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Authors

Lo, Christopher Yong-Zyn

Khor, Qian Hui

Abdullatif, Victor A

et al.

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Review

Systematic review of pharmacological, complementary and alternative therapies for the prevention of calcium oxalate stones

Christopher Yong-Zyn Lo [a,*], Qian Hui Khor [b],
Victor A. Abdullatif [c], Cesar Delgado [d], Yadong Lu [e],
Jonathan Katz [d], Roger L. Sur [d], Christopher YZ. Lo [a],
Qian Hui Khor [b], Victor A. Abdullatif [c], Cesar Delgado [d],
Yadong Lu [e], Jonathan Katz [d], Roger L. Sur [d]

[a] Duke-NUS Medical School, Singapore, Singapore
[b] Changi General Hospital, Singapore, Singapore
[c] Ascension Macomb Oakland Hospital, Department of Urology, Warren, MI, USA
[d] University of California San Diego Health, Department of Urology, CA, USA
[e] Singapore General Hospital, Department of Urology, Singapore, Singapore

Abstract *Objective*: Several therapeutic modalities for the prevention of calcium oxalate (CaOx) stones have been studied, but only a select few of these modalities have been incorporated into the American Urological Association guidelines. Our study aimed to organize and interrogate existing research that may be promising for CaOx prevention.

Methods: A literature search was conducted using MEDLINE and Embase from inception to November 16th, 2022. Our study population included adults with or without a history of CaOx kidney stones. Studies in which patients were treated with pharmacotherapies, herbal supplements, or uncategorized research chemicals that are not included in the current American Urological Association guidelines for preventing CaOx stones were included. Nonoriginal research was excluded.

Results: Out of the 6155 identified articles, 38 were included in the final analysis. The five distinct categories of interventions for stone prevention were "medications", "herbal supplements", "food and macronutrients", "micronutrients", and "enzymes and probiotics". Modalities that were found to reduce known urinary risk factors were tolvaptan, cranberry juice, magnesium citrate, oxalate-degrading enzyme ALLN-177, and malic acid. Prophylaxis that reduced stone formation were sodium-glucose cotransporter-2 inhibitors (SGLT2i),

* Corresponding author.
    E-mail address: clo@u.duke.nus.edu (C. Yong-Zyn Lo).
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eicosapentaenoic acid, ethane-1-hydroxy-1, and 1-disphosphonate. Therapies that reduced urinary risk factors and stone formation were *Phyllanthus niruri*, rice bran, and magnesium hydroxide.

Conclusion: Our systematic review comprehensively summarized the research on CaOx stone prevention in the clinical setting. Several of the identified therapies may provide prophylactic benefits for CaOx stone formation and may be useful for inclusion in guidelines for kidney stone prevention.

1. Introduction

Nephrolithiasis is a common urological disease with an estimated global prevalence of up to 13% [1]. Not only can it be a painful condition, it is also associated with an increased risk of chronic kidney disease and end-stage renal disease [2,3]. After initial stone treatment with medical expulsive therapy or surgical intervention, approximately 35% of untreated patients experience another symptomatic stone event within 5 years of the first occurrence [4], which represents a significant healthcare and economic burden [5]. Hence, it is of great interest to prevent stone recurrence.

Calcium oxalate (CaOx) stones are the most common type of kidney stone [6]. Reviews for the prevention of CaOx stones have various areas of focus, either on evidence-based therapies already recognized in the American Urological Association (AUA) guidelines [7] or more general reviews of complementary and alternative therapies [8]. However, few reviews have systematically identified literature for the elucidation of promising therapies for the prevention of CaOx stones outside of the existing guidelines.

The AUA guidelines currently recommend lifestyle, dietary modifications, and pharmacotherapy for recurrent CaOx stones depending on urinary abnormalities [9]. Despite advancements in the understanding of stone formation, accepted recommendations for preventive therapy have largely remained unchanged for years, and recently, staples of treatment such as thiazides have been challenged [10]. Furthermore, while pharmacotherapy can be effective, patient compliance may be low due to unwanted side effects, inconvenience, or cost [11]. Therefore, novel, well-tolerated interventions are needed to prevent CaOx stone recurrence. This report aims to provide a comprehensive review of the current landscape of non-guideline approved interventions for the prevention of CaOx stones.

2. Methods

The present study aimed to evaluate promising treatments for the prevention of CaOx stones. The "PIO" model was used to define the research question as follows:

- Population: adult non-CaOx stone formers and adult male and female patients diagnosed with single or multiple CaOx stones.
- Intervention: the use of any medicine, supplement, or uncategorized research chemical that has not been previously endorsed in the AUA guidelines for the prevention of CaOx stones.
- Outcomes: urinary biochemical markers, reduction in kidney stone burden as measured by a reduction in symptoms, a decrease in stone size on imaging, or stone episode rate (defined as the number of stone episodes per patient per year).

2.1. Information sources and search strategy

A literature search was conducted using MEDLINE and Embase from inception to November 16th, 2022. The methodology for this systematic review was based on the Cochrane Handbook for Systematic Reviews of Interventions [12]. Boolean operators were utilized (*i.e.*, ['nephrolithiasis'/exp OR nephrolithiasis] AND ['prophylaxis'/exp OR prophylaxis OR 'prevention'/exp OR prevention]). All the results were imported into COVIDENCE systematic review software (Veritas Health Innovation, Melbourne, Australia) for abstract screening and full text review. The reference lists of relevant articles were manually searched for additional reports. Our systematic review protocol was prospectively registered on PROSPERO (CRD42023440913). The search strategy used is available in the appendix (Supplementary Table 1).

2.2. Inclusion criteria and exclusion criteria

Studies were included if the researchers evaluated healthy adults or adults with a history of kidney stones. The study designs included randomized controlled trials (RCTs), non-RCTs, intervention studies without concurrent controls, pre-post intervention studies, crossover trials, and observational studies. Review papers (including systematic reviews), case reports, study protocols, and conference proceedings were excluded.

Regarding interventions and outcomes, studies that implemented pharmacotherapy or herbal supplements that are not included in the current AUA guidelines as effective modalities for treating or preventing kidney stones were included. Articles that evaluated interventions already endorsed by the AUA guidelines were excluded.

2.3. Study selection

Utilizing COVIDENCE systematic review software (Veritas Health Innovation, Melbourne, Australia), the titles and abstracts of all the retrieved articles were independently reviewed by two authors (Lo CYZ and Khor QH), and any discrepancies were resolved by a third author (Abdullatif VA). Subsequently, the full-text articles were retrieved and reviewed in the same fashion as the title and abstract screening.

2.4. Data extraction

Full-text articles that met the inclusion criteria had information regarding study design, study population, study methods, and outcome measures extracted for analysis in a pre-populated form in Microsoft Excel (Redmond, Washington, United States). Two authors independently extracted the data (Lo CYZ and Khor QH), and any discrepancies were resolved by a third author (Abdullatif VA).

2.5. Quality assessment

Included RCTs were evaluated using the Cochrane Collaboration's risk of bias 2 tool [12] to determine internal validity. Each study was assessed on the following categories: adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and free of other bias. Categories that were rated as "some concerns" were evaluated as "moderate" risk of bias. The overall risk of bias for each study was reported as low, moderate, or high. Non-randomized studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [13]. Each study was assessed across seven domains: confounding bias, participant selection bias, classification of intervention bias, deviation from intended intervention bias, missing data bias, outcome measurement bias, and reported result selection bias. Risk of bias in each category for these articles were reported as low, moderate, serious, and critical [13]. Two authors (Lo CYZ and Khor QH) independently assessed the study quality and any discrepancies were resolved by a third author (Abdullatif VA).

3. Results

3.1. Study selection

The Preferred Reporting Items for Systematic reviews and Meta-Analyses study selection flowchart summarizes the selection process for the papers included in the analysis (Fig. 1). A total of 6155 papers were identified from MEDLINE and Embase. After removal of duplicates, 5813 studies were screened using titles and abstracts. Of these studies, 102 were identified for full-text review. Thirty-eight studies were included in the final analysis. An overview of the included studies is shown in Table 1.
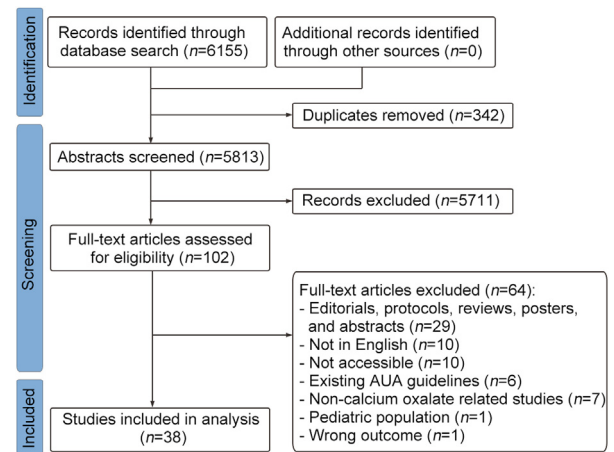
Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart of selected studies. AUA, American Urological Association.

3.2. Changes in urinary risk factors for CaOx stone formation

Table 2 provides a summary of the changes in urinary parameters relevant for CaOx stone formation from each of the 38 included studies.

3.3. Individual study findings

3.3.1. Medications
Of the 38 studies, 12 included medications as the intervention. These medications included SGLT2i, tolvaptan, bisphosphonates, diphosphonates, calcium channel blockers, sodium thiosulfate, cellulose phosphate, nonsteroidal anti-inflammatory drugs, sodium pentosan polysulfate, and methylene blue.

An observational study conducted by Kristensen et al. [14] investigated the association between the initiation of SGLT2i and the risk of nephrolithiasis. Using data from the Danish National Patient Registry, patients initiating SGLT2i or glucagon-like peptide-1 (GLP1) agonists were identified and matched 1:2 on propensity scores. The primary outcome was incident nephrolithiasis, defined as a recorded inpatient or outpatient diagnosis of ureteric and/or renal calculi in the registry. Patients started on SGLT2i had a lower rate of nephrolithiasis than patients initiated on GLP1 agonists a rate difference of −1.9 per 1000 person-years (95% confidence interval [CI] −2.8, −1.0) and a hazard ratio (HR) of 0.51 (95% CI 0.37, 0.71). Compared to patients initiated on dipeptidyl peptidase 4 inhibitors, the incidence rate difference was −1.5 per 1000 person-years (95% CI −2.6, −0.4), and the HR was 0.61 (95% CI 0.41, 0.88). For recurrent nephrolithiasis, the difference in incidence rate between the SGTL2i and GLP1 agonist groups was −17 per 1000 person-years (95% CI −33, −1.5), and the HR was 0.68 (95% CI 0.48, 0.97).

In a RCT conducted by Cheungpasitporn et al. [15], researchers compared urinary calcium oxalate, calcium phosphate, and uric acid supersaturation between tolvaptan and placebo. Tolvaptan was found to increase urine

Table 1 Summary of all included studies.

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
Medications						
Backman et al., 1980 [21]	Interventional study without concurrent control	35 recurrent Ca stone formers (mostly CaOx containing stones)	5 mg sodium cellulose phosphate TDS	Historical controls compared with patient population on thiazide or nil intervention in other studies	Sodium cellulose phosphate is an ion-exchange cellulose with special affinity for divalent cations; when mixed with intestinal content, sodium is exchanged for Ca, reducing both dietary and secreted Ca absorption in the gastrointestinal tract	2 years
Baumann et al., 1978 [24]	Non-RCT	9 patients with idiopathic recurrent CaOx containing stones	4.4 mmol/day EHDP	Crossover	Interference of CaOx crystal aggregation	12 months
Cheungpasitporn et al., 2016 [15]	RCT crossover	21 Ca stone formers	45 mg/day tolvaptan	Crossover	Increase urinary free water losses that result in increased urine volume, decreased urinary osmolality, and decreased urinary CaOx supersaturation	1 week
Hemal et al., 1989 [22]	Pre- and post-intervention	31 recurrent CaOx nephrolithiasis patient without hypercalciuria or hyperuricosuria	50 mg diclofenac-Na TDS	Pre-intervention	Decrease urinary Ca	4 weeks
Kristensen et al., 2021 [14]	Cohort study	Patients newly initiated on either SGLT2is or GLP1 receptor agonists as identified on the Danish health	SGLT2i	Patients newly initiated on GLP1 agonist, matched 1:1 on propensity scores	Decrease renal reabsorption of glucose, leading to osmotic diuresis and increased urinary flow,	2 years

(*continued on next page*)

Table 1 (*continued*)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
		registries (n=24 290 and n=19 576, respectively)			reducing concentration of lithogenic substances in urine	
Norman et al., 1984 [25]	Non-RCT	Healthy subjects without history of stone disease (n=6); recurrent idiopathic Ca stone formers (n=8); recurrent stone disease due to primary hyperoxaluria (n=2)	250 mg BD sodium pentosan polysulfate	Control	SPP is a semi-synthetic GAG-like substance that reduces the growth rate and agglomeration of CaOx crystals	10 days
Okada et al., 2008 [17]	RCT	25 healthy men on bed rest defined as 6° head-down tilt bed for 90 days	Intravenous pamidronate 60 mg 2 weeks before initiation of bed rest (n=7); resistive exercise every 3 days (n= 9)	Control (n=9)	Inhibit bone mineral loss and prevent hypercalciuria and crystallization of Ca-related salts	180 days
Okonkwo et al., 2013 [20]	Pre- and post-intervention	Healthy (n=5); idiopathic hypercalciuric Ca stone forming adults (n=5)	10 mmol sodium thiosulfate BD	Pre-intervention	Thiosulfate binds urinary Ca and is excreted as a highly soluble Ca thiosulfate salt; thiosulfate inhibits Ca stone crystallization directly or indirectly	7 days
Ruml et al., 1995 [16]	Double-blinded RCT	8 healthy male subjects	20 mg alendronate	Placebo (n=8)	Inhibition of bone mineral loss, prevention of hypercalciuria and increased propensity for the crystallization of stone-forming Ca	2 weeks

(*continued on next page*)

Table 1 (continued)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
					salts that occurs during strict bedrest	
Sarica et al., 2006 [19]	RCT	50 patients with CaOx stones treated with ESWL without biochemical abnormalities	PO verapamil HCl 120 mg TDS beginning 3 days before ESWL and continued 4 weeks after procedures ($n=25$); enforced fluid intake program (urine output >2.5 L/day) ($n=25$)	20 CaOx stone formers treated with ESWL on no specific medication apart from close follow-up	CCB-induced vasodilation increasing renal blood flow to compensate for tissue damage as a result of ESWL, which prevents stone recurrence and regrowth of any residual fragments.	30.4 months
Smith 1975 [23]	Interventional study without concurrent control	68 patients with renal calculi without biochemical abnormality	65 mg methylene blue TDS	None	Methylene blue is postulated to act through three mechanisms: coat the nidus/central nodule of crystal; disrupt intramolecular bonds; direct intracellular effect to prevent crystallization	5 years
Yasui et al., 2009 [18]	Pre- and post-intervention	12 post-menopausal patients with osteoporosis and Ca stones	5 mg/day of PO alendronate OM for 3 months	Pre-intervention	Inhibition of bone mineral loss, prevention of hypercalciuria and increased propensity for the crystallization of stone-forming Ca salts that occurs during strict bedrest.	3 months
Herbal supplements Erickson et al., 2011 [26]	Double-blinded RCT crossover	10 recurrent kidney stone formers with	Cystone 2 tabs BD	Crossover	Decreased urinary supersaturation,	6 weeks of each treatment with 1-

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Table 1 (continued)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
		documented CaOx stones			micropulverization, and expulsion of kidney stones	week washout between 1-year open label to assess renal stone burden
Lin et al., 2013 [27]	RCT	28 patients with recurrent CaOx stones	2 mg WLS formula TDS (n=14)[a]	Placebo (n=14)	Macromolecules in WLS have antilithic properties, preventing CaOx crystallization and growth	1 month
Pucci et al., 2018 [28]	Non-RCT	56 patients with kidney stones of <10 mm	*Phyllanthus niruri* tea preparation	Crossover	*Phyllanthus niruri* promotes diuresis and has anti-inflammatory properties	12 weeks of intervention, followed over 26 weeks
Food and macronutrients						
Ebisuno et al., 1986 [30]	Uncontrolled clinical trial	164 patients with hypercalciuria with Ca-containing stones	Rice bran 10 g BD	Pre-intervention	Phytate in rice bran lowers urinary Ca in patients with idiopathic hypercalciuria	2 years
Fakier et al., 2020 [29]	Pre/post intervention	Healthy males (n=7)	Restrict intake of food rich in phytate and oxalate for 18 days; on Days 15−18 dietary phytate 800 mg supplementation	Pre-intervention	Phytate inhibits CaOx crystallization and lowers urinary Ca	3 days
Koff et al., 2007 [31]	Non-RCT	21 stone formers	LT (standard recipe of 30 mL of ReaLemon lemon juice with 3/4 cups of water and sweetener TDS) or KC (2160 mg kC 3 times daily for 60 mEq/day)	Crossover	Citrate from lemonade increases urinary citrate	5 days
McHarg et al., 2003 [33]	RCT crossover	20 men without history of kidney stones	500 mL cranberry juice diluted in 1500 mL tap water	Crossover	Cranberry juice may have antibacterial properties that inhibit attachment	2 weeks

(*continued on next page*)

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Table 1 (*continued*)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
					of CaOx crystals and stone-forming bacteria	
Penniston et al., 2007 [32]	Non-RCT	Patients with CaOx stone formation with three or more clinic visits from 1996 to 2005 and three or more UroRisk profiles (LT alone [n=63]; LT and KC [n=37]).	LT: 4 ounces of lemon juice (5.9 g citric acid) diluted in water daily or 32 oz of low-sugar or sugar-free lemonade daily; LT and KC (20—90 mEq/day, mean dose 40 mEq/day)	LT and KC	Citrate from lemonade increases urinary citrate	40 months
Rodgers et al., 2014 [35]	Pre- and post-intervention	8 healthy subjects	1200 mg/day malic acid	Pre-intervention	Malic acid increases urinary citrate excretion by inducing systemic alkalinization	7 days
Siener et al., 2011 [37]	Pre- and post-intervention	15 healthy subjects	900 mg EPA and 600 mg DHA daily	Pre-intervention	Possibly decreased cellular oxalate exchange attributable to an altered fatty acid pattern of membrane phospholipids with concomitant changes in oxalate transporter activity	5 days
Siener et al., 2016 [38]	Pre- and post-intervention	12 healthy subjects	Standardized diet for 6 days, then 1500 mg L-methionine on Day 6	Pre-intervention	Urinary sulfate from metabolized L-methionine binds to urinary Ca, decreasing the supersaturation of CaOx	6 days
Trinchieri et al., 2002 [34]	Non-RCT	7 healthy subjects	20 mL/kg body weight over 60 min of soft drink containing grapefruit juice	Cross over	Grapefruit juice increases urinary citrate and Mg	One-time treatment, urine collection for 180 min afterwards

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Table 1 (continued)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
			diluted (10%) in mineral water			
Yasui et al., 2008 [36]	Pre- and post-intervention	29 patients after therapy for nephrolithiasis	Highly purified preparation of 1800 mg/day EPA	Pre-intervention	EPA modification of membrane phospholipid compositions decreases cellular oxalate exchange and affects oxalate transporter activity in the body	Exposure 36.4±22.0 (mean±SD) months, observed over 8 years
Micronutrients						
Ettinger et al., 1976 [48]	Double blinded RCT	71 recurrent CaOx stone formers	1.4 g/day elemental phosphorous in form of potassium phosphate ($n=25$) vs. low Ca diet only ($n=26$)	Placebo ($n=20$)	Phosphorous and its metabolic products may reduce CaOx crystallization in urine	2.9 years
Gershoff et al., 1967 [41]	Pre- and post-intervention	36 patients who had formed ≥ 2 CaOx stones during 2 years prior to enrolment in study	PO MgO 100 mg OM and PO pyridoxine (vitamin B6) 10 mg OM	Pre-intervention	Mg may decrease urinary oxalate excretion; pyridoxine may reduce oxalate excretion	5 years
Johansson et al., 1982 [39]	Non-RCT	55 patients with recurrent Ca stone disease without Mg deficiency (41 males and 14 females)	500 mg Mg^{2+} in $Mg(OH)_2$	43 recurrent Ca stone formers without medical therapy (35 Males and 8 Females)	The solubility product of Mg oxalate is greater than CaOx; increased Mg excretion and unchanged Ca excretion decrease the likelihood of crystallization, aggregation and stone growth as a result of increased Mg/Ca ratio; Mg also increases urinary citrate	Up to 4 years
Lindberg et al.,	Pre/post intervention	Normal ($n=7$);	(1) Mg citrate QDS	Pre-intervention	Mg binds to oxalate in	2 weeks

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Table 1 (continued)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
1990 [40]		recurrent CaOx nephrolithiasis with low or low normal urinary Mg ($n=4$)	without food (10 mEq); (2) MgO QDS without food (10 mEq).		the gastrointestinal tract, reducing dietary oxalate absorption, and forms soluble complexes with oxalate in urine to lower urinary saturation of CaOx	
Lu et al., 2022 [45]	RCT open label	Patients with proven CaOx stones ($n=58$ [total]); mineral water group ($n=32$)	1.25 L bicarbonate-rich mineral water	Plain water group ($n=26$)	Mineral water rich in bicarbonate may favorably increase Mg and citrate excretion	12 weeks
Moyad et al., 2009 [47]	Double-blinded RCT crossover	50 healthy adults	Vitamin C with metabolites (Ester-C) vs. 1000 mg/day for 5 days and 2000 mg/day for an additional 5 days	Crossover	Ester C formulation contains several metabolites and is bound to Ca in a non-acidic formulation; Ca reduces dietary oxalate absorption and urinary oxalate	10 days
Prien et al., 1974 [42]	Pre- and post-intervention	3 groups: (1) 4—5-year history of stones before starting therapy; (2) 4—5 year history of stones before therapy but unable to recover stones and had symptoms of stone disease; (3) study dropouts with 3 years or less of treatment	300 mg MgO and 10 mg pyridoxine daily	Pre-intervention	Mg has solubilizing effect on urine; MgO reduces excretion of oxalate; pyridoxine also increases solubilizing tendency of urine	6 years
Rodgers 1997 [43]	Crossover RCT	CaOx stone formers (20 males and 20 females)	1.5 L Vittel mineral water for 3 days	20 male 20 female non-stone formers	Synergistic effect of high Ca, Mg, and water intake reduces urinary	3 days

Table 1 (*continued*)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
					CaOx supersaturation; Ca binds to oxalate in the gastrointestinal tract to decrease urinary oxalate excretion	
Rodgers 1998 [44]	Crossover RCT	CaOx stone formers (24 males and 7 females)	1.5 L mineral water for 3 days, either Schoonspruit or Caledon	27 male and 27 female non-stone formers	Mineral water contains relatively high concentrations of Ca and Mg; Ca binds to free oxalate in the gastrointestinal tract to reduce the absorption of dietary oxalate; Mg reduces supersaturation of CaOx	3 days
Enzymes and probiotics and others						
Langman et al., 2016 [52]	Double-blinded RCT crossover study, Phase I study	30 healthy volunteers with hyperoxaluria induced by ingestion of high oxalate low Ca diet	ALLN-177 (7500 units/meal, 3 times/day) derived from recombinant oxalate de-carboxylase enzyme in *Bacillus subtilis* and expressed in *Escherichia coli*	Placebo	ALLN-177 is an oral formulation of recombinant microbial enzyme oxalate decarboxylase, which degrades dietary oxalate in the gastrointestinal tract to reduce dietary oxalate absorption and subsequently urinary excretion	7 days
Lieske et al., 2010 [50]	Double blinded RCT	40 patients with mild hyperoxaluria, idiopathic CaOx stone formers (all were subjected to	Agri-King Synbiotic preparation ($n=12$) or probiotic (Oxadrop; $n=14$)	Placebo ($n=14$)	Probiotics increase oxalate metabolism	1 week

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Table 1 (*continued*)

Therapeutic category (study)	Study design	Population	Intervention	Comparator group	Theoretical mechanism	Study follow up period
		controlled diet)				
Lieske et al., 2005 [49]	Non-RCT	10 patients with chronic fat malabsorption, CaOx stones, and hyperoxaluria	Increasing doses of lactic acid bacteria mixture (Oxadrop): 1 month, 1 dose per day; 2 nd month, 2 doses per day; 3rd month, 3 doses per day	Crossover	Intestinal microbiota utilize oxalate to limit intestinal oxalate absorption	3 months
Tavasoli et al., 2021 [51]	Double blinded RCT	Recurrent Ca stone formers with hyperoxaluria	Probiotic supplement (*n*=34)[b]	Placebo (*n*=30)	Intestinal microbiota utilize oxalate to limit intestinal oxalate absorption	4 weeks

TDS, thrice daily; Ca, calcium; CaOx, Ca oxalate; EHDP, ethane-1-hydroxy-1,1-diphosphonate; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP1, glucagon-like peptide 1; BD, twice daily; GAG, glycosaminoglycan; RCT, randomized controlled trial; ESWL, extracorporeal shockwave lithotripsy; CCB, Ca channel blocker; PO, per oral; OM, once morning; WLS, Wu Ling San; KC, potassium citrate; LT, lemonade therapy; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Mg, magnesium; MgO, Mg oxide; MgOH, Mg hydroxide; CFU, colony-forming unit; OD, once daily; QDS, take four times daily; EHDP, ethane 1-hydroxy-1, 1-diphosphonate; SD, standard deviation; SPP, sodium pentosan polysulphate.

[a] Five herbs were *Rhizoma alismatis, Poria cocos Wolf, Polyporus umbellatus Fries, Rhizoma Atractylodis Macrocephalae,* and *Ramulus Cinnamomi Cassiae*; the weight of each is in a ratio of 4:3:3:3:2.

[b] Each capsule of the supplement contained 1.8×10^9 CFU of the following species *Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium bifidum*, and *Bifidobacterium longum*. with the ratio of 1:1:1:1, 2 caps OD dose.

Table 2 Urinary parameters of included studies.

Study	Therapy	Urinary calcium	Urinary pH	Urinary citrate	Urinary oxalate	Urinary magnesium	Urinary sodium	Urinary volume	Urinary uric acid	CaOx supersaturation	Other parameters
Backman et al., 1980 [21]	Cellulose phosphate	↓***	NA	NA	NA	↓***	NA	NA	NA	NA	NA
Baumann et al., 1978 [24]	EHDP	NA	NS	NA	↑***	NA	NA	NS	↑***	NA	NA
Cheungpasitporn et al., 2016 [15]	Tolvaptan	NS	NS	NS	↑***	NS	NA	↑***	NS	↓***	NA
Hemal et al., 1989 [22]	Diclofenac	NS	NA	NA	NA	NA	NA	NS after 4 weeks	NS	NA	24 h urinary excretion of GAGs ↓***; urinary concentration of GAGs ↓***
Kristensen et al., 2021 [14]	SGLT2i	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Norman et al., 1984 [25]	Pentosan polysulfate	NS	NS	NA	healthy: ↓* SF: NS overall: NS	NA	NA	NS	NS	NA	NA
Okada et al., 2008 [17]	Bisphosphonates	↓ in pamidronate*	NA	NA	NA	NA	NA	NS	NA	↓ in pamidronate*	NA
Okonkwo et al., 2013 [20]	Sodium thiosulfate	NS	↓** in both SF and NSF	↓* in hypercalciuric SF	NS	NS	NS	NS	NA	NS	NA
Ruml et al., 1995 [16]	Alendronate	↓**	NS	NS	NS	NS	NA	NA	NS	↓**	Urinary ammonium ↓**
Sarica et al., 2006 [19]	Verapamil	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Smith 1975 [23]	Methylene blue	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yasui et al., 2008 [36]	Alendronate	NS	NS	NS	NS	NS	NA	NS	NA	NA	AP (CaOx) index NS; serum Ca ↓*; serum PO4 ↓*; serum uric acid NS; serum Cr NS
Erickson et al., 2011 [26]	Cystone	NS	NS	NS	NS	NS	NS	NS	NS	NS	NA
Lin et al., 2013 [27]	Wu Ling San	NS	NS	NA	NA	NA	NA	↓*	NS	NA	NA
Pucci et al., 2018 [28]	Phyllanthus niruri	NS	NS	NS	Hyperoxaluric patients: ↓**	NS	NS	NS	Hyperuricosuric patients ↓**	NA	NA
Ebisuno et al., 1986 [30]	Rice bran	↓***	NA	NA	↑*	NS	NA	NS	NS	NA	NA
Fakier et al., 2020 [29]	Phytate	NS	NS	NS intragroup difference after treatment for B but p<0.05 at Day 18 for White participants	NS	NS	NS	NS	NA	NA	NS in MSL and crystallization kinetics
Koff et al., 2007 [31]	Lemonade therapy	NA	LT NS, KC ↑***	Overall: KC ↑**, LT NS; hypocitraturia patients: LT NS, KC NS	NA	NA	NA	LT NS, KC ↓*	NS	NA	NA
McHarg et al., 2003 [33]	Cranberry juice	↓**	↓*	↑**	↓***	NS	NS	↓***	NA	↓***	PO4 ↓* compared to control and NS compared to water; CaOx MSL ↑** compared to control but NS compared to water

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Table 2 (continued)

Study	Therapy	Urinary calcium	Urinary pH	Urinary citrate	Urinary oxalate	Urinary magnesium	Urinary sodium	Urinary volume	Urinary uric acid	CaOx supersaturation	Other parameters
Penniston et al., 2007 [32]	Lemonade therapy	NA	↑** in both groups	LT group as well as LT and KC group: maximal change both ↑***; LT group: sustained change NS; LT and KC group: sustained change ↑***	NA	NA	NA	↑*** for LT group as well as LT and KC group	NA	NA	NA
Rodgers et al., 2014 [35]	Malic acid	NS	↑*	↑**	NS	↑**	NS	NS	NA	NS	NA
Siener et al., 2011 [37]	n-3 fatty acid	NS	NS	NA	↓** after 30 days of supplementation	NS	NS	NS	NS	NS	NA
Siener et al., 2016 [38]	ʟ-methionine	NS	↓**	NS	NS	NS	NS	↓*	NA	NA	CaOx RS NS
Trinchieri et al., 2002 [34]	Grapefruit juice	NS	NS	NS	NS	NS	NS	↑*** for treatment; ↑*** for mineral water	NA	NS	NA
Yasui et al., 2008 [36]	n-3 fatty acid	NS	NA	NA	NA	NS	NA	NS	NS	NA	NA
Ettinger 1976 [48]	Phosphate	↓ attributed to restriction of dietary calcium alone (no p-value)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gershoff and Prien 1967 [41]	MgO and vitamin B6	↑***	NA	↑**	NS	NS	NA	NA	NA	NA	NA
Johansson et al., 1982 [39]	MgOH	NS	NA	↑*	NA	↑***	NA	NA	NA	NA	NA
Lindberg et al., 1990 [40]	Mg citrate and MgO	↑*	NS	↑*	NS	↑*	NA	NA	NA	NS	NA
Lu et al., 2022 [45]	Mineral water	NS	↑ (95% CI 0.149 −0.804)	NS	NS	↑ (95% CI 1.01, 2.781)	NS	↑ (95% CI 206.7, 1081.3)	NA	NA	Tiselius index NS
Moyad et al., 2009 [47]	Vitamin C with metabolites	NA	NA	NA	NS	NA	NA	NA	NA	NA	NA
Prien et al., 1974 [42]	MgO and B6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rodgers, 1997 [43]	Mineral water	Male ↑*; female ↑**	NA	NS	NS	Male ↑***; female NS	NA	NA	NA	CaOx stone former MSL: ↑* (male); NS (female)	NA
Rodgers, 1998 [44]	Mineral water	NA	NS	Male: ↑*	Male ↓* for both Caledon and Schoonspruit; female ↓* for Schoonspruit	Male ↑* for Schoonspruit; female NS	NA	Male ↑* for Schoonspruit and Caledon	NA	NA	Male risk index ↓* for Caledon and Schoonspruit; CaOx RS ↓** for Caledon and Schoonspruit; female risk index and CaOx RS both ↓* for Schoonspruit, however NS change for Caledon
Langman et al., 2016 [52]	ALLN-177	NS	NS	NS	↓***	NS	NA	NS	NS	NA	NA

(continued on next page)

Table 2 (continued)

Study	Therapy	Urinary calcium	Urinary pH	Urinary citrate	Urinary oxalate	Urinary magnesium	Urinary sodium	Urinary volume	Urinary uric acid	CaOx supersaturation	Other parameters
Lieske et al., 2010 [50]	Probiotic	NS	NS	Diet: ↓**; probiotics: NS	Diet: ↓***; probiotics: NS	NS	Diet: ↓**; probiotics: NS	NS	NS	Diet: ↓***; probiotics: NS	Oxalate-restricted diet
Lieske et al., 2005 [49]	Probiotic	NS	NS	NA	NS	NS	NS	NS	NA	NS	NA
Tavasoli et al., 2021 [51]	Probiotic	NS	NA	NS	↓* but NS to placebo	NS	NS	NA	NS	NS	NA

EHDP, ethane-1-hydroxy-1,1-diphosphonate; CaOx, calcium oxalate; Ca, calcium; Cr, creatinine; PO4, phosphate; LT, lemonade therapy; KC, potassium citrate; MSL, metastable limit; RS, relative supersaturation; NS, not significant; NA, not applicable; Mg, magnesium; MgO, magnesium oxide; MgOH, magnesium hydroxide; B6, pyridoxine; AP, activity product; CI, confidence interval; SF, stone former; NSF, non-SF; B, black; W, white.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

volume (4.8 L vs. 1.8 L, $p<0.001$), decrease urinary osmolality (204 vs. 529 mOsm/kg, 1 mOsm/kg = 1 mmol/kg, $p<0.001$) and decrease urinary supersaturation of CaOx (0.01 vs. 0.95 kJ/mol for 38 °C, $p<0.001$; dG = −deltaG, where deltaG is calculated in units of kJ/mol for 38 °C) in calcium stone formers. Notably, nearly half of the patients were already taking thiazides prior to enrollment.

Three studies investigated the effect of bisphosphonates on CaOx stone prevention. Ruml et al. [16] used a model of 21-day bedrest immobilization in 16 healthy male participants to artificially induce hypercalciuria. Fourteen days prior to bedrest, the participants were started on oral alendronate 20 mg/day, which was continued throughout the duration of the study. Urinary parameters such as calcium, oxalate, and citrate levels were recorded and used to calculate the urinary saturation of calcium oxalate. The use of alendronate was associated with a reduction in urinary calcium in both pre-bedrest (75 mg/day vs. 209 mg/day, $p<0.05$) and bedrest (121 mg/day vs. 267 mg/day, $p<0.05$) phases and reduced saturation of CaOx ($p<0.05$ for both pre-bedrest and bedrest), which was maintained throughout the 3-week bed rest period. No statistically significant differences in citrate or oxalate levels were recorded. In a similar study of bedrest immobilization, Okada et al. [17] investigated the prevention of calcium-related stone formation by pamidronate in healthy young men on 90 days of bed rest. Pamidronate was given 14 days prior to the initiation of bed rest. In the control group, urinary calcium excretion increased during bed rest and decreased toward the recovery period, while in the pamidronate group, urinary calcium excretion remained at a significantly lower level ($p<0.01$) until the late bed rest period. Urinary oxalate levels in both the control and pamidronate groups were stable, except for a significant increase from Day 90 of bed rest to Day 1 of the recovery period ($p<0.05$) before rapidly returning to baseline. CaOx supersaturation significantly decreased in the pamidronate group before the initiation of bed rest ($p<0.05$) and remained lower until Day 14 of bedrest. No stones were detected in the pamidronate group, while three patients in the control group developed stones by the end of the recovery period. However, the difference in stone incidence was not statistically significant (pamidronate vs. control; $p=0.48$). Researchers concluded that pamidronate may be useful for preventing renal stone formation during and after bed rest. Yasui et al. [18] investigated the ability of alendronate to prevent calcium stone formation in post-menopausal women with osteoporosis and a history of calcium-containing stones. Treatment with alendronate did not significantly change the urinary calcium, oxalate or phosphate concentration, or the ionic activity product of CaOx index, but did significantly reduce the activity product of calcium phosphate index (1.53 vs. 0.89, $p<0.05$).

A prospective study conducted by Sarica et al. [19] investigated the effect of verapamil on residual stone fragments and the stone-free rate (SFR) following shock-wave lithotripsy. Patients were categorized based on whether they were stone free or had residual stones post-extracorporeal shockwave lithotripsy (ESWL) and were allocated to the verapamil, high-fluid, or placebo group. For patients who were stone free post-ESWL, the SFR after long-term follow-up (4–6 years) in the verapamil group was

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60%, which was not significantly different from the placebo group ($p>0.05$). However, compared with those in the placebo and verapamil groups, 91.7% of the patients in the high-fluid group (urinary volume of >2.5 L) was stone free ($p<0.05$). In participants with residual-fragment post-ESWL, long-term SFRs were comparable between the verapamil and high-fluid groups (47% and 46.1%, respectively) and the long-term SFR was greatly improved compared with those in the placebo group (18%).

Okonkwo et al. [20] recruited five healthy volunteers and five hypercalciuric stone formers who were given sodium thiosulfate over a course of 7 days. Urine levels of sulfate and ammonium increased while urinary pH and citrate decreased in stone formers. Overall, no statistically significant change in CaOx supersaturation was observed.

A trial conducted by Backman et al. [21] revealed that cellulose phosphate decreased urinary calcium levels by 40% (8.40 mmol/24h *vs.* 5.20 mmol/24h, $p<0.001$) and decreased urinary magnesium levels (5.00 mmol/24h *vs.* 3.10 mmol/24h, $p<0.001$). This reduction in urinary calcium was more pronounced in patients with hypercalciuria, and the urinary magnesium/calcium ratio remained unchanged. The recurrence rate after 2 years of treatment with sodium cellulose phosphate was not significantly different from patients who did not receive any specific treatment. This study revealed that a high dropout rate was associated mainly with gastrointestinal side effects. In addition, two patients experienced acute arthralgia, which subsided gradually with the discontinuation of treatment.

A study by Hemal et al. [22] evaluated the effect of diclofenac-Na on patients with recurrent CaOx nephrolithiasis who were not hypercalciuric or hyperuricosuric. After 2 weeks of treatment, there was a significant decrease in urinary excretion (17.04 μmol$-$11.54 μmol, $p<0.001$) and concentration of glycosaminoglycans (10.77 μmol$-$6.03 μmol/L, $p<0.001$) without a reduction in urinary excretion of calcium. The authors concluded that the use of diclofenac in patients without hypercalciuria may increase the risk of stone formation.

A non-randomized clinical trial by Smith et al. [23] investigated the effects of methylene blue in recurrent stone formers. When supplemented with methylene blue, those who had prior uninfected stones had a lower recurrence rate of CaOx stones than individuals with prior infected stones (54% *vs.* 33% had no further stones during the five-year study).

A study conducted by Baumann et al. [24] investigated the use of ethane 1-hydroxy-1,1-diphosphonate (EHDP) in nine patients with idiopathic recurrent calcium stones. Surprisingly, urinary oxalate and uric acid levels increased after 12 months of therapy ($p<0.001$ for both) and returned to baseline by 12 months post-discontinuation of EHDP therapy. The urinary pyrophosphate concentration increased from the abnormally low to the normal range ($p<0.005$). The inhibitory effect of CaOx precipitation was not reported. Increased excretion of pyrophosphate was observed up to 12 months after EHDP therapy was discontinued. The mean rate of stone formation per patient per year decreased from 2.4 to 0.2 during treatment and remained low during the following 24 months of follow-up.

Sodium pentosan polysulfate (SPP) is a semi-synthetic glycosaminoglycan-like substance. In a study by Norman et al. [25], oral administration of SPP in 16 subjects resulted in an overall increase in the polyanionic inhibition of CaOx crystallization in urine, as measured by zeta potential ($+1.5$ mV, 8% compared to pre-treatment, $p<0.01$), and a non-significant decrease in urinary oxalate (0.06 mmol compared to pre-treatment). However, when the participants were stratified, the inhibitory effects of SPP were significant only for healthy control participants ($n=6$) and not for stone formers ($n=8$) or patients with primary hyperoxaluria ($n=2$). This study was limited by its small sample size and lack of correlation with clinically significant stones.

3.3.2. Herbal supplements

Three supplements that met the inclusion criteria for our review were Cystone®, *Wu-Ling-San* (WLS), and *Phyllanthus niruri*.

Cystone® is an herbal blend that is composed of shilapuspha (*Didymocarpus pedicellata*), Pasanabheda (*Bergenia ligulata*), Manjishtha (*Rubia cordifolia*), Nagarmusta (*Cyperus scariosus*), Apamarga (*Achyranthes aspera*), Gohija (*Onosma bracteatum*), Sahadevi (*Vernonia cinerea*), Shilajeet (purified), and Hajrul yahood bhasma [26]. A study by Erickson et al. [26] revealed that Cystone® was not associated with alterations in urinary chemical parameters after short- or long-term usage. The total stone burden did not change significantly according to the use of the volumetric scoring system ($p=0.07$) or Agatston scoring system ($p=0.10$). The authors concluded that the study did not support the efficacy of Cystone for treating CaOx stone formers.

WLS is an herbal blend that contains *Rhizoma alismatis*, *Poria cocos Wolf*, *Polyporus umbellatus Fries*, *Rhizoma Atractylodis Macrocephalae* and *Ramulus Cinnamomi Cassiae*. Lin et al. [27] conducted a prospective study on patients with recurrent CaOx nephrolithiasis. WLS did not significantly affect the serum calcium, phosphate, sodium, potassium, creatinine, or uric acid levels. Urinary calcium and uric acid levels were also not significantly different from those of the placebo group.

Pucci et al. [28] investigated the effect of 12 weeks of supplementation with *P. niruri* (*P. niruri*) tea on serum and urinary electrolytes. Supplementation with the herb increased the magnesium/creatinine ratio (baseline *vs.* washout: 58.0 *vs.* 69.1, $p=0.01$) and the potassium/creatinine ratio (baseline *vs.* washout: 39.3 *vs.* 51.3, $p=0.008$). Urinary oxalate levels were lower in patients with hyperoxaluria (baseline *vs.* washout: 59.0 *vs.* 33.0; $p<0.001$). In addition, *P. niruri* decreased the number of stones in 38 patients (from 3.2 to 2.0; $p<0.001$), accounting for 67.8% of the cohort.

3.3.3. Food and macronutrients

A study in Cape Town, South Africa, queried 32 participants on diet [29]. The dietary intake of phytate was calculated, and during the test period of 18 days, all individuals were asked to restrict their intake of foods containing phytate and oxalate. Food diaries were obtained on Days 0, 15, and 18 to monitor nutritional intake. On Days 15$-$18, all the subjects were given a supplement containing 800 mg of phytate. The study found no changes in urinary risk factors for stone formation during the study.

Rice bran supplementation decreased urinary calcium levels ($p<0.001$), but increased urinary oxalate levels in hypercalciuric patients ($p<0.05$) [30]. Sixty-one patients with recurrent calcium stones who underwent treatment with rice bran for at least 1 year were monitored for stone formation. For this group, the frequency of new stone episodes decreased from 0.462 to 0.101 per patient-year before and after rice bran supplementation, respectively. A subset of these individuals were "active recurrent stone formers", defined as individuals who experienced more than two stone episodes in the previous 3 years. This group experienced a reduction in stone formation from 1.439 to 0.151 per patient-year. The study noted no side effects, and those who withdrew from the study found the rice bran unpalatable.

In 2007, Koff et al. [31] compared lemonade with added sweetener to lemonade with potassium citrate for increasing urinary citrate concentration. In this crossover study, 24-h urine parameters were measured in 21 patients with recurrent renal stones after each intervention. Intervention with lemonade did not significantly increase urinary citrate levels compared to potassium citrate (446 mg/day vs. 583 mg/day, $p<0.01$ for potassium citrate). Overall, there was no statistically significant difference in urinary parameters between patients receiving lemonade therapy and those receiving potassium citrate therapy, suggesting that lemonade therapy is noninferior to potassium citrate therapy. In addition, the low side effect profile of lemonade may be favorable for patients unable to tolerate gastrointestinal side effects associated with potassium citrate. In the same year, a separate retrospective study by Penniston et al. [32] compared lemonade therapy alone versus lemonade and potassium citrate combination therapy in patients with recurrent CaOx stone formation. One hundred participants who had three or more visits to the study's stone clinic and three UroRisk profiles were identified. Both groups noted an increase in urinary citrate of 203 mg/day in the lemonade-only group and 346 mg/day in the lemonade and potassium citrate groups ($p<0.001$ for both).

Twenty healthy male volunteers without any history of kidney stones were given either cranberry juice or tap water for 2 weeks, followed by washout for 2 weeks, then crossed over [33]. After treatment with cranberry juice, participants' urinary oxalate excretion decreased to 0.11 mmol/24 h compared to both baseline and tap water (both 0.16 mmol/24 h, $p<0.001$). Urinary citrate concentration was greater in the cranberry juice group (3.72 mmol/24 h) than those in the control (2.83 mmol/24 h, $p<0.01$) and water (2.55 mmol/24 h, $p<0.001$) groups. The urinary volume increased in both the tap water and cranberry juice regimens (both $p<0.001$ compared to baseline but the p-value was not significant between water and cranberry juice), and the calcium concentration decreased ($p<0.05$ and $p<0.01$ compared to baseline, respectively; the p-value was not significant between water and cranberry juice).

Healthy individuals ($n=7$) with no history of stone formation participated in a crossover study in which the initial therapy consisted of a single dose of soft drink containing sweetened grapefruit juice diluted in mineral water in a fasting state; then, the patients underwent a washout period of 1 week and subsequently underwent an oral load with mineral water alone for comparison [34]. The results showed an increase in urine volume in both the grapefruit juice and

mineral water arms ($p<0.05$ and $p<0.01$, respectively). Urinary calcium, citrate, and oxalate concentrations were not significantly different in the grapefruit arm.

Malic acid was studied in eight healthy subjects who ingested 1200 mg/day of malic acid for 7 days [35]. Analysis of the urinary samples revealed statistically significant increases in pH (6.48 vs. 6.13, $p<0.05$) and urinary citrate concentration (3.42 mmol/24 h vs. 2.18 mmol/24 h, $p<0.01$). No side effects were reported.

Yasui et al. [36] investigated the relationship between the consumption of n-3 polyunsaturated fatty acids found in fish or fish oil and the risk of kidney stone formation. The study period was divided into three phases: phase 1 consisted of the first clinical encounter and the initiation of eicosapentaenoic acid (EPA); phase 2 was the period during which the EPA was administered; and phase 3 was the end of the EPA administration and the end of the follow-up study. Twenty-nine patients who were known CaOx stone formers and had been treated with EPA for more than 24 months were included. The incidence rates were 0.23 episodes/year, 0.07 episodes/year, and 0.17 episodes/year for Phases 1, 2, and 3, respectively. The incidence of nephrolithiasis was significantly lower in Phase 2 than before and after the administration of EPA (both $p<0.05$). A separate study by Siener et al. [37] investigated the role of docosahexaenoic acid and EPA in preventing CaOx stones. Thirty days of supplementation was associated with a 23% reduction in the relative supersaturation of CaOx ($p=0.023$), which was attributed to a significant decrease in urinary oxalate excretion ($p=0.006$).

A German study on the administration of L-methionine included 12 healthy male subjects with no prior history of stone formation [38]. Urinalysis revealed no changes in urinary calcium excretion compared to that in the control group.

3.3.4. Micronutrients
A non-randomized clinical trial by Johansson et al. [39] investigated the use of magnesium hydroxide in recurrent calcium stone formers compared to controls. In the recurrent stone formers, the urinary magnesium calcium ratio and urinary citrate concentration increased at 24 months after therapy and approached the corresponding values in healthy individuals without stone disease (0.69–1.05, $p<0.01$ and 2.6 to 3.0, $p<0.01$, respectively). There was no significant change in urinary calcium. During treatment, the mean stone removal rate decreased from 0.8 stones/year to 0.08 stones/year. Of patients who were followed up for more than 4 years, 86% remained stone free whereas 59% of patients in the control group developed stones during the same period. In another trial by Lindberg et al. [40], magnesium citrate and magnesium oxide were both associated with a significant increase in urinary magnesium and citrate (both $p<0.05$). Urinary calcium also increased (both $p<0.05$). When magnesium citrate was given with meals, an additional statistically significant increase in urinary citrate was observed compared to that in the magnesium citrate treatment without meals ($p<0.05$). Furthermore, both urinary oxalate and urinary CaOx saturation were reduced by magnesium citrate supplementation together with meals (both $p<0.05$). Gershoff et al. [41] conducted a trial with 36 patients who had two or more CaOx stones formed within 2

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years prior to enrollment in the study. The patients were given 100 mg of magnesium oxide and 10 mg of pyridoxine once daily over the course of 5 years. They found that this supplementation regimen increased urinary citrate levels ($p < 0.01$) and increased urinary calcium levels ($p < 0.001$), without any statistically significant increase in urinary magnesium. Furthermore, 30 out of 36 patients showed no recurrence or decreased recurrence of stone formation compared to prior supplementation. A follow-up study by the same group, Prien et al. [42], investigated the use of magnesium oxide with pyridoxine combination therapy on 265 calcium stone formers over 5 years. Among the 149 patients who had an accurate count of the number of stones formed while on the supplement, the average number of stones per year decreased from 1.3 to 0.1 while on magnesium oxide and pyridoxine supplementation. In 18 patients who did not recover stones and had symptoms while on medication, they reported milder symptoms of ureteral colic than did previous pre-treatment stone episodes. A total of 98 patients dropped out within 3 years, with the majority being lost to follow-up. Researchers concluded that magnesium oxide and pyridoxine combination therapy was effective at preventing the recurrence of idiopathic CaOx stones.

In two separate studies, South African researchers Rodgers et al. [43,44] explored several different mineral waters containing calcium and magnesium on known risk factors for CaOx stone formation. In both studies, mineral water rich in calcium and magnesium (Schoonspruit and Caledon) positively influenced urinary parameters for the prevention of CaOx stone formation (Table 2), with greater benefit for male CaOx stone formers. A study by Lu et al. [45] examined differences in the urinary parameters of CaOx stone formers who were given either mineral-rich water or plain water. After 12 weeks, patients who drank mineral water had overall greater urinary volume (difference 644.0 mL/24 h; 95% CI [206.7, 1081.3]), urinary Mg (difference 1.89 mmoL/24 h; 95% CI [1.01, 2.78]), and pH (difference 0.48; 95% CI [0.15, 0.80]). There was no significant difference noted in urinary oxalate or urinary citrate levels. The authors concluded that drinking carbonate-rich mineral water was associated with increased urinary excretion of citrate and Mg and modest urinary alkalinization when compared to patients drinking plain water. There was no significant change in CaOx saturation.

Vitamin C supplementation is associated with hyperoxaluria, as it produces oxalate as its primary metabolite [46]. A RCT by Moyad et al. [47] revealed that there was an overall non-significant decrease in the urine oxalate concentration from baseline to 10 days after treatment with vitamin C with metabolites (Ester-C) compared to the non-significant increase in the ascorbic acid group. Other urinary parameters related to kidney stone formation were not reported.

A study in 1976 revealed that potassium phosphate prophylaxis was not associated with any change in the stone passage rate in patients with recurrent CaOx stones [48].

3.3.5. Enzymes and probiotics

In one study, researchers found that patients with chronic fat malabsorption, CaOx stones, or hyperoxaluria secondary to iatrogenic or pathological causes had reduced urinary oxalate levels when supplemented with lactic acid bacilli probiotics (Oxadrop) for up to 5 months [49].

In another study, researchers used two formulations of lactic acid bacilli probiotics (Oxadrop and Agri-King Synbiotic) to assess changes in urinary oxalate levels in patients with mild hyperoxaluria [50]. They found that dietary restriction of oxalate alone was effective, with no additional benefit from probiotic supplementation. Similarly, a study by Tavasoli et al. [51] revealed that probiotic consumption did not decrease urinary oxalate levels.

ALLN-177 is a recombinant oxalate decarboxylase enzyme obtained from *Bacillus subtilis* and expressed in *Escherichia coli*. A phase I trial revealed that, compared with placebo, ALLN-177 supplementation at 7500 units per meal three times daily was associated with a decrease in the urinary oxalate concentration of 11.6 ± 2.7 mg/day ($p < 0.001$) in a group of 30 healthy volunteers [52].

3.4. Stone formation rates and definitions

Table 3 summarizes the definitions of new stone formation and the reported stone formation rates. Among the included studies, the radiographic modalities included plain X-ray [17,19,23,30,36,48], ultrasound [17,19,28], CT [19,26,28], and pyelography [23]. In some studies, clinical evidence has also been used for recording new stone events, such as the passage of stones [23,26,30,48] or renal colic [26,36]. Definitions of stone formation typically required either clinical or radiographic evidence. Other infrequently used definitions included the Agatston scoring system [26] and surgical removal of a new stone [30].

3.5. Quality assessment

For randomized studies, the risk of bias was generally low to moderate. Older studies prior to 2004 did not have a pre-published protocol prior to publication of results. For non-randomized studies, many of the older studies had serious or critical risks of bias across all domains, which raises concerns of study quality (Supplementary Tables 2 and 3).

4. Discussion

Herein, we contextualize our findings by reviewing the potential risks and benefits associated with the successful alternative interventions summarized above.

4.1. Medications

SGLT2is are used to treat type 2 diabetes mellitus. Exploratory analyses of RCTs of SGLT2i have indicated a 30%–50% reduction in stone events in patients with diabetes [53]. An observational study by Kristensen et al. [14] revealed SGLT2i to be superior to GLP1 agonists for preventing new stone formation events, which they postulated may be due to the SGLT2i effect of increased urinary flow and urine dilution secondary to osmotic diuresis. The nature of the study precluded the ability to compare stone episode rates to those of the placebo. In a meta-analysis of 15 000 patients on empagliflozin or placebo, incident urinary tract stone events (originally recorded as adverse

Table 3 Definitions of new stone formation and reported stone formation rates.

Study	Definition of new stone formation	Outcomes on the stone episode rate
Backman et al., 1980 [21]	Passage, removal, or radiographic visualization of a stone that was not seen on previous radiograph	- There was a 47% recurrence rate after 2 years, similar to patients without any specific treatment in historical controls - Cellulose phosphate appeared to have a reduction of mean stone episode rate as average number of stones decreased from 0.7 to 0.2 per year; control stone episode rate was not reported
Baumann et al., 1978 [24]	Passage, removal or radiographic visualization, or clinical evidence of new stone formation	- Average rate of stone formation per patient per year decreased from 2.4 to 0.2 during treatment with EHDP and remained low during the following 24 months follow-up
Kristensen et al., 2021 [14]	Incident nephrolithiasis, recorded as an inpatient or outpatient diagnosis of calculus of the kidney and ureter (*i.e.*, upper urinary tract stones not including bladder stones) in the Danish National Patient Registry	- Nephrolithiasis rate was 2.0 per 1000 person-years in SGLT2i initiators compared with 4.0 per 1000 person-years in GLP1 agonist initiators, with a rate difference of -1.9 per 1000 person-years (95% CI -2.8, -1.0) and an HR of 0.51 (95% CI 0.37, 0.71) - For recurrent nephrolithiasis ($n=731$ patient pairs), the rate difference was -17 per 1000 person-years (95% CI -33, -1.5) and the HR was 0.68 (95% CI 0.48, 0.97)
Okada et al., 2008 [17]	XR abdomen, US abdomen	- Kidney stone formation in 22.2% (control); 44.4% exercise group, no stones in the pamidronate group (exercise *vs.* control, $p=0.376$; pamidronate *vs.* control, $p=0.476$, exercise *vs.* pamidronate; $p=0.089$)
Sarica et al., 2006 [19]	XR (including renal tomography), US kidney	- Overall stone recurrence rate: 14% - Stone free after ESWL (Group 1 [verapamil]: 40%; Group 2 [urinary volume>2.5 L]: 8.3%; Group 3 [no intervention]: 55%; $p<0.05$ between Group 2 and the other two groups but $p>0.05$ between 1st and 3rd groups) - Residual stones after ESWL $<$ 5 mm (Group 1 [verapamil]: 20%; Group 2 [urinary volume $>$ 2.5 L]: 15.3%; Group 3 [no intervention] 64%)
Smith 1975 [23]	Plain abdominal XR; excretory pyelograms only if clinically warranted, passage of stones	- Among patients with the CaOx stones (excluding struvite stone formers): of those without initial UTI, 19/35 had new stones; of those with initial UTI, 5/15 had new stones - Overall for calcium oxalate stone formers: 46% reported no further stones; 20% reported improvement; 27% of infected stones reported benefit; no *p*-values reported
Erickson et al., 2011 [26]	CT scan analysis: volume and Agatston scoring, radiologist impression of stones and clinical events/spontaneous passage	- Mean total stone burden per kidney did not change significantly over this time period as assessed by the volumetric scoring system (93−114 mm^3; $p=0.07$

Table 3 (*continued*)

Study	Definition of new stone formation	Outcomes on the stone episode rate
		by matched pairs analysis) or the Agatston scoring system (108—136 Agatston units, $p=0.10$ by matched pairs analysis)
Pucci et al., 2018 [28]	US or CT	- Number of kidney stones decreased from 3.2 ± 2 to 2.0 ± 2 (mean$\pm$SD) per patient ($p<0.001$); 10 patients had no change in number of stones; 8 patients experienced an increase in the number of kidney stones
Ebisuno et al., 1986 [30]	Spontaneous passage of a new stone, the appearance of a new stone on serial XR, surgical removal of a new stone or clear growth in size of a pre-existing stone	- Of 61 with recurrent calcium stones and treatment of at least 1 year, stone formation rate decreased from 0.462 to 0.101 per patient year - Thirty-nine patients had experienced more than two stone episodes in the previous 3 years and were described as "active recurrent stone formers"; their stone formation rate decreased from 1.439 to 0.151 per patient year
Yasui et al., 2008 [36]	Stone recurrence by plain XR and stone passage episode and/or renal colic	- The incidence rates of nephrolithiasis (times/year) before, during, and after the administration of EPA were 0.2283, 0.0693 and 0.1742, respectively; the incidence rate of nephrolithiasis during the administration of EPA was significantly lower compared to those before and after its administration ($p<0.05$)
Ettinger et al., 1976 [48]	Stone passage and lithotomy, roentgenogram	- Group 1 (phosphate) stone passage reduced by 52% during treatment; Group 2 (placebo) stone passaged reduced by 93% during treatment; Group 3 (low-calcium diet) stone passage reduced by 51% during treatment
Johansson et al., 1982 [39]	Number of stones passed per patient per year	- The stone episode rate dropped from 0.8 to 0.08 per patient-year, while control stone episode rate dropped from 0.5 to 0.3 per patient-year only
Gershoff et al., 1967 [41]	Crystallographic examination of calculi	- Over 5 years, 30/36 patients showed no recurrence or decreased recurrence of stone formation
Prien and Gershoff 1974 [42]	Number of stones passed per patient per year	- The stone episode rate for treatment Group 1 decreased from 1.3 to 0.1; Group 2 recovered no stones but had stone symptoms, so were classified as "symptomatic failures"

XR, X-ray; US, ultrasound; SGLT2i, sodium-glucose co-transporter 2 inhibitor; GLP1, glucagon-like peptide 1; HR, hazard ratio; CI, confidence interval; EHDP, ethane 1-hydroxy-1, 1-diphosphonate; ESWL, extracorporeal shockwave lithotripsy; CaOx, calcium oxalate; f, urinary tract infection; EPA, eicosapentaenoic acid.

events in their respective cardiovascular RCTs) were analyzed [54]. Empagliflozin was associated with an incidence rate ratio of 0.64 (95% CI 0.48—0.86) when compared to placebo. According to the sensitivity analysis, the results were similar (incidence rate ratio 0.62; 95% CI 0.45—0.85]) in favor of empagliflozin. These results suggest that empagliflozin is beneficial for kidney stone prophylaxis, especially in patients with type 2 diabetes mellitus. An ongoing RCT (SWEETSTONE trial) is investigating the impact of empagliflozin on the urinary supersaturation of CaOx,

calcium phosphate, and uric acid in non-diabetic kidney stone formers [55]. The results of this study may broaden our understanding of the effect of SGLT2i on different stone types with or without urinary biochemical derangements. Future studies may include other SGLT2is to determine whether these observations are class effects. As the number of approved indications for SGLT2i has increased in recent years, its role in CaOx stone prophylaxis may be indicated, especially for diabetic populations.

Tolvaptan is a V2 receptor antagonist primarily used to treat euvolemic hyponatremia. A study by Cheungpasitporn et al. [15] demonstrated that this medication was able to increase patients' urine volume and decrease supersaturation of CaOx, despite many participants already receiving thiazide therapy. Previous studies have also shown that increasing urine volume decreases the activation product of CaOx, increasing the minimum supersaturation required for spontaneous CaOx nucleation and thereby decreasing CaOx stone formation [56]. Further studies on tolvaptan should explore the efficacy of tolvaptan supplementation, especially in patients who are resistant or unable to increase water consumption. Notably, one major limitation of the widespread adoption of this intervention is its risk of liver failure, which results in the need for monitoring liver enzymes when taking this medication [57].

Bisphosphonates are antiresorptive agents commonly used to treat osteoporosis. Ruml et al. [16] and Okada et al. [17] found that alendronate and pamidronate were associated with reduced CaOx supersaturation in healthy male volunteers on a bedrest protocol. Yasui et al. [18] reported no significant change in activity product of CaOx after 3 months of alendronate treatment in postmenopausal women. The same group also conducted a separate study in osteoporotic men without hypercalciuria with a history of calcium-containing stones [58]. In this group, urinary calcium excretion (162 mg/day to 116 mg/day; $p<0.05$) and activity product of CaOx were significantly reduced (1.55−0.89; $p<0.05$). These data suggest that bisphosphonates may reduce the risk of CaOx stone formation in select populations, such as those with prolonged immobilization and/or osteoporotic men. However, the results of these studies are limited by the small population size, short follow-up duration, and, in some cases, lack of placebo controls. Future studies could explore the use of bisphosphonates in known CaOx stone formers with hypercalciuria in both pre- and postmenopausal women.

Baumann et al. [24] suggested that EHDP may play a role in reducing overall stone episode rates secondary to increased pyrophosphate excretion; however, urinary risk factors for CaOx stones, such as urinary oxalate levels, were elevated. It is unclear from these studies whether the EHDP influences CaOx stone formation directly. Overall, larger and more comprehensive studies should be performed to assess the efficacy of EHDP as a medical prophylaxis for CaOx stones.

4.2. Herbal supplements

P. niruri is a common medicinal plant reported to have several possible benefits and is marketed internationally for several purposes, including the prevention of kidney stones [59]. A study by Pucci et al. [28] showed that hyperoxaluric patients had reduced urinary oxalate levels during and after *P. niruri* supplementation. Furthermore, the patients' total stone burden was significantly reduced. Two independent review papers found studies showing that *P. niruri* reduced urinary calcium in hypercalciuric patients and increased the SFR in patients who took *P. niruri* extract post-ESWL [60,61]. More recently, a study in 2018 showed that after 3 months of supplementation, patients with hyperoxaluria experienced a reduction in urinary oxalate [28]. Future studies should assess the role of *P. niruri* in CaOx stone prevention on a larger scale and whether the administration of *P. niruri* as a tea is necessary.

4.3. Food and macronutrients

Urolithiasis often results from electrolyte abnormalities, which are correlated with diet [62]. Dietary recommendations are often made based on urinary electrolyte abnormalities to decrease the rate of new stone formation. Similarly, we summarized our findings regarding potential novel dietary supplements for the prevention of calcium-based nephrolithiasis.

Fakier et al.'s study [29] was unable to provide sufficient evidence that phytate acts as a stone inhibitor, as there were no significant intra- or inter-group changes in urinary risk factors or stone formation parameters except for increased urinary citrate excretion in the white population post-supplementation. These findings challenge previous *in vivo* studies that have suggested phytate acts as a crystallization inhibitor in both intrapapillary tissue and urine [63] and that phytate can inhibit crystal aggregation kinetics in healthy male subjects [64]. Furthermore, the Nurses' Health Study II revealed that dietary phytate had a beneficial effect on kidney stone prevention [65]. These equivocal findings demonstrate the need for a high-quality RCT before being able to recommend this approach to patients for CaOx-related kidney stone prevention. Ebisuno et al. [30] reported that rice bran therapy was associated with a reduction in urinary calcium excretion and the frequency of stone episodes in hypercalciuric patients with calcium stones. The authors postulated that, like other cation exchange resins, phytin binds to calcium in the intestine, hence increasing oxalate excretion in the urine. In their long-term study of up to 94 months, urinary calcium was reduced, while urinary phosphate and oxalate were increased. The SFR was reduced from 0.721 to 0.120 events per patient-year; 61.2% of patients remained in remission during treatment [66]. Jahnen et al. [67] performed a comparative study with rice, soy, and wheat bran on healthy women on a standardized calcium-rich diet. Rice and soy bran were associated with decreased urinary calcium (both $p<0.01$); however, rice and wheat bran increased oxalate excretion. The authors postulated these results were partially attributed to the oxalate content of the brans. The relative supersaturation of CaOx was unchanged in this study. Overall, rice bran appears to be promising for calcium stone prophylaxis in the absence of hyperoxaluria.

Lemonade therapy alone (RealLemon lemon juice with water and sweetener) significantly improved urinary parameters, though not as much as when combined with potassium citrate therapy [32]. Similarly, Koff et al. [31] reported that lemonade therapy (diluted lemon juice or low-sugar lemonade) was able to increase urinary citrate and total urinary volume. A prospective, blinded crossover study by Cheng et al. [68] compared the effects of lemonade and diet lemonade on urinary risk factors for calcium stone formation. They observed increased urine volume with lemonade therapy; however, only diet lemonade was found to increase urinary citrate and reduce supersaturation of CaOx. The authors concluded that diet lemonade may be an effective low-calorie, low-sugar prophylactic therapy for CaOx stone formation. Another single-center study by Ruggenenti et al. [69] followed up with patients for more than 2 years while on lemon juice (60 mL, equivalent to 6 g of citric acid daily). One-year follow-up found that, after adjustment for age, sex, and citraturia status, participants who consumed lemon juice had a significant reduction in stone recurrence (HR 0.45, 95% CI 0.20–0.93; $p = 0.036$). However, the authors noted that adherence to treatment was poor, decreasing from 68% at the 1-year follow-up to 48% at the 2-year follow-up. Lemonade therapy is a promising alternative source of citrate that may be particularly useful for patient populations who prefer non-pharmacological methods for preventing kidney stones or who do not tolerate potassium citrate. A challenge associated with lemonade supplementation is the unpalatable taste of unsweetened lemon juice. However, the benefits of lemonade are diminished when sweeteners are added.

Cranberry juice has long been used as a remedy for urinary tract infections. McHarg et al. [33] showed that, in healthy individuals, urinary oxalate and CaOx supersaturation decreased, while urinary citrate increased. However, a separate study by Gettman et al. [70] revealed that cranberry juice increased the risk of CaOx stone formation by increasing urinary calcium, urinary oxalate, and supersaturation of CaOx in known CaOx stone formers. Both studies were limited by small sample sizes ($n = 20$ and $n = 24$, respectively) and short follow-up durations. Future studies should use McHarg's cranberry juice formulation in known CaOx stone formers to assess urinary parameters and possibly stone formation rates. Overall, cranberry juice appears to have questionable value in preventing both CaOx stones and recurrent urinary tract infections.

Rodgers et al. [35] reported that malic acid supplementation was associated with increased urinary citrate. However, the study's utility is limited by the small sample size ($n = 8$) and did not include any reports of stone formation rates. This study suggested that malic acid may be another promising therapy for the conservative management of kidney stones. Larger studies to assess the efficacy of these therapies in comparison to current gold standard therapies, such as potassium citrate therapy, may be useful.

Two studies on EPA supplementation were included in our analysis with promising findings [36,37]. Siener et al. [37] reported a reduction in both urinary oxalate excretion and relative supersaturation of CaOx during 30 days of supplementation with docosahexaenoic acid and EPA. Yasui et al. [36] reported a reduction in kidney stone formation risk in patients treated with n-3 polyunsaturated fatty acids for 24 months. However, Yasui et al.'s study [36] did not reveal any significant difference in urinary parameters, which challenges their previous study in which they found that EPA supplementation was associated with reduced urinary calcium [71]. The evidence for the association between polyunsaturated fatty acid (PUFA) supplementation and CaOx urinary risk factors is mixed. Isolated cases of other PUFAs, such as evening primrose oil containing the n-6 FAs linoleic acid and γ-linolenic acid, have also shown potential for producing favorable changes in urinary calcium [72], while a large prospective observational study using three cohorts (summative $n = 234\,426$) by Taylor et al. [73] reported that dietary PUFA intake alone was not consistently associated with the rate of development of kidney stones. Overall, larger prospective trials may be useful for confirming the association between n-3 fatty acid (such as EPA) administration and CaOx stone prevention.

4.4. Micronutrients

Micronutrients such as calcium and magnesium have been studied extensively in search of CaOx stone prophylaxis. While magnesium supplementation is usually well tolerated, it may cause gastrointestinal adverse effects such as diarrhea, nausea, and vomiting [74]. Many studies have explored the use of magnesium supplements, such as magnesium hydroxide, magnesium citrate, magnesium dioxide, and magnesium oxide-pyridoxine combination therapy, in various forms to prevent CaOx stone formation [39–42]. When taken with meals, both magnesium citrate and magnesium oxide supplementation increased urinary magnesium and citrate with concomitant decreases in urinary oxalate. In a larger study ($n = 256$), magnesium oxide-pyridoxine combination supplementation was associated with a decrease in stone formation, from 1.3 stones per patient-year to 0.10 stones per patient-year during therapy [42]. Magnesium hydroxide supplementation had similar results as magnesium citrate and magnesium oxide supplementation, with increased urinary magnesium, a magnesium/calcium ratio, and citrate [39,40]. Furthermore, over the course of the study, the mean stone rate per patient per year decreased tenfold from 0.8 to 0.1 stones per patient per year during treatment during treatment compared to control (0.5–0.3 stones per patient year) [39]. In 2005–2006, according to the National Health and Nutrition Examination Survey, both pediatric and adult populations consumed magnesium at levels less than the estimated average requirements (22%–89% depending on age group and sex category) [75]. Given the beneficial effects of magnesium supplementation on CaOx stone risk, the safe risk profile of supplementation, and the fact that many adults are likely to be magnesium deficient, it may be beneficial to consider magnesium supplementation for the reduction of CaOx stone formation.

Researchers in South Africa have explored the effects of several different mineral waters containing calcium and magnesium on known risk factors for CaOx stone formation [43,44]. In both studies, mineral water rich in calcium and magnesium was superior to tap water in favor of adjusting urinary parameters for CaOx stone formation, with greater

benefit for male CaOx stone formers. However, a recent study by Lu et al. [45] examined differences in the urinary parameters of CaOx stone formers who were given either mineral-rich water or plain water and observed only transient differences in urinary parameters. The evidence for the effectiveness of mineral waters in improving the urinary parameters of CaOx stone formers appears inconclusive, which may be due to the differences in ionic concentrations between the mineral water brands used in these studies. Nonetheless, larger studies using mineral water formulations that have shown favorable effects on urinary parameters in preliminary studies should be pursued.

4.5. Enzymes and probiotics

Several probiotics and enzymes have been shown to reduce the risk of CaOx stones through increased oxalate metabolism and/or decreased dietary oxalate absorption. Of the studies selected for this review, none of the probiotics were able to confer an additional reduction in urinary oxalate beyond what dietary restriction achieved [49−51]. However, in the phase I trial of ALLN-177, urinary oxalate levels were reduced in healthy volunteers. Future studies on CaOx stone formers with hyperoxaluria may be promising.

5. Limitations

There are several limitations to our study. First, older studies often have ambiguous methodologies and results, causing difficulty in extraction and analysis. Often, studies would only report select urinary risk factors, which may have led to premature conclusions about the clinical efficacy of the therapy of interest.

Many of the studies included in our analysis were non-RCTs, such as prospective cohort studies. Furthermore, some studies did not include comparator groups or placebo controls, which limits the ability to draw meaningful conclusions, especially from studies with small sample sizes.

With respect to the population, many of the included studies' populations were either healthy participants, specific subgroups of CaOx stone formers, or had mixed stones (such as mixed calcium phosphate and CaOx). The heterogeneity of the studied populations limits the generalizability of the results of the included studies. Furthermore, the study sample sizes were small, which increases the possibility of erroneous conclusions regarding therapeutic efficacy.

We found little consensus on the definition of new stone formation, which makes comparisons across studies challenging. The included studies measured stone progression by either an imaging modality (*e.g.*, X-ray, ultrasound, CT) and/or stone events based on a combination of symptoms, surgery, or passed stones.

While our review has been conducted to be systematic and exhaustive, we note that only nine studies in our analysis have been published in the last 10 years. In addition, 13 of the included studies have been published before 2000. These findings highlight the lack of recent robustly designed and executed clinical trials for the prevention of CaOx stones, which raises the concern of insufficient new

evidence to advance the preventative therapies used to treat recurrent stone formers. Furthermore, many of these older studies were assessed to have serious or critical risk of bias that may have compromised the integrity of the study findings.

Finally, there is the risk of positive results bias, wherein it is easier to obtain a novel treatment published if it has a statistically significant finding but more challenging if there was a null finding, which may lead to the overestimation of the efficacy of the treatments described.

6. Conclusion

We believe this is the first report that provides a comprehensive review of promising non-guideline-approved therapeutic interventions for the prevention of CaOx stones. In this review, we identified several categories of therapeutics that have been studied for CaOx stone prevention but are not currently included in the AUA guidelines, including pharmacotherapy, herbal supplements, macronutrients, micronutrients, and probiotics. Several studies have demonstrated promising improvements in abnormal urinary parameters, while many popular traditional remedies have been shown to adversely influence the risk of CaOx stone formation. In the right settings, medications such as SGLT2i, tolvaptan, and bisphosphonates are promising medical therapies for CaOx stone prevention. Non-pharmacological therapies such as *P. niruri*, rice bran, unsweetened lemonade, malic acid, n-3 fatty acids, and magnesium supplementation have also shown promising results that warrant further investigation. We suggest evaluation of these studies for possible integration into clinical practice guidelines to supplement and augment the existing armament of preventative therapies for recurrent CaOx stone formers. Furthermore, we recommend standardization of the definition of kidney stone formation in the context of stone prevention.

Author contributions

Study concept and design: Christopher YZ Lo, Jonathan Katz, Roger L Sur.
Methodology: Christopher YZ Lo, Victor A Abdullatif.
Data acquisition: Christopher YZ Lo, Qian Hui Khor, Victor A Abdullatif, Cesar Delgado.
Data analysis: Christopher YZ Lo, Victor A Abdullatif, Qian Hui Khor.
Drafting of manuscript: Christopher YZ Lo, Qian Hui Khor, Victor A Abdullatif, Cesar Delgado, Yadong Lu.
Critical revision of the manuscript: Christopher YZ Lo, Jonathan Katz, Roger L Sur, Yadong Lu.
Visualization: Christopher YZ Lo, Qian Hui Khor, Victor A Abdullatif.
Supervision: Jonathan Katz, Roger L Sur.
Project administration: Jonathan Katz, Roger L Sur.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2024.04.006.

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