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Oxidative Stress in Urolithiasis

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Abstract

Oxygen is absolutely essential for the survival of our life. However, metabolic consumption of oxygen inevitably yields reactive oxygen species (ROS). Imbalance of ROS production and antioxidant capacity causes oxidative stress that potentially damages biomolecules leading to cell injury and death. In fact, ROS have two-faceted functions. Under physiologic condition, ROS function as signaling molecules and participate in maintaining redox balance. In pathology, ROS induce oxidative stress that critically involves in the development of several diseases including urolithiasis (UL). UL or urinary stone disease is a common urologic condition in all countries with progressively increasing prevalence. Most of UL are multifactorial with polygenic susceptibility and highly recurrent nature. Formation of urinary stones is driven by supersaturation of urinary lithogenic ions, and calcium oxalate (CaOx) is the most prevalent stone type. Oxidative stress clearly plays an active role in UL development. In vitro, lithogenic crystals induce ROS generation in renal tubular cells leading to oxidative stress, cell injury and release of inflammatory mediators. In nephrolithic rats, oxidative stress and CaOx deposit are gradually increased in the rats' kidneys. Intervention with antioxidants efficiently reduces oxidative damage and crystal deposits. Human studies show that patients with UL have increased oxidative stress and renal tubular injury relative to the non-stone-forming individuals. Increased oxidative lesions and inflammation are observed in the stone-containing kidneys of the patients. Furthermore, renal fibrosis mediated through tubular epithelial-mesenchymal transition is observed in kidneys of stone patients. Increased renal fibrosis is significantly associated with decreased kidney function. From therapeutic point of view, nutraceutical regimens that are able to reduce oxidative stress may be clinically useful alternatives for preventing stone formation and recurrence. This chapter has an intention to provide a basic knowledge of ROS generation and oxidative stress and up-to-date research findings of oxidative stress in UL based on the published articles as well as the author's studies.

Keywords: oxidative stress, reactive oxygen species, urolithiasis, kidney stone, treatment

1. Introduction

Aerobic living organisms require oxygen for their metabolism mainly to generate adenosine triphosphate (ATP) through the electron transport chain (ETC). In the aerobic metabolism, molecular oxygen (O_2) is sequentially reduced to water (H_2O), and reactive oxygen species (ROS) are generated (**Figure 1**) [1, 2]. Therefore, it is no doubt that oxygen is absolutely essential for aerobic life, but it can be very harmful under the condition that ROS are excessively generated. These good and evil faces of oxygen are called “oxygen paradox” [3–5]. A complete reduction of O_2 to H_2O requires stepwise addition of four electrons, and three ROS, viz., superoxide anion ($\cdot O_2^-$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($\cdot OH$) are respectively produced (**Figure 1**). In addition to ETC, another significant endogenous source of ROS is from oxidase and oxygenase enzymes [6]. Oxidases use oxygen as electron acceptor [7]. They catalyze the transfer of two electrons from electron donor to oxygen, and H_2O_2 is usually a byproduct. In case of oxygenases (monooxygenases and dioxygenases), they catalyze an incorporation of oxygen into substrate [7]. Dioxygenases incorporate both atoms of oxygen into substrate, while monooxygenases add one oxygen atom to substrate to yield hydroxyl substrate and water. Exogenous source of ROS includes UV/ionizing radiation, toxins, environmental pollutants, heavy metals, drugs, xenobiotics, pathogens and inflammatory cytokines [8–10]. Exposure to these substances causes increased production of ROS that further involves in the initiation of disease development. Besides ROS, reactive nitrogen species (RNS), such as nitric oxide and peroxynitrite [11–13], and reactive chloride species (RCS), such as hypochlorous acid [14, 15], also play important physiological and pathological roles in human. Fundamentally, RNS and RCS are produced by reacting with ROS, for example, peroxynitrite is formed from reaction of superoxide anion and nitric oxide. Overproduction of ROS in cells creates a tense condition called oxidative stress.

Oxidative stress is defined as an imbalance condition between amount of generated oxidants (mainly ROS) and antioxidant contents in the body, which further causes oxidative damage and injury (**Figure 2**). Oxidative stress is associated with a number of human diseases such as neurodegenerative diseases, cardiovascular diseases and cancers, and it has been

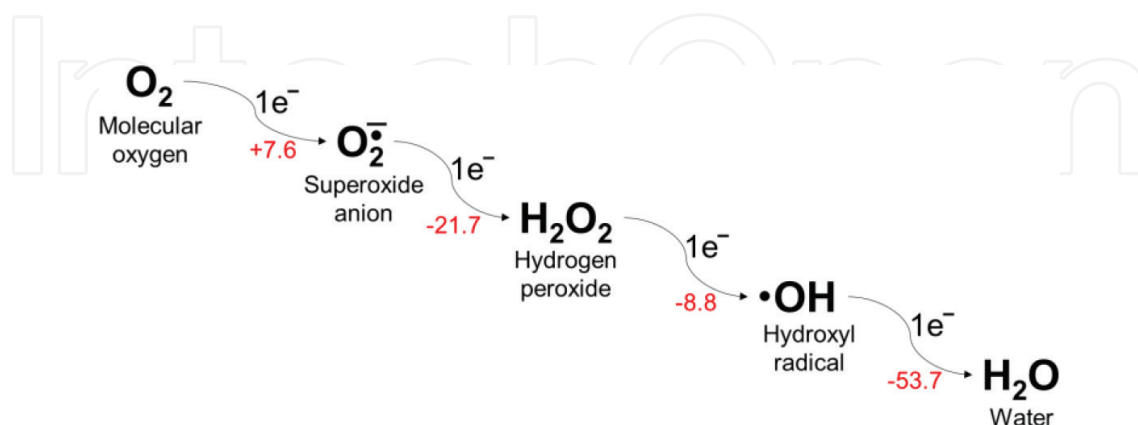


Figure 1. Stepwise reduction of O_2 to H_2O (sequential addition of four electrons). Numbers indicate the difference in Gibb’s free energy (Kcal/mol) for each reaction.

experimentally proved to mediate the disease development [16–18]. The term oxidative stress is first described by Helmut Sies in 1985 [19]. ROS are primarily generated in an aerobic metabolism, and they have a powerful oxidizing capability to damage all kinds of biomolecules in the cells [20]. Therefore, some say oxidative stress may be viewed as the price that we have to pay for the use of oxygen in our metabolism [21]. However, our body has an antioxidant defensive system to scavenge ROS, deter oxidative damage and remove oxidized lesions in order to prevent the development of oxidative stress-mediated diseases (**Figure 3**). Both enzymatic and non-enzymatic scavenging antioxidants are the first line defense to combat ROS and inhibit the formation of oxidative lesions [22]. Once lesions formed, the second line of defensive system is to fix the lesions (mostly oxidized DNA) via repairing mechanisms [23–26] or to degrade them (mostly oxidized proteins) through proteasome and turnover mechanism [27–29]. The signaling pathway that regulates cytoprotective response to ROS is the Nrf2 (nuclear factor erythroid 2 [NF-E2]-related factor 2)-Keap1 (Kelch-like ECH-associated protein 1) pathway [30–32]. In response to ROS, transcription factor Nrf2 is activated and moves to the nucleus to bind to antioxidant responsive element (ARE) in the regulatory region of target genes to initiate transcription of antioxidative genes involved in the maintenance of cellular redox homeostasis (called redox biology) [33–35]. In pathological conditions, ROS are overwhelmingly generated, and antioxidant defense systems are not sufficient to counteract resulting in oxidative injury and disease progression. Therefore, activation of Nrf2 pathway and intervention with antioxidants have been considered to be a clinically useful alternative to ameliorate oxidative stress, delay aging and reduce risk of oxidative stress-related diseases [36]. However, clinical evidences of antioxidant supplement for disease prevention are still controversial and not conclusive [37, 38]. Intake of natural antioxidants through diets, rather than commercial supplements, is believed to be a better effective way to naturally boost up antioxidative capacity in the body. In summary, ROS are a part of normal human metabolism. When ROS are chronically produced and antioxidant systems are overwhelmed, excessive ROS directly attack cellular biomolecules, cause tissue injury and eventually lead to pathology [22, 39, 40]. However, oxidative stress may not solely act as the only causative factor for disease development. It rather acts in concert or interacting with other cellular processes in order to initiate and promote the pathogenesis of diseases.

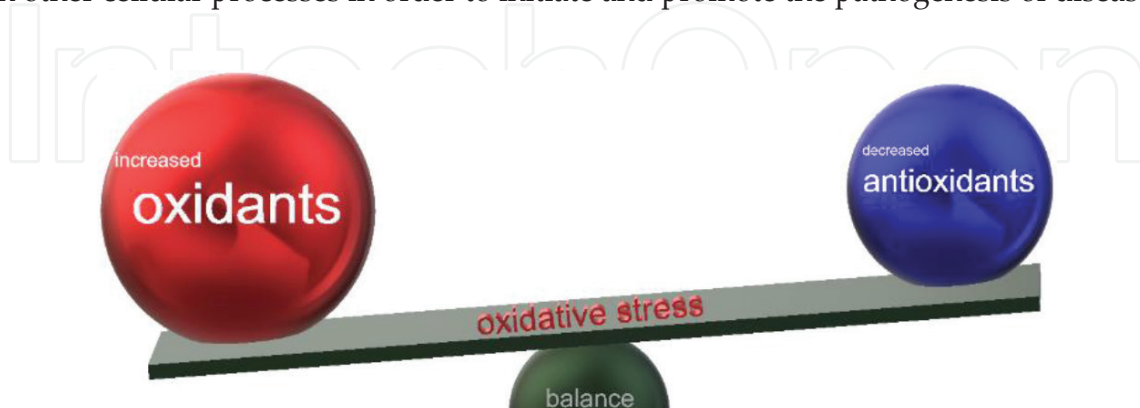


Figure 2. Oxidative stress is firstly conceptualized in 1995 by Helmut Sies as a disturbance in the oxidant-antioxidant balance in favor of oxidant, potentially leading to oxidative damage [19, 41–45].

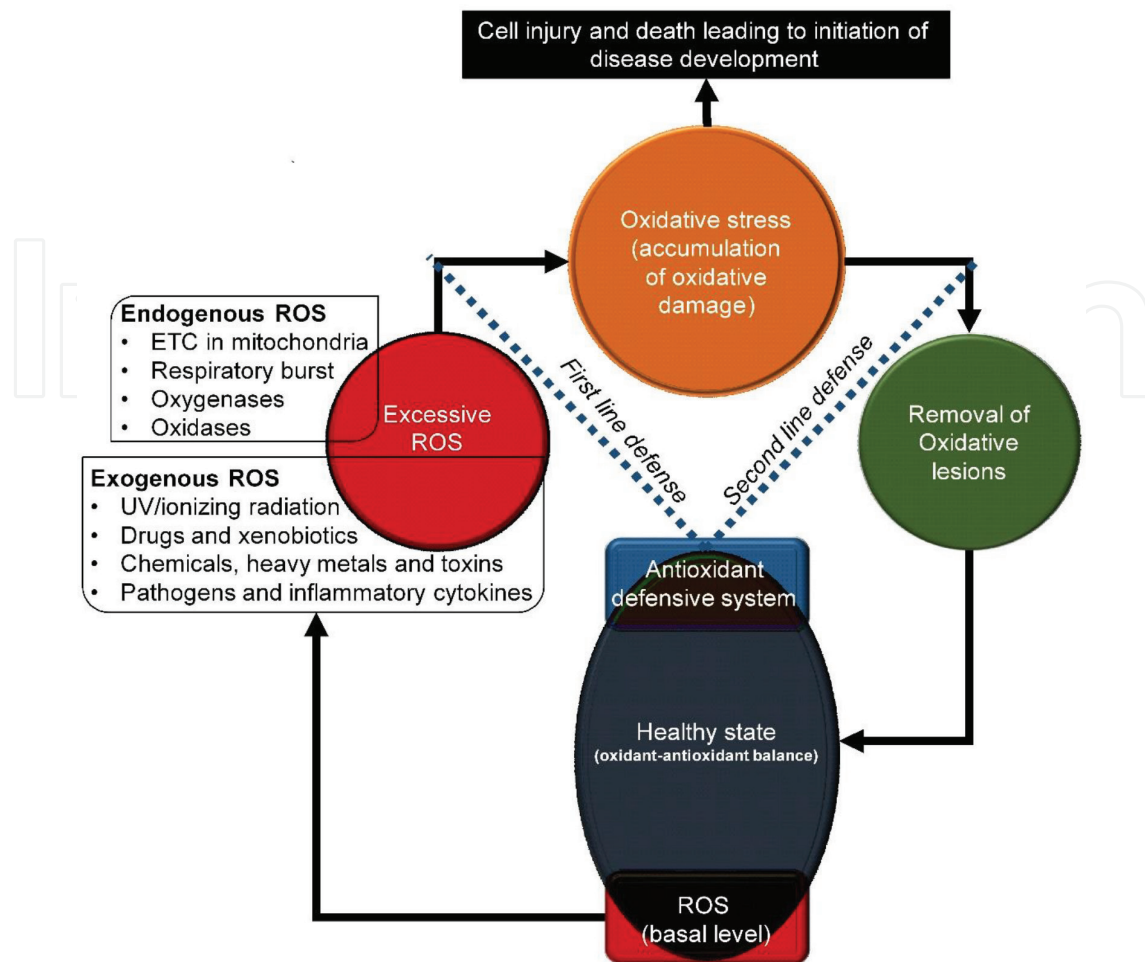


Figure 3. ROS generation, antioxidant defensive system, oxidative stress and consequences. Increased ROS production leads to oxidative damage. Antioxidant defensive system is activated to prevent oxidative injury. The first line defense is enzymatic and dietary antioxidants that directly scavenge the generated ROS. The second line defense is pathways to repair the oxidized lesions (repairing process) or degrade the oxidatively modified biomolecules (turnover process). Failure of these defensive mechanisms causes accumulation of oxidative lesions and increased degree of oxidative stress leading to cell injury, apoptosis and eventually initiation of disease development.

2. Oxidative stress

Oxygen is essential for our metabolism, but at the same time harmful ROS are produced during the reduction of oxygen to water (**Figure 1**). This two-faceted effect of oxygen is called “oxygen paradox” that is firstly conceptualized through an observation of a massive deleterious effect of reoxygenation in myocardium [46, 47]. The well-known oxygen paradox in clinical setting is a reperfusion injury [48]. In hypoxic tissues, xanthine oxidase appears to be a major source of superoxide anion after reoxygenation, and this superoxide is further reduced to form other ROS and cause an oxidative injury (**Figure 4**) [49, 50].

Excessive production of ROS and inadequacy of antioxidants cause an imbalance of oxidant-antioxidant system and result in oxidative stress. The term oxidative stress has gained more recognition and used in several research fields even in the public outside scientific community.

Usage of this term is sometimes overstressing or misusing. Therefore, the refined definition of oxidative stress is suggested in 2007 as follows: an imbalance between oxidants and antioxidants in favor of the oxidants, leading to the disruption of redox signaling and control and/or molecular damage [44, 51].

Increase in ROS production is the most common cause of oxidative stress in human body. There are at least six conditions that cause overproduction of ROS (**Table 1**). First, consumption of energy-rich diets directly increases aerobic metabolism and oxidative phosphorylation leading to increase in mitochondrial ROS production [52]. Mitochondrial superoxide anion is usually formed from an electron leakage in complexes I and III of ETC [53–55]. Second, high rate of oxygen use by strenuous work, competitive sport and exhaustive exercise is known to increase ROS generation through metabolic reactions [56–58]. Third, during reperfusion in surgery and organ transplantation, ROS are excessively generated, and ischemia or reperfusion injury is an unavoidable consequence (**Figure 4**) [59]. Forth, exposure to radiation such as UV (non-ionizing) and X-rays (ionizing) directly initiates ROS formation and causes damages to cellular biomolecules [60]. Fifth, excessive activation of phagocytic cells through respiratory burst consumes large amount of oxygen to generate superoxide anion, hydrogen peroxide and hypochlorous acid (HOCl) [61]. Sixth, exposure to toxicants activates cytochrome P450 monooxygenase (CYP450) in phase I xenobiotic biotransformation. Many reactive metabolites are unavoidably formed to cause oxidative damage [62].

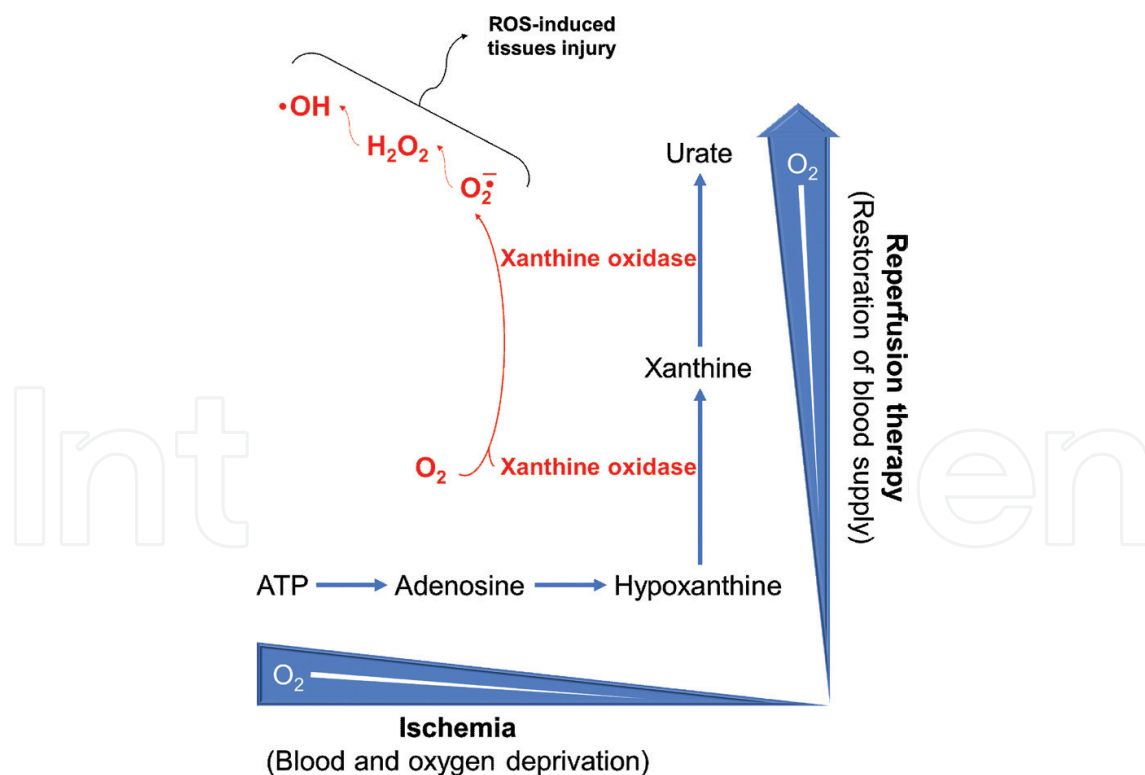


Figure 4. Proposed mechanism of excessive ROS production during reoxygenation leading to a reperfusion injury. Reduction of blood flow causes decreased oxidative phosphorylation and ATP production. Subsequently, purine precursor used in ATP synthesis is degraded to hypoxanthine. Restoration of blood supply and oxygen triggers conversion of the accumulated hypoxanthine into xanthine and uric acid by xanthine oxidase. This reaction generates superoxide anions and other ROS that further initiate oxidative tissue injury. Modified from Refs. [49, 50].

Increased ROS production	Decreased antioxidant capability
High intake of energy-rich foods	Inadequate intake of dietary antioxidants
High rate of oxygen consumption	Genetic mutation of antioxidant enzymes
Ischemic reperfusion	Depletion of glutathione as a consequence of increased rate of xenobiotic detoxification (via glutathione conjugation)
Exposure to radiation	
Excessive activation of phagocytic cells	
Exposure to xenobiotics activates CYP450 monooxygenase to produce reactive metabolites	

Table 1. Conditions contributed to disturbance between oxidants and antioxidants leading to oxidative stress in human body.

On the other side, decrease in antioxidant content in the body is attributed by at least three ways as follows: inadequate intake of dietary antioxidants, mutations in antioxidant genes and depletion of cellular glutathione as a consequence of detoxification of a large amount of xenobiotics (**Table 1**). Increased production of ROS beyond capability to cope by antioxidants leads to progressive augmentation of oxidized lesions that further promote pathogenic process such as in aging [63], atherosclerosis [64], neurodegenerative diseases [18, 65, 66] and cancers [67–71].

2.1. Generation of ROS

Reactive species include free radicals and other molecules that are themselves capable of converting to free radicals or have a powerful oxidizing property. By definition, free radicals are atoms or molecules having an unpaired valence electron. These molecules are chemically unstable and highly reactive towards other molecules. In fact, oxygen (O_2) in the air has two unpaired electrons, thus it is a biradical or diradical. Parallel spin of the unpaired electrons in oxygen molecule makes it chemically stable and inactive. This state of oxygen is a ground state or triplet oxygen (3O_2). However, if triplet oxygen is activated by sufficient energy to create an antiparallel spin of unpaired electrons, a highly reactive non-radical species, called singlet oxygen (1O_2), is formed. UVA exposure and phagocytosing neutrophils appear to be main sources of singlet oxygen formation in the human body [72]. Like other ROS, singlet oxygen is deleterious and capable of oxidizing lipids, proteins and nucleic acids leading to tissue damage and inflammation [73]. Common ROS and RNS found in the biological system are shown in **Figure 5**.

Superoxide anion is the first ROS generated in the stepwise reduction of oxygen, and it is a free radical precursor of hydrogen peroxide and hydroxyl radical (**Figure 1**). Superoxide anion is principally produced in mitochondrial ETC through complex I (NADH:ubiquinone oxidoreductase) and complex III (ubiquinol:cytochrome c oxidoreductase) [74]. The other clinically significant source of superoxide anion is from oxidases, particularly NADPH oxidase in the respiratory burst and xanthine oxidase in the reperfusion therapy [61].

NADPH oxidase is usually found in plasma membrane and phagosomes of phagocytic cells. Xanthine oxidase is primarily expressed in liver and small intestine located on outer surface of plasma membrane and in cytoplasm. Once activated, these oxidases produce large amount of superoxide anion. Superoxide anion itself is not highly reactive, and it has a relatively short half-life. Moreover, superoxide anion is negatively charged that is unable to cross the lipid membrane. Thereby, attack of superoxide anion to cellular biomolecules is confined at the site of origin. However, superoxide anion is capable of converting into a more diffusible reactive species, hydrogen peroxide. In addition, superoxide anion is able to react with other reactive species to produce more powerful oxidants, for instance, its interaction with nitric oxide (NO^\bullet) generates peroxynitrite (ONOO^-) [55]. Peroxynitrite is a very powerful non-radical oxidant that is injurious to cells and has crucial roles in pathogenesis of many diseases [75]. Reactive species that are derived from nitric oxide is collectively termed RNS (**Figure 5**), and a cellular stress that is caused by RNS with elevated level of nitrosylation marker (e.g., nitrotyrosine) is called “nitrosative stress” [75]. As it is beyond the scope, RNS, nitrosative stress and their contribution to disease development are not elaborated in this chapter.

Hydrogen peroxide (H_2O_2) is an uncharged non-radical species with reactive potential. Dismutation of superoxide anion produces hydrogen peroxide, and this reaction can be spontaneously occurred or catalyzed by superoxide dismutase (SOD) enzyme. SOD is first observed in 1969 [76]. The rate of hydrogen peroxide formation in SOD-catalyzed dismutation is much greater than the spontaneous one. In human, SOD has three distinct forms with a comparable reaction rate constant, i.e., SOD1 or Cu/Zn-SOD in cytosol, SOD2 or Mn-SOD in

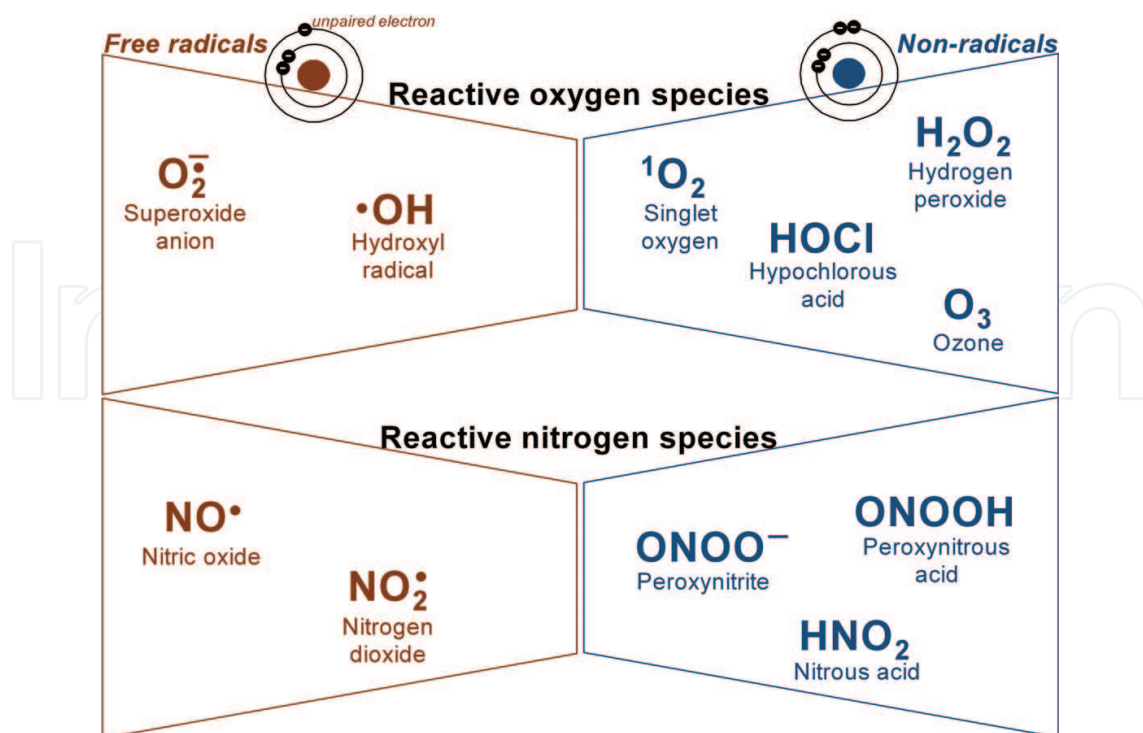


Figure 5. Common radical and non-radical species of ROS and RNS generated in the body.

mitochondria and SOD3 or extracellular SOD (Cu/Zn-ecSOD). To detoxify H_2O_2 , catalase and glutathione (GSH) peroxidase are employed to convert H_2O_2 into water. These two enzymes have been shown to have an equal contribution of H_2O_2 disposal in human red blood cells [77]. In addition to its direct toxic effect, H_2O_2 can be converted into two main ROS, including hypochlorous acid (HOCl) by myeloperoxidase (MPO) in phagocytes and hydroxyl radical ($\cdot OH$) by reacting with transition metals. In the actual fact, H_2O_2 per se is poorly reactive under a condition without transition metals [78].

Hydroxyl radical ($\cdot OH$) is the most destructive ROS with the strongest oxidizing capacity to attack biomolecules in cells. The well-known reaction for the production of hydroxyl radical is Fenton reaction [79, 80]. Ferrous ion (Fe^{2+}) reacts with hydrogen peroxide to give ferric ion (Fe^{3+}) and hydroxyl radical. The Fenton chemistry was first delineated by H.J.H Fenton an over century ago, based on an observation of tartaric acid oxidation by H_2O_2 in the presence of Fe^{2+} [81, 82]. In addition to Fe^{2+} , other transition metals such as Cu^{2+} can catalyze the Fenton reaction [22]. The other reaction that is closely related to the Fenton reaction is Haber-Weiss reaction [83, 84]. It was firstly described (in German) by Haber and Willstätter in 1931 [85], secondly demonstrated its kinetics by Baxendale et al. in 1946 [86] and experimentally verified that hydroxyl radical is produced from an interaction between hydrogen peroxide and superoxide anion by Weiss in 1949 [87]. This reaction indeed enlightens the toxicity of superoxide anion to generate a detrimental ROS, hydroxyl radical. In biological system with a presence of iron, generation of hydroxyl radical is mainly mediated through the iron-catalyzed Haber-Weiss/Fenton reaction (**Figure 6**) [22, 83, 87]. Therefore, in conditions with iron overload, ROS are increasingly generated via this iron-catalyzed Haber-Weiss/Fenton reaction causing accumulation of oxidative damage that further promotes disease progression [88–90].

2.2. Roles of ROS in physiology and pathology

ROS are poisonous and pathogenic at the uncontrollable high concentration, but they are our good friend exerting many beneficial functions at the nontoxic physiological level. These two paradoxical functions of ROS, depended on how well our body can regulate and control their production, can be viewed as the Janus faces (**Figure 7**). ROS under normal circumstance exert critical actions in cells such as signal transduction, gene transcription and immune response [91]. Superoxide anion produced by NADPH oxidase is vitally important in killing invaded pathogens in phagocytic cells (macrophages, monocytes, neutrophils, eosinophils) through respiratory burst or oxidative burst (**Figure 8**). SOD converts superoxide anion into H_2O_2 to be used by myeloperoxidase (MPO) to form hypochlorous acid (HOCl). In the presence of iron, $\cdot OH$ can be produced from H_2O_2 . These generated ROS are believed to be responsible for destroying the engulfed pathogens in the phagolysosome. Mutation in genes encoding for NADPH oxidase complexes resulting in insufficient ROS production that is a direct cause of chronic granulomatous disease (CGD) [92]. CGD is a rare inherited immune disorder caused from the inability of phagocytes to kill the ingested microbes, and its typical manifestation is frequently recurrent subcutaneous abscess formation together with hyperinflammation. There is still an argument that ROS and MPO-mediated halogenation are not the main killing system for the invaded microorganisms [93, 94].

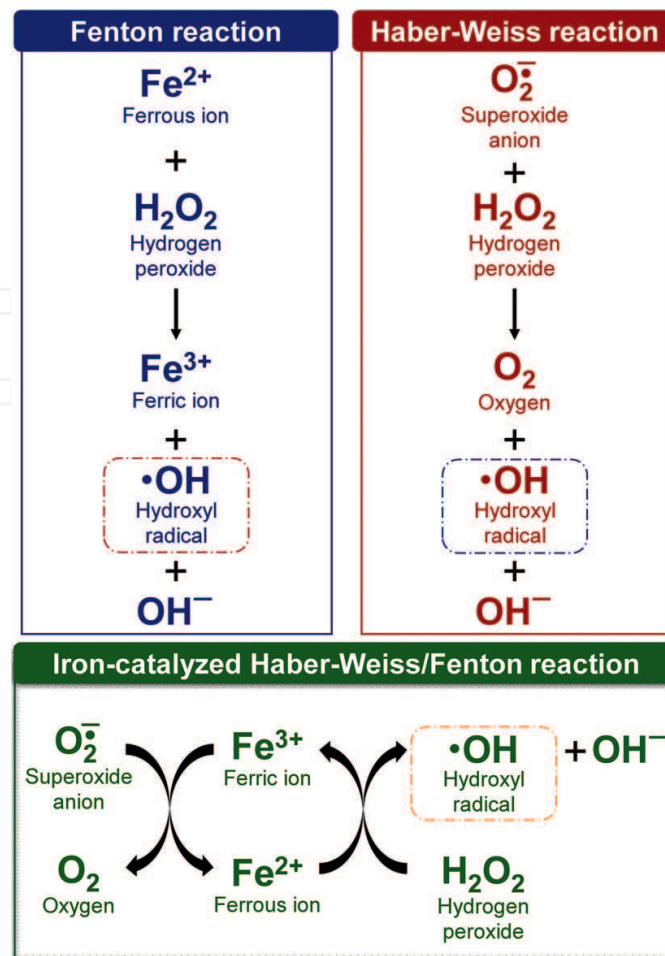


Figure 6. Fenton reaction and Haber-Weiss reaction for generation of hydroxyl radical. In the body with availability of iron ions, hydroxyl radical is principally produced via the iron-catalyzed Haber-Weiss/Fenton reaction.

ROS, particularly H₂O₂, are known to activate a stress-regulated transcription factor NF- κ B to withstand the physiological stress, and that activated NF- κ B induces transcription of a number of genes requiring for survival, apoptosis resistance and inflammatory response [95–97]. Some ROS act as substrate for enzymes, for instance, H₂O₂ is a substrate for heme-peroxidases involved in iodination of thyroid hormone [98]. H₂O₂ has been considered as a key cellular redox sensor and signaling molecule. At physiological levels (1–10 nM), it regulates redox signaling to maintain physiological stress (called oxidative eustress), and at higher level, it activates Nrf2/Keap1/ARE signaling pathway to initiate cytoprotective response and NF- κ B activation to promote cell survival. At the extremely high or supraphysiological concentrations (>100 nM), H₂O₂ damages cellular biomolecules, disrupts redox signaling and causes oxidative distress leading to pathological development [99].

Nitric oxide, originally discovered as endothelium-derived relaxing factor, is the best-known free radical with signaling characteristic. It participates in several cellular and organ functions such as relaxation and proliferation of vascular muscle cells, leukocyte adhesion, platelet aggregation and angiogenesis. Nitric oxide is synthesized from L-arginine and oxygen by nitric oxide synthase (eNOS in endothelial cells, nNOS in neurons and iNOS in many cell

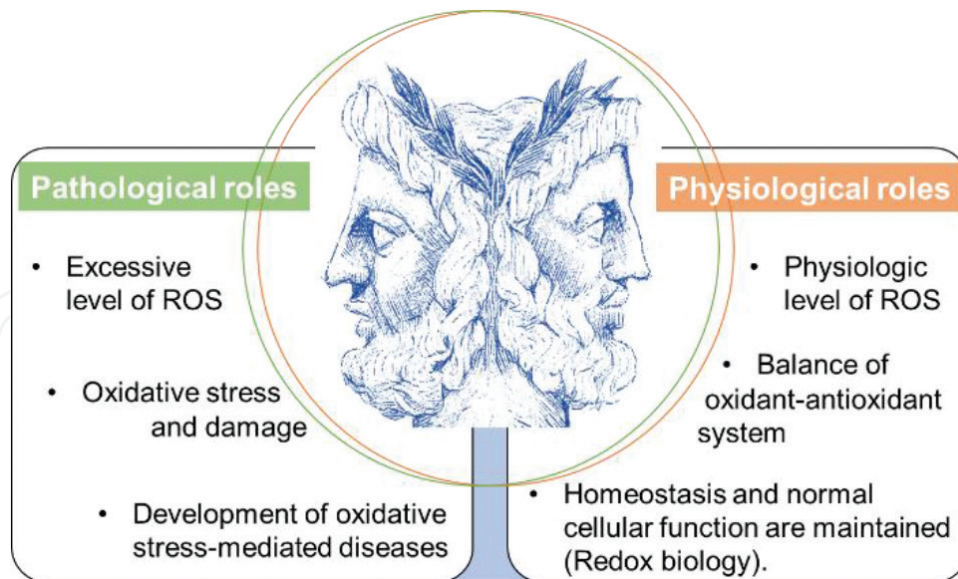


Figure 7. Janus faces of ROS in the human body regarding their physiologic and pathogenic functions. The process that ROS function as signaling molecules to maintain the physiological function is called “redox biology” [101], and the maintenance of intracellular redox homeostasis requires cooperative action and network of various antioxidants such as glutathione, peroxiredoxin, thioredoxin and antioxidant enzymes [102].

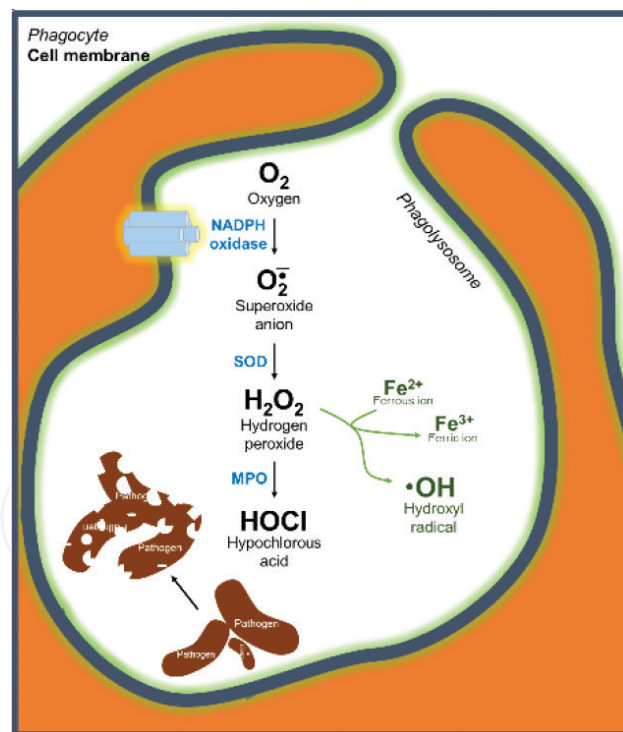


Figure 8. Respiratory burst for killing pathogens in phagocytes. In the presence of iron ions, hydroxyl radical can be formed through Fenton reaction and/or iron-catalyzed Haber-Weiss/Fenton reaction.

types following induction) using NADPH as electron donor. Sildenafil (VIAGRA®), a well-known drug for treating erectile dysfunction, is developed to interfere the nitric oxide signaling cascade in vascular smooth muscle cells [100]. Nitric oxide synthesized from endothelial

cells activates soluble guanylyl cyclase to convert GTP into cGMP leading to relaxation of vascular smooth muscle cells and vasodilation. The drug inhibits the cGMP degrading enzyme (phosphodiesterase-5), and this inhibition in turn causes a persistent increase in cGMP to stimulate vascular relaxation.

2.3. Oxidative stress in diseases

Oxidative stress is critically involved in the pathogenesis of almost all diseases ranging from infection to chronic diseases including cancers. Many infectious agents are well recognized to trigger the production of ROS and RNS [103]. *Helicobacter pylori*, a well-known bacterial agent implicated in the development of gastritis, peptic ulcer and gastric carcinoma, is shown to induce ROS generation, oxidative stress and apoptosis in human gastric epithelial cell lines [104]. Oxidative stress induced by influenza virus is clearly demonstrated in many studies, and antioxidant intervention is an alternative therapeutic strategy to combat the virus [66]. In hepatocellular carcinoma (HCC), oxidative stress induced by hepatitis B and C viruses is a well-established mechanism to drive malignant transformation of hepatocytes [105]. Toxicity and carcinogenicity induced by heavy metals (e.g., Hg, Cd, Ni, As) are demonstrated to mediate through ROS formation (mainly via Fenton reaction) yielding oxidatively modified products with highly carcinogenic and mutagenic potential [106, 107]. Undoubtedly, pathogenesis and complication of diabetes [108, 109], atherosclerosis [110, 111] and Parkinson's disease [112] is critically involved ROS generation and oxidative damage. ROS directly cause oxidized lesions on DNA. Increased formation of oxidized lesions together with failure of DNA repair introduces a bunch of genetic mutations. Cancer is a disease of accumulated genetic mutations, and ROS production in cancer cells is markedly higher than normal cells. It is well established that ROS and oxidative stress have both direct and indirect contributions to carcinogenesis and progression of cancers [69, 113, 114]. The question is that how do cancer cells survive under the highly oxidative microenvironment. It turns out that cancer cells cope with the oxidative stress by reprogramming their metabolism and empowering the antioxidative capability through Nrf2/Keap1/ARE pathway [115–119]. In this chapter, it is focused only on oxidative stress in urinary stone disease.

3. Urolithiasis

UL or urinary stone disease is a condition with mineral masses in the urinary system. It is indeed an ancient condition. The oldest urinary stone was found in the pre-historic Egyptian tomb by Professor G. Elliot Smith in 1901. He observed the calculus lying among the pelvic bones of a 16-year-old boy mummy. This bladder stone composed of several types of minerals including uric acid (UA), calcium oxalate (CaOx), calcium phosphate (CaP) and magnesium ammonium phosphate (MAP). It was dated before 4500 B.C., meaning that the first evidenced urinary stone occurred over 7000 years ago [120, 121]. Even though UL is a long-standing disease staying with us since the origin of human history, the mechanism of urinary stone formation is still not fully understood. Moreover, UL cannot be cured completely. Surgical treatment of stones removes only symptoms, not causes. The challenging issue of stone disease management is how to prevent the stone recurrence.

According to the location of stones in the urinary tract, stone disease is classified into three main forms as follows: kidney or renal stone (nephrolithiasis), ureteric stone (ureterolithiasis) and bladder stone (vesical calculi). Kidney stone is the most prevalent one. Bladder stone is accounted approximately 5% of all stones. It is prevalent in children in the developing countries, and diet is the main risk factor [122]. Stone lodged in the ureters (ureteric stone) is found about 20% of all stones [123]. It is believed that ureteric stone has a kidney origin. Kidney stone moves downwards to ureter due to the flush of urine flow and the size of stone (normal ureter diameter: 3–4 mm). Size does matter for spontaneous passage of ureteric stones, as ureteric stones about 4 mm in width have a spontaneous passage rate over 80% [124].

Prevalence of UL is progressively increasing in all countries across the world [125–127], especially in the tropical regions [128]. The lifetime risk of stone formation in the USA is over 12 and 6% in men and women, respectively [129]. In Japan, the lifetime prevalence is of 15.1% in men and 6.8% in women [130, 131]. Overall kidney stone prevalence in Europe is ranged between 5% and 10% [132]. In Germany, data in 2001 show stone prevalence of 4.7% in men and 4.0% in women [133]. The highest lifetime prevalence of 20% is reported in Saudi Arabia, a country with desert climate [130]. In Thailand, UL is endemic in the northeastern region, and the disease rate examined by abdominal ultrasound in 1997 is of 16.9% [134]. Our preliminary unpublished data of a community survey in 2017 for detecting asymptomatic urinary stones in villagers who reside in the northeastern region using computed tomography scan reveal the prevalence of asymptomatic stones at 12%, which is relatively high. Additionally, pattern of stone onset greatly varies among regions, for instance, the ureteric stone is much more common in the southern region of Thailand compared to the other regions [135]. In sum, the data of stone prevalence clearly indicate that stone formation varies across countries, depending greatly on climate. Stone prevalence is lower in colder countries, but higher in warmer countries.

Change in lifestyle and dietary habit is believed to have major contribution to an increasing stone prevalence [136]. Stone disease is a disease of urine concentration. Fluid intake and fluid loss due to hot climate are greatly contribute to urinary stone formation. An impact of global warming on rising in stone prevalence was first reported in 2008 in the USA [137]. Later, the adverse effect of climatic change on increase in UL onset is confirmed by studies [138] from various countries, viz., Korea [139, 140], Iran [141] and USA [142, 143]. In our ongoing research of climate change and UL onset, a trend of global warming in Thailand is observed. Increased temperature is positively associated with increased UL onset. Contrary, rainfall has a negative association with onset of urinary stone. Our finding confirms a significant contribution of global warming to UL development.

Stones are built from lithogenic crystals formed in the supersaturated urine. Type of urinary stones is, therefore, classified according to primary mineral components into four main types, namely CaOx, CaP, MAP and UA stones. Miscellaneous stones, including cystine and xanthine stones, are usually caused by genetic mutations of certain genes, and they are found mainly in children. CaOx is the highest prevalent stone type that is found up to 80% of all stones, and it is frequently mixed with CaP or hydroxyapatite. MAP or struvite stone is

formed in the alkali urine and associated with urinary tract infection of urea-splitting microorganisms such as *Proteus*, *Klebsiella*, *Serratia*, *Pseudomonas*, *Staphylococcus* and *Mycoplasma*. Nowadays, prevalence of struvite stone is decreasing, perhaps due to a widespread use of antibiotics. UA stone is the second most common urinary stones found up to 40%, and its formation is associated with acidic urine [144]. Precipitation of UA depends chiefly upon urine pH. UA has a pKa of 5.75 [145]. In urine pH over 5.8, it exists as urate and readily solubilizes in water, whereas in urine pH below 5.8 it predominantly presents in the form of insoluble UA. Our hospital-based data from four main regions of Thailand (Northeast, North, Central and South) revealed that CaOx, CaP, UA and MAP stones were found at 74, 5, 16 and 5%, respectively [146]. This is consistent with the global picture of urinary stone types as CaOx is the most common one followed by the UA stone.

Urinary stone has multifactorial etiology with polygenic susceptibility. It mainly affects adults. Monogenic stone condition, such as cystinuria (found approximately at 1% of all stones and 7% of stones in children) and primary hyperoxaluria, is a relatively rare condition that is often found in children, so-called childhood UL [147, 148]. Cystinuria is an autosomal recessive trait caused by mutations in *SLC3A1* or *SLC7A9* gene resulting in an inborn error in transport of urinary cystine, ornithine, lysine and arginine (commonly known as COLA) that subsequently initiate cystine stone formation. Stone formation without any identifiable clinical causes is labeled “idiopathic,” which is commonly observed in the CaOx formers [149]. However, it has been suggested that genetic screening should be performed in the previously classified idiopathic calcium UL in order to certainly rule out an underlying genetic susceptibility [148].

Stone formation is more prevalent in males than females. Male-to-female ratio varies from 3.13:1 (in Germany) to 1.15:1 (in Iran) [126, 150]. In Thailand, we found a much lower of male-to-female ratio at 1.1–1.2:1 implying that Thai men and women have a comparable chance to develop urinary stones [146, 151]. For age, a peak of prevalence is found between 40 and 50 years old for CaOx stone, but for UA stone the age peak is shifted to 60–70 years old [126, 146, 150, 151]. Increased body mass index and diabetes are associated with increased risk of UL, particularly UA stone formation [152–154]. Certain anatomical abnormality of kidneys also increases the risk of stone formation [155]. UL is known as the most frequent complication of horseshoe kidneys, which can be found up to 60% [156]. Likewise, up to 50% of patients with calyceal diverticula are inflicted with stones [157].

Family history is another factor known to increase a risk of stone formation. The data from study in the USA show that men with positive family history have 2.57 times higher risk of incident stone formation than those without [158]. Familial aggregation of kidney stone disease is more prominent in the northeastern region of Thailand with a relative risk of 3.18 among members of the affected families [159]. Based on our data, a positive family history is accounted for 32–35% implying that contribution of genetic susceptibility to drive stone formation is observed only in one-third of cases [146, 151]. Stone formation in the majority of cases (two-third) is chiefly influenced by environmental and behavioral factors, especially diets. Inadequate fluid intake (recommended at 2 liters per day), increased consumption of food rich in animal protein and lithogenic substances (such as oxalate and purines) and low

intake of food containing antilithogenic substances (especially citrate) markedly contribute to stone development [136]. However, argument is raised from a prospective study of the large cohorts in the USA that demonstrates that dietary oxalate (as well as spinach intake) is not a major risk factor for incident nephrolithiasis [160]. For protective factor, dietary calcium and intake of fruits and vegetables reduce a risk of stone formation [161, 162]. In sum, dietary factor has a large contribution to stone formation; therefore, development of UL is possibly preventable.

Exposure to risk factors mentioned above causes changes in concentrations of urinary substances, including lithogenic substances (called stone promoters) and antilithogenic substances (called stone inhibitors). Disproportion of urinary stone promoters and inhibitors predisposing to crystallization and stone formation is defined as metabolic risk factor or metabolic abnormality. Metabolic abnormality includes an increase in urinary stone promoters, e.g., hypercalciuria, hyperoxaluria and hyperuricosuria, and a decrease in urinary stone inhibitors, e.g., hypocitraturia, hypokaliuria and hypomagnesiuria. Although hypercalciuria is found in UL patients more frequent than hyperoxaluria, evidence suggests that mild degree of hyperoxaluria has much more influence on CaOx stone formation than hypercalciuria [163]. Citrate is the most potent stone inhibitor in urine, and low urinary citrate excretion is a common manifestation found in UL patients. Hypocitraturia in UL is reported between 20% and 60% in western studies [164]. In endemic area, hypocitraturia is much more prevailing, plausibly due to difference in lifestyle and dietary habit [165, 166]. Our data demonstrate that hypocitraturia (80–100%) and hypokaliuria are the most common metabolic risk factors found in Thai stone patients. In addition, we show that individuals with hypocitraturia have about 10 times higher risk for kidney stone development than those without [167, 168].

Mechanism of kidney stone formation has been proposed, although it is not entirely understood (**Figure 9**). Building blocks of stones are lithogenic crystals, such as CaOx, CaP and UA crystals, formed in the urine. Chemically, CaOx crystals have three forms, i.e., calcium oxalate monohydrate (COM), calcium oxalate dihydrate (COD) and calcium oxalate trihydrate (COT), but the most deleterious form with highest lithogenic potential is COM. A process of crystallization from solution has two phases. The first phase is birth of new crystals (called nucleation), and the second phase is growth of crystals to get larger size (called crystal growth). Supersaturation of urine, caused by increase in concentration of lithogenic ions and/or decrease in urine volume and stone inhibitors, triggers nucleation in renal tubules. The crystals grow and aggregate to reach sufficient sizes and retain in the kidney. Surplus crystals are toxic and injurious to renal tubular cells resulting in renal tubular injury. Injured tubule is a suitable site for crystal attachment and retention. Nidus (site of stone origin) is then formed, grown and finally become stone. There are pathological changes occurred during the lithogenic process. Excessive crystals induce ROS production in the exposed renal tubular cells leading to oxidative stress and renal tubular damage. Crystals also induce production and release of inflammatory mediators to activate inflammatory response that further enhances tubular injury. Both oxidative stress and inflammation cause release of various proteins and sloughing of cell debris into urine creating a vicious cycle to enhance crystal formation, aggregation, retention and finally stone formation (**Figure 9**).

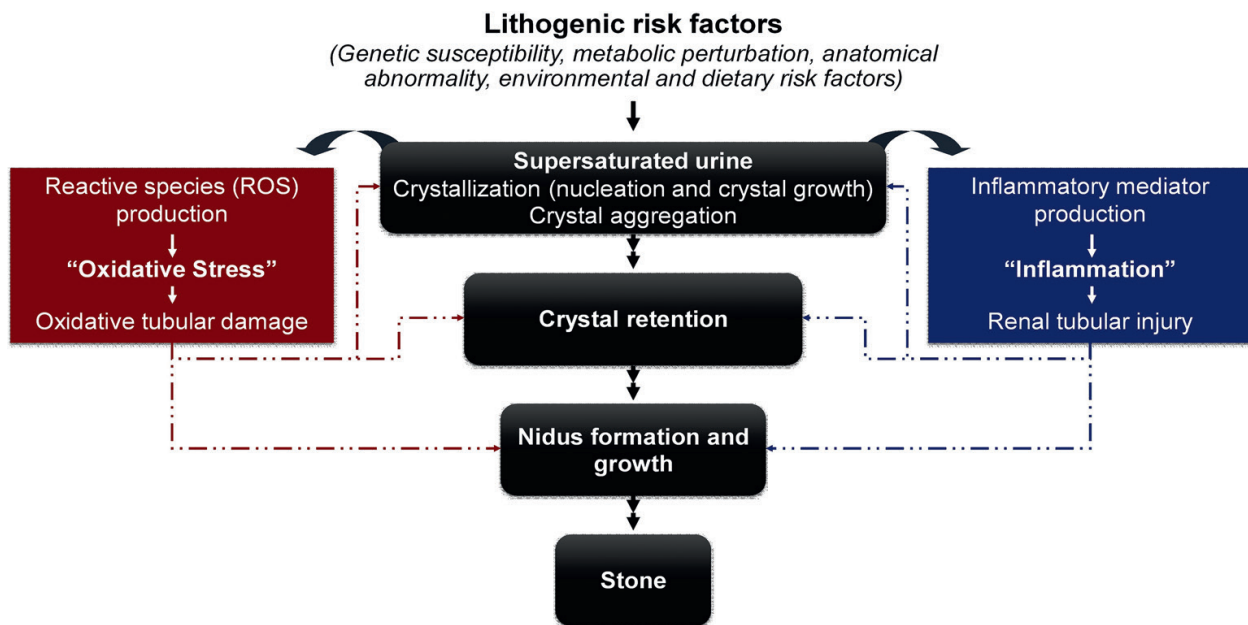


Figure 9. Key mechanistic steps in the process of kidney stone formation (see text for detail).

Although it is known that urinary crystals are building blocks for building urinary stone, it is not precisely known how the microscopic crystals transform to be a macroscopic stone. Crystal aggregation is one of the critical steps in lithogenic process. Urinary crystals have to adhere to each other to form a bigger mass. If urinary crystals do not adhere or bind to each other, stone cannot be formed—similar to granulated sugar that each minute granule stays separately without clumping. Studies show that stacking of urinary crystals to form stone requires biological glue to adhere crystals together, and that glue is called stone matrix [169]. Stone matrix contributes about 5% of the stone mass composing of cellular biomolecules, cell debris and whole cells. We investigated lipid and protein constituents in stone and urine samples of nephrolithiasis patients. We found that glycolipids and phospholipids released into urine are actively incorporated into stone matrix [170]. Majority of proteins in stone matrix and nephrolithiasis urine are inflammatory and fibrotic proteins [171]. We also demonstrate that S100A8 is an abundant inflammatory protein found in urine and stone matrix of the patients, and it could be a marker to indicate an extent of intrarenal inflammation in nephrolithiasis patients.

4. Oxidative stress in urolithiasis

ROS are experimentally proved to have a critical role in the pathogenesis of kidney stone [172]. Oxidative stress and inflammation are clearly demonstrated to mediate lithogenic process [173, 174]. Exposure of renal tubular cells to oxalate, COM, CaP and UA crystals causes increases in ROS production and oxidative stress leading to cell injury [175, 176] as well as release of monocyte chemoattractant protein-1 (MCP-1) [177–179] and interleukin-6 (IL-6) [180]. Our human data show an elevated urinary excretion of oxidative DNA lesion, 8-hydroxydeoxyguanosine

(8-OHdG), along with rise in renal tubular injury in patients with nephrolithiasis [181]. We also show an increased expression of 8-OHdG lesion in stone-containing renal tissues [182]. MCP-1 and IL-6 mRNA expression in stone-containing kidney tissues are increased, and their increment is related to declined creatinine clearance [183]. Our findings indicate that patients with nephrolithiasis persistently have increased oxidative stress and intrarenal inflammation, and these pathological changes contribute to renal impairment. An inevitable consequence of chronic inflammation is fibrosis. We show an evidence of renal fibrosis in the kidneys of nephrolithiasis patients, and the renal fibrogenesis at least in part mediates through transforming growth factor-beta 1 (TGF- β 1)-induced epithelial-mesenchymal transition (EMT) [184]. In **Figure 10**, we propose the putative cellular mechanism of crystal-induced inflammation leading to interstitial fibrosis in nephrolithiasis patients. Lithogenic crystals are readily formed in the supersaturated urine. In healthy individuals, crystals are flushed out by the urine flow without any harm. In contrast, crystals grow, aggregate and adhere to renal tubular cells in stone-forming patients. Crystals are internalized to be dissolved in lysosomes, and the remnants are exocytosed into renal interstitium. Alternatively, lithogenic ions such as calcium, phosphate and oxalate ions may diffuse through tubular lining towards the renal interstitium to form interstitial crystals. Crystals as well as oxalate ions induce oxidative damage to renal tubular cells via increased ROS generation. MCP-1, osteopontin (OPN), IL-6 and TGF- β 1 are

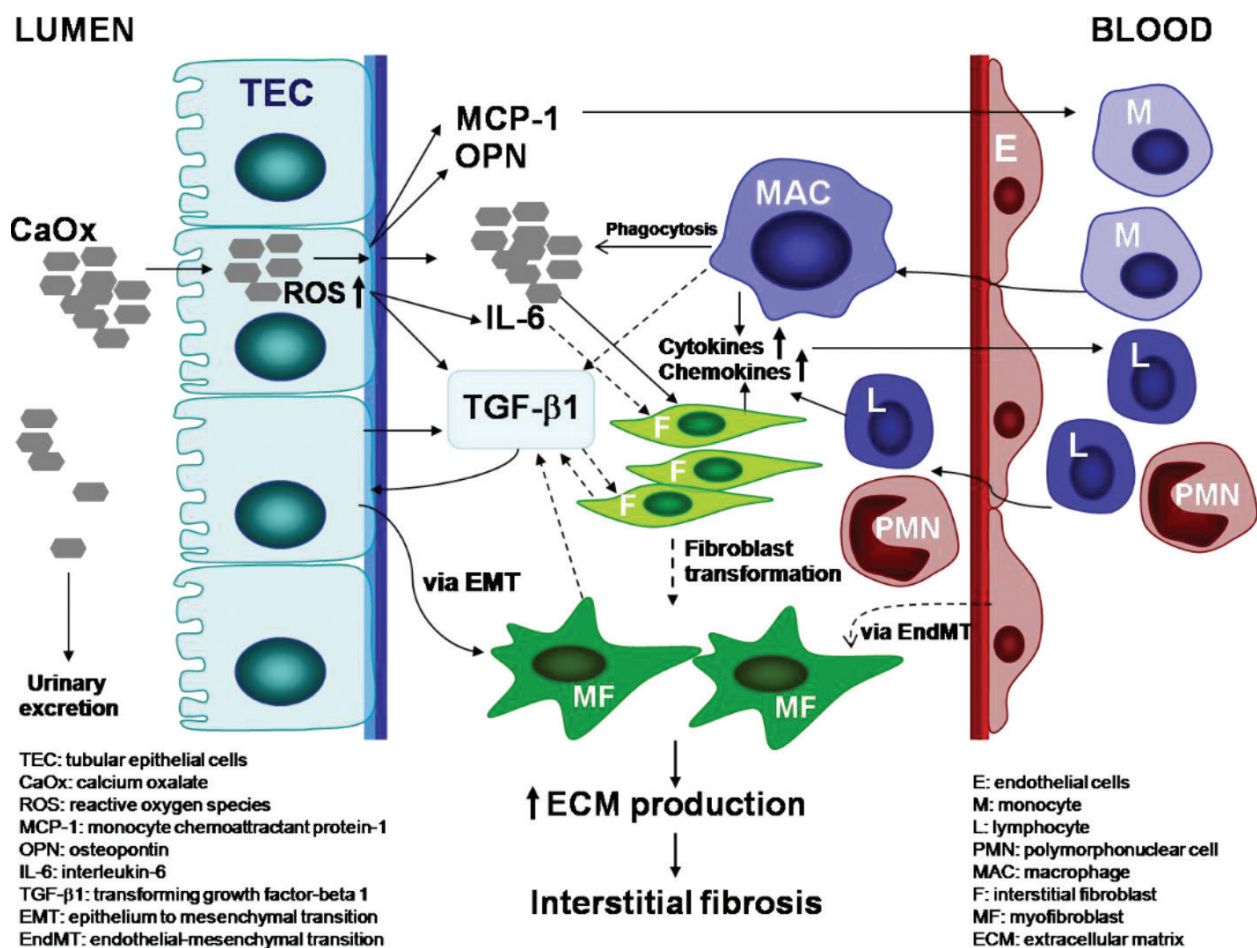


Figure 10. Putative cellular mechanism of crystal-induced inflammation leading to interstitial fibrosis in nephrolithiasis patients. Solid lines indicate demonstrated pathways and dash lines represent hypothesized pathways.

upregulated in the crystals/oxalate-exposed renal tubular cells. MCP-1 and OPN exert chemotactic activity to recruit monocytes and macrophages into the renal interstitium and initiate inflammatory response. The infiltrated immune cells phagocytose the interstitial crystals and release a variety of cytokines, chemokines and growth factors, leading to further recruitment of leukocytes and inflammatory amplification. Excessive and chronic inflammatory reaction causes renal damage and activates wound healing process. IL-6 might stimulate the proliferation of renal tubular cells and interstitial fibroblasts in order to replace the severely injured and dead renal cells. TGF- β 1 produced by tubular cells in stone-forming kidneys activates the transformation of interstitial fibroblasts into α -smooth muscle actin (α SMA)-expressing/extracellular matrix (ECM)-producing myofibroblasts and induces the transdifferentiation of renal tubular cells via EMT leading to overproduction of myofibroblasts and ECM. TGF- β 1 is also capable of inducing endothelial-mesenchymal transition to generate myofibroblasts from endothelial cells. TGF- β 1 is in turn overproduced by monocytes/macrophages, fibroblasts and myofibroblasts. Chronic inflammation is further amplified. Excessive repairing process causes excessive deposition of ECM proteins leading to scar formation. Thereby, lithogenic crystals that actively and chronically form in the nephron of nephrolithiasis patients cause a sustained inflammatory injury and excessive repair, which eventually lead to renal fibrosis. Urinary obstruction by large stone mass also initiates the renal fibrogenic cascade through TGF- β 1.

The goal of UL therapy is to remove stones and prevent stone recurrence. Removal of stones requires surgical approaches while prevention of stone relapse requires medical management. The current drug of choice for stone therapy is potassium citrate [185, 186]. The drug delivers citraturic and urine alkalinizing effects to elevate urinary citrate and increase urine pH. According to the stone management guideline, treatment with potassium citrate requires at least 6 months to effectively reduce the likelihood of recurrent stone formation [187]. Since citrate is a key therapeutic ingredient for inhibiting stone formation, citrus fruits (such as orange, lemon, lime and grapefruit) and non-citrus fruit (such as melon) with high content of citrate have been considered as alternatives for stone treatment [188]. Intervention with antioxidants is shown to effectively inhibit CaOx crystal deposits in experimental nephrolithic rats [189, 190]. Regarding this, herbs and medicinal plants with high antioxidant property that have been traditionally used for treating stone disease in various countries are suggested to be alternative nutraceuticals or complementary therapeutic options for stone disease [191]. Banana stem (*Musa sapienta* L.), which is an Ayurveda remedy to treat kidney stones, had been shown to significantly reduce urinary stone risk in hyperoxaluric rats [192]. We have been investigated the clinical efficacy of lime juice and banana stem beverage as alternatives for UL treatment. We show that our inhouse limeade-based regimen, designated lime powder regimen (LPR), efficiently delivers citraturic, alkalinizing and antioxidative actions in nephrolithiasis patients [193]. Our preclinical and phase 1 clinical trial reveals that LPR inhibits COM crystal growth and attenuates oxidative stress in vitro and is capable of increasing urine citrate, pH and antioxidant capacity in healthy individuals [194]. Importantly, LPR is well tolerated and safe for daily intake.

Based on our research experience over 10 years three major etiological factors are identified in UL patients including (1) an inadequate intake of water, (2) low urinary excretion of citrate and (3) increased oxidative stress. We have developed an innovative beverage-based regimen for preventing urinary stone formation, named HydroZitLa (patent pending). Our inhouse HydroZitLa beverage contains therapeutic dose of citrate and naturally antioxidants

derived from banana stem, *Clitoria ternatea* L. and *Caesalpinia sappan*. In vitro, HydroZitLa efficiently inhibits COM crystal aggregation and exerts antioxidative action to reduce oxidative damage in COM-treated HK-2 cells as well as H₂O₂-treated bladder cancer cells. In vivo experiment reveals an antilithogenic efficacy of HydroZitLa in inhibiting CaOx deposits in kidneys of ethylene glycol-induced nephrolithic rats. The antilithogenic effect of HydroZitLa is comparable to that of potassium citrate drug (Uralyt-U). Our findings indicate a promising clinical potential of LPR and HydroZitLa as alternative nutraceuticals for UL treatment.

5. Conclusion

ROS are both friend and enemy. At physiological level, they are required for metabolic reactions and play a vital role in redox biology. At the uncontrollable high level, they are very destructive. High rate of oxygen consumption (through ETC and oxidases/oxygenases) and presence of transition metals are the main factors to generate ROS in an excessive amount. Cells combat ROS through activation of the cytoprotective Keap1-Nrf2-ARE signaling pathway. Chronically excessive production of ROS causes oxidative stress that disrupts redox signaling and control resulting in damage to biomolecules and cell injury. Oxidative stress mediates pathogenesis of a number of diseases ranging from infection to cancer. Evidences from in vitro, animal and human studies strongly support the active involvement of oxidative stress in urinary stone formation. Lithogenic crystals formed in urine directly induce ROS generation in renal tubular cells causing oxidative damage and release of inflammatory mediators. Sustained tubular injury, oxidative stress and inflammation in turn accelerate crystal formation, growth and aggregation and ultimately stone formation. Renal fibrosis is also found in the stone-containing kidneys of the patients and believed to be a main contributing factor to kidney dysfunction in the stone patients. Stone disease is greatly contributed by environmental and behavioral factors, and the disease is frequently recurrent. Based on our research experiences, major risk factors of stone formation (in particular CaOx stone) include inadequate daily intake of fluid, low urinary excretion of citrate (hypocitraturia) and low antioxidative capability (high oxidative stress). Therefore, regimens or approaches to recuperate these depleted conditions are promising to be a new therapy for UL. Citrate is a potent stone inhibitor, and potassium citrate is a current drug used for preventing the stone recurrence. We recently developed a novel herb-based antilithic drink (called HydroZitLa, patent pending) containing a therapeutic dose of citrate and high amount of natural polyphenol antioxidants. Our in vitro and animal studies show a great promise of HydroZitLa to be an alternative for preventing urinary stone formation. Clinical trials are now planning to be conducted to observe the side effect and to test the clinical efficacy of HydroZitLa in reducing the risk of stone formation in the real clinical setting.

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Conflict of interest

C. Boonla is one of the inventors of HydroZitLa (Patent pending).

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