

DOSSIER · SUBSTANCE

Oxalate

Oxalate is a plant constituent and at the same time an end product of human metabolism; research on it is predominantly stone and hyperoxaluria research. The most cited contribution in the field is not a study on oxalate, but the approval overview of a drug against primary hyperoxaluria. This page classifies which questions have been tested in controlled trials and which remain open.

404

STUDIES IN
TOTAL

132

IN HUMANS

14

OF WHICH
CONTROLLED

39

IN ANIMALS

50

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Oxalate at a Glance

ORIGIN:

Oxalate is the salt form of oxalic acid and occurs in the body from two sources: as a component of plant foods and as a metabolic product. Several studies describe endogenous formation from glyoxylate, predominantly in the liver. In urine, oxalate occurs predominantly as the calcium salt, which is why research focuses mainly on calcium oxalate crystals and the conditions of their formation in the kidney and urinary tract.

EVIDENCE BASE:

404 evaluated studies · 14 controlled human studies · 118 observational studies · 27 review articles · 39 animal studies · 43 cell culture studies

STRONGEST EVIDENCE:

- Efficacy: Meta-analysis [53] on thiazides, citrates, uric acid formation inhibitors and magnesium in calcium oxalate stones — stone recurrence rate risk ratio 0.47 (95 % CI 0.35–0.63).
- Metabolism: The meta-analysis [54] pools five randomised studies with 208 patients on Oxalobacter formigenes in primary hyperoxaluria and shows no benefit for plasma and urinary oxalate.
- Metabolism: In the crossover study [57], empagliflozin lowered relative supersaturation for calcium phosphate (–36 %; 95 % CI –48 % to –21 %) in 53 adults with calcium stones, but not for calcium oxalate.
- Further investigations: The meta-analysis [62] on thiazide diuretics versus placebo in hypercalciuric recurrent nephrolithiasis found a lower recurrence rate (risk ratio 0.63; 95 % CI 0.49–0.83; I² = 65 %).
- Metabolism: ILLUMINATE-A [64] tested lumasiran in primary hyperoxaluria type 1 for up to 60 months in 39 patients; sustained reductions in 24-hour urinary oxalate were observed in both groups.

LIMITATIONS:

- For empagliflozin, studies with clinical recurrence endpoints and longer treatment duration are still outstanding; validated surrogates were measured over two weeks each.
- Whether colonisation with oxalate-degrading intestinal bacteria or oxalate degradation leads to a reduction in stone recurrence rate remains an open question.
- Treatment with lanthanum carbonate [51] involved four patients; whether the effect is confirmed in larger cohorts remains to be clarified.

CLASSIFICATION:

Oxalate is a metabolic end product with a narrow window: research has focused primarily on urine measurements and stone recurrence rates; the path from the measured value to the stone event remains open.

1. What Oxalate Is

Oxalate is the salt form of oxalic acid and occurs in the body from two sources: as a component of plant foods and as a metabolic product. Several studies describe endogenous formation from glyoxylate, predominantly in the liver; one observational human study links increased hepatic oxalate production to metabolic liver diseases. In urine, oxalate occurs predominantly as the calcium salt, and this is precisely what most research revolves around: **calcium oxalate crystals** and the conditions under which they form in the kidney and urinary tract. Oxalate is therefore not a nutrient in the strict sense, but a metabolic end product with a narrow window — little is unremarkable, much becomes a risk. The studies distinguish genetically determined forms with very high production from diet- and gut-related forms with moderate excretion.

For the evaluation of all studies it is crucial that oxalate is almost never captured directly, but via urine: as **24-hour excretion**, as crystalluria or as a supersaturation index. These are measured values. Whether a stone or a recurrence develops from them is another question. Added to this is the diversity of forms: **primary hyperoxaluria** is based on rare genetic defects of liver enzymes, secondary or enteric hyperoxaluria follows absorption disorders of the intestine, and the idiopathic form often remains without a clear cause. Intestinal bacteria, particularly oxalate-degrading species, intervene in absorption, yet their colonisation varies between individuals and is not stable. Anyone transferring findings from one of these groups to another overextends them.

2. What the Studies Show in Detail

The key human studies and the most important reviews — by application area, with population, duration, preparation, measured variable and result, as reported in the original studies. Numbers appear only where the study states them.

Distribution of **controlled human studies** by application area — the numbers are not additive, as one study may be assigned to several areas:

APPLICATION AREA	CONTROLLED STUDIES
Safety and tolerability	5
Gut and microbiome	3
Metabolism	3
Absorption and bioavailability	1

APPLICATION AREA	CONTROLLED STUDIES
Inflammatory processes	1

Metabolism

The controlled crossover study [57] tested empagliflozin in 53 adults (≥ 18 and < 75 years) with calcium ($n = 28$) or uric acid stones ($n = 25$) without diabetes (HbA1c $< 6.5\%$, no diabetes therapy). It was administered once daily at 25 mg for two weeks each, followed by placebo or vice versa. Primary endpoints were the relative supersaturation ratios (RSR) for calcium oxalate, calcium phosphate and uric acid. In calcium stone formers, empagliflozin lowered RSR CaP (relative difference versus placebo -36% ; 95% CI -48% to -21% ; $P < 0.001$), but not RSR CaOx and RSR UA. In uric acid stone formers, RSR UA decreased (-30% ; 95% CI -44% to -12% ; $P = 0.002$), but not RSR CaOx and RSR CaP. No serious or predefined adverse events occurred. The RSRs are validated surrogates; treatment duration was two weeks each.

The randomised parallel-group study [11] compared, in 72 recruited and 44 evaluable recurrent calcium stone formers with idiopathic hyperoxaluria, a calcium citrate dose of 800 mg (in two doses at midday and evening, with limited dairy intake) with adequate calcium intake from the diet. Over eight weeks, 24-hour urinary oxalate (B Time effect -10.06 ; 95% CI -13.70 to -6.42 ; $p < 0.001$) and the calcium oxalate supersaturation index (B Time effect -2.54 ; 95% CI -4.06 to -1.02 ; $p = 0.001$) decreased in both arms. The fact that 28 of 72 participants did not complete the study limits the strength of the evidence; the adjusted analysis is not fully reported in the excerpt given.

Study [65] examines hepatic oxalate overproduction in metabolic dysfunction-associated steatohepatitis (MASH). In livers of patients and mice with MASH, AGXT was suppressed and LDHA activated. Preclinical experiments linked these changes to increased oxalate formation and showed that oxalate inhibited PPAR α transcription and fatty acid β -oxidation and promoted monocyte chemotaxis via CCL2. In male mice with diet-induced MASH, hepatocyte-specific AGXT overexpression or pharmacological LDHA inhibition reduced steatohepatitis and fibrosis. The effects of these interventions in humans were not investigated. The review [69] classifies dietary, lifestyle and pharmacological approaches for the prevention of calcium oxalate stones and names hyperoxaluria as the most common metabolic disorder in calcium oxalate stone formation.

What is missing: For empagliflozin, studies with clinical recurrence endpoints and longer treatment duration are still outstanding; for calcium citrate administration in idiopathic hyperoxaluria, confirmation in larger, fully evaluated cohorts is the next open question.

Gut and Microbiome

Study [51] tested an enteric-coated capsule containing 500 mg lanthanum carbonate, released in the distal gastrointestinal tract (radiologically confirmed), in four patients with primary hyperoxaluria and an estimated glomerular filtration rate > 60 ml/min per 1.73 m^2 . After 2.5 months of treatment in three patients and 18 months in one patient, the urinary oxalate concentration decreased markedly below $0.51\text{ mmol}/24\text{ h}$ per 1.73 m^2 ($45\text{ mg}/24\text{ h}$ per 1.73 m^2), the value set as the upper limit of normal. The number of treated patients is very small at four; the question of whether the effect is confirmed in larger cohorts remains open.

Phase-II study [8] enrolled 23 patients who underwent ureterorenolithripsy for calcium oxalate stones with crystalluria and a normal metabolic profile. After discharge they received daily for 20 days 1 billion *Lactobacillus paracasei* LPC09, 1 billion *Lactobacillus plantarum* LP01, 1 billion *Bifidobacterium breve* BR03, potassium (520 mg), citrate (1400 mg) and magnesium (80 mg). Crystalluria was monitored by polarised-light microscopy at 1, 3, 6 and 12 months. After one month no patient reported crystalluria; after three months none of the 20 patients examined; after six months it occurred in three patients (15%) and after twelve months in five patients (25%).

Proof-of-concept study [68] gave 22 healthy adults without a history of stones and without colonisation by *Oxalobacter formigenes* an oxalate- and calcium-controlled diet. After a single dose of approximately 10^{10} cells all 22 participants became colonised; 10 remained colonised for at least one year. In 11 colonisation was lost, of whom 9 reported antibiotic intake; 6 were redosed and 5 were successfully recolonised. Faecal oxalate concentration fell by 54%, urinary oxalate excretion by 14%, with differing time courses between participants.

Review [70] describes *Oxalobacter*, *Lactobacillus* and *Bifidobacterium* as intestinal colonisers that participate via enzymes in the degradation of oxalate salts, and discusses oxalate-degrading bacteria as starter cultures in fermented foods. Review [71] summarises probiotics, including recombinant strains, intended to promote oxalate degradation in the intestine. What is missing: controlled studies that derive a reduction in stone recurrence rate from colonisation or oxalate degradation.

Inflammatory Processes

Multicentre, double-blind, placebo-controlled study [59] enrolled 173 patients with calcium oxalate urolithiasis after successful stone removal from six clinics in Thailand. They received either a phytochemically rich lime-based preparation (LPR) or placebo for 24 months. The primary endpoint was the CT-confirmed stone recurrence rate; secondary endpoints were urinary protein excretion and urinary interleukin-8 (IL-8), a pro-inflammatory cytokine. The recurrence rate is the clinical endpoint on which benefit over the 24 months is decided; the course of IL-8 is a laboratory marker.

Review [67] examines studies in human stone formers. Histological and molecular analyses of renal tissue show increased density of immune cells and altered gene expression, with clear differences between calcium oxalate and brushite stones. Phenotyping according to tissue mineralisation – for example Randall's plaque or tubular plugging – reveals considerable heterogeneity of tissue damage. Systemic markers such as elevated serum C-reactive protein suggest a link between active stone disease and inflammation, with relationships varying by age, sex and comorbidities.

Review [72] discusses how uropathogenic *Escherichia coli* may contribute to calcium oxalate stone formation via oxidative stress, inflammation and altered citrate metabolism, and addresses the role of macrophages. Review [73] describes that calcium oxalate crystals generate reactive oxygen species in renal tubular epithelial cells, and that selected antioxidants reduce crystal accumulation in renal tissue in animal models. Review [74] classifies interleukins and chemokines: pro-inflammatory interleukins such as IL-1 β can promote crystal deposition via NLRP3 inflammasome, NF- κ B and MAPK, anti-inflammatory interleukins protect via M2 macrophage polarisation, and IL-6 acts in both directions. What is missing: inflammation-related longitudinal data in patient groups separated by stone type and tissue findings.

Safety and Tolerability

Systematic review with meta-analysis [53] evaluated randomised controlled trials of thiazides, citrate preparations, uric acid synthesis inhibitors and magnesium preparations in calcium oxalate stones with abnormal urine chemistry. Pharmacotherapies markedly lowered the stone recurrence rate (risk ratio 0.47; 95 % CI 0.35–0.63). At the same time, adverse drug reactions leading to study discontinuation (risk ratio 2.51; 95 % CI 1.09–5.75) and adverse drug reactions and events overall (risk ratio 1.95; 95 % CI 1.07–3.56) increased. The reported adverse effects were predominantly mild and rarely required discontinuation (2 %–16 %).

Systematic review with meta-analysis [54] pooled five randomised controlled trials with 208 patients on the administration of *Oxalobacter formigenes* in primary hyperoxaluria. Compared with placebo there was no advantage in plasma oxalate values (mean difference -0.00 mmol/day; 95 % CI -0.01 to 0.00 ; $P = 0.06$) or urinary oxalate values (mean difference -0.01 mmol/day; 95 % CI -0.12 to 0.10 ; $P = 0.86$). Adverse events (odds ratio 0.44; 95 % CI 0.14–1.39; $P = 0.16$) and serious adverse events (odds ratio 0.80; 95 % CI 0.29–2.25; $P = 0.67$) did not differ significantly.

Phase-3 study ILLUMINATE-A [64] investigated lumasiran in primary hyperoxaluria type 1 for up to 60 months. Patients aged 6 years and older with genetically confirmed disease, an estimated glomerular filtration rate ≥ 30 ml/min per 1.73 m² and a mean 24-hour urinary oxalate excretion ≥ 0.70 mmol/24 h per 1.73 m² were included. Of 39 enrolled patients, 24 of 26 in the lumasiran group and 13 of 13 in the placebo group completed the study. Sustained reductions in 24-hour urinary oxalate were observed in both treatment groups. The most common adverse events were mild injection-site reactions.

Systematic review with meta-analysis [50] on RNA interference in primary hyperoxaluria concludes that an early start of treatment is favourable for preserving renal function and that high-dose, long-lasting therapy may be clinically more effective; combination with haemodialysis appears promising. What is missing: independent replications and larger, well-planned studies that confirm these observations.

Further Investigations

Updated systematic review with meta-analysis and sequential testing analysis [62] evaluated randomised controlled trials of thiazide diuretics versus placebo in hypercalciuric patients with recurrent nephrolithiasis. From 10 articles, 650 patients entered the intervention group and 672 the placebo group. The recurrence rate was lower under thiazides (risk ratio 0.63; 95 % CI 0.49–0.83; $P = 0.0007$; $I^2 = 65$ %). The heterogeneity of 65 % indicates that the studies did not yield uniform results.

Randomised study [9] compared an empirical (Emp) with a 24-hour urine-test-guided (Sel) strategy in adults with recurrent stone disease. In the Emp group dietary oxalate intake fell by 33 % ($p = 0.02$), without significant changes in water, sodium, animal protein or fruit and vegetable portions; urine volume and sodium excretion also did not change. The URINE study [13] compared the same strategies in 56 participants (mean age 44.5 years, standard deviation 13.2; 30 women, 54 %), of whom 29 were in the empirical and 27 in the selective group.

Three-arm randomised study [12] tested a low potential renal acid load diet versus sustained-release potassium citrate and a control group over four weeks in 46 participants (diet $n = 14$, medication $n = 16$, control $n = 16$). The medication group improved urinary potassium and potential renal acid load after two weeks and up to the fourth week ($p < 0.001$). In the diet group the urinary changes over time were not significant; a slight shift in urinary potassium and pH towards alkalisation was discernible, without significant change in stone-forming potential.

Non-randomised, uncontrolled pilot study [14] examined a polyherbal Ayurvedic preparation twice daily together with dietary counselling over two weeks in 58 patients (20–60 years) with confirmed recurrent calcium oxalate stones. Morning urine pH rose from 5.55 ± 0.39 to 5.80 ± 0.51 ($p = 0.001$), uric acid fell from 311.38 ± 161.87 to 275.12 ± 149.82 mg/day ($p = 0.017$), potassium rose from 28.09 ± 14.58 to 35.16 ± 16.30 mmol/day. Without a control group the effect cannot be separated from the dietary counselling.

Randomised, controlled, double-blind study [5] tested four toothpastes in 120 adults with dentine hypersensitivity (118 completed the study): potassium nitrate, stannous fluoride, an experimental paste with 1.5 % oxalate and a negative control. Brushing was performed twice daily for eight weeks, followed by three weeks with the negative control. All treatments relieved thermal sensitivity more than the negative control ($p \leq 0.004$). The stannous fluoride paste was stronger than potassium nitrate in week 2 ($p = 0.021$). Review [66] places glyoxylate metabolism with the involvement of several organs and derives consequences for siRNA-based therapies in primary hyperoxaluria. What is missing: controlled studies that directly test dietary strategies against standard drug therapy over longer periods.

Immune System

Study [75] examined the regulation of ferroptosis in renal tubular epithelial cells under high oxalate load in HK-2 cell cultures and in glyoxylate-induced mouse models of oxalate nephropathy. High oxalate doses triggered ferroptosis in a dose-dependent manner and activated the Hippo signalling pathway with phosphorylation and inactivation of YAP1. Proteomic and multi-omics analyses identified YAP1 as a central regulator and SLC7A5 as a direct transcriptional target via TEAD1. High oxalate disrupted the binding of YAP1/TEAD1 to the SLC7A5 promoter and downregulated SLC7A5. Loss of SLC7A5 mediated ferroptosis under YAP1 inhibition by limiting leucine availability and dampening the mTOR pathway; leucine supplementation or reactivation of mTOR abolished ferroptosis.

These findings derive from cell cultures and animal models and are therefore preclinical. They describe a mechanism by which oxalate intervenes in tubular cells via the Hippo-YAP1/TEAD1-SLC7A5 signalling pathway and the leucine-mTOR axis. What is missing: human studies that examine whether this pathway can be exploited therapeutically in stone formers or in patients with oxalate nephropathy.

Overall Picture

Across the fields a pattern emerges: the most robust statements concern surrogate endpoints such as supersaturation ratios, urinary oxalate and crystalluria, whereas clinical recurrence endpoints are rarer and mostly obtained in smaller cohorts. The meta-analyses on thiazides [62] and on pharmacotherapy overall [53] rest on several randomised studies and demonstrate a reduction in recurrence, but at the cost of increased, predominantly mild adverse effects. In contrast, colonisation with *Oxalobacter formigenes* [68] and the probiotic reviews [70, 71] are at an early stage: they demonstrate changes in oxalate metabolism, but not a reduction in recurrence rate.

The situation differs for the rarer diseases. For primary hyperoxaluria, therapies such as lumasiran [64] and RNA interference [50] achieve sustained reductions in urinary oxalate; administration of Oxalobacter formigenes performed no better than placebo in meta-analysis [54] of 208 patients. The inflammatory and immunological studies [67, 72, 73, 74, 75] predominantly supply mechanisms from cell and animal models. Where the evidence is still at an early stage, the next testable question is named in each case: clinical recurrence endpoints, independent replications and human studies.

Overall Picture

Urinary Oxalate Is a Marker, Not a Disease Course

A large proportion of the controlled studies measure **OXALATE EXCRETION IN URINE**, crystalluria or calcium oxalate-related supersaturation. These values can be standardised well and respond quickly to an intervention — yet they are not patient events. A stone recurrence takes time, and only some of the studies track it at all. Anyone who infers a reduced recurrence rate from reduced excretion turns a **marker** into an endpoint. Every assessment must disclose precisely this gap, especially in reviews that pool studies with different endpoints.

The methodologically strongest studies concern **PRIMARY HYPEROXALURIA**, a rare disorder with very high endogenous production. There, RNA interference, mRNA replacement and deliberately colonised gut microbes target a clearly named cause. In idiopathic or diet-related hyperoxaluria the contribution of the same pathways is smaller, and the evidence there consists predominantly of observational data and Phase-2 studies on excretion. Both fields share the word oxalate, but not the mechanism — and therefore not the transferability. A positive Phase-3 finding in primary hyperoxaluria says nothing about the ordinary stone patient.

3. How Robust the Research Is

Of the human studies, the great majority are **observational**; controlled trials form a small group and are distributed across safety, gut, metabolism, bioavailability and inflammation. The thematic centre lies on **nephrolithiasis** and primary hyperoxaluria, not on oxalate as a dietary constituent. A second block addresses genetic-engineering and microbial approaches intended to alter oxalate production or uptake itself — from RNA interference via mRNA replacement therapy to deliberately colonised gut microbes. Nutritional and agricultural research forms a separate field that deals predominantly with food technology and fermentation.

Methodologically the field rests on two legs. On one side stand systematic reviews and meta-analyses — on thiazides, on Oxalobacter formigenes in primary hyperoxaluria, on RNA interference and as the basis of a Japanese guideline; they pool several randomised trials and carry the furthest. On the other side **preclinical** research from animal and cell models forms a substantial part. Many controlled human studies are Phase-2 trials with small groups, short durations and surrogate endpoints; a Phase-3 evaluation exists for one rare genetic form. Robustness therefore varies greatly according to the question.

4. What Is Frequently Claimed — and What the Data Provide

CLAIM	EVIDENCE BASE
Targeted dietary therapy reduces stone recurrences	Controlled studies examine a targeted versus an empirical dietary therapy and a diet with low renal acid load in recurrent stone formers. The studies predominar
Probiotics or Oxalobacter formigenes reduce oxalate load	A meta-analysis of randomised studies investigates Oxalobacter formigenes in primary hyperoxaluria; review articles describe mechanisms. This carries no stat
Calcium-rich diet increases stone risk	A randomised study compared calcium citrate with normal calcium intake in recurrent stone formers with idiopathic hyperoxaluria and examined metabolic risk f
Fermented foods with oxalate-degrading bacteria	There is also a review on food technology. It addresses starter cultures and product development, not the application in humans.

5. Profile: Molecule and Charge

Oxalate is not a single molecule but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; that is exactly what the next section addresses.

6. Charge, Electrons, Radicals

Oxalate appears above all as a trigger of reactive oxygen species: elevated systemic oxalate levels promote ROS formation and activate NF-κB, MAPK and the NLRP3 inflammasome ²⁶. One metabolite inhibited fatty-acid oxidation via PPARδ-CPT1A and increased ROS and lipid peroxidation in the tubule ²⁵. In humans, ROS, apoptosis and inflammation were determined in cell and tissue samples from stone patients ²³; ROS by immunofluorescence and apoptosis by TUNEL ³⁰. In TCMK-1 and HK-2 cells, ROS, MDA, apoptosis rate and crystal adhesion were recorded after COM administration ^{24 20}. It remains open whether ROS precede crystal formation; this would need to be examined in humans.

Urine proteins from calcium-oxalate-stone patients were fractionated according to their isoelectric point by FPLC on a GigaCap-Q-650M column ²⁷; the aggregation-promoting activity correlated positively with the number of oxalate-binding sites per protein and the isoelectric point ²⁹. In artificial urine, polyhydroxycarboxylic acids and phytate complex calcium thermodynamically; hydroxycitrate showed the strongest complexation, phytate additionally inhibited crystallisation ^{28 28 28}. In ternary vanadium(IV) systems, oxalate was characterised as a ligand by EPR and ESI-MS ³¹. An electron transfer at the oxalate ion itself has not been investigated; the measurement remains to be done.

7. Interactions with Other Substances

With which other substances on the platform this substance has been **jointly** investigated or discussed in human studies and reviews — combination, comparison or shared mechanism of action. The number indicates studies in which both appear.

SUBSTANCE	JOINT STUDIES	OF WHICH CONTROLLED IN HUMANS
Acceptance and Commitment Therapy (ACT)	33	1
Gut Microbiome	30	0
Vitamin C	26	5
Chronic Inflammation	25	1
Magnesium	23	10
Stress, Cortisol and Inflammation	22	1
Probiotics	13	4
Art Therapy	12	2
Palmitoylethanolamide (PEA)	8	0
High-Intensity Interval Training (HIIT)	7	4

For oxalate, a preanalytical interaction is described: fluoride-oxalate tubes for blood collection deliver comparable values to K3-EDTA tubes in HbA1c measurement, without clinically significant differences ^{32 32}. An absorption, CYP or binding interaction is not described for oxalate. In stone formation, urine supersaturation is the primary concern: Tolvaptan, a vasopressin V2 receptor antagonist, can lower supersaturation through increased urine volume and thereby reduce stone risk ³⁶. It has been suggested to examine whether a low dose of a selective V2 receptor antagonist prevents new stones in these patients ³⁵.

Combinations mainly concern the treatment of primary hyperoxaluria. One child received Lumasiran 6 mg/kg subcutaneously together with pyridoxine 10 mg/kg/day on the sixth day of life ³⁴. The efficacy of RNAi with haemodialysis is described as promising and requires larger studies ^{14 14}. In stone composition, calcium oxalate and uric acid occurred together in 13.2 % of two-component stones ³⁷; uric acid with a phosphate component was found in 2.9 % of cases ³⁸. A prediction model from morning urine profiles and BMI achieved an AUC of 0.8439 ^{33 33}. It remains open which metabolic pathways are suitable for intervention.

8. Overdosage, Tolerability, Limitations

In oxalate-associated diseases, the available controlled human studies show an overall favourable safety profile for several investigated substances. In one study on Lumasiran in primary hyperoxaluria type 1, predominantly mild or moderate adverse events occurred, most frequently injection-site reactions; the safety profile was rated as acceptable ^{9 9 9 9}. For Oxalobacter formigenes, no significant adverse events (OR 0.44; 95 % CI 0.14–1.39; P = 0.16) and no serious adverse events (OR 0.80; 95 % CI 0.29–2.25; P = 0.67) were observed ². A lime-based supplement with citrate and flavonoids was well tolerated, with minimal adverse effects, and no serious adverse events were reported ^{4 4 5}.

In contrast, there are indications of relevant adverse effects with established pharmacotherapies. One controlled human study reports that pharmacotherapies increased adverse drug reactions with study discontinuation (risk ratio 2.51; 95 % CI 1.09–5.75) as well as adverse drug reactions or adverse events (risk ratio 1.95; 95 % CI 1.07–3.56)³. For potassium citrate, effective recurrence reduction is described; however, costs and gastrointestinal side effects limit long-term use due to poor adherence⁴. Thiazides are recommended in guidelines for nephrolithiasis with hypercalciuria, although uncertainties in optimising prescription in hypercalciuric patients persist¹¹. It would be necessary to examine how these adverse-effect profiles behave at different oxalate doses and treatment durations and whether tolerability can be improved by accompanying measures.

9. The Most Robust Studies

Ordered by strength of evidence, not by familiarity: review articles and studies with many participants first. The complete evaluation comprises considerably more studies; the most robust ones are presented here.

Controlled Human Studies

- ¹ Thiazide diuretics for preventing calcium oxalate recurrent kidney stones: an updated systematic review, meta-analysis and trial sequential analysis ... (2025) — Review article, 672 participants
- ² Efficacy and safety of Oxalobacter formigenes in patients with primary hyperoxaluria: A systematic review and meta-analysis of randomized controlled ... (2025) — Review article, 208 participants
- ³ Pharmacotherapy for patients with calcium oxalate stones and abnormal urine chemistry: A systematic review and meta-analysis for the Japanese ... (2025) — Review article
- ⁴ Lime-based supplement reduces calcium oxalate stone recurrence: A multicenter randomized controlled trial (2025) — 173 participants
- Randomized clinical trial evaluating kinetic benefits of desensitizing agents: Magnitude, onset, and stability of relief (2025) — 120 participants
- ⁵ Empagliflozin in nondiabetic individuals with calcium and uric acid kidney stones: a randomized phase 2 trial (2025) — 53 participants
- ⁶ A Targeted Release Capsule of Lanthanum Carbonate: a New Efficient Cheap Treatment for Primary Hyperoxalurias (2025) — 4 participants
- ⁷ Oral supplementation with probiotics, potassium citrate, and magnesium in reducing crystalluria in stone formers: A phase II study (2024) — 23 participants
- ⁸ Targeted versus empiric approach for prevention of recurrent kidney stones: Insights on diet therapy from a randomized trial (2026)
- ⁹ Final Results of the ILLUMINATE-A Phase 3 Clinical Trial of Lumasiran for Primary Hyperoxaluria 1 (2026) — 39 participants
- ¹⁰ Comparing the effect of calcium citrate supplement with normal calcium diet on metabolic risk factors in recurrent calcium stone formers with ... (2024) — 44 participants
- ¹¹ Effect of low-potential renal acid load diet intervention on urinary lithogenic parameters in recurrent calcium urolithiasis patients ... (2025) — 46 participants
- ¹² Urinary Supersaturation in a Randomized Trial Among Individuals with Recurrent Nephrolithiasis Comparing Empiric Versus Selective Preventive Therapy ... (2026) — 56 participants
- ¹³ Effectiveness of Subap Plus, a Polyherbal Medicine, on 24-Hour Urinalysis and Early Morning Urine pH in Recurrent Calcium Oxalate Stone Formers: A ... (2025) — 58 participants

Observational Studies in Humans

- ¹⁴ The efficacy and safety of RNA interference for the treatment of primary hyperoxaluria: a systematic review and meta-analysis (2025) — Review article
- ¹⁵ Systematic review of pharmacological, complementary, and alternative therapies for the prevention of calcium oxalate stones (2025) — Review article
- ¹⁶ Where does endogenous oxalate come from? - a systematic review of endogenous sources of urinary oxalate (2026) — Review article
- ¹⁷ Variations in Renal Tract Calculus Composition Between South Asian and Non-South Asian Ethnicities in North West England (2025) — 1.890 participants
- ¹⁸ Metabolic Insights From Composition-Based Analysis of Kidney Stones: A Retrospective Study of 506 Patients (2026) — 506 participants
- ¹⁹ Sex Differences in Admission Urine Culture Positivity, Pathogen Distribution, and Clinical Characteristics Among Patients with Calcium Oxalate Stones (2026) — 1.257 participants
- ²⁰ Clinical features of Escherichia coli positive calcium oxalate stones and effects of outer membrane vesicles on tubular epithelial ... (2026) — 1.976 participants
- ²¹ Distribution of urinary stone composition and its associations with age, sex, and temporal factors among 3901 patients in Xiamen: A 13-year ... (2026) — 3.901 participants
- ²² Integrated Serum Lipidomics, Renal Transcriptomics, and Mendelian Randomization Reveal Glycerophospholipid Dysregulation in Calcium Oxalate Kidney ... (2026) — 9.713 participants
- 24-h urine test application in patients with kidney stone disease: a population-based study in a primary care setting (2025) — 21.907 participants

10. Summary

PROVEN

Randomised trials and meta-analyses carry the greatest weight, and they almost always centre on stone disease rather than oxalate as a dietary component. The meta-analysis [53] shows that thiazides, citrates, uric acid synthesis inhibitors and magnesium produce a clear reduction in stone recurrence rate (risk ratio 0.47; 95 % CI 0.35–0.63) together with more frequent adverse drug reactions (risk ratio 2.51; 95 % CI 1.09–5.75). The meta-analysis [62] confirms a lower recurrence rate for thiazides (risk ratio 0.63; 95 % CI 0.49–0.83; $I^2 = 65\%$). The meta-analysis [54] finds no benefit for *Oxalobacter formigenes* in primary hyperoxaluria with respect to plasma and urinary oxalate. Decisive for assessment: oxalate is almost never measured directly, only via the urine.

PLAUSIBLE

Part of the mechanism of action rests on preclinical work. The reviews [72], [73] and [74] describe how calcium oxalate crystals generate reactive oxygen species in tubular epithelial cells, how pro-inflammatory interleukins can promote crystal deposition via the NLRP3 inflammasome, NF- κ B and MAPK, and how anti-inflammatory interleukins protect via M2 macrophage polarisation; IL-6 acts in both directions. Study [65] links hepatic oxalate overproduction in MASH with suppressed AGXT and activated LDHA. **Hypothesis:** If inflammation and crystal formation mutually reinforce each other, patient groups separated by stone type and tissue findings could respond differently to inflammation-directed approaches.

The first point to clarify is the path from measured value to clinical event: studies with clinical recurrence endpoints and longer treatment duration are still outstanding, and calcium citrate administration in idiopathic hyperoxaluria requires confirmation in larger, fully evaluated cohorts. Independent replications and larger, well-designed trials are still outstanding for RNA interference in primary hyperoxaluria. Inflammation-related course data in groups separated by stone type and tissue findings would be the next step, as would controlled trials that derive a reduction in stone recurrence rate from colonisation or oxalate degradation in the gut.

11. What Remains Open

- **Endpoint:** Does a reduced urinary oxalate excretion actually lower stone recurrences, or does it merely alter the marker?
- **Transferability:** Can the principles tested in primary hyperoxaluria be transferred to idiopathic and diet-related forms?
- **Microbiome:** How stably can the gut be colonised with oxalate-degrading bacteria, and in whom does this permanently alter excretion?

12. Further Paths

Topics, mechanisms and pathways in which this substance occurs — for all those who wish to look beyond the substance.

- Interaction network

Frequently Asked Questions

Is oxalate a nutrient or a risk factor?

The studies treat oxalate as a metabolic end product that is excreted via the kidney, and as a component of plant-based diet. An independent benefit is not the subject of research; the focus is on excretion, crystal formation and ways to reduce excretion. Practically important is the distinction between genetically determined and nutrition- or gut-related overproduction.

What do the controlled human studies examine?

They are distributed across safety, gut, metabolism, bioavailability and inflammation. The measurements are predominantly urine parameters such as 24-hour excretion, crystalluria or supersaturation, partly in phase-2 designs. Randomised studies on recurrence prophylaxis exist, among others, for thiazides, for a calcium-containing preparation and for a targeted versus an empirical dietary therapy.

Can the gene-therapy approaches be transferred to ordinary stone patients?

Currently not. The larger controlled and the phase-3 studies concern almost exclusively primary hyperoxaluria, a rare disease with very high hepatic production. In idiopathic or nutrition-related hyperoxaluria the production is far lower and the cause is heterogeneous. Whether a reduction in excretion is accompanied by fewer recurrences there is not answered by these studies.

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Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
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