



**MACROTYLOMA UNIFLORUM (LAM.) VERDC., PHASEOLUS LUNATUS LINN., AND PHASEOLUS VULGARIS LINN. SEEDS: NATURE'S POTENTIAL CANDIDATES AGAINST UROLITHIASIS BY VIRTUE OF MULTIDIMENSIONAL PHARMACOLOGY**

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**ABSTRACT**

Urolithiasis arises from disturbances in physicochemical balance and hydro dynamic system in urinary tract. Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of various ailments. A comprehensive literature search of antiurolithiatic plants reported worldwide revealed family Fabaceae with highest number of cited species. The members, *Macrotyloma uniflorum* (Lam.) Verdc., *Phaseolus lunatus* Linn. and *Phaseolus vulgaris* Linn. have been selected and hidden versatile weapons of their seeds against urolithiasis such as analgesic, antioxidants, astringent, diuretic, emollient, high soluble oxalate contents, insoluble fibers, magnesium, potassium, phytic acid, pyridoxine (vitamin B<sub>6</sub>), have been discussed on scientific basis to rationalize the folkloric use.

**KEYWORDS:** *Macrotyloma uniflorum*, *Phaseolus lunatus*, *Phaseolus vulgaris*, urolithiasis, natural weapons.

**INTRODUCTION**

Urolithiasis is the combination of two Greek words *ouron* (urine) and *lithos* (stone). Urolithiasis or urinary stone formation is a complex physicochemical process comprises of supersaturation, nucleation, growth, aggregation and retention of stone within the urinary

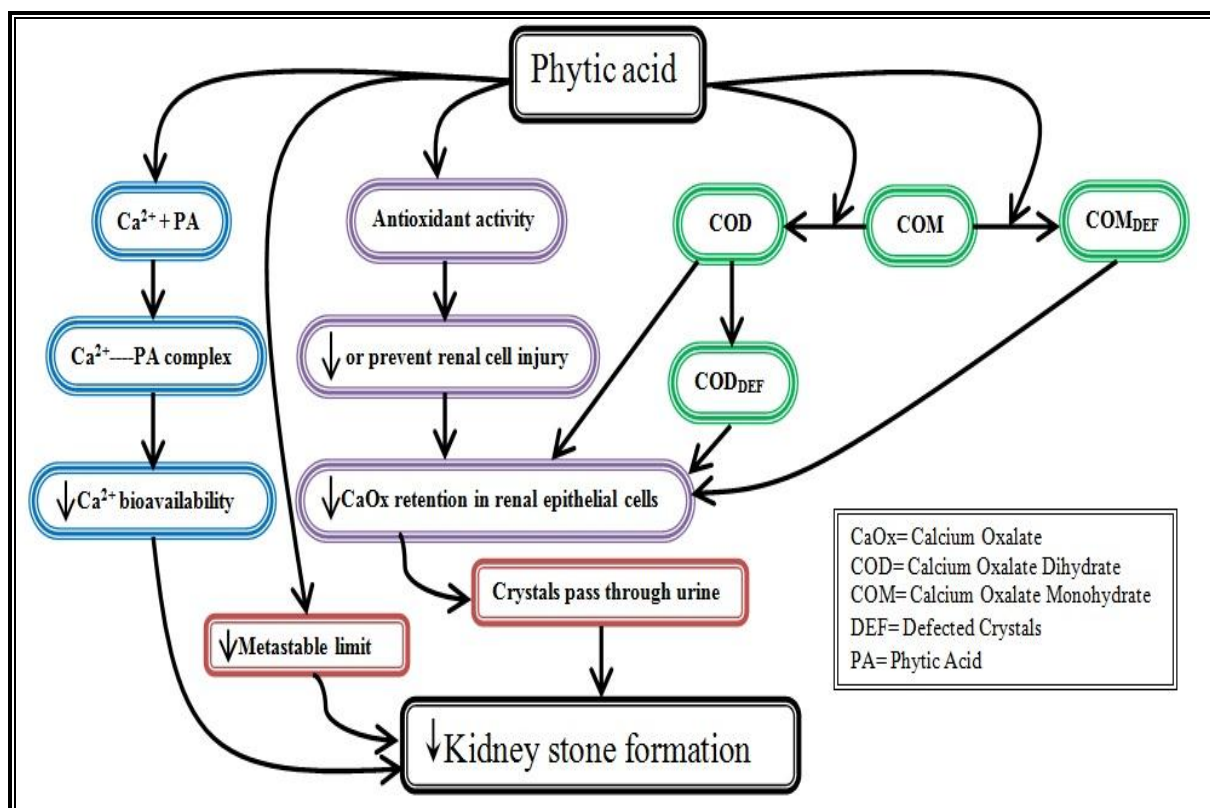
tract. At the initial level the stones are as small as a grain of sand and gradually increase in size as large as a pearl or even a golf ball by the process of crystal growth and aggregation. Smaller stones may go down to the urinary tract and excreted without bringing any manifestation. Whereas, bigger stones may get stuck in the urinary tract and cause urinary tract obstruction with dysuria, hematuria, nausea and vomiting. Individuals are at the risk for stone recurrence if they have stone before or any family history of urolithiasis. Other risk factors are not drinking enough water, protein, sodium and sugar rich diet, being obese or experiencing gastric bypass surgery<sup>[1,2]</sup>.

Medicinal plants are the gift of nature and play an important role as a part of our diet to maintain health. They also serve as a versatile weapon to combat against a number of diseases. Every civilization has its own experience and knowledge of therapeutic uses of plants. The belief and observations regarding traditionally used medicinal plants, increasing the interest of people to use them against urolithiasis. A comprehensive literature search of antiurolithiatic plants reported worldwide suggests family Fabaceae with highest number of cited species<sup>[3]</sup>. The members, *Macrotyloma uniflorum* (Lam.) Verdc., and *Phaseolus vulgaris* Linn. have been selected in the present study as Pakistani Fabaceous plants having ethnomedicinal background against urolithiasis. Although, no authenticated report regarding ethnomedicinal evidence of *Phaseolus lunatus* Linn. against urolithiasis was found in current literature review, yet it was selected being the member of family Fabaceae and reported supporting pharmacological effects against urolithiasis<sup>[4]</sup>. The seed infusion and decoction of *M. uniflorum* and *P. vulgaris* used against urolithiasis in different countries like Haiti, Jordan, India, Iran, Nepal and Pakistan<sup>[5]</sup>. *M. uniflorum* and *P. vulgaris* have been successfully used against urolithiasis in Ayurvedic and Unani system of medicines as mono and polyherbal formulation. Sushruta Samhita an important Sanskrit text on Ayurvedic medicine prescribed seed decoction of *M. uniflorum* for kidney stones. A 100 ml decoction of *M. uniflorum* prepared from 2-5 g used twice a day for 30 days. 1 cup of seeds (approximately 150 g) boiled in 500ml water till reduces to 100 ml and then 2 teaspoon of crushed *Punica granatum* seeds mixed in decoction, mixed well and drink daily<sup>[6-8]</sup>. In Unani system of medicine, seeds are used as polyherbal formulation. *Hajr-ul-Yahood* (*Lapis judaicus*) 100 g is ground in *Aab-e-Turb* (*Raphanus sativus* leaves juice) 1.5 L and cake is prepared. Simultaneously, *M. uniflorum* 400g was soaked overnight in water to obtain an aqueous paste which is finally wrapped around the cake to produce a final preparation. Kept in earthen discs and sealed with the process of *Gil-e-Hikmat* till further use. 125-200mg taken

daily against kidney stone<sup>[9]</sup>. In Ayurvedic system, 60g of *P. vulgaris* seeds boiled in 4 L of water for 4-5 hr and is recommended to drink one glass (approximately 200 ml) every two hours for seven days<sup>[8]</sup>. In Unani system, the 100 ml decoction prepared from 2-5g seed powder of *M. uniflorum* used twice daily for 30 days to eliminate kidney stones<sup>[7]</sup>.

Plants have complex molecular structures which act through multiple biochemical pathways to produce desired therapeutic effects. Some of these secondary metabolites are biologically active, having great selectivity of cellular targets. In contrast, some having multiple cellular targets which may combine together to produce specific biological activity. Some exerts greater effect than individual bio active compound(s) through synergistic mechanism. Some inactive adjuvant substances enhance the potency of bio active compounds, known to act simply through potentiation. Plants also contain by-products which may increase absorption rate or solubility of active phytochemicals or may induce metabolic enzyme(s)<sup>[10]</sup>. The presence of different antioxidants such as anthocyanins (cyanidin, delphinidin, malvidin, petunidin), flavonoids (daidzein, genistein, kaempferol, myricetin, quercetin) and phenolic acids (caffeic acid, chlorogenic acid, ellagic acid, ferulic acid, gallic acid, kaempferol, *p*-coumaric acid, *p*-hydroxybenzoic acid, protocatechuic acid, quercetin, rutin, sinapic acid, syringic acid, tocopherol and vanillic acid), minerals (magnesium and potassium) and phytic acid in the seeds of *M. uniflorum*, *P. lunatus* and *P. vulgaris* behave as versatile weapons against urolithiasis. Whereas, analgesic, astringent, emollient and diuretic effects play supporting role in this regard<sup>[3]</sup>. Oxalate forms strong chelates with calcium in the renal glomeruli and contributes to stone formation. Soluble oxalate, not the total oxalate is the absorbable part and thus responsible for renal oxalate formation. This soluble oxalate causes membrane injury of renal epithelial cells which invites calcium oxalate binding with renal epithelia and provides support to grow kidney stones<sup>[11]</sup>. Antioxidants reduce renal cell injury, decreases calcium oxalate retention in renal epithelial cells. Due to this, calcium oxalate crystals pass through urine and do not participate in kidney to form stone. Hence antioxidants, play an important role in prophylactic management of kidney stones<sup>[12]</sup>. The total oxalate contents (mg/g) in the seeds of selected plants reported as 1.24 in *M. uniflorum*, 1.77 in *P. lunatus* and 1.71 in *P. vulgaris*. Whereas, soluble oxalate (mg/g) have been reported as 0.24 (19.50%) in *M. uniflorum*, 0.26 (15.08%) in *P. lunatus* and 0.27 (15.88%) in *P. vulgaris*. In view of the data presented and various earlier studies, it can be assume that the regular consumption of *M. uniflorum*, *P. lunatus* and *P. vulgaris* would significantly increase the daily oxalates intake but lower soluble oxalate would not pose any risk to people who are

at risk of recurrent kidney stones<sup>[11]</sup>. Different types of antioxidants make these plants more effective against kidney stones. *M. uniflorum* contains anthocyanins, flavonoids and phenolic acids<sup>[13]</sup>. Phenolic acids are reported in *P. lunatus* and *P. vulgaris*<sup>[14-16]</sup>. Chemical literature search suggest the presence of phytic acid contents (mg/g) in *M. uniflorum* 1.02-10.20<sup>[17-19]</sup>, *P. lunatus* 1.86-69.50<sup>[20-23]</sup> and *P. vulgaris* 9.80-58.00<sup>[23-26]</sup>. Phytic acid plays an important role in whewellite and brushite crystallization inhibition by forming calcium-phytic acid complex, reduces calcium bioavailability and decreases calcium containing stone formation. Its antioxidant property also takes part against urolithiasis<sup>[27-31]</sup>. Phytic acid not only makes whewellite / calcium oxalate monohydrate (COM) crystals defected but also modulate COM into calcium oxalate dihydrate (COD). COD crystals are unable to attach with renal epithelial cells and thus pass through urine<sup>[12]</sup>. Phytic acid also inhibits intracellular calcium and phosphate accumulation, prevents calcium phosphate deposits (Figure – 1). Thus, inhibiting brushite nucleation and crystal growth by blocking calcium phosphate precipitation<sup>[32]</sup>.



**Figure-1: Proposed antiurolithiatic mechanism of Phytic acid.** Adopted from Ahmed, S., Hasan, M. & Mahmood, Z. 2016. Inhibition and modulation of calcium oxalate monohydrate crystals by phytic acid: An *in vitro* study. *Journal of Pharmacognosy and Phytochemistry*, 5(2): 91-95.

Magnesium and potassium supplements are effectively used for prophylactic management of urolithiasis. Magnesium 200-400mg/day orally is recommended for prophylactic management of calcium oxalate stones<sup>[33]</sup>. The reported magnesium contents (mg/g) are *M. uniflorum* 0.40 - 1.90<sup>[13]</sup>, *P. lunatus* 1.08-3.08<sup>[34-38]</sup> and *P. vulgaris* 0.16-4.00<sup>[26,37,39-41]</sup>. Magnesium compete with calcium for oxalate and form magnesium oxalate complex instead of calcium oxalate, which is more soluble form<sup>[42]</sup>. It is further reported that magnesium ion has the property to destabilize calcium oxalate ion pairs and thus reduces the size of the aggregates<sup>[43]</sup> (Figure – 2). The magnesium ion’s inhibitory effect remains stable in an acidic environment and synergistic with citrate<sup>[44]</sup>. The significant synergistic effect between magnesium and phytate on calcium oxalate crystallization suggests that a combination of these 2 compounds may be useful as an antiurolithiatic therapy<sup>[45]</sup>. The reported potassium contents (mg/g) of *M. uniflorum*, *P. lunatus* and *P. vulgaris* are 2.63-14.78<sup>[13]</sup>, 8.17 - 18.81<sup>[36-38]</sup> and 10.50-23.24<sup>[36, 37, 39-41, 46]</sup> respectively. Low urinary citrate excretion is a known risk factor for the development of kidney stones<sup>[47, 48]</sup>. Potassium promotes urinary citrate excretion and together with magnesium, it further inhibits crystal formation. Alkali therapy using potassium or magnesium citrate is reported to boost citrate excretion in patients having calcium oxalate stones with hypocitraturia<sup>[49]</sup>. In case of calcium phosphate stone, potassium citrate therapy is recommended to inhibit calcium phosphate crystallization<sup>[50]</sup> and is also useful in the management of uric acid urolithiasis<sup>[51]</sup>.

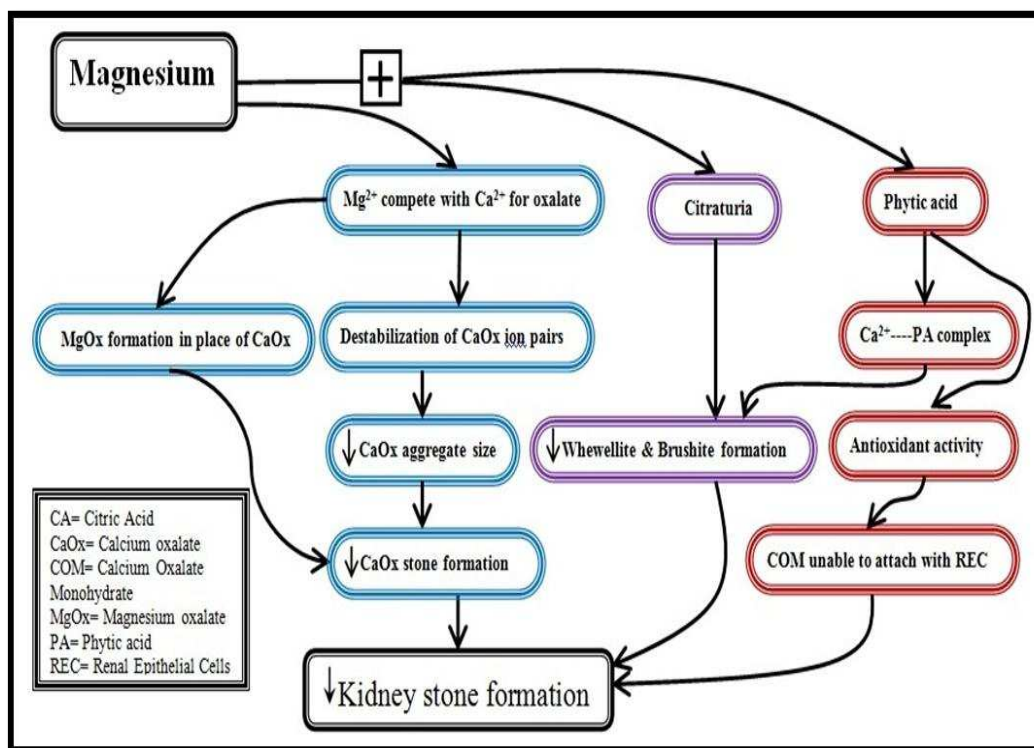
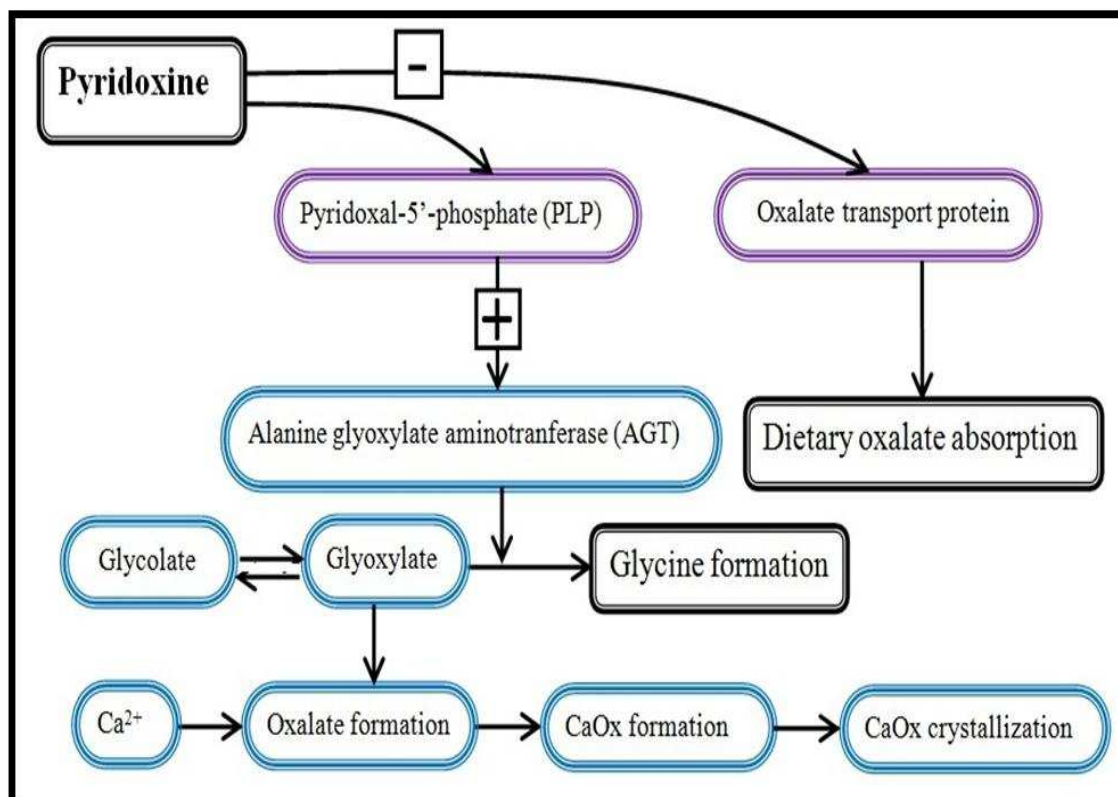


Figure- 2: Proposed antiurolithiatic mechanism of magnesium.

Vitamin B<sub>6</sub> (pyridoxine) traps glyoxylate, the oxalate precursor in the liver. Pyridoxine is a precursor of pyridoxal-5'-phosphate (PLP) a coenzyme enhances alanine glyoxylate aminotranferase (AGT) activity. AGT catalyses the transamination of glyoxylate to glycine, thus decreasing the glyoxylate amount for conversion to oxalate. As a result, oxalate is not transported to the blood for its excretion through the kidneys and to make calcium oxalate crystals. Furthermore, pyridoxine inhibits dietary oxalate absorption by suppressing the oxalate transport protein present in the intestinal bursh border membrane<sup>[52, 53]</sup>. Figure – 3 showing the proposed antiurolithiatic mechanism of pyridoxine. Hypercalciuria and hyperoxaluria contribute urolithiasis by precipitating calcium oxalate in urinary tract. Long term oral pyridoxine therapy significantly lower urinary oxalate level and benefited in hyper oxaluric calcium urolithiasis<sup>[54]</sup>. European Association of Urology suggests pyridoxine 5-20 mg/kg body weight orally for calcium oxalate stones prevention<sup>[33]</sup>. United States Department of Agriculture (USDA) nutrient index data reported the presence of pyridoxine (mg/100g) as 0.32 in *P. lunatus* and 0.39 in *P. vulgaris*<sup>[55,56]</sup>.



**Figure- 3: Proposed antiurolithiatic mechanism of pyridoxine.**

Considering the supporting effects against urolithiasis, the seeds of *M. uniflorum*, *P. lunatus* and *P. vulgaris* are reported to possess diuretic activity<sup>[3, 57]</sup>. Pyroglutaminylglutamine in *M. uniflorum*<sup>[58, 59]</sup> and phaseoluside A,B,C,D and E glycosides in *P. vulgaris* are reported as

diuretic compounds<sup>[60]</sup>. The diuretic action flushes out the deposits by increasing the quantity of fluid going pass through the kidneys and decreasing the saturation of salts. Which prevents the precipitation of the crystals at physiological pH<sup>[3]</sup>. *M. uniflorum* possess analgesic, anti inflammatory<sup>[13]</sup>, astringent<sup>[3]</sup>; *P. lunatus* analgesic, astringent and emollient<sup>[57]</sup> and *P. vulgaris* declared analgesic and anti inflammatory properties<sup>[61]</sup>. Insoluble dietary fibers are also proposed to have supported effect against urolithiasis. Insoluble fibers contain non digestible compounds, including lignin and non starch polysaccharides combines with calcium in the intestines, so the calcium is excreted with the stool rather than through the kidneys. Hence, not able to take part in calcium stone formation. However, earlier studies have demonstrated blended results and the relationship between fiber intake and stone formation is still unclear<sup>[62, 63]</sup>. Previous studies on insoluble dietary fiber (mg/g) by using AOAC enzymatic-gravimetric method reported 216.10 in *M. uniflorum*<sup>[64]</sup> and 171.00 in *P. vulgaris*<sup>[65]</sup>.

## CONCLUSION

In conclusion, it can be proposed that *M. uniflorum*, *P. lunatus* and *P. vulgaris* may provide prophylactic treatment in urolithiasis through a combination of analgesic, antioxidant, astringent, diuretic and emollient properties. Proposed multidimensional pharmacology could produce greater levels of efficacy by multiple targets and could be less prone to resistance than mono targeted pharmacology. This study also suggests the co-existence of biologically active antiurolithiatic compounds. However, much remains to be discovered by using *in vitro*, *in vivo* studies, clinical trials not only to rationalize the folkloric use of studied plants against urolithiasis but explore the natural, safe and effective antiurolithiatic agents from *M. uniflorum*, *P. lunatus* and *P. vulgaris*.

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