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Alkalinizing Agents: A Review of Prescription, Over-the-Counter, and Medical Food Supplements.


Karen L. Stern
Mayo Clinic

Noah Canvasser
University of California Davis

Michael Borofsky
University of Minnesota

Vanessa M. Gleason
Thomas Jefferson University

Guido Kamphuis
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Authors

Karen L. Stern, Noah Canvasser, Michael Borofsky, Vanessa M. Gleason, Guido Kamphuis, Marawan M. El Tayeb, Ryan Hsi, and Kymora B. Scotland

TITLE: Alkalinizing agents: a review of prescription, over-the-counter, and medical food supplements

Karen L. Stern MD, Noah Canvasser MD, Michael Borofsky MD, Vanessa M Gleason PharmD BCCP, Guido Kamphuis MD, Marawan M. El Tayeb MD, Ryan Hsi MD, Kymora B Scotland MD PhD

Corresponding author:

Kymora Scotland, MD, PhD

Corresponding author address

Department of Urologic Sciences

Faculty of Medicine

Gordon & Leslie Diamond Health Care Centre

Level 6, 2775 Laurel Street

Vancouver, BC Canada V5Z 1M9

Fax: 604-875-5604

Tel: 604-875-5003

Email: Kymora.scotland@ubc.ca

Co-Author addresses:

Karen L. Stern

Mayo Clinic, 5777 E Mayo Blvd, Phoenix, AZ 85054

Stern.karen@mayo.edu

Noah Canvasser

University of California Davis, 4860 Y St Suite 2200, Sacramento, CA 95817

ncanvasser@ucdavis.edu

Michael Borofsky

University of Minnesota, 420 Delaware St SE, Box 394 Mayo, Minneapolis, MN 55455

mborofsk@umn.edu

Vanessa Gleason

Thomas Jefferson University Hospital, 111 S 11th St, Philadelphia PA 19107

Vanessa.gleason@jefferson.org

Guido Kamphuis

Meibergdreef 9, 1105 AZ Amsterdam, Netherlands

g.m.kamphuis@amc.uva.nl

Marawan El Tayeb

Baylor Scott & White Hospital, 2401 S 31st St, Temple, TX 76508

marawaneltayeb@gmail.com

Ryan Hsi

Vanderbilt University, 1211 Medical Centre Dr, Nashville, TN 37232

Ryan.hsi@vumc.org

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ABSTRACT

Introduction

Kidney stones affect 1 in every 11 people in the United States each year. There is a significant high recurrence rate without a stone prevention protocol. Alkali citrate is beneficial in decreasing stone recurrence, but due to the cost and gastrointestinal side effects there is a low adherence rate. This study aims to serve as a review of some of the most commonly used alkalinizing over-the-counter supplements that are advertised to prevent and treat kidney stones.

Methods

Data was gathered by a comprehensive online literature search and company inquiries for kidney stone prevention supplements. An additional informal poll of the authors selected supplements that are most commonly taken by their patients. A total of eight supplements were evaluated for cost, alkali equivalent provided, dosing and regulatory information.

Results

Eight of the most commonly used supplements were reviewed with a focus on alkalinizing agents. Information reviewed revealed dosing recommendations resulting in decreased citrate alkali equivalents per day compared to prescription-strength potassium citrate. Cost, peer-reviewed study results and regulatory data were reviewed, tabulated and analyzed. Cost per alkali equivalent was substantially decreased for each supplement compared to the prescribed drug. All supplements were found to be readily available online.

Conclusion

Over-the-counter alkalinizing agents are available to patients and may be an appropriate alternative to cost prohibitive potassium citrate when treating urolithiasis patients. Additional testing will be necessary in the future to determine the efficacy of these supplements in the treatment and prevention of urinary stone disease.

INTRODUCTION:

Kidney stones affect 1 in every 11 people in the United States each year.¹ Unfortunately, without dietary and/or medical management kidney stones can have a significant recurrence rate, highlighting the importance of prevention.² The American Urological Association (AUA) guidelines recognize the effectiveness of medical management at decreasing the recurrence of stone disease and recommend that clinicians offer pharmacologic therapy to recurrent stone formers.^{3,4} Several clinical trials have demonstrated the effectiveness of potassium citrate in decreasing stone recurrence.^{5,6} However, among kidney stone patients prescribed potassium citrate for stone management, only 13% are adherent with the medication.⁷ Low adherence to stone preventative therapy is likely multifactorial. Side effects associated include abdominal pain and diarrhea.⁹

Another significant barrier to medication adherence is its cost. Potassium citrate retails at an average cost of \$154.80 for a one-month supply of the generic formulation at a dosage of 15 milli equivalents (mEq) twice daily (BID).¹⁰ This is notable considering that the urine alkalization is a long-term therapy. Anecdotally, patients often report insurance formularies do not cover commonly prescribed potassium citrate formulations. The combination of the effectiveness of the medications with the prohibitory cost of the prescription has led to the development of multiple over-the-counter supplements that promise to alkalize the urine and/or decrease the risk of future kidney stones.

A simple Amazon search for “kidney stone medicine” returns more than 250 results. Although the manufacturing of over-the-counter options is not regulated, and many are not scientifically tested to the same degree as prescribed alkali citrate, they may be effective and the affordability may increase patient compliance and adherence.

We review the more common over-the-counter supplements advertised to prevent or directly treat kidney stones, specifically focusing on alkalizing agents. The intent of this review is to educate providers on the supplements available to their patients, especially patients who frequently self-educate and self-prescribe without direct oversight from the treating physician. Shared decision making is a critical part of a patient-provider

relationship, and knowledge of treatment options beyond the standard prescriptions is essential in strengthening that relationship. While the goal of this review is not to promote or advertise for any of the described supplements, a baseline knowledge of these options may prove useful in the event patients inquire about them or self-administer.

Urinary Alkalinization

The common Western diet includes a large acid load, predominantly from animal protein intake. In the kidneys, acid loads cause increased citrate uptake in renal cells leading to lower urinary citrate and increased supersaturation of calcium salts. Urinary citrate is thought to decrease stone recurrence by complexing with calcium in the urine, which increases the solubility and reduces the concentration of free calcium in the urine, as well as by binding the surface of crystals to prevent agglomeration and growth.⁸ *In vitro*, citrate has been shown to inhibit calcium oxalate precipitation and decrease calcium phosphate growth.^{11,12} Hence, alkali supplementation to raise urine pH and limit urine citrate uptake is recommended for stone formers with low urine pH and/or urinary citrate.⁴

Multiple ingestible forms of alkali exist. Baseline knowledge of urinary alkalinization is important when reviewing over-the-counter alkali preparations. The most commonly prescribed alkali for stone prevention is potassium citrate, which has demonstrated as high as a 75% risk reduction of kidney stone recurrence, with a long-term durable response in some patients.^{13,14} Although similar, citric acid, a protonated form of citrate, is less effective at increasing urinary citrate due to the counterproductive acid load.¹⁵

These differences have potential significance when dietary beverages are being used to prevent stones. For example, lemonade therapy is commonly recommended to stone formers as a way to increase urinary citrate. Orange juice, however, may in fact be more effective given a greater portion of potassium citrate versus citric acid.^{16,17} Coconut water, due to a large malate as alkali component, can also increase urinary citrate if ingested in large quantities.¹⁸ In addition, some citrus-flavored carbonated beverages also contain large portions of alkali due to citrate and malate content, however, substantial volumes of these beverages would need to be ingested to match the alkali content of prescribed potassium citrate.¹⁹

Bicarbonate is another useful alkali, with both sodium bicarbonate and potassium bicarbonate demonstrating similar efficacy to potassium citrate at raising urine pH and urine citrate.^{20,21}

The cation associated with each alkali salt can have important consequences. Sodium administration can increase blood pressure and decrease bone mineral retention. Most importantly for kidney stone patients, it has a hypercalciuric effect that can be counterproductive.²⁰ Magnesium citrate also increases urine pH, but is associated with significant gastrointestinal effects which can counterproductively increase urinary oxalate through malabsorption.²² Additionally, magnesium can decrease intestinal absorption of oxalate. Lastly, potassium lowers urine calcium and increases urine citrate²⁰ but can be dangerous for patients with renal failure or significant cardiac disease, and therefore requires close monitoring.¹³

Regulation

The Food and Drug Administration (FDA) is the governing body regulating the content and sale of domestically produced food and pharmaceuticals in the United States. For approved pharmaceuticals, good manufacturing processes (GMPs) are regulated by the FDA to ensure the identity, strength, quality, and purity of drug products is maintained. Generally Recognized as Safe (GRAS) is a FDA designation that a chemical or substance is considered safe by experts. Any substance added to a food is subject to review and approval by the FDA, unless said substance is identified as GRAS.

Many over-the-counter treatments for kidney stone formers are marketed as medical foods or supplements. Per the FDA and based on the United States Orphan Drug Act, a medical food is “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation”.²³ The FDA does not approve supplements. The United States Pharmacopeia Convention is a non-profit organization that publishes an annual compendium of drug information, the United States Pharmacopeia (USP). In order to assure quality among supplements and protect

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consumer health, the USP works with manufacturers in an attempt to verify the quality of ingredients and products. A multi-step evidence-based process is used to confirm the accuracy of the information supporting the quality of each product being verified in a particular program. However, it is important to note that USP has no role in enforcement of these standards. Hence, manufacturer claims must be carefully considered. In particular, only supplements that have been tested and meet the USP program requirements are allowed to display the *USP Verified Dietary Supplement* mark. This is not equivalent to manufacturers who claim to adhere to USP standards without verification.

METHODS:

A comprehensive search for “kidney stone medications” and “kidney stone medicine” was performed on online shopping websites that are likely visited by patients (i.e., Amazon, Google). In addition, an informal poll of the authors was undertaken to determine the supplements that are most commonly taken by their patients. Product information was obtained from manufacturer websites and *via* company inquiries. Scientific literature search was performed via PubMed, with manuscripts reviewed and summarized in the results. Any additional available literature regarding the various products was reviewed and reported.

RESULTS:

Eight supplements were reviewed, with a focus on alkalizing agents. See Table 1 for summary of the alkali containing supplements. Commercial potassium citrate comes in three doses: 5, 10, or 15 mEq of alkali. As seen in Table 1, most supplements provide a fraction of this amount.

Pure Alkalizing Agents:

A search for “Potassium Citrate” on Amazon returned 213 products; we reviewed three of these products. NOW[®] Potassium Citrate is “Amazon’s Choice,” BulkSupplements is the most reviewed potassium citrate product with over 1400 reviews, and Litholyte[®] was selected based on its popularity among patients.

There are numerous versions of potassium citrate that are currently online. Two of the more commonly reviewed products are BulkSupplements (Hard Eight Nutrition LLC, Henderson, NV, USA) and NOW[®] Potassium Citrate (NOW, Bloomingdale, IL, USA).^{24,25} Each of these is available as a powder. The BulkSupplements formulation has 99 mg of potassium citrate (0.92 mEq of alkali) per serving of 275 mg (3.33 mEq of alkali/1 gm supplement) whereas the NOW[®] Potassium Citrate powder has 448 mg of potassium citrate (4.15 mEq of alkali) per serving of 1.4 grams (2.96 mEq of alkali/1 gm supplement). NOW[®] Potassium Citrate also comes in a 99 mg vegetarian capsule (0.92 mEq of alkali). Again, for comparison commercial potassium citrate contains between 5-15 mEq of alkali per tablet. BulkSupplements is made in an FDA-registered facility.

Litholyte[®] (Litholyte Corporation, New Bern, NC, USA) is a powdered mixture of potassium citrate, magnesium citrate and sodium bicarbonate developed by urologist Ryan Holland, MD.²⁶ Each packet contains 10 mEq of alkali and the manufacturers recommend twice daily dosing (see Table). It has zero calories and is unflavored to allow incorporation into a liquid of the patient's choice. The inventors note there is no citric acid in this product leading to a net alkali effect on systemic pH. There are currently no peer-reviewed publications evaluating Litholyte[®]. However, the manufacturer cites studies that demonstrate the benefit of sodium bicarbonate or combination potassium and magnesium citrate versus placebo.^{25,26} This is not marketed as a prescription medication. It is still patent pending but has been classified by the FDA as a medical food.

Combination Alkalinizing and Vitamin Supplements:

There are several available alkalinizing supplements that combine citrate with vitamin B6 and magnesium including TheraLith[®] XR, StoneStop[™], KSPTabs, Kidney C.O.P.[®] and Lithobalance[™]. TheraLith[®] XR (Theralogix LLC, Aston, PA, USA) is a supplement that contains vitamin B6 (7.5 mg), magnesium (180 mg) and potassium citrate (99 mg/0.92 mEq), in a delayed-release coating.²⁷ The magnesium included is both magnesium citrate (1.2 mEq) and magnesium oxide. The supplement is dye-free, gluten-free and is made in the United States. The recommended dosage is two tablets twice a day with food. A study in 2006 at Stony Brook University Hospital found normalization of urinary magnesium and

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urinary citrate levels after two months of consistent intake in patients with known low urinary magnesium and citrate.²⁸ TheraLith[®] XR retails for \$60.00 per bottle (90 day supply).

StoneStop (StoneStop LLC Wilmington, DE, USA) is an over-the-counter pH-neutral mixture of citrate, magnesium, and vitamin B6 in individual packets.²⁹ StoneStop was developed by urologist Kyle Wood, MD. The dosage of each ingredient is not immediately available to consumers. Each packet is mixed into 16 ounces of water and dissolved, and the recommendation is to consume two packets daily. Like Litholyte[®], it is advertised as a medical food and recommended to be used under medical supervision. Since the cation complexed with citrate is magnesium, rather than sodium or potassium, the dosage may be limited by gastrointestinal side effects, specifically, diarrhea. Retail price is 30 packets for \$29.99.

KSPTabs (Austin, TX, United States) are dissolving effervescent tablets developed by urologist Michael Trotter, MD.³⁰ Manufacturer recommendation is to consume one tablet in 16 ounces of water, 2-3 times per day. One KSPTab contains vitamin B6 (7.5 mg), magnesium (64 mg), sodium bicarbonate (170 mg/ 2 mEq) and potassium bicarbonate (100 mg/1mEq). The tablets come in two flavors, lime and berry, and are advertised as gluten-free, vegan friendly and all-natural. They are sweetened with dextrose and stevia. Each tablet is 10 calories and has 1 gram of sugar. The company has made available a self-produced study investigating urinary parameters in 35 nephrolithiasis patients who had taken the supplement. The study found increased urinary outputs and urine pH, citrate and magnesium with decreased urinary calcium and super saturation of uric acid on 24-hour urine analysis following administration of KSPTabs. This study is available on their website.³⁰ However, there are currently no peer-reviewed studies reported using KSPTabs to prevent kidney stones. Eighty tablets (approximately 1-month supply) retail for \$59.95.

Kidney C.O.P.[®] (Calcium Oxalate Protector, Calcium Oxalate Labs Inc., Ft. Lauderdale, FL, USA) is a patented formulation that combines five ingredients, each suggested to prevent stone growth.³¹ In addition to citric acid (4.5 mEq), vitamin B6 and magnesium, Kidney C.O.P.[®] also includes Phytin and Musa Paradisiaca. Phytin (Inositol) is a known

crystallization inhibitor of calcium salts that has been shown to have a synergistic effect when combined with magnesium *in vitro*.^{32,33} *Musa Paradisiaca* (Banana Stem) has traditionally been used as a natural remedy for stone prevention. Formal evidence supporting this is sparse in the literature, but proposed mechanisms include a diuretic effect as well as decreased activity of liver enzymes that are involved in oxalate production. One small series suggested efficacy when used among a rat model of ethylene glycol induced nephrolithiasis.³⁴ The Kidney C.O.P.[®] website claims that *in vitro* testing of the patented formula led to a 99% inhibition of calcium oxalate growth rate; these findings could not be verified by peer-reviewed literature at the time of publication. Furthermore, the website's disclaimer notes that the proposed stone prevention mechanism has not been evaluated by the FDA.

LithoBalance[™] (AmPurity Nutraceuticals[™], Fenton, MO, USA) is a combination of vitamin B6, magnesium citrate and potassium citrate sweetened with stevia leaf extract.³⁵ The recommended serving size is one scoop (10 grams), dissolved in 12-16 ounces of water, 2 to 3 times daily with meals. One scoop contains 20 mg vitamin B6, 43 mg (0.6 mEq) magnesium citrate, 410 mg (3.8 mEq) potassium citrate and 150 mg Stevia leaf extract. No artificial colors, sweeteners or flavors are claimed to be added. The product is claimed to have been developed by a team of clinical urologists and research scientists. The website refers to several publications related to the effect on stone formation of potassium citrate, magnesium citrate, vitamin B6, and magnesium oxide (dihydrate). In the referenced studies, there are several combinations and dosages of these ingredients mentioned, however there is no published literature on the specific combination and quantities of the materials in LithoBalance[™] in the literature, and no publications on LithoBalance[™] specifically. One container contains 90 servings (approximately 1-month supply) and retails for \$49.89.

Chanca Piedra- containing Supplements:

A simple online search for “kidney stone medicine” will lead patients to dozens of products with *Phyllanthus niruri* (Chanca Piedra). *Phyllanthus niruri* (*Chanca Piedra*, Spanish for “stone breaker”) is a plant used in both Ayurvedic systems of medicine in India and in folk

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medicine in Brazil and Peru. It is neither cytotoxic nor genotoxic.³⁶ There are some studies indicating that Chanca Piedra has a role in decreasing kidney stones, increasing urine potassium, and decreasing urinary oxalate and urinary uric acid.³⁷⁻³⁹ However, the need for additional rigorously performed studies persists. Given that the scope of this paper is to focus on alkalinizing agents, products containing *Phyllanthus niruri* were not reviewed in great detail here.

DISCUSSION:

The high prevalence of kidney stone disease makes access to medical therapies a necessity for patients. Unfortunately, the high cost and side effects of prescription potassium citrate is prohibitive for many patients and results in low adherence.⁷ A 2013 survey found that 72% of patients look online for health information.⁴⁰ Patients are likely using similar search engines to find accessible and affordable alternatives to expensive prescription medications. Providers need to be aware of these formulations to appropriately counsel patients on the risks and benefits of such therapies.

It must be emphasized that none of these products are FDA approved for the treatment of kidney stones and they have little to no scientific data to support the manufacturers' claims. In fact, KSPTabs and TheraLithXR are the only supplements reviewed here that are associated with any documented studies on the product.^{28,30} Litholyte[®] and StoneStop are classified as medical foods. The medical food category became popular in the late 1980s and 1990s and has grown into a lucrative business, valued at \$12.3 billion in 2015 and expected to surpass \$24 billion by 2025.⁴¹ As mentioned above, a medical food is a product designed to be consumed for the specific dietary management of a disease or condition.²³ Medical foods are not regulated by the FDA but manufacturing of the products must comply with the FDA regulations for food.²³

This review briefly discusses a few of the more popular alternatives to prescription potassium citrate. The alkalizing formulations available deserve further study. The non-alkalizing supplements were included so providers have basic knowledge of the products marketed to urolithiasis patients. Providers should use this guide as a tool for an open

discussion with patients who may seek over-the-counter alternatives, rather than a guide for medication or supplement recommendations.

CONCLUSIONS:

Over-the-counter alkalizing agents are available to patients and may be an appropriate alternative to cost prohibitive potassium citrate when treating urolithiasis patients. Additional testing will be necessary in the future to determine the efficacy of these supplements in the treatment and prevention of urinary stone disease.

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Abbreviations

American Urological Association	AUA
Food and Drug Administration	FDA
Good manufacturing processes	GMP
Generally Recognized As Safe	GRAS
United States Pharmacopeia	USP
milli-equivalent	mEq

Table 1: Comparison of Potassium Citrate and Alternative Supplements*

Name	Main Ingredients	Dosing	Alkali Equivalent Per Serving*	Price (US \$)	Approximate Price Per Day**	Regulatory Information
UroCit-K	<ul style="list-style-type: none"> K citrate (5, 10, or 15 mEq tabs) 	1-4 tablets BID	5-15 mEq	\$231/100 tablets (10 mEq) \$388/100 tablets (15 mEq)	\$15.52	FDA approved Prescription Required
Potassium citrate (generic)	<ul style="list-style-type: none"> K citrate (5, 10, or 15 mEq tabs) K citrate packets 	1-4 tablets BID Varies	5-15 mEq	\$138/120 tabs (15 mEq) \$186/120 packets	\$4.62 \$6.19	Several generics FDA approved Prescription Required
Bulk Supplements	<ul style="list-style-type: none"> 99mg K citrate per 275 mg powder serving 	1 serving daily	0.92 mEq	\$11.96/250 g	\$0.40	Made in FDA registered facility
NOW® Potassium	Capsule Form: <ul style="list-style-type: none"> K+ Citrate 	1 capsule	0.92 mEq	\$11.99/180	\$0.07 per pill	Follows GMP

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Alkalinizing agents: a review of prescription, over-the-counter, and medical food supplements (DOI: 10.1089/end.2019.0292)

Citrate	(99 mg =0.9 mEq) Powder Form: <ul style="list-style-type: none"> K+ Citrate (448 mg= 4 mEq) 1.4 gm 	1-5x daily ¼ teaspo on 1-2x daily	4.15 mEq	capsules \$12.99/1 2 ounces		
Litholyte®	<ul style="list-style-type: none"> K+ Citrate (4 mEq) Mg Citrate (2.5 mEq) Na Bicarbonate (3.5 mEq) 	1-2 packets BID	10 mEq	\$30/ 60 packets	\$1.00	Follows GMP
TheraLith® XR	<ul style="list-style-type: none"> B6 (7.5mg) Mg citrate+oxide (180 mg = 1.2 mEq Mg citrate) K+ Citrate (99 mg= 0.9 mEq) 	2 tabs BID	2.12 mEq	\$60/bottle (360 tabs)	\$0.67	Follows GMP
Kidney C.O.P.®	<ul style="list-style-type: none"> Pyridoxine HCl (5 mg) Mg Citrate (45 mg = 0.6 mEq) Citric Acid 	2 tabs daily	5.1 mEq	\$29.95/ bottle (60 capsules)	\$1.00	GRAS Follows GMP

	<ul style="list-style-type: none"> (350 mg =4.5 mEq) Phytin (Inositol) (200 mg) Musa Paradisiaca (200 mg) 					
KSPtabs	<ul style="list-style-type: none"> B6 (7.5 mg) Mg (64 mg = 0.9 mEq Mg citrate) Na Bicarbonate (170 mg = 2 mEq) K+ Bicarbonate (100 mg = 1 mEq) 	2-3 tabs Daily	2.92 mEq	\$59.95/80 tabs	\$1.50	
StoneStop	<ul style="list-style-type: none"> Citrate Magnesium B6 <p>No information on alkali equivalents or</p>	2 packets daily	Unknown	\$29.99/30 packets	\$2.00	Follows GMP

	contents by weight					
LithoBalanc e™	<ul style="list-style-type: none"> Vitamin B6 (20 mg) Mg Citrate (43 mg = 0.6 mEq) Potassium citrate (410 mg =3.8 mEq) 	1 scoop (=10 grams) 2-3 times a day	4.4 mEq	\$49.89 / 90 servings	\$1.11	

* **The over-the-counter supplements provide alkali equivalents that are a fraction of the recommended dosage.**

** **The Price per day column reflects the suggested dose by the manufacturer only, not the recommended dosage**