INTRODUCTION

Nephrolithiasis is a chronic disease involving imbalance between crystallization of largely calcium salts & inhibition of crystal formation or their dissolution [1]. Despite detection of urinary stones hundreds of years ago, their pathogenesis & prevention/cure are not fully understood. It is a multifactorial disease owing to multiple genetic or environmental factors that regulate calcium salt precipitation in the urinary system. With its multifactor f
ty and high rate of recurrence, urinary tract stone disease provides a medical challenge [2].

Calcium oxalate (CaOx) is the most common type of human kidney stone, of which hyperoxaluria is the major risk factor. The mechanism by which a CaOx stone is formed is complex, and many factors are believed to be involved. However, the exact mechanism of renal stone formation is poorly understood [3]. Although it involves a cascade of events including one or more of the following: urinary super saturation, crystal nucleation, growth, and aggregation; retention of crystals in the renal tubules or interstitium and growth of a calculus upon a tubular plug or interstitial deposit so-called Randal’s Plaque. Oxalate (Ox) is a naturally occurring, highly oxidized organic compound with powerful chelating activity that can cause death at high concentrations in animals and occasionally humans due to its toxic corrosive effects on cells [4]. A higher concentration of Ox in human fluids can cause a variety of pathological disorders, including hyperoxaluria, cardiomyopathy, cardiac conductance disorders, renal failure and, in particular calcium oxalate (CaOx) nephrolithiasis.

Studies with animal models as well as tissue culture model systems, have demonstrated injury to the epithelial cells of the kidney in the presence of calcium oxalate crystals [5]. It has been confirmed that injury of renal epithelial cells is mediated by the overproduction of reactive oxygen species (ROS), produced mostly from mitochondria or nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The interaction between injured renal tubular epithelium and CaOx crystals and/or oxalate ions is likely to play a critical role in the formation of urinary calculi [6].

ABSTRACT

Renal injury and inflammation caused by ROS play a major role in stone formation. Under the hyperoxaluric condition, crystal deposition results in angiotensin II (Ang II) activation. NADPH Oxidase is stimulated by activated Ang II, leading to ROS production, which can damage renal cells. Oxidative stress also results in mitochondrial dysfunction and release of pro-apoptotic factors from depolarized mitochondria that result in apoptosis that leads to renal injury. Crystal retention in the kidney requires tubular epithelial injury accompanied by luminal expression of HA, OPN, and CD44. The expression of these molecules turns a non-crystal-binding epithelium into a crystal-binding one, thereby setting the stage for crystal retention. Recently many antioxidants have been studied that prevent hyperoxaluria mediated nephrolithiasis. Antioxidant treatment significantly reduces CaOx crystal deposition in kidneys. Naturally occurring antioxidants such as Vitamin E, Apocynin, Phycocyanin, Fucoidin, Gallotannins, Rottlerin, Lupeol, Curcumin, etc. have shown significant effect in combating renal injury which is an early event in nephrolithiasis. These findings point towards a great potential for the therapeutic application of antioxidants and free radical scavengers to reduce stone occurrence particularly under hyperoxaluric conditions. This review article attempts to compile various naturally occurring antioxidants used in treatment of nephrolithiasis.

Keywords: Calcium oxalate, Oxidative stress, Hyperoxaluria, Reactive oxygen species, antioxidants
for the activation of Renin–angiotensin system and NADPH Oxidase when cells are exposed to high Ox and CaOx/CaP crystals [19]. Under the hyperoxaluric condition, crystal deposition results in angiotensin II (Ang II) activation [20]. As depicted in Fig. 1, NADPH Oxidase is stimulated by activated Ang II, and through phosphorylation of the former’s cytosolic subunit p47phox and translocation to the membrane assembling the catalytic complex of active Oxidase leading to ROS production, which can damage renal cells [21]. The Ox and CaOx crystals exposure to renal epithelial cells in culture cause changes in the expression of various subunits which in turn effect activation of NADPH Oxidase. Significant correlation was seen between CaOx crystal-induced up regulation of p22phox and p47phox and NADPH Oxidase activation and associated cell injury [6]. These are two basic mechanisms that have been proposed for development of OS that leads to apoptosis and renal injury.

One of the major findings was that there is no crystal retention in the absence of tubular injury/ regeneration. The cell or tissue injury leads to exposure of molecules on cell surface which are not normally accessible to crystals resulting in crystal attachment [22]. The hyaluronic acid (HA) has been identified as a major crystal binding molecule at the surface of human renal tubular cells in primary culture [23]. In addition, it was found that crystal-binding cells expressed not only HA at their apical surface but also osteopontin (OPN) and CD44 [24]. The transmembrane protein CD44 is a cell surface receptor for HA and OPN and it is up regulated during inflammation in the kidney. Although the expression of HA, OPN, and CD44 by injured/regenerating tubular epithelial cells most likely is aimed at reestablishment of the epithelial barrier integrity and restoration of renal function but a negative side effect could be that it turns a non-crystal-binding epithe liver into a crystal-binding one, thereby setting the stage for crystal retention. Cell injury provokes the retention of calcium oxalate crystals, which forms the nidus and grows by a cascade of events to stone formation.

**Role of antioxidants in treatment of hyperoxaluric**

Management of urolithiasis mainly involves techniques like extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy (PCNL). However, the recurrence of stone formation is quite common. Besides, these treatments cause undesirable side effects such as haemorrhage, hypertension, tubular necrosis and subsequent fibrosis of the kidney leading to cell injury and recurrence of renal stone formation [7]. Experiments have shown that supplementation of agents which could decrease oxidative stress was able to rescue the cells from oxalate-induced toxic effects.

**Natural antioxidants**

Several recent studies have highlighted the potential efficacy of several Oriental medicinal herbs or natural compounds for the treatment of nephrolithiasis. Now a day various phytotherapeutic agents have been proposed as useful alternative or complementary therapies for the management of urolithiasis, in part due to their anti-oxidative effects. There are various antioxidants which have been shown to reduce oxidative stress. The present review includes natural antioxidants with their chemical structure (Figure 2) and proven beneficial effects (Table 1).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Systematic name / Functional group</th>
<th>Mechanism of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vitamin E</td>
<td>(2R)-2,5,7,8-Tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-6-chromanol / Tocotrienols and Tocopherols</td>
<td>Major lipid per oxidation chain-breaking antioxidant</td>
<td>[25]</td>
</tr>
<tr>
<td>2.</td>
<td>Phycocyanin</td>
<td>Tetrapyrrole chromophore</td>
<td>Free radical scavenger &amp; antioxidant activity</td>
<td>[26]</td>
</tr>
<tr>
<td>3.</td>
<td>Lupeol</td>
<td>(3β,13β)-4-Lup-20(29)-en-3-ol / Pentacyclic triterpene</td>
<td>Antioxidant activity</td>
<td>[27]</td>
</tr>
<tr>
<td>4.</td>
<td>PGG</td>
<td>1,2,3,4,6-Pentakis-O-{(3,4,5-trihydroxybenzoyl)-β-D-glucopyranose}/1,2,3,4,6-Penta-O-galloyl-beta-D-glucose</td>
<td>Protect against ROS induced renal cell injury and reduce renal hyaluron expression</td>
<td>[28]</td>
</tr>
<tr>
<td>5.</td>
<td>Gallotannin</td>
<td>1,3,6-Tris-O-{(3,4,5-trihydroxybenzoyl)-β-D-glucopyranose}/Polyphenolic hydrolysable tannin</td>
<td>Inhibit COM crystal growth and adhesion to renal epithelial cells</td>
<td>[29]</td>
</tr>
<tr>
<td>7.</td>
<td>Apocynin</td>
<td>4-hydroxy-3-methoxy-acetophenone</td>
<td>NADPH oxidase inhibitor</td>
<td>[4]</td>
</tr>
<tr>
<td>8.</td>
<td>Rottlerin</td>
<td>(2E)-1-[6-(3-Acetyl-2,4,6-trihydroxy-5-methylbenzyl)-5,7-dihydroxy-2,2-dimethyl-2H-chromen-8-yl]-3-phenyl-2-propen-1-one / Polyphenol</td>
<td>PKC-δ inhibitor</td>
<td>[31]</td>
</tr>
<tr>
<td>9.</td>
<td>Curcumin</td>
<td>(1E,6E)-1,7-Bis[(4-hydroxy-3-methoxyphenyl)-1,6-hexahydro-3,5-dione] / Polyphenol</td>
<td>PKC-δ inhibitor</td>
<td>[32]</td>
</tr>
<tr>
<td>10.</td>
<td>Thymoquinone</td>
<td>2-Isopropyl-5-methyl-1,4-benzoquinone</td>
<td>Antioxidant and antibacterial activity</td>
<td>[33]</td>
</tr>
<tr>
<td>11.</td>
<td>Fucoids</td>
<td>Sulphated polysaccharides</td>
<td>Normalize the redox status</td>
<td>[34]</td>
</tr>
<tr>
<td>12.</td>
<td>Atorvastatin</td>
<td>(3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-5,3-dihydroxyheptanoic acid / Statins</td>
<td>Inhibit renal crystal retention</td>
<td>[35]</td>
</tr>
</tbody>
</table>
Vitamin E

It refers to a group of eight fat-soluble compounds that include both tocopherols and tocotrienols. Tocopherols have a saturated phytol tail attached to their chromanol ring, whereas tocotrienols have an unsaturated aliphatic tail. The structure is shown in Fig. 2A. Naturally occurring alpha-tocopherol is found in lipid rich plant products and vegetable oils, while rice bran and palm oil have high concentrations of tocotrienols. It is the major lipid peroxidation chain-breaking antioxidant in lipid domains and thought to be an effective radical scavenger. It also has immunostimulatory activity [25]. The beneficial effect of vitamin E in reducing CaOx accumulation is due to attenuation of tubular cell death and enhancement of the defensive roles of OPN and Tamm–Horsfall protein (THP). It can also preserve renal function and reduce levels of free radicals, vasoconstrictive thromboxanes, and tubulointerstitial fibrosis in nephrotoxicity model in rats [38].

Phycocyanin

The main source of phycocyanin is Spirulina, a cyanobacteria. Phycocyanins function as a highly potent hydroxyl or peroxyl free radical scavenger. Due to its free radical quenching capacity against oxalate mediated tissue injury it acts as a neuroprotective agent [26]. A biliprotein pigment containing an open chain tetrapyrrrole chromophore is known as phycocyanobilin (Fig. 2B) [39]. Administration of phycocyanin significantly reduces the levels of urinary risk factors such as oxalate, creatinine, calcium and protein. Phycocyanin was found to be diuretic and it also regulated the excretion of calcium. Under hyperoxaluric conditions, the activity of brush border enzymes such as ALP, ACP and γGT increased but in phycocyanin pretreated rats [40]. Phycocyanin administration resulted in a significant improvement in the thiol content of renal tissue and RBC lysate via increasing glutathione and reducing malondialdehyde levels in the plasma of oxalate induced rats [41]. This effect might be helpful in reduction in OS and prevention of stone formation.

Lupeol & Lupeol linoleate

Lupeol is a pentacyclic triterpene (Fig. 2C). It has been isolated from stem bark of Cretaceaewaurola. It has diuretic properties. Treatment with this triterpene significantly reduced the risk of calcium oxalate nephrolithiasis by increasing the urinary volume, which results in reduction in the calcium oxalate supersaturation in the urine [22]. Lupeol is also able to normalize the increased excretion of renal enzyme in urine during lithogenesis and thus shows its renoprotective effect. The derivatefficient of Lupheol has been proved to be more effective than lupeol due to its more bioavailability, penetration and retention ability into the cell membrane and these compounds act by inhibiting some steps of oxalate synthesis from glycolic acid. The possible mechanism behind the stabilizing effect of these compounds may be due to increase in surface area/volume ratio of cells which is achieved by an expansion of membrane or shrinkage of the cell through an interaction of these compounds with membrane protein. Hyperoxaluric conditions lead to increased conversion of xanthine dehydrogenase to xanthine oxidase. This abnormal elevation in enzyme activity is normalized with both lupeol and its derivative treatment [27]. They also found to enhance the activities of SOD, CAT etc and ester of Lupheol is found to be more effective as compared to lupeol. They also protect from oxidative stress caused by ADP/Fe²⁺ and Cu²⁺, which might be due to reduction in overall concentration of oxalate [42].

1,2,3,4,6-Penta-O-galloyl-beta-D-glucoside

1,2,3,4,6-Penta-O-galloyl-beta-D-glucose (PGG) is a water soluble gallotannin (Fig. 2D). It has been isolated from a gallnut of Rhus chinensis MILL or Paonia lactiflora. It can affect the surface of CaOx crystal and renal cells that ultimately decrease their propensity to adhere and hence is more efficient at higher concentration. It effectively decreased the calcium and oxalate excretion and proved to be diuretic [28]. PGG significantly reduced the urinary oxalate excretion and also reduced the ROS production in EG induced human primary renal epithelial cells (HRCs). It also restored the SOD expression, CAT and glutathione peroxidase activity. It has been found to decrease the OPN expression and hyaluronan expression in dose dependent manner. This suggests that it can prevent renal cell injury under hyperoxaluric conditions [43].

Gallotannin

It is polyphenolic hydrolysable tannin (Fig.2E). It is commonly found in green tea. It has antioxidant properties and it effectively blocks renal calculus formation. It reduces the production of ROS and MDA and also enhanced activity of the antioxidant enzyme SOD in oxalate-treated HRCs. Gallotannin inhibited COM crystal growth and adhesion to renal epithelial cells. RT-PCR analysis revealed that it also attenuated the mRNA and protein expressions of MCP-1, OPN, NADPH oxidase subunit p22phox and p47phox after oxalate treatment in HRCs [29].

Berberine

It is an isoquinoline alkaloid (Fig. 2F). It is widely distributed in nature and exists as main constituent of several plants including Hydrastis canadensis (goldenseal), Coptis chinensis (copsis or goldenthread), Berberis aquifolium (Oregon grape), Berberis aristata (tree turmeric) and Berberis vulgaris (barberry) [44]. Berberine is therapeutically effective for both prevention as well as treatment of calcium oxalate urolithiasis, exhibiting these effects through a combination of antioxidant, diuretic, hypocalciuric and urine alkalizing activities. Berberine has been tested in vitro for the antioxidant effect and in vivo for diuretic and antiurolithic effects on an animal model of calcium oxalate urolithiasis [45]. It exhibited concentration-dependent (50–150 μg/ml) antioxidant effect and increased the urine output accompanied by increased pH and Na+ and K+ excretion and decreased Ca²⁺ excretion. It prevented as well as eliminated calcium oxalate crystal deposition in renal tubules and protected against deleterious effects of lithogenic treatment including weight loss, impaired renal function and oxidative stress, manifested as increased malondialdehyde and protein carbonyl content, depleted GSH and decreased antioxidant enzyme activities of the kidneys. These findings suggest berberine as active principle of the plants used in urolithiasis [30].

Apocynin

It is 4-hydroxy-3-methoxy-acetophenone (Fig. 2G). It is a natural nontoxic compound isolated from a medicinal plant, Picrorhiza kurroo [6]. It prevents activation of NADPH oxidase by blocking the association of cytosolic units with the membrane complex. Oral treatment with apocynin, reversed not only the transcriptome profile of the NADPH Oxidase-associated genes, but also multiple molecular pathways involving numerous cell components. These data raise the possibility that apocynin is a broad-spectrum antioxidant [4, 36].

Rottlerin

It is (5, 7-dihydroxy-2,3-dimethyl-6-(2,4,6-trihydroxy-3-methyl-5-acetylbenzyl)-8-cinnamoyl-1,2-chromone), also called maitolaxin (Fig. 2H). It is primarily present in the gland hair covering the fruit of Mallotus philippinenis (Euphorbiaceae), an evergreen rain forest

<table>
<thead>
<tr>
<th>14.</th>
<th>Losartan</th>
<th>2-butyl-4-chloro-1-[2-[(1H-tetrazol-5-yl)[biphenyl]-4-yl][methyl]-1H-imidazol-5-yl]methanol</th>
<th>Competitive</th>
<th>Angiotensin II type 1 receptor antagonist</th>
<th>[36]</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td>N-Acetyl cysteine (NAC)</td>
<td>2-Acetamido-3-sulfanylpropanoic acid</td>
<td>Antioxidant activity</td>
<td></td>
<td>[37]</td>
</tr>
</tbody>
</table>
tree that is inedible and only used by indigenous populations of Southeast Asian tropical regions [31]. It displays specificity as an inhibitor of PKC-δ activity in vitro, and on this basis it has been a component of patent applications to consider it for therapeutic use [46]. PKC-δ is reportedly a key signaling molecule in the ROS-induced apoptotic pathway through generation of active catalytic fragments by proteolytic cleavage and also inhibits translocation of PKC-δ.

**Curcumin**

It is a polyphenol obtained from the spice turmeric (*Curcuma longa*, Zingiberaceae) and is responsible for the yellow colour of turmeric (Fig. 2I). Curcumin is a dietary antioxidant and has been known since ancient times to possess therapeutic properties. It has been reported to scavenge oxygen free radicals, to inhibit lipid peroxidation, and has anticarcinogenic activities in experimental models [32]. The possible nephroprotective effect of curcumin is inhibition of lipid peroxidation. Recent studies reported that curcumin decreases PKC protein levels by forming tight complexes with the enzyme and generating tyrosine phosphorylated PKC fragments. It has been found that by forming hydrogen bonds with the activator binding domain of the enzyme, curcumin and its analogues could change PKC-δ conformation and influence activation and membrane translocation properties [31].

**Thymoquinone**

Thymoquinone is a phytochemical compound found in the plant *Nigella sativa* (Fig 2J). It is active quinine, has antioxidant effect, scavenges free radicals and superoxide anions, and inhibits cyclooxygenase and 5-lipoxygenase pathways; therefore, it inhibits inflammatory products [47]. Thymoquinone has an antibacterial effect, and, therefore, calcium with a bacterial origin such as struvite calculi may be prevented by thymoquinone [48]. Urinary oxalate concentration was also decreased by thymoquinone which is in agreement with its preventive effects on the CaOx kidney calculi [33].

**Fucoidans**

These are sulfated polysaccharides from brown algae (Fig. 2K). They are rich in the sugar, fucose. These naturally occurring glycossaminoglycans from edible seaweeds were able to modulate the altered redox status in hyperoxicuric rats [49]. They are reported to have blood anticoagulant, anti-tumour, anti-mutagenic, anti-complementary, immunomodulating, hypoglycaemic, antiviral, hypolipidemic and anti-inflammatory activities [50]. It possesses antioxidant potential which is unique to polysaccharides of marine origin. Fucoidans administration is able to normalize the redox status of the renal cells under hyperoxaluria, and also prevent the mitochondrial damage as was evident from biochemical investigations and electron microscopic analysis [34].

**Atorvastatin**

Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reduction inhibitor (Fig. 2L). It is a high cholesterol lowering drug with anti-inflammatory and antioxidative activities [51]. It has an inhibitory effect on renal tubular cell injury and on oxidative stress by ROS. Atorvastatin treatment also decreases the apoptosis of renal tubular cells and the formation of renal crystal deposits in kidney tissue. It stimulates the production of SOD which converts super oxide ions into $\text{H}_2\text{O}_2$ and catalase which converts $\text{H}_2\text{O}_2$ into $\text{H}_2\text{O}$ and $\text{O}_2$. The possible mechanism of action behind its antioxidative activity is that it decreases the NADPH Oxidase (NOX) activity by reducing the expression of NADPH oxide subunits in a rat stone forming kidney model. Therefore, one of the mechanisms by which it inhibits the renal tubular cell injury and oxidative stress caused by ROS, is the inhibition of NOX-1 [52]. It has been found that atorvastatin inhibited the expression of TGF-β. TGF-β increases the activity of NADPH oxidase and leads to the production of ROS ultimately resulting in oxidative stress. The suppression of TGF-β in kidney tissue was thought to be additional mechanism to inhibit renal crystal retention by atorvastatin [35].

**Taurine**

It is 2-aminoethanesulfonic acid, one of the few known naturally occurring sulfonic acids (Fig. 2M). Taurine is a derivative of cysteine, an amino acid which contains a thiol group so it is an amino sulphonic acid [53]. It occurs naturally in food, especially in seafood and meat. It is a major constituent of bile and can be found in the large intestine and in the tissues of many animals, including humans [54, 55]. Taurine is known to have antioxidative activity and shows renoprotective effect. It has been found to localize in mitochondria where it serves as mitochondrial matrix buffer so it has been proposed that by stabilizing the environment in the mitochondria, it would prevent leakage of the reactive compounds formed in the reactive mitochondrial environment and thus indirectly acts as an antioxidant. Taurine treatment repairs the oxidative injury of the kidney, improved SOD and GSH-Px activities, as well as the mitochondrial membrane injury, with lesser crystal depositions in the kidney [36]. In this way, it protects the kidney from oxidative injury through mitochondrial-linked pathway.

**Losartan**

Losartan is a selective, competitive angiotensin II type 1 (AT1) receptor antagonist (Fig. 2N). Treatment with Losartan resulted in reduction of urinary 8-IP and a decrease in renal p47phox expression. It has been shown that administration of AT1 receptor blockers or ACE inhibitors significantly reduced hyperoxaluria-induced production of renal lipid peroxides [4]. OS is a key component of both oxalate and angiotensin-induced renal injury. Also, losartan treatment may act by lowering the Bax and caspase-3 expression and decrease the apoptotic cell numbers in hyperoxicuric rat model [36].

Our group is also actively involved in identification of novel calcium oxalate inhibitor molecules from various natural sources like, a novel dimeric protein DAP (98 kDa) from *Dolichos biflorus* seeds has been purified. Based on its ability to inhibit calcium oxalate crystallization *in vitro* it is postulated to have anti-lithiatic activity. We proposed that DAP, which is CYN, Calnexin like protein has a calcium binding site, which might also be responsible for its ability to inhibit CaOx crystallization [56]. Recently, our group has also purified an anticalcifying protein from the seeds of *Trachyspermum ammi* (TAP). The anti-lithiatic potential of TAP was confirmed by its ability to maintain renal function, reduce renal injury and decrease crystal excretion in urine and retention in renal tissues [57]. Also N-acetylcysteine (NAC) has been extensively studied, with some reports indicating its outstanding efficacy in the renal protection. NAC has been shown to reverse hyperoxicuric manifestations in rat liver. The thiol group of NAC reduces the level of free radicals responsible for the lipid peroxidation and thus decreases the level of malondialdehyde, the end product of peroxidation. This shows that NAC is a potential free radical quencher in renal tissue and it reduces oxalate induced free radical damage which is evident from histological analysis [37]. In one more study *Achyranthes aspera* extract has been checked for its ability to maintain renal functioning and reduced renal injury [58]. This treatment reduced changes in the architecture of renal tissue and also decreased the size of crystals thereby helping in quick expulsion of the crystals [59]. The anti-lithiatic potency of the protein biomolecules of *Tribulus terrestris* has been checked by various biochemical methods and was tested on the oxalate induced injury on renal epithelial cell lines (NRK 52E) [60]. The protective potency of TTP on NRK 52E was quite comparable to the aqueous extract of cystone. These findings suggest that this purified protein biomolecule from *Tribulus terrestris* could open new vista in medical management of urolithiasis [61]. Coconut water has also potential to inhibit the genes of oxidative stress to push the activity of these enzymes towards normal. The re-balancing of activated antioxidative enzyme gene expression by coconut water treatment, reduced mineral deposits in kidney tissue further substantiated the prophylactic nature of coconut water in nephrolithiasis.
ameliorating hyperoxaluria induced oxidative stress and renal cell injury in urolithiasis. Further research on these molecules is required to explore their potential and confirm their candidature as an antiurolithic drug.

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