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Review

The mechanistic insight of polyphenols in calcium oxalate urolithiasis mitigation

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ABSTRACT

About 12% of world population is affected by different forms of urolithiasis of which the recurrence rate in female is 47–60% and in male is 70–80%. Standard therapeutic agents (allopurinol, citrate, cystone and thiazide diuretics) are used to prevent and treat urolithiasis but these are not universally-effective due to common kidney stone relapse and other side effects. Surgical treatment causes long-term renal damage, hypertension and stone recurrence. Polyphenols, the plant-derived bioactive molecules, have showed protection against cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases, among a number of other ailments. The role of these phytochemicals in urolithiasis management is emerging. Hence, the present review discusses peer-reviewed published literature till date on this aspect and highlights that polyphenols could effectively inhibit the formation of calcium oxalate urinary stones (most common renal stone), correlating with their antioxidant, anti-inflammatory, diuretic and angiotensin-converting enzyme (ACE) inhibition. Further, we have proposed the prospects and challenges in developing the plant polyphenols into drugs against kidney stone prevention. This review might be a stepping stone for further investigation into the clinical implications of the polyphenols in urolithiasis remediation.

1. Introduction

Urolithiasis, characterized by uroliths or mineral deposition in urinary system, is a common health problem, with worldwide occurrence and high recurrence. This pathology is estimated to affect 12% of the world population with 70–80% and 47–60% recurrence in males and females, respectively [1]. Due to disturbed urine flow rate, uric acid excretion rate, and urine pH, the stones are formed. Increased bone resorption, hypercalciuria and hyperphosphaturia are risk factors of calcium oxalate kidney stones. Urease-producing bacteria such as *Proteus* cause struvite (magnesium—ammonium—phosphate) stones, which can cause severe aching and sepsis. Stones with ammonium hydrogen urate in the core result due to poor nutrition and dehydration.

The dissolution and prevention of the stone relapse are the main focus of urolithiasis treatment. Medications are prescribed to resolve the pain and stones pass out their own. Standard pharmaceutical drugs such as allopurinol, citrate, cystone and thiazide diuretics are used to prevent and treat urolithiasis [2], but these are not effective in all patients, due to common kidney stone recurrence and potential side effects. Surgical treatment causes long-term renal damage, hypertension and reformation of stones. Now, the Extracorporeal Shock Wave Lithotripsy (ESWL) and percutaneous nephrolithotomy, have almost become the standard procedure for eliminating the kidney stones but the traumatic effect of shock waves, persistent residual stone fragments as potential nidus for new stone formation, acute renal injury, decrement in the renal function and an increment in stone recurrence, ESWL induced hypertension, severe hematuria, steinstrasse (multiple small stone blocking the ureter), pancreatitis and infection are reported as repercussions [1]. These complications can lead to large perfusion of the collecting system, extravasations of irrigating fluid, urosepsis, ureteral injury. Further, ESWL is less effective in calcium oxalate monohydrate (COM) and cystine stones. In this regard, benign but effective therapy is being sought-after.

Antiurolithiatic plants are used since ancient times, in the form of

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decoction, infusion, or juice, to eliminate kidney stones and to prevent their recurrence. Although medicinal plants have milder efficacy and longer therapy duration, these are affordable and less expensive, with fewer side effects. On the basis of available ethnopharmacological information, more scientific studies are needed to explore natural and safe antiurolithiatic compounds [3]. Phytochemicals have complex molecular structures which act through multiple biochemical pathways to produce desired therapeutic effects. Some of these secondary metabolites are bioactive, having great selectivity of cellular targets. In contrast, some of the metabolites have multiple cellular targets, which may combine together to produce specific biological activity. Some of the phytochemicals exert biological effect by synergistic mechanism. Some inactive adjuvant substances enhance the potency of bioactive compounds. Plants also contain byproducts which may increase the absorption rate or solubility of active phytochemicals or may induce metabolic enzymes [4].

Over the years, plant-based products have demonstrated broad-range of therapeutic potentials [5–10]. Polyphenols encompass anthocyanins, chalcones, flavones, isoflavones, flavonols, phenolic acids and stilbenoids. Cyanidin, delphinidin, malvidin are anthocyanins [11]; curcumin is grouped under chalcones [12–14]; apigenin, diosmin and luteolin are classified under flavones [15]; genistein and daidzein are reported as isoflavones [16] ; catechin, kaempferol, quercetin, rutin are the examples of flavonols. Phenolic acid consists of hydroxycinnamic and hydroxybenzoic acids [17]. Hydroxycinnamic acids comprise caffeic, chlorogenic, coumaric, ferulic and sinapic acid; whereas hydroxybenzoic acid includes gallic, protocatechuic, syringic and vanillic acid. Resveratrol is a stilbenoid [11]. Each of the polyphenol members boast thousands of scientific validation reports regarding their health benefits.

2. Pathophysiology of calcium oxalate urolithiasis

Oxalate is widely distributed in plant-based foods as potassium, sodium and ammonium oxalates (water-soluble form) and as insoluble calcium oxalates. It is being recommended to limit the intake of oxalate-rich foods, specifically for individuals at risk for kidney stone formation [18]. Oxalate is poorly absorbed under non-fasting conditions. It has been demonstrated that only 2–12% of oxalate (soluble form) is absorbed from foods but that once absorbed, free oxalate binds to calcium ions to form insoluble calcium oxalate [19]. Oxalate has been shown to be toxic to renal epithelial cells of cortical origin. It has been observed that the exposure of renal epithelial cells to oxalate leads to the disruption of the normal activities of the renal epithelium, caused changes in gene expression, impairment of mitochondrial function, forming reactive oxygen species and thus, decreased cell viability [20]. Membrane injury is considered to be the prime reason for the binding of calcium oxalate crystal and subsequent growth into kidney stones. Oxalate-induced membrane injury is mediated by lipid and protein peroxidation through the generation of ROS with altered biochemical reactions, including the depletion of the antioxidant defensive system and failure of the calcium pump. Calcium and oxalate accumulate and then precipitate in the presence of membrane fragments to form stones [21]. Renal epithelial cell injuries in renal papilla invites calcium oxalate to form attached renal calculi and the development of calcium oxalate papillary calculi. Antioxidants play an important role in the avoidance of calculi formation [22], and by protecting membrane injury. These stones attached to tips renal papilla and prevent calcium oxalate retention [21]. Calcium oxalate crystals are generally grown from microns to several centimeters. These stones attach to the tips of renal papilla and when detached, hinder urine flow due to their large size. These crystals have a stronger affinity for the membranes of renal epithelial cells and therefore they make strong adhesion contacts with these cells, and form stable aggregates instead of excretion and lead to the retention of mineral in renal collecting ducts for urolithiasis development [23]. Fig. 1 illustrates the mechanism of stone formation (Table 1).

3. The mechanistic insight of polyphenols in oxalate urolithiasis

Pumpkin (*Cucurbita* sp.) seeds ingestion has been observed to avoid kidney stones. *Hibiscus sabdariffa* aqueous extract significantly lowered the stone formation risk in the kidneys and serum of rat models. Although in earlier studies caffeic acid [24], catechin [25], curcumin, rutin [26], diosmin [27], quercetin [28,29] and resveratrol [30] have prevented the ethylene glycol-induced calcium oxalate crystallization in rats, the mechanistic insights underlying these effects have been barely-explained. The antioxidant, anti-inflammatory, ACE-inhibitory, and diuretic activities of polyphenols are contributive to the calcium oxalate calculi prevention [31].

4. Antioxidant

ROS are free radicals comprising of singlet oxygen superoxide anion ($O2^{*-}$), hydroxyl (OH^{*-}) and peroxy (ROO*) radicals, as well as non-radical molecules, such as hydrogen peroxide and hypochlorous acid [32]. Free radicals quickly react with lipids and proteins, render them unstable, and initiate a cascade of chain reactions. Under normal physiologic conditions, these reactions are important for immune response, gene expression, signal transduction and growth regulation. But the overproduction of ROS, injure and damage renal epithelial cells [32–34]. Free-radical scavenging enzymes such as catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, heme oxygenase-I, superoxide dismutase and endogenous antioxidants as vitamin C, vitamin E, reduced glutathione, not only maintain the normal physiologic concentration of free radicals, but also provide protection against endothelial oxidative damage. Renal exposure to oxalates causes lipid peroxidation and produce ROS followed by renal cell injury and inflammation. The resultant loss of membrane integrity promotes fibrosis and collagen formation, facilitates calcium oxalate adhesion, retention and subsequent stone formation. The ROS triggers phospholipase A2 activation through nuclear transcription factor NF-κB. The activation of phospholipase A2 generates arachidonic acid, which increases ROS production which in turn causes inflammation, cellular damage and crystal formation [35–37]. Thus, the vicious cycle continues. Antioxidants are compounds that can delay, inhibit or prevent the oxidative degeneration by decreasing localized oxygen concentrations, scavenging ROS or RNS species and their intermediates, binding or chelating with metal ions and decompose lipid peroxides [38]. *In vitro* and *in vivo* studies suggest that the antioxidant activity of natural polyphenols play an important in the prevention of calcium oxalate monohydrate type urolithiasis, particularly by inhibiting renal endothelial tissue injury caused by cytotoxic substances with oxidative capacity [22,39–41]. By scavenging free radicals, increasing endogenous antioxidant enzymes level and chelation of transition metals, and lowering membrane lipid peroxidation, the polyphenols protect the cells against oxidative stress.

Catechin [42,43], curcumin [44], daidzein, genistein [45], kaempferol [46], luteolin [47,48], quercetin [46] and syringic acid [32] are reported to scavenge peroxide free radicals. Superoxide dismutase is useful in protecting tissue injury, and glutathione participates in membrane stabilizing during oxidative stress [49]. Catechin [50], cyanidin, malvidin [51], caffeic acid [52,53], diosmin [54], *p*-coumaric acid [55], gallic acid [56], protocatechuic acid [57,58], apigenin [59], resveratrol [30] and vanillic acid [60] are reported to inhibit lipid peroxidation by increasing the activity of endogenous antioxidants such as CAT, SOD, and GSH.

Transition metals such as copper and iron play an important role in generation of free radicals leading to lipid peroxidation [33]. Cyanidin, delphinidin, malvidin [38], caffeic, chlorogenic, ferulic [33], gallic [56], protocatechuic [57,58], syringic acid [32], rutin [61] and curcumin [44] reduced lipid peroxidation by forming chelate with iron and