ferrostatin-1 (Fer-1) and its analogues for the prevention of ferroptosis in kidney stone-related renal injury. Ferroptosis can be therapeutically targeted by a couple of small molecules, including natural products and synthetic chemical compounds, which are collectively referred to as ferrostatins. The restoration of this axis via ferrostatin-1, Nrf2 activators or melatonin reinstates GPX4 activity, limits lipid peroxidation, and attenuates CaOx-induced injury and stone formation, thereby identifying the GSH-GPX4 axis as a feasible therapeutic target for nephrolithiasis (2,57,83,84,91,104-106). Several high-quality compounds with acceptable pharmacodynamic and pharmacokinetic properties are currently under development (16,107), and the initiation of clinical trials appears imminent.

Fer-1, as a lead molecule, inhibits ferroptosis by scavenging initiating alkoxyl radicals produced by ferrous iron from lipid hydroperoxides (107). In both *in vivo* and *in vitro* models, Fer-1 upregulates the key ferroptosis regulators GPX4 and SLC7A11, downregulates HO-1 and SOD2, attenuates mitochondrial damage, reduces ROS levels and lipid peroxidation, decreases tubular epithelial cell apoptosis and renal tissue injury, reverses the aberrant expression of fibrosis markers including E-cadherin, vimentin and α-SMA, and significantly suppresses CaOx crystal deposition (108). In CaOx models, Fer-1 partially restores the downregulated expression of the hub ferroptosis-related genes lysosome-associated membrane protein 2 and mouse double minute 4, which further enhances

its protective effects against oxalate-induced kidney injury and stone formation (109).

However, Fer-1 has a low *in vivo* functionality due to potential metabolic and plasma instability. Multiple attempts have been made to improve the potency of this type of molecule (110). A more stable and readily soluble series of Fer-1 analogues have been synthesized in recent studies (110-115). The Fer-1 analog, XJB-5-131, exhibits low nanomolar efficacy against erastin- and RSL3-induced ferroptosis, as well as ferroptosis in AKI and subsequent chronic kidney disease (116). By contrast, has been shown to JP4-039 display significantly higher EC50 values of 3.58 and 1.27 μM, correlating with its lower mitochondrial enrichment (117,118). XJB-5-131 and JP4-039 are multifunctional mitochondria-targeted protective molecules that have been shown to exert tissue-protective effects in various disease models by inhibiting ferroptosis, scavenging ROS, preventing apoptosis and promoting mitophagy (116-120).

New analogues, such as UAMC-3203, UAMC-3234, UAMC-3206 and UAMC-3240, have significantly longer microsomal half-lives and improved solubility, addressing the limitations of Fer-1. Molecular dynamics simulations suggest that these analogues rapidly insert into phospholipid bilayers, consistent with their role in inhibiting lipid peroxidation (111,121). Another Fer-1 analog, Srs11-92, was found to mitigate brain infarct size, neuronal damage and neurological deficits in the mouse model of middle cerebral artery occlusion and reperfusion by inhibiting iron overload, ROS accumulation and neuroinflammation. This was achieved through the upregulation of GPX4, Nrf2 and HO-1, while concurrently suppressing HMGB1 and NF-κB p65 in the injured hippocampus or Alzheimer's disease models (112,122,123). Beyond the analogs listed above, numerous Fer-1 derivatives have been comprehensively reviewed and are summarized in Table I.

Calcium oxalate crystals adhere to renal tubular epithelial cells, inducing substantial ROS generation, which leads to lipid peroxidation and the release of iron ions. This stimulus causes a decrease in GPX4 expression and an upregulation of ACSL4 in renal tubular epithelial cells, ultimately resulting in ferroptosis (82-85,124). The inhibitory effects of Fer-1 and its analogues on ferroptosis have been well-documented in various experimental models; however, their roles in oxalate-induced kidney injury and nephrolithiasis remain largely understudied, and whether they exert protective effects against crystal-induced renal damage remains unclear.

Natural products for the prevention of ferroptosis in kidney stone-related renal injury. Numerous natural products have been reported to exhibit significant anti-ferroptotic effects, highlighting their potential as therapeutic agents for diseases involving ferroptosis, including urolithiasis. For example, ursolic acid (UA) exerts antitumor effects in malignant tumors of the urinary system (prostate cancer/bladder cancer/renal cell carcinoma) by inducing ferroptosis, specifically by promoting SLC7A11-mediated ferroptosis; however, in subarachnoid hemorrhage, UA inhibits ferroptosis via brain-targeted nanodelivery, thereby exerting neuroprotective effects (125,126). Additionally, UA can alleviate CaOx-induced injury to renal tubular epithelial cells by suppressing oxidative stress and inflammation (127). UA exerts reverse effects in different types of disease, which may be attributed to the expression levels of SLC7A11 or the state of oxidative stress. The application of nanomaterial-based delivery systems to achieve neuroprotection may also be related to how these delivery systems modulate the local concentration, targeting specificity, and functional selectivity of UA. As an upstream multi-target protective agent (inhibiting oxidative stress and inflammation), UA directly alleviate CaOx-induced RTEC injury, suggesting its potential for further research and clinical application in the management of renal stone disease.

Similarly, 6-gingerol can promote ferroptosis in prostate cancer, while inhibiting ferroptosis in inflammatory, metabolic or vascular diseases (15,125,128,129). As an NRF2 activator, 6-gingerol ameliorates atherosclerosis and protects against diabetic cardiomyopathy by inhibiting ferroptosis via NRF2-mediated anti-ferroptotic pathways (15,128,129). It can also alleviate inflammation and oxidative stress by suppressing the JAK/STAT signaling pathway (130), reduce high glucose-induced inflammation and cytotoxicity in THP-1 cells by inhibiting the TLR4/NF-κB pathway (131), and attenuate NNK-induced oxidative damage in lung cells by activating the NRF2 pathway (132).

Talaroconvolutin A inhibits RSL3-induced ferroptosis, likely by alleviating lipid peroxidation and upregulating NRF2 expression (133). Baicalin activates signaling pathways, such as Nrf2/GPX4, PI3K/AKT/GPX4 and SIRT3/GPX4, thereby reducing lipid peroxidation and ROS accumulation. Additionally, baicalin can directly chelate iron ions, reducing iron deposition and oxidative damage (134-138). Kukoamine A has been shown to exert protective effects in a model of osteoarthritis by inhibiting inflammation and ferroptosis via the SIRT1/GPX4 signaling pathway, and to alleviate nephrolithiasis by inhibiting endogenous oxalate synthesis through the IL-6/JAK/STAT3/D-amino acid oxidase signaling pathway (139,140).

Collectively, these natural products demonstrate significant potential in modulating ferroptosis, either by directly inducing ferroptosis or by protecting cells from ferroptotic damage. Their mechanisms involve regulating key pathways, such as iron metabolism, lipid peroxidation and antioxidant defense systems. These findings provide preliminary evidence that numerous natural products may hold therapeutic potential for the prevention and treatment of kidney stone disease by modulating ferroptosis; however, this remains to be validated by further mechanistic and clinical studies.

Existing drugs for preventing ferroptosis in kidney stone-related renal injury. A series of existing drugs exhibit novel therapeutic indications. For example, mMetformin, an approved and core first-line medication for type 2 diabetes, can reverse COM-induced oxidative stress by activating the Nrf2/HO-1 signaling pathway, thereby simultaneously inhibiting CaOx crystal formation (dissolving COM and promoting COD conversion) and mitigating renal tubular injury (106). However, metformin also exerts antitumor effects in breast cancer cells by inhibiting the UFMylation of SLC7A11, thereby promoting ferroptosis (141). These opposite effects on ferroptosis may be due to differences in SLC7A11 expression levels across different disease types, as well as the diverse pharmacological effects of metformin in distinct disease contexts.

Table I. Agents for ferroptosis-targeted therapy.

Type of agent	Agent name	Targets	Mechanism	(Refs.)
Ferrostatin-1 (Fer-1) and its' analogues	Ferrostatin-1 (Fer-1)	PL-O; Fe^{2+}	Inhibits lipid peroxidation and complements the enzymatic pathway of GPX4	(107,162,168)
	XJB-5-131/ JP4-039	ROS	Inhibit ferroptosis by scavenging free radicals generated during mitochondrial lipid peroxidation	(16,116,117)
	UAMC-3203, UAMC-3234, UAMC-3206, UAMC-3240	Lipid peroxide radical	Trapping free radicals and inhibiting lipid peroxidation	(111,121)
	Srs11-92	ROS	It functions in the iron-dependent lipid peroxidation pathway; similar to Fer-1, exerts an inhibitory effect on ferroptosis	(112,122)
	SRS 1022, SRS 16-86	ROS	Prevents ROS production from lipid peroxidation	(16,169)
Natural products	Ursolic acid (UA)	SLC7A11	Promotes Mcl-1-dependent apoptosis and SLC7A11-mediated ferroptosis	(125,126,137)
	6-Gingerol	Nrf2/HO-1 Pathway	6-Gingerol inhibits EMT and induces autophagy and ferroptosis in prostate cancer; in diabetic cardiomyopathy, 6-Gingerol inhibits ferroptosis by activating the Nrf2/HO-1 signaling pathway	(125,170,171)
	Erianin	Nrf2/GPX4,	Inactivation of the Nrf2 pathway leads to iron-dependent lipid ROS accumulation, depletion of glutathione (GSH), and downregulation of GPX4/xCT expression, collectively inducing ferroptosis.	(125,172)
		ALOX12/P53	Induces ALOX12/P53 mRNA m^6A modification, thereby promoting Fe^{2+} accumulation	(125,173)
		PDP2/JNK, GPX4/SLC7A11	Induces ferroptosis via JNK or GPX4 downregulation	(125,174-176)
	Talaroconvolutin A (TalaA)	ROS; MAPK pathway	TalaA induces ferroptosis by elevating ROS levels and inhibiting MAPK-mediated phosphorylation	(177,178)
	Baicalin	JAK2/STAT3/ GPX4	Baicalein blocks the JAK2/STAT3/GPX4 axis, leading to downregulation of GPX4 expression, which promotes the accumulation of lipid peroxidation and thereby triggers ferroptosis.	(179,180)
		Nrf2/HO-1↑; GPX4↑/xCT↑; ACSL4↓	Baicalein suppresses ferroptosis by upregulating GPX4/xCT expression and modulating the ACSL4/ACSL3 axis.	(29,135)
	Kukoamine A (KuKA)	SIRT1/GPX4	Inhibits inflammation and ferroptosis via SIRT1/GPX4	(140)
	IPolyphyllin I (PPI)	Nrf2/HO-1/GPX4 axis	PPI regulates the Nrf2/HO-1/GPX4 antioxidant axis by binding to Nrf2, HO-1, and GPX4 proteins, thereby enhancing mitochondrial disruption and inducing ferroptosis.	(181)
	Sanguinarine chloride (S.C.)	ROS	S.C. induces ferroptosis in prostate cancer cells through ROS-mediated BACH1 degradation and HMOX1 upregulation.	(125,182,183)

Table I. Continued.

Type of agent	Agent name	Targets	Mechanism	(Refs.)
	Icariin	miR-7/mTOR/ SREBP1	Icariin induces autophagy and ferroptosis via miR-7, disrupting lipid metabolism by inhibiting the mTOR/SREBP1 pathway.	(125,184)
		Nrf2/ HO-1↓	Inhibition of the Nrf2/HO-1 signaling pathway	(185)
		Xc^-/GPX4	Inhibition of ferroptosis via the Xc^-/GPX4 axis protects synovial cells; it also regulates cellular iron homeostasis and downregulates the expression of cell death-associated genes	(186)
	Luteolin	TFEB nuclear translocation	Triggers ferroptosis via TFEB-driven ferritin degradation, causing iron buildup and lipid peroxidation	(125,187)
		Nr4a1/SLC7A11-GPX4 axis	Targeting Nr4a1 activates the SLC7A11-GPX4 antioxidant axis, reduces lipid peroxidation, inhibits ferroptosis, and thereby alleviates CaOx-induced renal injury	(188)
	Artemisinin	GPX4; System Xc^-; ROCK1/ ATF3; HO-1; HSD17B4	Artemisinin generates ROS and leads to oxidative stress in cancer cells, which contributes to cell death. Its derivatives kill cancer cells depending on the presence of ferric iron ions (Fe^{3+}).	(16,189-192)
	Sinularin	Nrf2/GPX4 signaling axis	Sinularin induces ferroptosis by increasing intracellular ROS levels, depleting glutathione, and downregulating the Nrf2 and GPX4 signaling axis.	(125,193)
	Evodiamine	GPX4	Evodiamine triggers ferroptosis by inhibiting GPX4 and inducing lipid peroxidation.	(125,194)
	Abietic acid (AA)	HO-1 and GPX4	AA selectively triggers cellular ferroptosis through HO-1 activation, GPX4 inhibition, and iron-dependent lipid peroxidation.	(125,195)
	Nodosin	HMOX1 ↑ and SLC7A11/ GPX4 axis↓	Nodosin induces ferroptosis by upregulating HMOX1 and modulating the SLC7A11/GPX4 axis.	(125,196,197)
		Oxidative stress, inflammation	Modulates and reduces oxidative stress, Inhibits inflammation, Inhibits ferroptosis	(197)
	Lycorine	GPX4↓ + ACSL4 ↑	Lycorine induces cellular ferroptosis by downregulating GPX4 and upregulating ACSL4.	(125,198)
	Icariside II (ICS II)	miR-324-3p ↑ → GPX4 ↓	ICS II downregulates GPX4 by upregulating miR-324-3p, leading to ROS and Fe^{2+} accumulation, lipid peroxidation, and reduced GSH.	(125,199)
Existing drugs	Metformin	SLC7A11↓	Inhibition of UFMylation leads to decreased protein stability of SLC7A11, thereby triggering ferroptotic cell death.	(141)
		Nrf2/HO-1 signaling	Activating the Nrf2/HO-1 signaling pathway, thereby simultaneously inhibiting calcium oxalate crystal formation and mitigating renal tubular injury	(106)
		Nrf2/GPX4↑	In cardiovascular and renal diseases, metformin exerts an anti ferroptotic effect primarily by activating the Nrf2/GPX4 pathway and upregulating Sirt1 signaling.	(200)

Table I. Continued.

Type of agent	Agent name	Targets	Mechanism	(Refs.)
		AMPKα ↑ → NOX4 ↓	Activation of AMPKα, downregulation of NOX4 (NADPH oxidase 4) expression, reduction of reactive oxygen species and lipid peroxidation, inhibition of ferroptosis	(201)
		Sirt1 ↑	Activate Sirt1, which in turn activates PGC-1α, then recruits NRF2 to the GPX4 promoter, co-activates GPX4 transcription, and ultimately suppresses ferroptosis.	(64)
	Reserpine	Activate Nrf2/SLC7A11/ GPX4	Reserpine upregulates Nrf2, thereby promoting the expression of its downstream target genes SLC7A11 and GPX4, which effectively inhibits ferroptosis.	(142,143)
	Propafenone	JNK/JUN pathway	Propafenone upregulates HMOX1 via the JNK/JUN pathway, leading to mitochondrial Fe^{2+} overload and thereby promoting ferroptosis.	(202)
	Omeprazole	Lipid peroxyl radicals	As a lipid peroxyl radical scavenger, exerts antioxidant activity	(147)
		ATP7A	Omeprazole, as a copper transporter inhibitor, acts on the ATP7A target to synergistically induce copper death and ferroptosis.	(148)
	Lidocaine	p38 MAPK pathway	Inhibits p38 MAPK; reduces lipid peroxidation; upregulates GPX4; attenuates ferroptosis	(149)
		miR-382-5p↑SLC7A11 ↓	Inhibits the expression of SLC7A11 and GPX4 in breast and ovarian cancer cells, triggering ferroptosis.	(203)
	Promethazine	Lipid peroxyl radicals	Scavenges lipid peroxyl radicals; antioxidant; anti-ferroptosis; anti-inflammatory	(147,150,151, 204,205)
	Cariprazine	DHCR7	A selective DHCR7 inhibitor that raises intracellular 7-DHC levels, inhibiting ferroptosis.	(153,206)
	Sulfasalazine	Nrf2/SLC7A11/ GPX4 axis	A classic System Xc^- (SLC7A11/SLC3A2) inhibitor that triggers ferroptosis by blocking cystine uptake.	(122,207,208)
	Lanperisone	System Xc-	Promotes ROS production and indirectly inhibits GPX4 activity via GSH depletion.	(16,209)
	N-acetyl-L-cysteine (NAC)	ROS	Scavenges cellular ROS	(16,210,211)
		-	As a precursor of acetylcysteine, it bypasses the System Xc^- transporter and directly replenishes intracellular cysteine.	(212)
		SIRT3	Activation of the SIRT3-SOD2/GPX4 pathway-maintenance of mitochondrial redox homeostasis	(213)
	Vitamin E	5-Lipoxygenase, GPX4	Maintains cellular redox homeostasis; scavenges free radicals, upregulates GPX4 expression	(16,214,215)
	Zileuton	5-Lipoxygenase (5-LOX)	Inhibits Alox5, thereby suppressing enzymatic lipid peroxidation	(16)
	Deferoxamine (DFO)	Fe^{2+}	Chelates intracellular Fe^{2+}/Fe^{3+}, thereby inhibiting the Fenton reaction.	(153,216,217)
	Sorafenib	System Xc-	Blocks system Xc- activity and GSH synthesis	(16,218,219)
Other molecules	TASIN-30	EBP	Selective EBP inhibitor that lowers intracellular 7-DHC levels, increasing susceptibility to ferroptosis.	(153)

Table I. Continued.

Type of agent	Agent name	Targets	Mechanism	(Refs.)
	Glutamate	System Xc-	Induce ferroptosis via competitive inhibition of System Xc^-	(16,220,221)
	Buthionine sulfoximine	GSH	Inhibits γ-glutamyl cysteine synthetase and GSH synthesis	(16)
	DPI2	GSH	Depletes GSH	(16)
	DPI7,10,12,13,17, 18,19	GPX4	Covalently binds to the GPX4 and promotes accumulation of lipid hydroperoxides	(16,222)
	GKT137831 (setanaxib)	Nox4	GKT137831 inhibits ferroptosis by attenuating ROS production through targeting the NADPH oxidase isoform 4 (Nox4).	(16,223)
	Mitoquinone	ROS	Inhibits mitochondrial superoxide generation	(16,224)
	Idebenone	ROS	Idebenone is an antioxidant that can inhibit ferroptosis by scavenging reactive oxygen species (ROS) and preventing lipid peroxidation.	(153)
	Necrostatin-1	RIPK1 and IDO	Inducing XCT (SLC7A11) expression enhances System Xc^-/cystine uptake, thereby maintaining GSH/GPX4 levels to suppress ferroptosis.	(162,212)
	Liproxstatin (Lip-1)	ROS	Prevents ROS production from lipid peroxidation	(162,168)
	Erastin	System Xc	Inhibiting System Xc^- (cystine/glutamate antiporter), depleting GSH, and thereby indirectly inactivating GPX4, the accumulation of lipid peroxidation is promoted, ultimately inducing ferroptosis.	(122,225)
	RSL3	GPX4	Covalent binding to GPX4 promotes the accumulation of lipid hydroperoxides, thereby inducing ferroptosis.	(122,226,227)
	Ferrous ammonium sulfate ($FeSO_4$)	ROS production	FeSO4 triggers ferroptosis by directly catalyzing lipid peroxidation via increased intracellular iron, catalyze the Fenton reaction	(111,228)
	FGF21	NRF2	Activating the Nrf2 signaling pathway, then upregulates SLC7A11 (maintaining the GSH/GPX4 antioxidant defense), downregulates ACSL4 (reducing lipid peroxidation substrates), and downregulates TFR1 (reducing iron uptake), thereby inhibiting ferroptosis.	(105,229)

Upward arrows indicate upregulation and downward arrows indicate downregulation. Right-pointing arrows indicate the direction of regulation. ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; EMT, epithelial-mesenchymal transition; GSH, glutathione.

Reserpine is a classic sympatholytic agent, belonging to anti-hypertensive drugs (142). Previous research has demonstrated that it exerts anti-ferroptotic and anti-inflammatory effects in the context of cisplatin-induced acute kidney injury (143).

Propafenone, a class Ic antiarrhythmic agent clinically applied for rhythm control in patients with atrial fibrillation and supraventricular tachycardia (144), exerts sodium channel blocking (145) and immunomodulatory effects (146). These effects may alleviate oxalate-induced cellular stress and inflammatory responses to a certain degree, thereby indirectly inhibiting ferroptosis and preventing kidney stone formation.

Omeprazole, a classic proton pump inhibitor that potently suppresses gastric acid secretion by irreversibly inhibiting the H^+/K^+-ATPase in gastric parietal cells. Recent studies have revealed that omeprazole also possesses non-antacid effects, including antioxidant activity, free radical scavenging, regulation of copper metabolism and exhibits ferroptosis-related activity in various disease models (147,148). Lidocaine attenuates hypoxia/reoxygenation-induced inflammation and apoptosis, and inhibits ferroptosis in lung epithelial cells by suppressing the p38 MAPK pathway, thereby exerting a protective effect (149). Promethazine exhibits non-histamine

receptor-dependent antioxidant and anti-ferroptosis activities, and can protect multiple organs from ferroptosis-related damage by scavenging lipid peroxyl radicals (147,150,151). Reduced vitamin K (VKH_2 and menadiol) possesses potent antioxidant activity and can inhibit ferroptosis by directly scavenging lipid peroxidation free radicals through various mechanisms (152).

Collectively, the examples discussed above, metformin, reserpine, propafenone, omeprazole, lidocaine, promethazine and reduced VKH_2, illustrate a compelling yet largely unexplored phenomenon: A range of established drugs, originally developed for distinct therapeutic purposes, may exert unexpected renoprotective and anti-lithogenic effects via the common pathway of ferroptosis inhibition. Given the vast arsenal of clinically approved drugs with previously unrecognized anti-ferroptotic properties, it is highly probable that a number of other molecules await identification and systematic evaluation. Future drug repurposing efforts, leveraging high-throughput screening, computational approaches and ferroptosis-specific biomarker assays, are urgently required to uncover additional candidates that could effectively prevent or treat nephrolithiasis by targeting ferroptosis. Such discoveries may open new avenues for non-surgical, mechanism-based intervention in kidney stone disease.

Other molecules for the prevention of ferroptosis in renal injury associated with kidney stones. 7-Dehydrocholesterol (7-DHC) is a direct precursor of cholesterol in the cholesterol biosynthetic pathway, produced from the catalytic reaction of 7-DHC reductase (DHCR7), and is also an endogenous sterol possessing a conjugated diene structure. Recently, Multiple studies have demonstrated that 7-DHC can inhibit phospholipid autoxidation through its conjugated diene structure, thereby protecting cells from ferroptosis (153-155). As a naturally occurring potent ferroptosis inhibitor, 7-DHC has been shown to protect renal tubular epithelial cells in a renal ischemia-reperfusion injury model (155). Ferroptosis can be significantly suppressed by either inhibiting DHCR7 or directly supplementing 7-DHC (153,154,156,157).

In 2019, Doll *et al* (158) first identified FSP1 (AIFM2) as a glutathione-independent ferroptosis suppressor. FSP1 reduces CoQ10 to ubiquinol in an NAD(P)H-dependent manner; ubiquinol then functions as a lipid peroxyl radical trapping agent, thereby inhibiting phospholipid peroxidation and ferroptosis (158). Mishima *et al* (155) found that FSP1 can also reduce vitamin K to its hydroquinone form, which is a potent lipid peroxyl radical trapping agent. Nakamura *et al* (159) demonstrated that phase separation leads to a loss of FSP1 function, inhibits its ability to suppress lipid peroxidation, thereby synergizing with GPX4 inhibitors to potentiate ferroptotic cell death, which represents a fundamentally new paradigm for pharmacological targeting of ferroptosis. Recently, Ye *et al* (12) demonstrated that *Fsp1* deficiency significantly exacerbated oxalate-induced AKI, as evidenced by aggravated renal function, enhanced oxidative stress and increased ferroptosis. Conversely, the overexpression of FSP1 in renal tubular epithelial cells markedly reduced CaOx-induced lipid peroxidation and cellular ferroptosis (12). Oxalate exposure downregulated the expression of endogenous FSP1 and GPX4, while upregulating the pro-ferroptotic gene, ACSL4, thereby disrupting the redox balance and promoting ferroptosis (12). These findings suggest that FSP1 may function as an endogenous protective factor that assists renal tubular cells in resisting oxalate-induced ferroptosis. Therefore, FSP1 may be a potential target for the prevention and treatment of kidney stone disease, particularly CaOx-associated renal injury; however, further validation is warranted.

With the rapid advancement of biochemical and structural biology techniques, novel small molecules and theoretical concepts for modulating ferroptosis have emerged continuously, opening up new directions for the treatment of ferroptosis-related diseases. However, current findings are based predominantly on *in vitro* cell lines and *in vivo* rodent models, which still have several limitations on their translational to human kidney stone disease. First, *in vitro* experiments rely almost exclusively on proximal tubular epithelial cell lines, whereas stones develop in the renal papilla, and the roles of other renal resident cells and infiltrating immune cells during stone formation remain unexplored (160). Second, current *in vivo* models do not fully reproduce human nephrolithiasis: Experimentally induced hyperoxaluria generates animal models with CaOx crystal deposition, which may more effectively represent hyperoxaluria-driven conditions than common idiopathic stone disease. Third, the association between ferroptosis and stone pathogenesis remains to be rigorously validated in humans. There is still a lack of clinical cohort data confirming whether ferroptosis biomarkers (e.g., GPX4 downregulation and lipid peroxide accumulation) are genuinely elevated in kidney stone patients, and whether targeting ferroptosis can reduce stone formation or recurrence in patients. Collectively, these model limitations underscore the need for more representative, human-relevant models for ferroptosis related therapeutic agent selection and investigation for nephrolithiasis.

5. Challenges in translating ferroptosis-targeting small molecules into clinical practice for the treatment of kidney stones

Despite the notable progress being made in identifying the role of ferroptosis in CaOx nephropathy, and the promising advances on anti-ferroptosis molecules, the clinical translation of ferroptosis-targeting strategies for kidney stone disease faces multifaceted challenges that require critical evaluation.

Foremost among these is the pharmacokinetic insufficiency of current ferroptosis inhibitors. The conventional anti-ferroptosis agent, Fer-1, suffers from both poor aqueous solubility, and a low metabolic and plasma stability (111,161). Its direct analog, SRS11-92, still retains the ester-based metabolic instability of the Fer-1 core (123). Although liproxstatin-1 displays a substantial bioavailability, it is constrained by a short plasma half-life (162). The optimized UAMC series, UAMC-3240 and UAMC-3234, exhibit marked species-dependent intrinsic clearance, while their earlier sulfonamide progenitors were limited by poor solubility *in vivo* (111). JP4-039 is limited not by solubility, but by its low mitochondrial enrichment, which markedly restricts its efficacy (118). Collectively, these pharmacokinetic and targeting drawbacks impair the bioavailability and renal tissue penetration.

A second challenge is the off-target toxicity and systemic safety concerns inherent to systemic ferroptosis modulation. The complete inhibition of ferroptosis may increase the risk of tumorigenesis by undermining the surveillance that ferroptosis exerts over potentially malignant cells, which has not been addressed in long-term safety assessments (9). Moreover, the complete inhibition of ferroptosis may disrupt iron homeostasis, and the lack of renal-specific drug delivery systems exacerbates this detrimental effect (10,163). The development of kidney-directed nanocarriers, exosomes, or antibody-drug conjugates is proposed (164-166), although this remains at the preclinical stage.

A third challenge is the absence of specific and standardized biomarkers to guide patient selection and monitor therapeutic response. Although BODIPY C11 staining combined with MDA and 4-HNE detection has been used to confirm the association between COM-induced cytotoxicity and ferroptosis in COM treated HK-2 cells, these methods are non-specific, as their signals can also be generated by mitochondrial-derived oxidative stress (44,64,161). Some emerging candidates, such as oxidized phospholipids and ferroptosis-related ncRNAs (e.g., LINC00239, lncRNA CRCMSL, and lncRNA HMG), lack standardized detection protocols and clinical validation (44,167).

Finally, the incompletely understood role of ferroptosis in kidney stone disease complicates rational drug screen and design. Studies using CaOx models have demonstrated that ferroptosis, oxidative stress, inflammation, autophagy and apoptosis function simultaneously, which indicates that single-target monotherapy may not achieve sufficient therapeutic effects (2-4,25,89). Current clinical stone therapy relies on pharmaceuticals that modulate urinary crystalloid supersaturation, and the integration of ferroptosis-targeting agents still requires additional clinical evidence verifying their specific efficacy in reducing stone burden. Overcoming these barriers, through renal-specific drug delivery systems, rigorous pharmacokinetic profiling, long-term safety profiling, validated biomarkers and combination therapeutic strategies, is essential before ferroptosis-targeting small molecules can become a cornerstone of kidney stone management.

6. Conclusions

Ferroptosis functions as a pivotal driver of oxalate crystal nephropathy by facilitating crystal nucleation and adhesion. Conversely, oxalate crystals exacerbate ferroptosis, thereby amplifying renal injury. This bidirectional positive feedback loop suggests that ferroptosis may represent a promising pharmacological target for the treatment of crystal nephropathy. Small molecules, including natural products and synthetic chemical compounds, have been found to exert certain efficacy in inhibiting or activating ferroptosis for disease treatment. In kidney stone disease, although novel findings shed light, considerable efforts are still warranted, and further evidence is required for the implication of ferroptosis regulators in disease treatment and prevention.

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Authors' contributions

ZW and HL proposed the topic of the review. QD and CX investigated the literature and prepared the manuscript. ZW and YZ revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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