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RESEARCH ARTICLE

KIDNEY STONE TREATMENT BY POMEGRANATE (PUNICA GRANATUM)

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ABSTRACT

Oxalate is via way of means of product that is obviously present in the body for metabolism, and in everyday people it's far excreted harmlessly. Oxalate may be poisonous due to its tendency to crystallize at physiological pH and shape calcium oxalate crystal. There changed into a minute correlation oxidative strain and extrude in urine evaluation with the pomegranate extract supplement. Stone formers have extensively extended tiers of oxidative strain, renal tubular harm, and DNA oxidative damage. After administration of ethylene glycol, produce excessive tiers of urinary calcium oxalate, results in speedy crystal deposition and nephrolithiasis. Pomegranate extract supplementation with 1,000 mg polyphenol extract each day can also additionally present a few modest advantages in reducing supersaturation of calcium oxalate. The iNOS-mediated NO production is extensively excessive while there may be accelerated tiers of oxidative strain. Renal tubular molecular harm ends in the formation of cystic fibrosis stem cells. There are numerous promoters of stone formation just like the Tamm-Horsfall proteins and osteopontin. The THP make a contribution closer to stone formation while the ionic electricity is excessive and the pH is low. But if the THP gene is inactivated in mouse embryonic stem cells, it effects in impromptu formation of calcium crystals. The formation of stones relies upon the stability among the promoters and inhibitors of urolithiasis.

KEYWORDS

lipid peroxidation, oxalate, oxidative stress, Renal tubular injury, crystal deposition, pomegranate extract supplementation, singular serum constituents, hyperoxaluria

INTRODUCTION

Hyperoxaluria (unrestricted urinary excretion of oxalate) is the major consequence for formation of stone disease[1].

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Oxalate is by product which is naturally present in the body for metabolism, and in normal individuals it is excreted harmlessly. However, Oxalate can be toxic because of its tendency to crystallize at physiological pH and form calcium oxalate(CaOx) crystal which are deposited in the kidney[3,4].Acute and chronic production of CaOx crystals leads to lipid peroxidation; therefore, this process plays an important role in CaOx stone formation[5].

Oxalate and calcium oxalate crystals cause damage to Renal epithelial cells[6,7] and induces lipid peroxidation which leads to functional impairment of cellular components by reactive oxygen species (ROS) such as

superoxide[8,9] . ROS act as mediators to signaling molecules such as p38-MAPK (mitogen-activated protein kinase) and transcription factors such as nuclear factor kappa-B (NF-kB) [10,11].
(NF-kB) is ubiquitous tanscriptional factors of the many genes including iNOS, host defences process[12] Mitogen-activated protein kinases (MAPK) are major mediators involved in the intracellular network of interaction proteins that transduce extracellular stimuli to intracellular responses[13].Three distinct MAPK pathways have been described: extracellular signal regulated and terminal kinase, and p38 MAPK[14].Both Ox and CaOx crystals selectively activated p38-MAPK signal transduction pathways in the proximal tubular epithelial cells[15,16]. The activation of p38-MAPK was found to be essential for the reinitiation of Ox- induced DNA synthesis.
Nitric oxide(NO) regulates inflammation and vasorelaxation and have a major role in eradication of tumor cells and pathogens[17]. Although in elevated production of NO is oxidized to ROS, which results in disruption of cell signaling and uncontrolled systemic inflammation[18].
Malondialdehyde (MDA) is a phenomenal marker of lipid peroxidation. In excessive amount it cause tissue injury and DNA damage. When combine with proteins, forms MDA-modified protein adducts[19].
Glutathione(GSH) is important intracellular antioxidant[20].

COMPONENTS OF POMEGRANTE

- Pomegranate is a rich source of potent polyphenolic, glucose, ellagic acid, garlic acid , flavonoids (anthocyanin effective in inhibition of lipid peroxidation[22,23]). Fresh juice is enriched with vitamin C and polyphenolic compounds[32].
- Edible parts of pomegranate fruit has 78% juice and 22% seeds[25].
- Fresh fruit contains 85% water, 10% total sugars and 1.5% pectin, ascorbic acid and polyphenolic flavoids[1].

Pomegrante seed is rich source of crude pectin, fibres and sugars[28]. It shows that pomegranate can act as a NF-kB inhibitory effect on kidney stone formation[29].

Pomegranate has become more popular because of major effective physiological properties, such as anticancer,[42,43] cholesterol lowering, cardioprotective,[44]etc. Many experiments have reported that pomegranate and its derivatives have free radical scavenger and potent antioxidant activity.[45,46,47] It has also been shown that pomegranate can suppress NF-kB activation through a novel mechanism in vascular endothelial cells.[48]

CHARACTERISTICS OF POMEGRANATE

Pomegranate is used as a traditional medicine from ancient time. It exhibit both anti-hypercalciuria and anti- urolithiasis effect . Its phytochemicals are responsible for muscle relaxation in the urinary tract which can easily remove stones from the kidney. The extract and juice of pomegranate inhibits the hyperoxaluria – induced oxidation renal tubular damages by reducing the levels of ROS, NO and NF-kB and regulates the level of creatinine , urea, and uric acid[1,8,9,18].

MATERIAL AND METHOD

Patients following, repetitive stone formers (RSFs; >2 earlier scenes), 18–70 years of age, were selected from our stone facility. Potential subjects needed to have been recently advised on broad dietary rules to diminish the "stone facility impact." Only patients with calcium containing (non-irresistible, non-uric corrosive, noncystine) stones who had gone through something like a 24-hrs urine study were included. There were chosen from an information base of volunteers and coordinated with three to one as to age, sex, and weight record (BMI). Subjects as of now on clinical treatment for stone anticipation or with any clinical inclination to stone arrangement were prohibited (i.e., essential gout, LeschNyhan condition, Von Gierke infection, persistent

loose bowels, insulin opposition, neoplastic issues, renal hyperuricosuria, hyperparathyroidism, renal cylindrical acidosis, innate hyperuricemia)[2].

SUPPLEMENT

Members got a solitary 1,000 mg pomegranate separate case day by day for 90 days administered by our exploration drug store. Pill checks were performed at the finish of the examination to evaluate adherence[2].

OXIDATIVE PRESSURE MARKERS

Urinary 8-hydroxy-deoxyguanosine (8-OHdG) is a marker of oxidative DNA get damage by receptive oxygen species (ROS)[33]. Lipid peroxidation (LPO) has been evidence to be associated with the pathogenesis of an assortment of infections, for example, end stage renal illness, coronary vein sickness, atherosclerosis, and stroke. As basal degrees of oxidation are regularly low and might be impacted by singular serum constituents, we utilized the free extreme generator 2.2′-azobis (2amidinopropane) hydrochloride to incite oxidation to quantify serum peroxides and assist with anticipating a person's capacity to react to oxidative pressure[34] . Basal and inducible oxidative states were estimated for every persistent during each stage[34]. AAPH prompted serum lipid peroxidation was controlled by incubating serum tests (weakens x 4 with Phosphate-cushioned saline) with AAPH (100 mol/L) for 2 hrs at 37 °C [21]. The degree of lipid peroxidation was then estimated by the TBARS[Thio barbituric corrosive responsive substances] examine and by the lipid peroxides test[24]. For correlation among gatherings, we used AAPH-prompted values, as it is the best address a person's capacity to react to oxidative pressure.

Exceptionally sensitive C-receptive protein (hsCRP) has been linked in elevating the level of oxidative pressure in diabetes and coronary artery disease[2].

STATISTICAL ANALYSIS

Values for demographic profile of patients, urine samples serum samples and oxidative stress markers were calculation for each individual patient earlier enlisted and following supplement intervention to pre and post examine. Linear mixed model analysis for repeated measures was used to test for differences in urine values and oxidative stress values between non stone formers and stone formers at pre and post changes between the groups. For correlation analysis between urine values and oxidative stress among stone formers could be detected with 0.80 power [2].

RESULT

17 recurrent stone formers, 5 non stone formers. There were no adverse effects reported from supplements during the study period. The standard age of participants was 40.4 years and 57% were female with standard BMI of 29. Baseline and post intervention values for markers of oxidative stress in RSFs and NSFs. RSFs patient had significantly increase oxidative state at baseline when compared to NSFs patient[2].

Urinary 8-OHdG was significantly increased in RSFs by 350%. Additionally, there was higher susceptibility of the patients' serum to AAPH-induced lipid peroxidation as measured by lipid peroxides and TBARS. However, there was no baseline difference between RSFs and NSFs in serum PON1 activity, or in the inflammatory marker hsCRP. Following supplementation serum PON1 activity was seen increased significantly in RSFs patients. Supplementation decreased the serum hsCRP levels insignificant by 29 % in the RSFs patients. 24 hrs urine analysis showed that RSFs had lower urinary pH and saturation of calcium phosphate and higher saturation of uric acid than NSFs at baseline. Following to pomegranate extract supplementation, the only difference in urinary analysis of RSFs patients was an increase in calcium, sodium, chloride, and magnesium for RSFs patient. Otherwise, no urinary risk factor Changes were seen significantly. In general the was a minute correlation oxidative stress and change in urine analysis with the pomegrante extract supplement. Although there was a negative correlation between lipid peroxides and uric acid i.e, a patient with higher baseline

lipid peroxides levels had a greater reduce in urinary uric acid with the following supplementation. Significant changes were seen in the levels of AAPH-induced serum TBARS, lipid peroxides, hsCRP, and urine 8-OHgG did not correlate with changes in urine analysis values following supplementation in RSFs. i.e, patients with high levels of PON1 pomegranate extract supplementation were more likely to have a decline in supersaturation of CaOx[2].

DISCUSSION

Stone disease has been linked to obesity, hypertension[35], diabetes[36], metabolic syndrome[37], and chronic kidney disease[38]. As these diseases have been associates to oxidative stress[39].

Oxidative stress also plays a pathophysiologic role in nephrolithiasis. Earlier studies in RSFs suggest that reactive oxygen species-induced renal cellular injury and inflammation are likely involved in idiopathic nephrolithiasis, as demonstrated by increased in level than normal levels of urinary gamma-glutamyl transpeptidase, angiotensin 1 converting enzyme, beta-galactosidase, Nacetyl-betaglucosaminidase (NAG) activity, TBARS, and 8-OHdG[33,40].

Stone formers have significantly increased levels of oxidative stress (in serum and urine), renal tubular injury, and DNA oxidative damage, than NSFs as showed by significant differences in urine 8-OHdG, serum TBARS, and lipid peroxide levels. The association between oxidative stress and calcium-containing crystals is not fully understood[2].

Tentatively studies suggested that renal epithelial exposure to high calcium oxalate results in significant increase in markers of oxidative stress[27], implicit that the stone constituents themselves may be an causing factor in renal tubular damage and ROS radical formation. Atypical, deposition of calcium apatite in the renal papillary interstitium may lead to production of ROS and recruitment of monocytes and macrophages, which phagocytize or coat crystals in macromolecules which causes further cellular damage[41]. If crystal formation continual unregulated, localized injury and inflammation cause collagen deposition, mineralization, and renal tubular damage, providing sites for crystal attachment. As crystals continue to enlarge, they ulcerate through the papillary urothelium, where exposure to pelvic urine leads to heterogeneous nucleation of calcium salts[50]. After administration of ethylene glycol produce high levels of urinary calcium oxalate, leads to rapid crystal deposition and nephrolithiasis [31].

Pomegranate plants, which are rich source of antioxidants, including polyphenols hydrolyzable tannins, anthocyanins, and ellagic acid derivatives[52], have been shown to suppress NF-kappaB activation in vivo and inhibit lipid peroxidation. In a intended diet-controlled study,[51,53] demonstrated that prophylactic pomegranate juice administration in rats receiving ethylene glycol helpfully no crystal formation compared to the development of severe crystallization and epithelial degradation seen in animals without any supplementation. Eventually[8, 9], in a similar type of animal nephrolithiasis. Found that crystal accumulation, inducible oxide synthase (iNOS), p38-MAPK and p65NFκB activity, and oxidative stress markers were decreased by pomegranate supplementation[30].It is concluded that p38-MAPK and NF-kB pathways are activated in a variety of models of renal inflammatory disease, including nephritis[49].The iNOS-mediated NO production is significantly high when there is elevated levels oxidative stress[26].

CONCLUSION

Recurrent stone formers have markedly excessive levels of oxidative stress than NSFs. Pomegranate extract supplementation with 1,000 mg polyphenol extract daily may present some modest benefit in lowering supersaturation of calcium oxalate.

The correlation between elevated serum PON1 activity with lower saturation of calcium oxalate may help explain the reduced risk of calcium oxalate stone formation with pomegranate shown in earlier animal studies[2].

FORMATION OF STONES

Factors causing "nidus" formation: - Lithogenic drugs, Altered pH, Microorganisms, Gout, Genetic Disorder, Solute precipitation

Nidus/Nucleus formation

Crystallization of nucleus

Crystal growth

Crystal aggregation on renal tubule

Crystal cell interaction

Renal tubular cell injury & these injured cells act as site of binding

Crystal retention

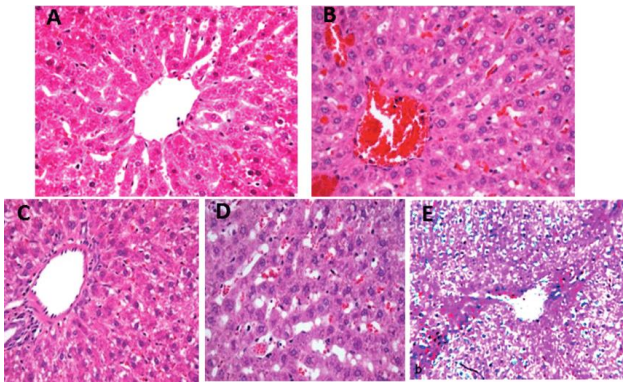
STONE FORMATION

There are several promoters of stone formation like the Tamm-Horsfall proteins and osteopontin. Some of the proofs indicate that a primary interstitial apatite crystal formation leads to CaOx stone formation (54). The lipids in human cellular membranes are chiefly involved in the crystal nucleation (55). The renal cells which get injured due the crystal sell interaction produce PT-1 or other anionic proteins lead to COM crystal aggregation (56). The THP contribute towards stone formation when the ionic strength is high and the pH is low (57). The THP is also assumed to provide protection from the stone agglomeration when it has low ionic strength and high pH, as reported by Hess (58). The mucopolysaccharides also act as the binders by increasing nucleation and aggregation (59). But according to a study, if the THP gene is inactivated in the mouse embryonic stem cells, it results in impromptu formation of calcium crystals. This is a conclusive confirmation theta the THP is an important inhibitor of stone formation (60). The presence of ROS due to oxalate can damage the mitochondrial membrane leading to apoptosis (61). According to a study, when oxalic acid is added to the HK-2 cells, it causes activation of IL-2R beta mRNA and IL-2R beta proteins that lead to inflammation. This whole process may activate the p38 MAPK signalling, however the mechanism is still not known (62). The promoters are the substances which promote urolithiasis by different mechanisms (63). The idiopathic stone formers are those in whom stone are formed due to various drugs. In these patients, the stones are attached to the interstitial site of the Randall's plaque (64). Some molecules like phosphatidylserine, CD44 and hyaluronan also act as binders for the stones (65, 66). The stone formation can be prevented by blocking the binding molecules like the monocyte chemoattractant protein-1, hyaluronic acid (67). There are also some promoters of urolithiasis which are the calcitriol hormones (69), phospholipids, cholesterol, glycolipids (68), oxalic acid, cystine, sodium, low urine volume, calcium (70). The formation of stone primarily depends upon the balance between the promoters and the inhibitors.

There are certain food colours which may have adverse effect on the kidneys and liver. According to a study Tartrazine and Carmoisine were administered in two male albino rats by the oral route in two divided doses amongst which one was low and the other was high. This was continued for 30 days. After the completion of the pre-determined duration of drug administration the tissue and serum samples

were collected and LFT, RFT, blood glucose, lipid profile was done.

The research data estimated an increase in the levels of urea, creatinine, albumin, ALT, AST, ALP, Total protein. The study concludes that both tartrazine and carnosine can unfavorably effect the biomarkers of organs like the liver and kidney not only at higher but also at lower doses (71).



Histopathology in livers of rats fed tartrazine (Tz) and ameliorative effects several doses of curcumin (CUR). A) Normal structure of liver tissue of control showing the central vein, normal arrangement of hepatic cords, normal blood sinusoids(s) and hepatocytes, HE, X 400; B) Liver tissue of rats exposed to Tz showing dilation of blood sinusoids, and central vein with hemorrhage and necrosis (*), HE, X 400; C) Liver tissue of rats fed Tz in combination with 1.0 g/ kg dry mass (dm) diet of CUR, showing less necrosis and moderate degenerative changes compared to the control and rats fed Tz alone (N), HE, X 400; D) Liver tissue of rats fed a diet containing Tz in combination with 2 g/ kg, dm diet of CUR, showing little necrosis (N) compared to the controls or rats exposed to lesser amounts of CUR. HE, X 400; E) Liver tissue of rats fed a diet containing Tz supplemented with 4.0 g/ kg, dm diet of CUR, showing little necrosis (N), H&E, X 400.

REFERENCE

1. Tugcu, V., Kemahli, E., Ozbek, E., Arinci, Y. V., Uhri, M., Erturkuner, P., ... & Tasci, A. I. (2008). Protective effect of a potent antioxidant, pomegranate juice, in the kidney of rats with nephrolithiasis induced by ethylene glycol. *Journal of Endourology*, *22*(12), 2723-2732.
2. Tracy, C. R., Henning, J. R., Newton, M. R., Aviram, M., & Zimmerman, M. B. (2014). Oxidative stress and nephrolithiasis: a comparative pilot study evaluating the effect of pomegranate extract on stone risk factors and elevated oxidative stress levels of recurrent stone formers and controls. *Urolithiasis*, *42*(5), 401-408.
3. Ilbey, Y. O., Ozbek, E., Simsek, A., Cekmen, M., Somay, A., & Tasci, A. I. (2009). Effects of pomegranate juice on hyperoxaluria-induced oxidative stress in the rat kidneys. *Renal failure*, *31*(6), 522-531.
4. Danpure, C. J. (1995). Primary hyperoxaluria, The Molecular and metabolic basis of inherited disease.
5. Tugcu, V., Kemahli, E., Ozbek, E., Arinci, Y. V., Uhri, M., Erturkuner, P., ... & Tasci, A. I. (2008). Protective effect of a potent antioxidant, pomegranate juice, in the kidney of rats with nephrolithiasis induced by ethylene glycol. *Journal of Endourology*, *22*(12), 2723-2732.
6. Thamilselvan, S., & Khan, S. R. (1998). Oxalate and calcium oxalate crystals are injurious to renal epithelial cells: results of in vivo and in vitro studies. *Journal of Nephrology*, *11*, 66-69.
7. Selvam, R., & Kalaiselvi, P. (2001). Studies on calcium oxalate binding proteins: effect of lipid peroxidation. *Nephron*, *88*(2), 163-167.
8. Ilbey, Y. O., Ozbek, E., Simsek, A., Cekmen, M., Somay, A., & Tasci, A. I. (2009). Effects of pomegranate juice on hyperoxaluria-induced oxidative stress in the rat kidneys. *Renal failure*, *31*(6), 522-531.
9. Xie, Q. W., Kashiwabara, Y., & Nathan, C. (1994). Role of transcription factor NF-kappa B/Rel in induction of nitric oxide synthase. *Journal of Biological Chemistry*, *269*(7), 4705-4708.
10. Thamilselvan, S., Hackett, R. L., & Khan, S. R. (1997). Lipid peroxidation in ethylene glycol induced hyperoxaluria and calcium oxalate nephrolithiasis. *The Journal of urology*, *157*(3), 1059-1063.
11. Xie, Q. W., Kashiwabara, Y., & Nathan, C. (1994). Role of transcription factor NF-kappa B/Rel in induction of nitric oxide synthase. *Journal of Biological Chemistry*, *269*(7), 4705-4708.
12. Angel, P., & Karin, M. (1991). The role of Jun, Fos and the AP-1 complex in cell-proliferation

and transformation. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1072*(2-3), 129-157.

13. BOKEMEYER, D., OSTENDORF, T., Kunter, U. T. A., LINDEMANN, M., KRAMER, H. J., & FLOEGE, J. (2000). Differential activation of mitogen-activated protein kinases in experimental mesangioproliferative glomerulonephritis. *Journal of the American Society of Nephrology*, *11*(2), 232-240.
14. Kumar, S., Boehm, J., & Lee, J. C. (2003). p38 MAP kinases: key signalling molecules as therapeutic targets for inflammatory diseases. *Nature reviews Drug discovery*, *2*(9), 717-726.
15. Koul, H. K., Menon, M., Chaturvedi, L. S., Koul, S., Sekhon, A., Bhandari, A., & Huang, M. (2002). COM crystals activate the p38 mitogen-activated protein kinase signal transduction pathway in renal epithelial cells. *Journal of Biological Chemistry*, *277*(39), 36845-36852.
16. Chaturvedi, L. S., Koul, S., Sekhon, A., Bhandari, A., Menon, M., & Koul, H. K. (2002). Oxalate Selectively Activates p38 Mitogen-activated Protein Kinase and c-Jun N-terminal Kinase Signal Transduction Pathways in Renal Epithelial Cells∗. *Journal of Biological Chemistry*, *277*(15), 13321-13330.
17. Lieberthal, W. (1998). Biology of ischemic and toxic renal tubular cell injury: role of nitric oxide and the inflammatory response. *Current opinion in nephrology and hypertension*, *7*(3), 289-295.
18. Chatterjee PK, Patel NS, Kvale EO, Cuzzocrea S, Bro wn PA, Stewart KN, et al. Inhibition of inducible nitric oxide synthase reduces renal ischemia/reperfusion injury. Kidney Int. 2002; 61: 862–871
19. Paul, J. L., Sall, N. D., Soni, T., Poignet, J. L., Lindenbaum, A., Man, N. K., ... & Raichvarg, D. (1993). Lipid peroxidation abnormalities in hemodialyzed patients. *Nephron*, *64*(1), 106-109.
20. Frei, B., Stocker, R., & Ames, B. N. (1988). Antioxidant defenses and lipid peroxidation in human blood plasma. *Proceedings of the National Academy of Sciences*, *85*(24), 9748-9752.
21. Aviram, M., Dornfeld, L., Kaplan, M., Coleman, R., Gaitini, D., Nitecki, S., ... & Fuhrman, B. (2002). Pomegranate juice flavonoids inhibit low-density lipoprotein oxidation and cardiovascular diseases: studies in atherosclerotic mice and in humans. *Drugs under experimental and clinical research*, *28*(2-3), 49-62.
22. Tsuda, T., Horio, F., & Osawa, T. (2002). Cyanidin 3-O-β-D-glucoside suppresses nitric oxide production during a zymosan treatment in rats. *Journal of nutritional science and vitaminology*, *48*(4), 305-310.
23. Buege, J. A., & Aust, S. D. (1978). [30] Microsomal lipid peroxidation. In *Methods in enzymology* (Vol. 52, pp. 302-310). Academic press.
24. El-Nemr, S. E., Ismail, I. A., & Ragab, M. (1990). Chemical composition of juice and seeds of pomegranate fruit. *Food/Nahrung*, *34*(7), 601-606.
25. Fischer, P. A., Dominguez, G. N., Cuniberti, L. A., Martinez, V., Werba, J. P., Ramirez, A. J., & Masnatta, L. D. (2003). Hyperhomocysteinemia induces renal hemodynamic dysfunction: is nitric oxide involved?. *Journal of the American Society of Nephrology*, *14*(3), 653-660.
26. Fischer, P. A., Dominguez, G. N., Cuniberti, L. A., Martinez, V., Werba, J. P., Ramirez, A. J., & Masnatta, L. D. (2003). Hyperhomocysteinemia induces renal hemodynamic dysfunction: is nitric oxide involved?. *Journal of the American Society of Nephrology*, *14*(3), 653-660.
27. Khan, S. R. (2013). Reactive oxygen species as the molecular modulators of calcium oxalate kidney stone formation: evidence from clinical and experimental investigations. *The Journal of urology*, *189*(3), 803-811.
28. Aviram, M., Dornfeld, L., Rosenblat, M., Volkova, N., Kaplan, M., Coleman, R., ... & Fuhrman, B. (2000). Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E–deficient mice. *The American journal of clinical nutrition*, *71*(5), 1062-1076.
29. Schubert, S. Y., Neeman, I., & Resnick, N. (2002). A novel mechanism for the inhibition of NFκB activation in vascular endothelial cells by natural antioxidants. *The FASEB Journal*, *16*(14), 1931-1933.
30. Rathod, N. R., Biswas, D., Chitme, H. R., Ratna, S., Muchandi, I. S., & Chandra, R. (2012). Anti-urolithiatic effects of Punica granatum in male rats. *Journal of ethnopharmacology*, *140*(2), 234-238.
31. Hackett, R. L., Shevock, P. N., & Khan, S. R. (1990). Cell injury associated calcium oxalate crystalluria. *The Journal of urology*, *144*(6), 1535-1538.
32. Bhandari, P. R. (2012). Pomegranate (Punica granatum L). Ancient seeds for modern cure?

Review of potential therapeutic applications. *International Journal of Nutrition, Pharmacology, Neurological Diseases*, *2*(3), 171.

33. Boonla, C., Wunsuwan, R., Tungsanga, K., & Tosukhowong, P. (2007). Urinary 8-hydroxydeoxyguanosine is elevated in patients with nephrolithiasis. *Urological research*, *35*(4), 185-191.
34. El-Saadani, M., Esterbauer, H., El-Sayed, M., Goher, M., Nassar, A. Y., & Jürgens, G. (1989). A spectrophotometric assay for lipid peroxides in serum lipoproteins using a commercially available reagent. *Journal of Lipid Research*, *30*(4), 627-630.
35. Obligado, S. H., & Goldfarb, D. S. (2008). The association of nephrolithiasis with hypertension and obesity: a review. *American journal of hypertension*, *21*(3), 257-264.
36. Lieske, J. C., de la Vega, L. S. P., Gettman, M. T., Slezak, J. M., Bergstralh, E. J., Melton III, L. J., & Leibson, C. L. (2006). Diabetes mellitus and the risk of urinary tract stones: a population-based case-control study. *American journal of kidney diseases*, *48*(6), 897-904.
37. Jeong, I. G., Kang, T., Bang, J. K., Park, J., Kim, W., Hwang, S. S., ... & Park, H. K. (2011). Association between metabolic syndrome and the presence of kidney stones in a screened population. *American Journal of Kidney Diseases*, *58*(3), 383-388.
38. Saucier, N. A., Sinha, M. K., Liang, K. V., Krambeck, A. E., Weaver, A. L., Bergstralh, E. J., ... & Lieske, J. C. (2010). Risk factors for CKD in persons with kidney stones: a case-control study in Olmsted County, Minnesota. *American Journal of Kidney Diseases*, *55*(1), 61-68.
39. Khan, S. R. (2012). Is oxidative stress, a link between nephrolithiasis and obesity, hypertension, diabetes, chronic kidney disease, metabolic syndrome?. *Urological research*, *40*(2), 95-112.
40. Baggio, B., Gambaro, G., Ossi, E., Favaro, S., & Borsatti, A. (1983). Increased urinary excretion of renal enzymes in idiopathic calcium oxalate nephrolithiasis. *The Journal of urology*, *129*(6), 1161-1162.
41. Escobar, C., Byer, K. J., & Khan, S. R. (2007). Naturally produced crystals obtained from kidney stones are less injurious to renal tubular epithelial cells than synthetic crystals. *BJU international*, *100*(4), 891-897.
42. Afaq, F., Saleem, M., Krueger, C. G., Reed, J. D., & Mukhtar, H. (2005). Anthocyanin-and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-κB pathways and inhibits skin tumorigenesis in CD-1 mice. *International journal of cancer*, *113*(3), 423-433.
43. Lansky, E. P., Harrison, G., Froom, P., & Jiang, W. G. (2005). Pomegranate (Punica granatum) pure chemicals show possible synergistic inhibition of human PC-3 prostate cancer cell invasion across Matrigel™. *Investigational new drugs*, *23*(2), 121-122.
44. Sumner, M. D., Elliott-Eller, M., Weidner, G., Daubenmier, J. J., Chew, M. H., Marlin, R., ... & Ornish, D. (2005). Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. *The American journal of cardiology*, *96*(6), 810-814.
45. De Nigris, F., Williams-Ignarro, S., Lerman, L. O., Crimi, E., Botti, C., Mansueto, G., ... & Napoli, C. (2005). Beneficial effects of pomegranate juice on oxidation-sensitive genes and endothelial nitric oxide synthase activity at sites of perturbed shear stress. *Proceedings of the National Academy of Sciences*, *102*(13), 4896-4901.
46. Balasundram, N., Sundram, K., & Samman, S. (2006). Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food chemistry*, *99*(1), 191-203.
47. Rosenblat, M., Hayek, T., & Aviram, M. (2006). Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. *Atherosclerosis*, *187*(2), 363-371.
48. Schmitz, M. L., Bacher, S., & Kracht, M. (2001). IκB-independent control of NF-κB activity by modulatory phosphorylations. *Trends in biochemical sciences*, *26*(3), 186-190.
49. Goligorsky, M. S., Brodsky, S. V., & Noiri, E. (2002). Nitric oxide in acute renal failure: NOS versus NOS. *Kidney international*, *61*(3), 855-861.
50. Khan, S. R. (2004). Crystal-induced inflammation of the kidneys: results from human studies, animal models, and tissue-culture studies. *Journal of Clinical and Experimental Nephrology*, *8*(2), 75-88.
51. Tugcu, V., Ozbek, E., Kemahli, E., Cekmen, M. B., Caner, N., Somay, A., ... & Tasci, A. I. (2007). Rapid Communication: Protective Effect of a Nuclear Factor κ B Inhibitor, Pyrolidium Dithiocarbamate, in the Kidney of Rats with Nephrolithiasis Induced by Ethylene Glycol. *Journal of endourology*, *21*(9), 1097-1106.
52. Gil, M. I., Tomás-Barberán, F. A., Hess-Pierce, B., Holcroft, D. M., & Kader, A. A. (2000). Antioxidant activity of pomegranate juice and

its relationship with phenolic composition and processing. *Journal of Agricultural and Food chemistry*, *48*(10), 4581-4589.

53. Tugcu, V., Kemahli, E., Ozbek, E., Arinci, Y. V., Uhri, M., Erturkuner, P., ... & Tasci, A. I. (2008). Protective effect of a potent antioxidant, pomegranate juice, in the kidney of rats with nephrolithiasis induced by ethylene glycol. *Journal of Endourology*, *22*(12), 2723-2732.
54. Knoll, T. (2010). Epidemiology, pathogenesis, and pathophysiology of urolithiasis. *European urology supplements*, *9*(12), 802-806.
55. Khan, S. R., Atmani, F., Glenton, P., Hou, Z. C., Talham, D. R., & Khurshid, M. (1996). Lipids and membranes in the organic matrix of urinary calcific crystals and stones. *Calcified tissue international*, *59*(5), 357-365.
56. Moryama, M. T., Domiki, C., Miyazawa, K., Tanaka, T., & Suzuki, K. (2005). Effects of oxalate exposure on Madin-Darby canine kidney cells in culture: renal prothrombin fragment-1 mRNA expression. *Urological research*, *33*(6), 470-475.
57. Lieske, J. C., Swift, H., Martin, T., Patterson, B., & Toback, F. G. (1994). Renal epithelial cells rapidly bind and internalize calcium oxalate monohydrate crystals. *Proceedings of the National Academy of Sciences*, *91*(15), 6987-6991.
58. Hess, B. (1992). Tamm-Horsfall glycoprotein-inhibitor or promoter of calcium oxalate monohydrate crystallization processes?. *Urological research*, *20*(1), 83-86.
59. Viswanathan, P., Rimer, J. D., Kolbach, A. M., Ward, M. D., Kleinman, J. G., & Wesson, J. A. (2011). Calcium oxalate monohydrate aggregation induced by aggregation of desialylated Tamm-Horsfall protein. *Urological research*, *39*(4), 269-282.
60. Mo, L., Huang, H. Y., Zhu, X. H., Shapiro, E., Hasty, D. L., & Wu, X. R. (2004). Tamm-Horsfall protein is a critical renal defense factor protecting against calcium oxalate crystal formation. *Kidney international*, *66*(3), 1159-1166.
61. Chaturvedi, L. S., Koul, S., Sekhon, A., Bhandari, A., Menon, M., & Koul, H. K. (2002). Oxalate Selectively Activates p38 Mitogen-activated Protein Kinase and c-Jun N-terminal Kinase Signal Transduction Pathways in Renal Epithelial Cells∗. *Journal of Biological Chemistry*, *277*(15), 13321-13330.
62. Koul, S., Khandrika, L., Pshak, T. J., Iguchi, N., Pal, M., Steffan, J. J., & Koul, H. K. (2014). Oxalate upregulates expression of IL-2Rβ and activates IL-2R signaling in HK-2 cells, a line of human renal epithelial cells. *American Journal of Physiology-Renal Physiology*, *306*(9), F1039-F1046.
63. Mandel, N. (1996, September). Mechanism of stone formation. In *Seminars in nephrology* (Vol. 16, No. 5, pp. 364-374).
64. Evan, A. P. (2010). Physiopathology and etiology of stone formation in the kidney and the urinary tract. *Pediatric nephrology*, *25*(5), 831-841.
65. Chhiber, N., Sharma, M., Kaur, T., & Singla, S. (2014). Mineralization in health and mechanism of kidney stone formation. *International Journal of Pharmaceutical Science Invention*, *3*, 25-31.
66. Yuen, J. W., Gohel, M. D. I., Poon, N. W., Shum, D. K., Tam, P. C., & Au, D. W. (2010). The initial and subsequent inflammatory events during calcium oxalate lithiasis. *Clinica Chimica Acta*, *411*(15-16), 1018-1026.
67. Aggarwal, K. P., Narula, S., Kakkar, M., & Tandon, C. (2013). Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. *BioMed research international*, *2013*.
68. Khan, S. R., & Kok, D. J. (2004). Modulators of urinary stone formation. *Front Biosci*, *9*(629), 1450-1482.
69. Centeno, V., de Barboza, G. D., Marchionatti, A., Rodriguez, V., & de Talamoni, N. T. (2009). Molecular mechanisms triggered by low-calcium diets. *Nutrition research reviews*, *22*(2), 163-174.
70. Basavaraj, D. R., Biyani, C. S., Browning, A. J., & Cartledge, J. J. (2007). The role of urinary kidney stone inhibitors and promoters in the pathogenesis of calcium containing renal stones. *EAU-EBU update series*, *5*(3), 126-136.
71. Amin, K. A. (2010). Abdel Hameid II H, Abd Elsttar AH. Effect of food azo dyes tartrazine and carmoisine on biochemical parameters related to renal, hepatic function and oxidative stress biomarkers in young male rats. *Food Chem Toxicol*, *48*(10), 2994-2999.

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