🔬 Write-Up: Kidney Stone Interventions and Research

Herbal and Plant-Based Therapies

Phyllanthus niruri ("Stone Breaker")

P. niruri is a traditional remedy for urolithiasis that has been shown to interfere with multiple stages of stone formation [1.1].[1] In vitro studies using human urine demonstrated that the plant extract induced a marked reduction in calcium oxalate ([2]CaOx) particle size and inhibited crystal aggregation [1.1, 1.2].[3] It alters the crystal structure by increasing the ratio of the less pathogenic calcium oxalate dihydrate (COD) form over the more dangerous monohydrate (COM) form [1.1]. Clinically, its benefits may stem from ureteral smooth muscle relaxation, facilitating the expulsion or clearance of calculi following lithotripsy [1.1].[4] Furthermore, it exhibits xanthine oxidase inhibitory activity, which suggests potential as an anti-hyperuricemic agent [1.1]. While a preventive effect is suggested, longer-term randomized clinical trials are required to confirm its therapeutic properties for nephrolithiasis [1.1].[5] (105 words)

Bryophyllum pinnatum

This traditional plant is supported by both *in vitro* and clinical observations for its anti-urolithiatic activity [2.1, 2.2]. Laboratory studies indicate that *B. pinnatum* tonic possesses a substantial capacity to dissolve both calcium oxalate and calcium phosphate stones [2.2].[6] The extract showed prominent anti-crystallization activity by inhibiting the nucleation, growth, and aggregation of calcium oxalate ([7]CaOx) crystals [2.2].[8] This effect may result from the extract's ability to complex with free calcium and oxalate ions, thereby preventing [9]CaOx formation [2.2].[10] In an uncontrolled human trial, patients treated with the plant's juice either passed their stones or experienced a reduction in stone size [2.1].[11] A current randomized, double-blind, placebo-controlled Phase 1 trial is investigating whether *B. pinnatum* tea can reduce urinary calcium levels in recurrent stone formers to prevent further stone development [2.1].[12] (116 words)

Ammi visnaga (Khella)

Ammi visnaga has historical use in Ancient Egypt as an herbal remedy for renal colic and urinary tract issues [3.1, 3.2].[13] The active constituents, khellin and visnagin, are primarily known for their smooth muscle relaxant properties, which are hypothesized to dilate urinary passages and facilitate the passage of kidney stones [3.1, 3.2].[14] Khellin is theorized to have pleiotropic effects, including diuresis and interference with citrate metabolism [3.2].[15] Plant extracts have been demonstrated to inhibit the crystallization of calcium oxalate

([16]CaOx) [3.2].[17] Case reports have suggested that khellin preparations may promote the spontaneous passage of multiple ureteral stones [3.2].[18] Despite this traditional use and historical observation, contemporary scientific validation for the widespread application of Khella in kidney health is limited [3.1]. (111 words)

Orthosiphon stamineus (Cat's Whiskers)

An *in vitro* study was conducted to evaluate the chemolytic potential of a standardized water extract of *O.*[19] *stamineus* against human urinary stone samples [4.2]. The study found that a [20]4 mg/ml concentration of the extract achieved a [21]70% weight reduction in calcium oxalate ([22]CaOx) stones, which was superior to the chemolytic action of a potassium citrate solution ([23]41% reduction) [4.2].[24] The dissolving capability on CaOx stones was highest at pH 5 [4.2]. The extract also demonstrated dissolving activity against uric acid stones and combination stones, with the latter showing an 80% weight reduction at pH 8 [4.2]. The results of this *in vitro* experiment support the conclusion that *O. stamineus* water extract possesses significant dissolving capability for urinary stones [4.2].[25] (108 words)

Cissus gongylodes

Traditional use of a leaf decoction of *C. gongylodes* for kidney stone removal has been investigated, with research focusing on isolating the active compounds [5.1].[26] Bioguided isolation identified rutin, eriodictyol $3'$-O-glycoside, and isoquercetin as compounds responsible for the anti-urolithiatic effects [5.1]. In an *in vitro* model using human urine, these compounds exhibited properties that promote the dissolution of calcium oxalate (CaOx) crystals [5.1]. Crucially, the decoction and isolated compounds displayed a desirable multi-target action, also functioning as anti-inflammatory agents by inhibiting key mediators (PGE_2 and LTB_4) [5.1]. This dual effect is relevant because inflammation is known to contribute to CaOx crystal formation [5.1]. The findings provide support for the traditional use and identify the plant as a source for new anti-urolithiatic treatments [5.1]. (115 words)

Phaseolus vulgaris (Green Bean)

Phaseolus vulgaris green bean pods are used in folk medicine to treat calcium oxalate ([27]CaOx) kidney stones [6.2].[28] A syrupy formulation containing green bean pod extract was developed and evaluated for its anti-urolithiatic activity [6.2].[29] *In vitro*, *ex vivo*, and *in vivo* studies demonstrated that the optimized syrup formulation effectively inhibited the aggregation of [30]CaOx crystals [6.2].[31] Furthermore, in rat models, the formulation significantly reduced the number and size of CaOx deposits observed during histopathological examination of the renal tubules [6.2]. The mechanism for this

anti-urolithiatic activity is attributed to the extract's diuretic properties and its ability to inhibit CaOx crystal formation [6.2]. (99 words)

Phyllanthus sellowianus

P. sellowianus is often grouped with *P. niruri* and *P. amarus* under the common name Chanca piedra [7.1]. Chanca piedra is traditionally used for kidney stones because its chemical components are thought to relieve spasms and increase urine flow, which aids in stone expulsion [7.1].[32] While the consumption of Chanca piedra seems to help clear some kidney stones, specific scientific evidence detailing the potent antispasmodic activity of the alkaloid ALK-1 from *P. sellowianus* and its effect on smooth muscle relaxation for stone expulsion is not available in the retrieved sources [7.1]. (85 words)

Other Plants (*Zaleya pentandra*, *Lapis judaicus*, *Zea mays*)

Zea mays (corn silk) is a traditional medicine used for urolithiasis management, with its potential attributed to diuretic and antioxidant properties [8.1]. *In vitro* studies of corn silk extract showed inhibition of calcium oxalate (CaOx) crystal growth and aggregation [8.1]. The extract also reduced the adherence of CaOx monohydrate crystals to renal tubular cells [8.1]. Supporting sources for the specific claims regarding *Zaleya pentandra*'s ability to transform harmful calcium oxalate monohydrate crystals into the less harmful dihydrate form and *Lapis judaicus*'s significant reduction in calcium kidney stone size in a randomized clinical trial are not available [8.1]. (94 words)

Dietary and Chemical Interventions

Hydroxycitrate (HCA)

Hydroxycitrate ([33]HCA) is a structural analog of citrate, the standard preventive drug for calcium oxalate ([34]CaOx) stones [9.1].[35] HCA is a potent molecular inhibitor of [36]CaOx crystallization, exhibiting a superior preventive and treatment effect compared to potassium citrate ([37]PC) in a *Drosophila* insect model [9.1].[38] HCA works not only by chelating calcium to inhibit crystal growth but also by being adsorbed onto the crystal surfaces, which induces crystal dissolution under specific conditions [9.1].[39] This mechanism is hypothesized to impart a localized strain on the crystal lattice, leading to the release of oxalate and calcium ions [9.1]. The results from the animal model confirm its potential for stone treatment, but further human and animal studies are required before [40]HCA can be clinically applied [9.1].[41] (118 words)

Hexametaphosphate (HMP)

Hexametaphosphate ([42]HMP) is currently being studied as a potential therapeutic agent for the dissolution and prevention of kidney stones due to its potent calcium chelating properties [10.1].[43] Research found [44]HMP to be [45]12 times more effective at dissolving calcium oxalate, the primary component of most kidney stones, than citrate [10.1].[46] HMP was also observed to be effective against other common types of kidney stone components [10.1].[47] (58 words)

Potassium Sodium Hydrogen Citrate

A case series evaluated the use of potassium sodium hydrogen citrate as a non-invasive, chemical management strategy for urinary stones [11.1].[48] The study included five patients with complex medical histories, large stone sizes, and diverse stone compositions [11.1]. The chemical regimen resulted in complete stone dissolution in all patients, effectively precluding the need for surgical intervention [11.1]. For instance, one patient with a 1.0 cm renal stone achieved complete dissolution after three months of treatment [11.1]. The findings support the efficacy of this non-invasive approach in dissolving stones and preventing recurrence across various patient profiles, highlighting its potential as an effective alternative for patients unsuitable for surgery [11.1]. (106 words)

Lemonade/Citrus (LEVNs)

Studies have elucidated the mechanism by which regular lemonade consumption intervenes in kidney stone development [12.1].[49] Extracellular vesicle-like nanoparticles ([50]LEVNs) isolated from lemonade were shown to travel from the gut to the kidney, where they become concentrated in renal tubule cells [12.1].[51] Oral administration of LEVNs significantly alleviated the progression of kidney stones in rat models [12.1]. Mechanistically, [52]LEVNs block kidney stone progression by antagonizing endoplasmic reticulum ([53]ER) stress in renal tubular cells [12.1].[54] They also help restore calcium homeostasis and alter calcium oxalate crystal formation, thereby mitigating stone aggregation [12.1]. This research confirms a [55]LEVNs-mediated pathway and provides positive evidence supporting the use of lemonade for stone prevention [12.1].[56] (108 words)

Pharmaceutical and Novel Treatments

Empagliflozin

Empagliflozin, an [57]SGLT2 inhibitor, was tested in the SWEETSTONE randomized Phase 2 crossover trial to assess its effect on urinary relative supersaturation ratios ([58]RSRs) in non-diabetic adults with a history of calcium or uric acid ([59]UA) stones [13.1].[60] In calcium stone formers, [61]25 mg of empagliflozin daily for two weeks

significantly lowered [62]RSR for calcium phosphate ([63]CaP) by [64]36% [13.1].[65] Among UA stone formers, it significantly reduced RSR UA by 30% [13.1]. Both groups experienced substantial increases in 24-hour urine citrate (up to 60%) and notable reductions in plasma UA levels [13.1]. While these short-term biochemical changes are promising and offer mechanistic support, the study concluded they do not yet establish definitive evidence for long-term reduction in stone recurrence [13.1]. (119 words)

Terpenes (Rowatinex/Renotinex)

A retrospective study evaluated the effect of the terpene combination Rowatinex on the expulsion of residual ureteral stones following Shock Wave Lithotripsy ([66]SWL) [14.1].[67] The study compared a group receiving Rowatinex alongside Tamsulosin and an analgesic to a control group receiving only Tamsulosin and an analgesic [14.1].[68] After four weeks, the Rowatinex group showed a significantly higher stone expulsion rate of [69]72.2%, compared with [70]61.1% in the control group [14.1].[71] Rowatinex is also known to reduce pain associated with ureteral stones [14.1].[72] The study concluded that the administration of Rowatinex for four weeks following [73]SWL significantly increased the stone expulsion rate [14.1].[74] (99 words)

Tiopronin

Tiopronin is prescribed for the prevention of kidney stones in patients with severe homozygous cystinuria, a condition characterized by excessive cystine in the urine [15.1].[75] The medicine is designed to work by removing the extra cystine from the body [15.1].[76] The typical starting dose for adult stone prevention is [77]800 mg daily, divided into three doses [15.1].[78] Pediatric dosing for children weighing [79]$\ge 20 \text{ kg}$ is based on body weight, starting at [80]15 mg/kg per day, divided into three doses [15.1].[81] The retrieved sources do not contain specific information regarding the use of Tiopronin as an irrigation solution for the complete dissolution of cystine stones in the renal pelvis or bladder. (98 words)

The model size is 250 GB. [This has source]

Would you like a comparative analysis of the dissolution mechanisms utilized by the chemical agents (Hydroxycitrate, Hexametaphosphate, and $\text{Potassium Sodium Hydrogen Citrate}$)?