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Review Article

Mitochondrial Reactive Oxygen Species and Nephrolithiasis

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Abstract

Mitochondrial redox/oxidative balance are vital for cellular life and death. Mitochondria are considered as the most important sub cellular site of reactive oxygen species production in mammalian organs. Reactive oxygen species produced by mitochondria can cause damage to mitochondrial components and initiate degradative processes. The kidney requires ample amount of mitochondria to remove waste from the blood and regulate fluid and electrolyte balance. Adverse conditions of organelle stress such as decreased altered energy metabolism in mitochondria contribute in the progression and development of kidney diseases. Nephrolithiasis is a kidney disease in which solid urinary components form crystals, precipitated out of the urine and shaped into stones. Studies have suggested that oxidative stress and associated renal injury paved the way for crystal deposition in the renal tissue. Mitochondria are anticipated as the foremost source of intracellular reactive oxygen species under oxalate induced nephrolithiasis. Persistent mitochondrial dysfunction results in the progression of nephrolithiasis. Although different approaches to minimize mitochondrial dysfunction through regulation of mitochondrial ROS production using antioxidants have been accomplished yet mitochondria specific antioxidants are the prerequisite. This review offers a glimpse into the role of mitochondrial reactive oxygen species in nephrolithiasis and the future perspective of potential antioxidant therapies.

Keywords: Mitochondria; Kidney; Hyperoxaluria; Nephrolithiasis; Reactive oxygen species; Antioxidants

Abbreviations

ATP adenosine triphosphate; CaOx calcium oxalate; COM calcium oxalate monohydrate; IMM inner mitochondrial membrane; MitoQ mitoquinone; mtDNA mitochondrial DNA; mETC mitochondrial electron transport chain; mPTP mitochondrial permeability transition pore; NAG N-acetyl-beta-glucosaminidase; NAC N-Acetyl cysteine; OMM outer mitochondrial membrane; OXPHOS oxidative phosphorylation; 4-PBA 4-phenylbutyrate; RNS reactive nitrogen species; ROS reactive oxygen species; SOD superoxide dismutase; SkQ1 plastoquinonyl-decyl-triphenylphosphonium; SkQR1 plastoquinonyl-decyl-rhodamine19

Introduction

Mitochondria are ubiquitous, intracellular organelles known as powerhouses of the cell [1]. Inside all eukaryotic cells, the mitochondria are involved in essential metabolic processes for production of the adenosine triphosphate (ATP), the energy-rich compound that drives important cell functions. Mitochondria participate in numerous cellular functions including ion homeostasis, heme and steroid synthesis, calcium signalling, apoptosis [2]. Besides this organelle comprises major pathways for apoptosis and accumulates DNA mutations that may be linked to augmented rates of oxidants production and a number of degenerative diseases [3]. Over the last few years, it has been demonstrated that perturbation in mitochondrial activities is one of the major culprit behind renal injury associated with kidney stone formation. This suggests the hypothesis that renal cells use intracellular stress responses to initiate crystallisation. In this regard, mitochondrial reactive oxygen species (ROS) are considered as the perfect connection. Calcium oxalate (CaOx) stones account for the vast majority of calculi in kidney stone formers wherein hyperoxaluria is the major cause. Recently a study with Metabolic syndrome (MS) showed that hyperoxaluria in rats causes severe morphological alterations with a significant impairment of renal function and kidney stone formation [4]. Also, autophagy antagonist chloroquine significantly attenuate oxalate-induced autophagy activation, oxidative injury and mitochondrial damage of renal tubular cells in vitro and in vivo, as well as hyperoxaluria-induced CaOx crystals depositions in rat kidney [5]. Due to high reoccurrence rate of nephrolithiasis, it is one of the most irksome diseases of the kidney, which may lead to chronic kidney disease or permanent renal failure. Its prevalence is rising globally with the increasing incidence in women and children [6]. Around the globe only few groups are engaged in studies to comprehend new roles for the mitochondria, particularly in nephrolithiasis. The aim of the present review is to discuss the role of the mitochondrial reactive oxygen species in the progression of nephrolithiasis and the future perspective of potential antioxidant therapies.

Mitochondria - a unique sub cellular organelle

Mitochondria are remarkable organelles with a specialized double-membrane structure which forms separate regions, termed as outer mitochondrial membrane (OMM), intermembrane space, cristae formed by inner mitochondrial membrane (IMM), and matrix. The OMM has pores that permit passive diffusion of molecules up to 5 kDa. Larger molecules enter the mitochondrion through the translocases present in OMM [7]. The permeability of the OMM increases due to irreversible harm to cells, and proteins located in the intermembrane space, such as cytochrome *c*, flow out and initiate the apoptosis program. Owing to the numerous folds of cristae with oxysomes, the area of the IMM is about five times greater than that of the OMM. The IMM is embedded with abundant proteins that perform redox reactions, synthesize adenosine

triphosphate (ATP), block ionic diffusion, and regulate mitochondrial dynamics. The IMM also encloses the matrix, where the oxidative phosphorylation (OXPHOS) enzyme and mitochondrial genetic material reside [8]. Mammalian mitochondria emerge and function through the co-ordinated action of two genomes: (a) Multiple copies of bacterial-like mitochondrial DNA (mtDNA) that encode for 22 transfer RNAs, 2 ribosomal RNAs, and 13 proteins implicated in oxidative phosphorylation, and (b) the nuclear genome (nDNA) that encodes for about another 1,500 structural and functional proteins [9].

Mitochondria play a vital role in providing the great amount of energy required for several different cellular functions. Substrates obtained from other intracellular processes, such as glycolysis or fatty acid metabolism, are converted to acetyl-CoA, which enters the tricarboxylic acid cycle (TCA), and its complete degradation is coupled with the production of NADH and $FADH_2$, which are the effective electron donors for the mitochondrial electron transfort chain (mETC) [10]. The energy is stored as an electrochemical gradient across the IMM, which explains the presence of the negative mitochondrial membrane potential ($\Delta\Psi$). F1Fo-ATP synthase allows H^+ to cross the IMM and re enter the matrix, coupling the energy derived from the proton gradient with the phosphorylation of ADP to produce ATP [11]. The new ATP molecules are then ready to leave the mitochondria.

Mitochondrial associated reactive oxygen species (ROS)

It was proposed that during the respiration, 0.4–4% of the total consumed oxygen is converted into superoxide radicals via electron leakage from the respiratory chain, which also acts as second messengers in cellular signaling pathways [12]. Further the released superoxide radicals are dismutated into hydrogen peroxide (H_2O_2) and O_2 by superoxide dismutase (SOD) in the matrix or intermembrane space. H_2O_2 combines with superoxide radicals to produce Hydroxyl radicals. Superoxide radicals, H_2O_2, and hydroxyl radicals are the major forms of ROS [13]. In normal conditions, mitochondria are equipped with antioxidant system such as the thioredoxin reductase/thioredoxin/ peroxiredoxin-3,5 system, glutathione peroxidase (GPx), and glutathione (GSH) [14]. Reactive oxygen species (ROS) can lead to mild uncoupling of mitochondria, and the consequential increase in proton conductance can have a negative feedback effect on ROS production [15]. Additionally, to reduce the electrochemical gradient, and to accelerate oxygen consumption, the mitochondrial permeability transition pore (mPTP) is opened which decreases ROS production. Conversely, upsurge ROS has deleterious effects on mitochondrial DNA (mtDNA) and potentially leads to mitochondrial dysfunction, cell injury, and even apoptosis [16]. Mitochondria were considered as the main source of intracellular ROS in both physiology and pathology [17]. The pioneering work of Chance and colleagues showed that isolated mitochondria produce H_2O_2 [18]. Several different sites of ROS production have been identified in mammalian mitochondria, including complex I and complex III of the mETC and the dihydrolipoamide dehydrogenase enzyme [19-22]. Complex I produces superoxide either by a reduced flavin mononucleotide (FMN) site on complex I (a high ratio of NADH/NAD+) or by reverse electron transfer from the coenzyme Q (CoQ) pool back to complex I [23]. Normally, ROS production by complex III is much lower than ROS production by complex I. But, the role of complex III in superoxide production is significant when it is inhibited. Contribution of Complex II (succinate dehydrogenase) to ROS formation is related to reverse electron transfer, the process by which electrons are transferred from succinate to ubiquinone

via complex II and then back to complex I, where ROS are produced [24,25]. Other than the respiratory chain complexes, mitochondrial enzymes also participate in ROS production, such as acyl- CoA dehydrogenase and glycerol α-phosphate dehydrogenase during the oxidation of lipid-derived substrates [26,27]. Monoamine oxidase, Dihydroorotate dehydrogenase, Pyruvate and α-ketoglutarate dehydrogenase enzymes are additional mitochondrial ROS sources [28,29]. The reactive nitrogen species (RNS) which are produced by reaction of anion superoxide with nitric oxide (NO) interact with mitochondrial components and results in alterations of mitochondrial respiration [30,31]. p66Shc protein acts as a redox-enzyme, generating H_2O_2 by binding cytochrome *c* [32].

The Kidney

Kidney has the second highest mitochondrial content and oxygen consumption after the heart thus it is considered as one of the most energy consuming organ in the human body [33]. Results from a study measuring the resting energy expenditure of different organs in healthy individuals found that the kidney and heart have the highest resting metabolic rates [34]. This high resting metabolic rate for the kidney is due to the requirement of plenty of mitochondria to supply adequate energy to perform various important tasks like removal of waste from the blood, reabsorbtion of nutrients, maintenance of acid–base homeostasis, blood pressure regulation, and maintaining the balance of electrolytes and fluid. Mitochondria are the exclusive source of energy to the sodium–potassium pump to produce ion gradients across the cellular membrane. The proximal tubule, the loop of Henle, the distal tubule and the collecting duct of the kidney require active transport to reabsorb ions [35]. On the other hand, glomerular filtration is a passive process which is dependent on the hydrostatic pressure in the glomeruli. Proximal tubules reabsorb 80% of the filtrate that passes through the glomerulus, hence require added active transport mechanisms in comparison to other renal cell types [36]. So, they have more mitochondria than any other structure in the kidney. The proper functioning of the proximal tubule depends upon the ability of mitochondria to sense and respond to changes in nutrient availability and energy demand by maintaining mitochondrial homeostasis [33]. Therefore mitochondrial dysfunction plays a crucial role in the pathogenesis of kidney diseases. Evidence is emerging that defects in mitochondrial function may lead to kidney chronic diseases [37-39].

Nephrolithiasis and mitochondria

Nephrolithiasis, a medical condition in which kidney stones are formed from crystals precipitating from the urine, and grow within the urinary tract, has been considered as a common, painful condition. Nephrolithiasis is not simply an isolated urologic disease, but instead a disorder with systemic complications, including an increased risk for chronic kidney disease [40]. Nephrolithiasis has become a rising problem and the third prevalent disorder affecting the urinary tract with high recurrence [41]. This disorder involves a complex of events, such as supersaturation, crystal nucleation, growth, aggregation, retention within renal tubules and migration to the renal papillary surfaces. The majority (up to 80%) of all stones are mainly composed of calcium oxalate (CaOx). Most research on the etiology and prevention of urinary tract stone disease has been directed toward the role of elevated urinary levels of oxalate, calcium, and uric acid in stone formation [42]. An elevated level of urinary oxalate (hyperoxaluria) is considered as an important factor of CaOx nephrolithiasis [43,44].

Oxalate, a by-product of metabolism, is primarily filtered at the glomerulus, where its concentration is usually, 1–5 µM; patients with kidney stone disease may have filtered oxalate loads that are 10–20 times higher [45]. Many laboratories have illustrated that exposure to such high oxalate concentrations can elicit an array of toxic responses at the level of renal cells. Early indication for renal oxalate toxicity was suggested indirectly by studies analyzing the urinary excretion of renal injury marker enzymes like N-acetyl-beta-glucosaminidase (NAG) in stone-forming and healthy individuals; higher than normal urinary enzyme values suggested the presence of tubular damage in patients with stones [46]. Rat models of nephrolithiasis have been used to study such damage in greater detail, revealing renal epithelial membrane disruption, increased incidence of inclusion bodies in tubular cells, discharge of cellular enzymes, epithelial erosion and the formation of plaques at the tips of the renal papillae [47,48]. Cultured renal epithelial cells exposed to elevated oxalate concentrations showed similar toxic effects *in vitro*: compromised cell integrity, release of cellular enzymes and necrotic and apoptotic cell death [49]. Many researchers have recommended that underlying renal cell injury augments the probability of crystal attachment to renal epithelial cells, both *in vivo* and *in vitro* in renal tubular cells [50-52]. Remnants of injured cells may also add to stone formation by forming nidi for crystal nucleation and by promoting crystal agglomeration [53,54].

Accumulating data have suggested that high oxalate concentration led to renal oxidative stress which could play a significant and adverse role in the initiation and progression of renal cell injury [55,56]. Reactive oxygen species may be produced in renal cells in response to oxalate exposure by several cellular mechanisms. Augmented free radical generation and related injury to the renal tubules are considered a prelude to the complex sequel of stone formation [57]. Studies have suggested that mitochondria are the key supplier of free radicals in oxalate toxicity, and the role of other non-mitochondrial sources is nominal [58-60] (Figure 1). Another study has shown that calcium oxalate monohydrate (COM) crystals were able to inhibit the mitochondrial respiratory chain in proximal tubular cells [61]. The *in vitro* and *in vivo* studies show that oxalate disturbs the electron transport chain in mitochondria and induces the leak of free radicals (Jonassen *et al.,* 2003). Isolated mitochondria reacted to oxalate exposure by the increase of ROS, lipid peroxides and oxidized thiol proteins [62]. Taurine treatment to hyperoxaluric rats has been shown to reverse mitochondrial changes in the kidneys and reduce the crystal deposition [63]. Mitochondrial damage is suggested to be induced by the opening of mitochondrial permeability transition pore (mPTP). Different factors such as calcium overload and oxidative stress results in the opening of the permeability transition pore in the inner mitochondrial membrane. This uncouples oxidative phosphorylation and compromises intracellular ATP levels finally leading to necrotic cell death [64]. Mitochondrial mPTP opening depends on the activation of cyclophilin D in the mitochondrial matrix by ROS produced by NADPH oxidase and is inhibited by cyclosporine A (CSA). CSA averted the depolarization of mitochondrial membrane, a decline in SOD expression, an increase in 4-hydroxy-2-nonenal (4-HNE) and discharge of cytochrome c into the cytosol in NR52E renal epithelial cells exposed to CaOx monohydrate crystals *in vitro. In vivo* CSA treatment resulted in reduced mitochondrial damage, oxidative stress and CaOx crystal deposition in the kidneys [65]. In view of above reports, mitochondria are not only an originator but also a target of ROS, hence mitochondrial ROS is a key factor in a vicious cycle by which oxidative stress is induced and promoted in nephrolithiasis (Figure 2).

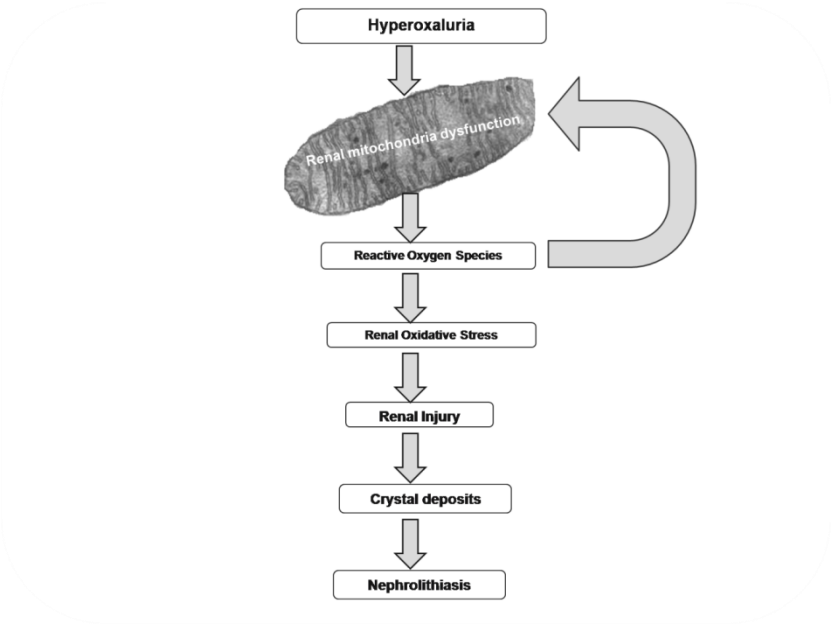

Figure 1: Potential mechanism for kidney stone formation via mitochondrial oxidative stress

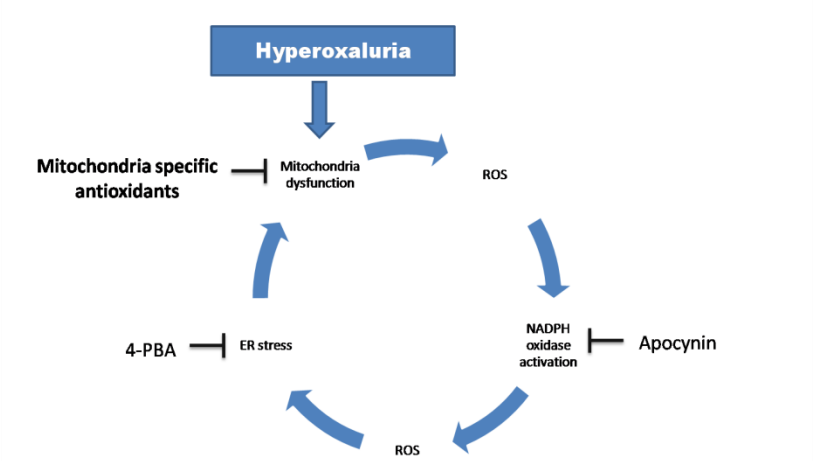

Figure 2: Hyperoxaluria generated vicious cycle of ROS in kidney

Anti-oxidants targeted to mitochondria

Therapeutic molecules that target reactive oxygen species induced mitochondrial dysfunction hold great promise in diseases that have confirmed involvement of oxidative stress. Nephrolithiasis emerges as one such case. Our research group have been working on kidney stones and its management from last three decades [59,66-72]. The studies in our lab described the critical role of mitochondrial oxidative stress in hyperoxaluria induced nephrolithiasis. N-Acetyl cysteine (NAC), an antioxidant and GSH precursor, proved to be beneficial in combating hyperoxaluria induced nephrolithiasis to

some extent (Sharma et al 2015). It has shown an outstanding efficacy in prevention of hyperoxaluria-induced mitochondrial damage. But subsistence of moderate crystalluria in NAC treated hyperoxaluric rats proposed an essential adjuvant therapy along with NAC. Thus a study was designed with NADPH oxidase inhibitor, Apocynin (4-hydroxy-3-methoxy-acetophenone), to evaluate the contribution of a possible feed-forward vicious cycle of ROS between mitochondria and NADPH Oxidase during nephrolithiasis. NAC in combination with Apocynin synergistically inhibited nephrolithiasis progression [59]. To describe systematically how mitochondrial proteins/pathways govern the renal damage and calcium oxalate crystal adhesion in hyperoxaluria large-scale proteomics was conducted. The study suggested that hyperoxaluria modified the levels of several important proteins involved in metabolism and oxidative phosphorylation in renal mitochondria. Also, alterations in mitochondrial molecular chaperones and proteins involved in antioxidant defence were reported [70].

However, the mitochondrion is not a single unit rather mitochondria and the endoplasmic reticulum (ER) are tightly associated. Under conditions of stress, Ca^{2+} is the most prominent signaling factor that is released from the ER and, at high concentration, mediates the transfer of an apoptosis signal to mitochondria as the executioner organelle for cell death. Therefore, to further explore the causes behind renal stone disease, a study was designed with a small chemical chaperone 4-phenylbutyrate (4-PBA), used as ER stress inhibitor, in hyperoxaluria [68]. Although 4-PBA decreased the hyperoxaluric manifestations yet mitochondria specific antioxidants are the prerequisite (Figure 2).

Some anti-oxidants were designed to amend the function of mitochondria which exploit the unique structural and functional characteristics of this organelle. Some important mitochondrial targets for therapeutic intervention include electron transport chain components, the permeability transition pore, and the mitochondrial membranes. Mitochondria-targeted antioxidants adjust the levels of ROS, thereby reducing mitochondria-driven cell death. At present, a number of compounds that are able to electrophoretically accumulate in mitochondria have been synthesized; they are effective at very low concentrations. The mitochondria-targeted antioxidants include substances like as SkQs and MitoQ. The formation of these chemical compounds was based on the studies by the group of V.P. Skulachev and E.A. Lieberman with lipophilic phosphonium cations [73]. These studies described that lipophilic ions with a delocalized charge shielded by bulky substituents freely penetrate into mitochondria and submitochondrial particles under the action of the electric field of the inner mitochondrial membrane. Results from various studies described that even small concentrations of mitochondria-targeted antioxidants such as MitoQ, SkQ1, SkQR1 were highly efficient in showing antioxidant activity in aqueous solutions, lipid micelles, liposomes, isolated mitochondria, and cell cultures. The protective effect of these substances was demonstrated in various models of ROS-associated diseases, including the models of such pathological states of the kidney as acute kidney injury, kidney ischemia-reperfusion.

MitoQuinone (MitoQ) is a positively charged lipophilic cation, it is accumulated in the negatively charged interior of mitochondria. The antioxidant component of MitoQ is the ubiquinone that is also found in coenzyme Q_{10}. By the action of the enzyme Complex II in the mitochondrial respiratory chain, ubiquinone part of MitoQ is rapidly activated to the active ubiquinol antioxidant. After detoxifying ROS, the ubiquinol part of MitoQ is converted to ubiquinone, which is by complex II be recycled back to active antioxidant

ubiquinol. This process makes MitoQ an effective mitochondria-targeted antioxidant. MitoQ reduced intracellular superoxide and inhibited cyst epithelial cell proliferation through extracellular signal-related kinase/MAPK inactivation in Autosomal Dominant Polycystic Kidney Disease [74]**.** A study investigated the effect of MitoQ in decreasing the severity of renal ischemia-reperfusion injury (IRI) in rats demonstrated that MitoQ can reduce the severity of renal damage in rodent IRI models using T2-weighted imaging and DCE-MRI [75]. Mitoquinone in phase II clinical trials reduced plasma ALT and aspartate aminotransferase in patients with chronic HCV infection [76].

Plastoquinonyl-decyl-triphenylphosphonium (SkQ1)

Several research groups from Russia and other countries synthesized (SkQs) comprising plastoquinone (an antioxidant moiety), a penetrating cation, and a decane or pentane linker. They selected SkQ derivatives with the highest permeability, namely plastoquinonyl-decyl-triphenylphosphonium(SkQ1),plastoquinonyl-decyl-rhodamine19 (SkQR1),and methylplastoquinonyl decyltriphenylphosphonium (SkQ3) to study the anti- and prooxidant properties of these substances [73]. In this compound named SkQ1, ubiquinone was replaced by plastoquinone [77]. SkQ1 manifested a strong therapeutic action on some already pronounced retinopathies, in particular, congenital retinal dysplasia [73]. The effect of SkQ1 on kidney IRI using a culture of kidney epithelial cells has been studied. Preincubation with SkQ1 increased survival of these cells and diminished mitochondrial fission induced by the anoxia/reoxygenation procedure [78].

Plastoquinonyl-decyl-rhodamine19 (SkQR1)

The same research group used a mitochondria-targeted compound containing a charged rhodamine molecule conjugated with plastoquinone named SkQR1 in another experiment [79]. Rats exposed to kidney IRI normalized the ROS level and lipid peroxidized products in kidney mitochondria after an intraperitoneal injection of SkQR1, they also showed significantly decreased BUN and blood creatinine levels. The SKQR1 lowered mortality of experimental rats compared to animals that were subjected to kidney IRI without any given drug. The study concluded that SkQR1 provided linked synergy between antioxidative effects and ischemic tolerance signaling mechanisms owing to the targeted delivery of this compound to mitochondria [80]. Besides SkQR1 reduces the death of kidney epithelium cells and decreases the severity of renal failure caused by gentamycin. SkQR1 also reduced the gentamycin induced hearing loss [81].

Conclusion

The information presented here demonstrated that the disruption in the renal mitochondrial homeostasis due to oxidative stress can result in mitochondrial dysfunction and renal damage. Although much is known about mitochondria functions but the precise role in renal disease remains to be determined. It is apparent; however, that mitochondrial dysfunction occurs early in kidney stone disease. Furthermore, the decrease in the mitochondrial antioxidant defence system after hyperoxaluria might lead to the continued impairment of renal mitochondria function, leading to renal injury and stone formation. Since the repair of renal cell and the recovery of renal function depend upon the ATP production ability of mitochondria, restoring mitochondrial function might reverse cellular injury and restore renal function. In the upcoming time, a more detailed study of the mechanisms of action of various types of mitochondria targeted antioxidants in the nephrolithiasis needs to be conducted, also their therapeutic values and toxicological properties are to be

analysed. Collectively, the research outcomes till date necessitate targeting mitochondrial homeostasis in hyperoxaluria induced nephrolithiasis to restore mitochondrial function and initiate renal repair to avoid advance renal dysfunction.

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Conflict of interest

The authors state no conflict of interest.

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