ISSN : 0974 - 7508 Volume 8 Issue 4

Trade Science Inc.

Natural Products

An Indian Journal

Review

NPAIJ, 8(4), 2012 [168-174]

Antiurolithiatic activity of edible plants and products

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Received: 28th February, 2012 ; Accepted: 28th March, 2012

INTRODUCTION

Urolithiasis is known to be an affliction to mankind from ancient eras and remains a major issue regarding health and well being today. Stone disease affects 10 to 12% of the population in industrialized countries with a peak incidence between 20 and 40 years of age[1].

There are many theories that explain the pathogenesis of stone formation, for example, the supersaturation theory and the inhibitors theory. Supersaturation occurs when there is an overabundance of solute in a solution[2]. Although, urolithiasis is a multifactorial disease, nutrition, especially fluid intake, with several underlying disorders of metabolism: that is why diet is an important treatment, especially in the prevention of recurrences[3,4]. Epidemiological studies reveal that about 80% of all kidney stones are composed of calcium salts (75% calcium oxalate), while about 5% are pure uric acid[5]. Kidney stones have previously been linked to higher rates of high blood pressure, obesity, diabetes and other heart disease risk factors. Researchers have speculated that the dietary approaches to hypertension (DASH) style diet could, also prevent kidney stones. The main components of the DASH diet includes fruit, vegetables, nuts and legumes, low fat dairy, whole grains, and lower intakes of salt, sweetened drinks, red meat and processed meat[6]. The DASH-style diet may reduce stone risk by increasing urinary citrate and volume. The small associations between higher DASH score and lower relative supersaturation of calcium oxalate and uric acid suggesting that unidentified stone inhibitors in dairy products and/or plants[7].

One of the important phenomena that characterizes urolithiasis is its high recurrence. Thus, a protective system is required including extracorporeal shock wave lithotripsy and medicament treatment. Unfortunately, these means remain costly and in most cases are invasive and with side effects. Therefore, great interest has arisen among both physicians and patients towards identifying effective measures to achieve analgesia during renal colic, promote stone passage or stone dissolution and prevent stone recurrence by natural products (phytotherapy)[8]. Recent years have shown a dramatic expansion in the knowledge of molecular mechanism of phytotherapeutic agents used to treat urolithiasis. The discovery and elucidation of the mechanism of action, in particular the clinical role of these herbal remedies, has made an important contribution to treatment for urinary stone disease as an alternative or adjunct therapy. We present a literature review of edible and herbal products in renal stone management.

THE ROLE OF CITRATE IN DIMINISHING RENAL STONE FORMATION

Saponins decrease blood lipids, lower cancer risks, and lower blood glucose response. A high saponin diet can be used in the inhibition of dental caries and platelet aggregation, in the treatment of hypercalciuria in humans, and as an antidote against acute lead poisoning.

In epidemiological studies, saponins have been shown to have an inverse relationship with the incidence of renal stones[9]. Nutritional intervention is based on a high water intake, physiological calcium intake, modest sodium and animal protein restriction and vitamin C intake < 2g daily. In case of diagnosed disorders of specific metabolic pathways, a low oxalate, low purine-diet should be advisable.

The hypocitraturia or low urinary citrate excretion is a common feature with nephrolithiasis, particularly in those with calcium stone disease. The protective role of citrate is linked to several mechanisms;

1- Citrate reduces urinary supersaturation of calcium salts by forming soluble complexes with calcium ions and by inhibiting crystal growth and aggregation.
2- Citrate increases the activity of some macromolecules in the urine (e.g. Tamm-Horsfall protein) that inhibit calcium oxalate aggregation.
3- Citrate seems able to reduce the expression of urinary osteopontin.

The therapy with potassium citrate, or magnesium potassium citrate, is commonly prescribed in clinical practice in order to increase urinary citrate and to reduce stone formation rates[10].

To reduce urine concentration consistently it is recommended that the fluid intake should be distributed more or less evenly over 24 h[11]. Diluting urine has two major consequences. First, by increasing urine output, the concentration of constituent ions and the saturation of stone-forming salts are lowered. Second, fluid composition has a direct influence on urine composition and crystal formation[12]. Depending on the stone composition, several fluids have been found to be suitable, e.g. orange juice[13], apple juice, fruit and herbal teas. Fluids containing lithogenic agents which may increase the risk of stone formation, such as coffee, black tea[14] and cola[15,16] should be avoided.

FRUITS AND VEGETABLES

Fruit and vegetable juices containing citrate may be recommended as an alternative in mild to moderate level hypocitraturic calcium stone formers who cannot tolerate pharmacological treatment. Tomato has been proved a citrate-rich vegetable. Tomato juice usage as citrate sources in hypocitraturic recurrent stone formers were evaluated in the light of the results of studies on orange and lemon juices. Fresh tomato juice may be useful in hypocitraturic recurrent stone formers due to its high content of citrate and magnesium, and low content of sodium and oxalate[17].

Meschi *et al*.[18] studied the effect of a two-week period of fruits (Oranges, pineapple, apples, pears, avocado, mango, bananas, apricots, peaches, persimmon, plums, kiwi, melons, and water melon) and vegetables (Asparagus, broccoli, cauliflower, cucumber, lettuce, onions, radishes, turnip, artichokes, fennel, radicchio, peppers, courgettes, tomatoes, carrots) elimination on urinary stone risk profile in 12 normal adults, and of supplementing the diet with a fair quantity of low-oxalate fruits and vegetables in 26 idiopathic calcium stone formers characterized by hypocitraturia and a very low fruit and vegetable intake in their usual diet. They found that the removal of fruits and vegetables from the diet decreased the urinary excretion of potassium, magnesium, citrate and oxalate, and increased that of calcium and ammonium. In contrast, the addition of these foods to the diet of hypocitraturic stone formers not used to eating them not only significantly increases citrate excretion without affecting oxalate excretion, but also decreases calcium oxalate and uric acid relative saturation.

Curhan *et al*[19,20] showed that the incidence of stone disease decreased in proportion to the increase of potassium in the diet. Most dietary potassium derives from meat, fruits, and vegetables, with an important difference, however, between these foods: whereas meat intake has an acidifying effect due to its high content of sulfuric aminoacids (methionine and cysteine), fruits and vegetables provide mainly an alkali load that increases urinary citrate. Various studies have shown that, unlike potassium chloride, potassium bicarbonate can reduce urinary calcium excretion in normal subjects[21,22] and patients with urinary stones[23]. On the other hand, Wabner and Pak[24] were the first to show that, owing to its high content in potassium and citrate, orange juice intake induces a significant increase in urinary citrate excretion in normal males, and in male stone formers with hypocitraturia. Seltzer *et al*[25] demonstrated that lemon juice has a similar effect to that of orange juice in hypocitraturic calcium stone formers. Moreover, it has been common knowledge for some time that pharmacologic treatment with potassium cit-

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rate protects against the formation of stones because it increases urinary citrate and reduces calciuria[26]. On the basis of such indirect evidence, today calcium stone formers are generally advised to consume fruits and vegetables regularly, and to limit their intake of animal proteins and sodium chloride, the indication of a reduced dietary calcium intake for subjects with idiopathic hypercalciuria being no longer acceptable[27].

Magnesium urinary excretion was, on the other hand, found to be consistent with the dietary intake, which decreased in the healthy subjects after fruit-vegetable withdrawal, whereas it increased in the hypocitraturic stone formers after fruit-vegetable supplementation, this being a favorable effect in the prevention of calcium renal stones[28].

CRANBERRY JUICE

A protective effect in the therapy of urinary tract infection was attributed to cranberry juice[29]. Kahn *et al*[30] observed an acidifying of the urine after ingestion of large amounts of cranberry juice and Howell *et al*[31] identified proanthocyanidins as the compounds in cranberries that are responsible for the inhibition of the adherence of *Escherichia coli* to uroepithelial cells.

Keßler *et al*.[32] evaluated the influence of plum, cranberry and blackcurrant juice on urinary stone risk factors in 12 healthy male received a standardized diet formulation. They found that cranberry juice decreased the urinary pH, whereas the excretion of oxalic acid and the relative supersaturation for uric acid were increased. Blackcurrant juice increased the urinary pH and the excretion of citric acid. The excretion of oxalic acid was increased too. The plum juice had no significant effect on the urinary composition. They concluded that blackcurrant juice could support the treatment and metaphylaxis of uric acid stone disease because of its alkalizing effect. Since cranberry juice acidifies urine it could be useful in the treatment of brushite and struvite stones as well as urinary tract infection.

GRAPEFRUIT JUICE

The effect of citrus fruit juice ingestion on the risk of calcium oxalate stone formation is still debated. Changes in urinary stone risk factors after administration of a soft drink containing grapefruit juice were investigated[33]. Seven healthy subjects, with no history of kidney stones, were submitted to an acute oral load (20 ml/kg body weight over 60 min) of a soft drink containing grapefruit juice diluted (10%) in mineral water. Urinary flow and urinary excretion of citrate were significantly increased after grapefruit juice compared to baseline. Citrus fruit juices could represent a natural alternative to potassium citrate in the management of nephrolithiasis, because they could be better tolerated and cost-effective than pharmacological calcium treatment. However, in order to obtain a beneficial effect in the prevention of calcium renal stones reduced sugar content is desirable to avoid the increase of urinary calcium due to the effect of sugar supplementation.

POMEGRANATE JUICE

Crystal depositions, inducible nitric oxide synthase, p38-mitogene-activated protein kinase and p65-nuclear factor-kB activity, and oxidative stress markers were found to be decreased by middle- and high-dose PJ treatment. Pomegranate juice was found to have inhibitory effects on renal tubular cell injury and oxidative stress caused by oxalate crystals by reducing nitric oxide synthase, p38-mitogene-activated protein kinase and p65-nuclear factor-kB expression on hyperoxaluria-induced oxidative stress and stone formation in rat kidneys[34].

RADISH

The effect of radish on urinary calcium oxalate excretion was evaluated[35]. Early morning midstream urine (MSU) samples collected from 36 subjects were analyzed continuously for a period of 14 days for the presence of calcium oxalate crystals. Of these, 21 cases were of renal stone and 15 were normal subjects. The subjects were advised to consume self-selected diet for a week and radish containing diet along with their self-selected diet for consecutive week. The study reveals that radish containing diet caused increased excretion of calcium oxalate compared to the self-selected diet and the crystals count in the urine were significantly higher in both genders.

RICE-BRAN

Rice bran has shown promising disease-preventing and health-related benefits in experimental research studies. Candidate products studied and under investigation include: inositol and related compounds, inositol hexaphosphate (IP6 or phytate), rice oil, ferulic acid, gamma-oryzanol, plant sterols, tocotrienols and RICEO, a new rice-bran-derived product[36]. Diseases in which preventive and/or nutraceutical effects have been detected include: cancer, hyperlipidemia, fatty liver, hypercalciuria, kidney stones, and heart disease. The efficacy of rice-bran therapy was studied in patients with hypercalciuria who were suffering from calcium stones. The frequency of stone episodes was reduced dramatically, especially in "active recurrent stone formers". Urinary calcium excretion was considerably reduced, while urinary phosphate and oxalate were slightly increased. Urinary magnesium, uric acid, serum calcium, phosphate, magnesium and uric acid were not affected. Rice-bran therapy is particularly useful in patients with hyperabsorptive hypercalciuria and it is effective in the prevention of recurrent urinary stone disease[37,38]. In this respect, Noronha *et al*.[39] treated ten patients with recurrent nephrolithiasis and hypercalciuria were given rice bran during 60 days. They found that hypercalciuria was reduced in all patients in an average of 40%. Urinary magnesium was reduced in 28% and oxalate excretion was increased in 28%. The rate of decrease of urinary calcium was 65% in the absorptive type and 33% in the renal type of hypercalciuria.

Zea mays

Zea mays has sufficient evidence to support their traditional use for urinary problems[40]. Cystine stones represent 1% of urinary calculi in adults and 10% in children and are especially recurrent. Administration of Zea mays extract for 4 weeks, results in complete dissolution of cystine stones. This effect may possibly due to the formation of complexes between cystine and polyhydroxylated molecules present in the extracts[41,42].

Trigonella foenum graecum (Fenugreek)

Despite considerable progress in medical therapy, there is no satisfactory drug to treat kidney stones. Therefore, the current study aimed to look for an alternative by using *Trigonella foenum graecum* on nephrolithiasic rats as a preventive agent against the development of kidney stones, which is commonly used in Morocco as a phytotherapeutic agent. The inhibitory effect of the aqueous extract of fenugreek seeds was examined on the formation of calcium oxalate renal stones induced by ethylene glycol with ammonium chloride. The results showed that the amounts of calcification in the kidneys and the total calcium amount of the renal tissue in rats treated with fenugreek were significantly reduced compared with the untreated group. Consequently, fenugreek may be a useful agent in the treatment of patients with calcic urolithiasis. Ahsan *et al*.[44] investigated the effect of *Trigonella foenum-graecum* seed on experimentally-induced kidney stones. Oxalate urolithiasis in male rats was produced by the addition of 3% glycolic acid to their diet. After 4 weeks, highly significant deposition in the kidneys was noticed and changes in water intake and body weight recorded. Daily oral treatment with *T. foenum-graecum* significantly decreased the quantity of calcium oxalate deposited in the kidneys thus supporting its use in folk medicine.

Nigella sativa

Nigella sativa L. or black seeds have been used in traditional medicine for centuries[45]. Black seeds have been reported to be increases glutathione in the kidney, and repairs kidney tissue of the nephrotoxicity[46]. Hadjzadeh *et al*[47] investigated the effects of the ethanolic extract of *Nigella sativa L* seeds on in rats received 1% ethylene glycol for induction of calcium oxalate calculus formation. They found that treatment of rats with ethanolic extract of *Nigella sativa* reduced the number of calcium oxalate deposits. *Nigella sativa* could also lower the urine concentration of calcium oxalate. N-butanol phase remnant fraction and aqueous-ethanolic extract have polar and intermediate compounds such as tannin, flavonoids and alkaloids. Flavonoids including quercetin, kaempferol and glyceride flavonoids also have anti-inflammatory and antioxidant effects[48]. Thus it may be suggested that the effects of NS seeds fractions in preventing of CaOx calculi formation in the present study are in part caused by anti-inflammatory and antioxidant action of NS seeds components. These compounds are able to inhibit the process of epithelial cell injury and inflammation induced by CaOx crystals[49].

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GREEN TEA

Recently, interest in green tea as a promising agent for the prevention or reduction of risk for many human diseases has increased worldwide and is a widely consumed beverage throughout the world second only to water[50]. Green tea contains multiple catechin components, though epigallocatechin-3-gallate (EGCG) is the primary catechin accounting for 50–80% in a brewed cup[51]. ECG epicatechin-3-gallate is the second most concentrated catechin component of green tea, and is associated with its anti-inflammatory/anti-oxidant properties[52]. Other major catechins found in green tea include epicatechin (EC) and epigallocatechin (EGC).

Previous studies have identified anti-inflammatory/ anti-oxidant properties of green tea in both in vivo and in vitro systems[53,54]. Indeed, due to its low cost, low cytotoxicity and widespread availability, green tea has enormous potential as a chemopreventative agent for a variety of human diseases. Consequently, because catechin components have been detected at measureable levels in human urine[55,56], green tea and other herbal supplements may be beneficial and under-utilized dietary resources to modulate lower urinary tract inflammation.

Jeong *et al*[57] evaluated whether EGCG a main constituent of green tea polyphenols, could protect against cellular toxicity by oxalate and whether green tea supplementation attenuates the development of nephrolithiasis in an animal model. The administration of EGCG inhibited free-radical production induced by oxalate. Green tea supplementation decreased the excretion of urinary oxalate and the activities of urinary gamma-glutamyl-trans-peptidase and N-acetyl-glucosaminidase. The number of crystals within kidneys in was significantly decreased. Green tea has an inhibitory effect on urinary stone formation, and the antioxidative action of EGCG is considered to be involved.

The antioxidative effect of green tea decreases the formation of calcium oxalate stones, osteopontin (OPN) expression, and apoptosis, and increases superoxide dismutase (SOD) activity in rat kidney tissues. The inhibitory effect of green tea on calcium oxalate urolithiasis is most likely due to its antioxidative effects[58]. Therefore, we examined oxidative stress *in vivo* applied to Madin-Darby canine kidney (MDCK) cells, to which catechin, an antioxidant, was added. Confluent cultures of MDCK cells were exposed to EGCG (0, 0.1, 0.5, 5.0 mg/ml) for 2, 4, 8 or 16 h to determine changes in protein secretion and apoptosis. Quantitative analyses showed that SOD activity decreased gradually in all groups. Only in the EGCG 0 mg/ml 16 h group were TUNEL-positive cells observed. In the other groups, TUNEL-positive cells were not detected. EGCG used as an antioxidant protects renal tubular cell from cellular injury caused by oxidative stress through SOD protein expression[59].

ASPARAGUS RACEMOSUS

The ethanolic extract of *Asparagus racemosus Willd* was evaluated for its inhibitory potential on lithiasis (stone formation), induced by oral administration of 0.75% ethylene glycolated water to adult male albino Wistar rats for 28 days. The high serum creatinine level observed in ethylene glycol-treated rats was also reduced, following treatment with the extract. The histopathological findings also showed signs of improvement after treatment with the extract. All these observations provided the basis for the conclusion that this plant extract inhibits stone formation induced by ethylene glycol treatment[60,61].

CONCLUSION

Phytotherapeutic agents could be useful as either an alternative or an adjunctive therapy in the management of urolithiasis. Further scientific researches should be instigated to determine the exact mechanism of action of these agents would be fruitful for willing investigators.

ACKNOWLEDGEMENT

This work was funded by Cairo university, Project No, 3/5 2009 Application of NB in the new millennium.

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