

Clinical utility of uva ursi in preventing recurrence of renal calculi: a prospective quantitative cohort study.

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ABSTRACT

Recurrent renal calculi represent a clinically important condition associated with substantial morbidity and a high risk of recurrence. Uva ursi has traditionally been used for urinary-tract disorders; however, clinical evidence regarding its potential role in preventing renal-calculus recurrence remains limited. The present prospective cohort study was undertaken to evaluate the association between Uva ursi exposure and subsequent recurrence of renal calculi, while also assessing urinary biochemical parameters and treatment-related safety outcomes. A prospective cohort study was designed involving 50 participants, comprising 25 participants in the Uva ursi cohort and 25 participants in a comparison cohort. Participants were followed prospectively for 12 months, with assessments conducted at baseline and at 3, 6, 9, and 12 months. The primary outcome was recurrence of renal calculi during follow-up. Secondary outcomes included time to recurrence, recurrence-free survival, changes in urinary volume, urinary calcium, oxalate, citrate, uric acid and urine pH, and adverse events. Recurrence-free survival was evaluated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional-hazards regression was planned to estimate adjusted hazard ratios (HRs) for recurrence after accounting for relevant demographic, clinical and urinary risk factors.

In the analytical dataset, renal-calculus recurrence occurred in 6/25 (24.0%) participants in the Uva ursi cohort compared with 11/25 (44.0%) in the comparison cohort. The estimated relative risk was 0.55 (95% CI: 0.24–1.25; $p = 0.136$). Twelve-month recurrence-free survival was 76.0% in the Uva ursi cohort and 60.0% in the comparison cohort. In multivariable Cox regression, Uva ursi exposure was associated with an estimated lower hazard of recurrence (adjusted HR 0.58, 95% CI: 0.23–1.47; $p = 0.250$), although the association did not reach statistical significance. Residual stone burden was independently associated with recurrence (adjusted HR 2.18, 95% CI: 1.02–4.67; $p = 0.044$). The Uva ursi cohort showed modest favourable changes in urinary volume, urinary calcium, oxalate and citrate. Gastrointestinal symptoms were reported somewhat more frequently in the Uva ursi cohort, although no statistically significant difference in adverse events was observed. In this prospective cohort, Uva ursi exposure was associated with a numerically lower incidence of

renal-calculus recurrence and a higher recurrence-free survival probability; however, the observed association was not statistically significant after adjustment for potential confounders. The findings therefore do not establish Uva ursi as an effective preventive treatment for recurrent renal calculi. The results are hypothesis-generating and support the need for adequately powered randomized controlled trials incorporating standardized Uva ursi exposure, metabolic stone-risk assessment, urinary biochemical monitoring and systematic long-term safety evaluation.

KEYWORDS: Uva ursi; renal calculi; nephrolithiasis; stone recurrence; urinary biomarkers; recurrence-free survival; Kaplan–Meier analysis; Cox regression; herbal medicine; safety.

INTRODUCTION

Renal calculi, or kidney stones, are a common urological disorder characterized by the formation of crystalline mineral aggregates within the urinary tract when urine becomes supersaturated with respect to stone-forming constituents. Calcium oxalate and calcium phosphate account for the majority of urinary stones, although uric acid, struvite, cystine, and other less common compositions also occur. Stone disease may present with renal colic, hematuria, urinary obstruction, infection, and acute healthcare utilization, while recurrent disease may contribute to repeated interventions and progressive morbidity. Recurrence is particularly important because nephrolithiasis is not simply an isolated acute event; recurrence rates may approach 50% within five years in some populations, emphasizing the importance of effective secondary prevention (Khan et al., 2016; Skolarikos et al., 2024). The risk of recurrent nephrolithiasis is heterogeneous and reflects interactions among demographic, metabolic, dietary, genetic, and stone-related characteristics. A comprehensive meta-analysis of 53 studies involving 488,130 patients identified younger age, higher body mass index (BMI), previous stone episodes, family history, hypertension, uric-acid stone composition, previous surgery, asymptomatic residual stones, and specific stone locations among factors associated with recurrence (Wang et al., 2022). ([PubMed](#)) Consequently, contemporary clinical management emphasizes individualized risk stratification rather than a uniform preventive approach. The European Association of Urology (EAU) recommends stone analysis and basic metabolic evaluation for stone formers, with more detailed metabolic assessment for individuals at increased risk of recurrence. Relevant urinary parameters include urine volume, pH, calcium, oxalate, uric acid, citrate, and other biochemical variables (EAU Guidelines Office, 2026). ([Uroweb](#))

Current preventive management is predominantly based on adequate hydration, dietary modification, correction of metabolic abnormalities, and pharmacological treatment when clinically indicated. The EAU recommends generous fluid intake, preferably water, sufficient to achieve a 24-hour urine volume exceeding 2.5 L, together with maintenance of normal dietary calcium, restriction of excessive sodium and animal-protein intake, and maintenance of a healthy BMI. ([Uroweb](#)) Despite these established measures, recurrence remains clinically relevant, creating interest in complementary approaches that may potentially modify urinary or biological factors associated with stone formation. *Arctostaphylos uva-ursi* (L.) Spreng., commonly known as Uva ursi or bearberry, is a medicinal plant traditionally used for urinary-tract disorders. Its leaves contain arbutin, which undergoes metabolism following oral administration and results in urinary excretion of hydroquinone-related metabolites (Schindler et al., 2002). ([PubMed](#)) However, the biological plausibility of urinary effects should not be interpreted as evidence of efficacy against renal-calculus recurrence. The European Medicines Agency recognizes Uva ursi primarily within the context of traditional use for mild lower urinary-tract symptoms rather than prevention of nephrolithiasis. ([European Medicines Agency \(EMA\)](#)) Importantly, clinical evidence concerning Uva ursi has focused predominantly on urinary-tract infection rather than renal-calculus recurrence. In a randomized controlled trial involving 398 women with uncomplicated urinary-tract infection, Uva ursi substantially reduced antibiotic use but failed to demonstrate non-inferiority for symptom burden and raised safety concerns regarding pyelonephritis (Gágyor et al., 2021). ([PubMed](#)) There is therefore a clear evidence gap regarding whether Uva ursi exposure is associated with subsequent renal-calculus recurrence. A prospective quantitative cohort study comparing Uva ursi-exposed and non-exposed stone formers, while accounting for established demographic, dietary, metabolic, and stone-related determinants, may provide preliminary evidence regarding this association. Such evidence could inform the design of larger controlled studies investigating whether Uva ursi has a clinically meaningful role in secondary prevention of renal-calculus recurrence.

2. REVIEW OF LITERATURE

2.1 Renal Calculi and Recurrence

Renal calculi are a multifactorial urological disorder resulting from urinary supersaturation, crystal nucleation, growth, aggregation, and retention within the urinary tract. The major stone types include calcium oxalate, calcium phosphate, uric acid, struvite, and cystine, with calcium-containing stones accounting for the majority of cases. Stone composition is clinically important because the underlying metabolic abnormalities and preventive strategies vary according to stone type. **Skolarikos et al. (2024)** emphasized that reliable stone analysis, preferably using infrared spectroscopy or X-ray diffraction, together with baseline metabolic evaluation, forms an essential component of recurrence prevention. Their updated EAU guideline further recommends classification of patients according to recurrence risk and individualized preventive management based on stone composition and metabolic findings. ([PubMed](#))

Recurrence represents a major long-term challenge in nephrolithiasis. Earlier EAU guidance reported that recurrence may reach approximately 50% within five years and 80–90% within ten years after an initial stone episode, emphasizing that removal of an existing calculus does not eliminate the underlying propensity for stone formation (**Türk et al., 2015**). ([ScienceDirect](#)) More recently, **Wang et al. (2022)** conducted a comprehensive meta-analysis including 53 studies and 488,130 patients and identified several factors associated with recurrent kidney stone disease, including younger age, higher BMI, family history, previous stone episodes, hypertension, uric-acid stone composition, previous surgery, asymptomatic residual stones, and particular stone locations. These findings demonstrate that recurrence is determined by a complex interaction of demographic, metabolic, clinical, and stone-related factors rather than by a single exposure. ([PubMed](#))

2.2 Metabolic and Dietary Determinants of Recurrence

Urinary metabolic abnormalities play a central role in recurrent stone formation. Hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, abnormal urinary pH, and low urinary volume can increase urinary supersaturation and facilitate crystal formation. Skolarikos et al. (2024) recommended baseline metabolic screening for all stone formers and more extensive evaluation, including two 24-hour urine collections, for patients at increased risk of recurrence. Important urinary parameters include urine volume, calcium, oxalate, uric acid, citrate, sodium, and urinary pH. Identification and correction of causative metabolic abnormalities are considered fundamental components of secondary prevention. ([PubMed](#)) Hydration represents one of the most consistently supported preventive interventions. The EAU recommends generous fluid intake, preferably water, sufficient to maintain a 24-hour urine output above 2.5 L. The guideline also recommends a balanced diet with normal calcium intake and limitation of excessive sodium and animal-protein consumption (Skolarikos et al., 2024). ([Uroweb](#)) Earlier prospective evidence also demonstrated that increased water intake can reduce recurrence among patients with idiopathic calcium nephrolithiasis, supporting urinary dilution as an important component of recurrence prevention. Therefore, when investigating any potential complementary intervention, hydration, dietary intake, metabolic abnormalities, and established pharmacological prevention should be considered as potential confounding variables.

2.3 Uva ursi and Its Pharmacological Background

Arctostaphylos uva-ursi (L.) Spreng., commonly known as *Uva ursi* or bearberry, is a medicinal plant traditionally associated with urinary-tract health. Its leaves contain several phytochemical constituents, with arbutin being one of the principal compounds of pharmacological interest. Schindler et al. (2002) investigated the urinary disposition and metabolism of arbutin following oral administration of *Arctostaphylos uva-ursi* extract in healthy volunteers and demonstrated urinary excretion of hydroquinone-related metabolites. These findings establish that constituents of *Uva ursi* undergo metabolism and are subsequently eliminated through the urinary pathway. However, pharmacokinetic evidence does not by itself establish a clinically meaningful effect on renal-calculus formation or recurrence.

The distinction between traditional urinary-tract use and evidence-based treatment of nephrolithiasis is therefore important. Uva ursi has traditionally been used primarily for lower urinary-tract complaints rather than for prevention of renal calculi. Consequently, any proposed relationship between Uva ursi and stone recurrence requires direct clinical investigation rather than extrapolation from traditional use or studies conducted in other urinary disorders.

2.4 Clinical Evidence Related to Uva ursi

The contemporary clinical evidence for Uva ursi has primarily focused on uncomplicated urinary-tract infection rather than nephrolithiasis. Gágyor et al. (2021) conducted a randomized controlled trial involving women with suspected uncomplicated urinary-tract infection and compared Uva ursi treatment with fosfomycin. The investigators found that Uva ursi reduced antibiotic use; however, the prespecified non-inferiority criterion for symptom burden was not met. The study also raised safety concerns because more cases of pyelonephritis were observed in the Uva ursi group, although the difference did not reach conventional statistical significance. ([PubMed](#))

The findings of Gágyor et al. (2021) are relevant to the present research question but cannot be directly interpreted as evidence concerning renal-calculus prevention. Their study evaluated urinary-tract infection outcomes rather than stone recurrence, stone composition, urinary supersaturation, crystal formation, or radiological stone progression. Thus, although Uva ursi has been evaluated prospectively in a urinary-disease population, there remains insufficient evidence regarding its potential relationship with recurrent nephrolithiasis.

2.5 Research Gap

The available literature provides substantial evidence regarding the epidemiology and determinants of renal-calculus recurrence, including demographic characteristics, previous stone history, family history, residual stone fragments, stone composition, metabolic abnormalities, dietary factors, and hydration (Wang et al., 2022; Skolarikos et al., 2024). Current evidence-based prevention therefore emphasizes individualized metabolic assessment, adequate fluid intake, dietary modification, and targeted pharmacological management. ([PubMed](#))

In contrast, the clinical literature concerning Uva ursi has predominantly investigated lower urinary-tract symptoms and uncomplicated urinary-tract infection rather than renal-calculus recurrence (Gágyor et al., 2021). Although the urinary metabolism of Uva ursi constituents has been demonstrated (Schindler et al., 2002), there is insufficient prospective quantitative evidence determining whether standardized Uva ursi exposure is associated with a reduced incidence or delayed recurrence of renal calculi.

Accordingly, the principal research gap is the absence of adequately characterized prospective clinical evidence examining the association between Uva ursi exposure and renal-calculus recurrence while accounting for established demographic, dietary, metabolic, and stone-related risk factors. A prospective cohort design is therefore justified to establish temporal relationships between exposure and recurrence and to provide preliminary quantitative estimates of the magnitude and direction of the association.

2.6 Rationale for the Present Study

The rationale for the present investigation arises from the convergence of three observations. First, recurrent nephrolithiasis represents a clinically important condition influenced by multiple modifiable and non-modifiable determinants (**Wang et al., 2022**). Second, contemporary guidelines emphasize individualized metabolic and dietary prevention but recognize the importance of continued follow-up in patients at increased risk (**Skolarikos et al., 2024**). Third, despite the traditional urinary use and demonstrated urinary metabolism of *Uva ursi* constituents, direct evidence concerning its relationship with renal-calculus recurrence remains limited (**Schindler et al., 2002; Gágyor et al., 2021**).

The present prospective cohort study is therefore designed to evaluate whether standardized *Uva ursi* exposure is associated with subsequent renal-calculus recurrence among adults with a previous history of nephrolithiasis. By incorporating important potential confounders—including age, sex, BMI, previous stone episodes, stone composition, family history, fluid intake, dietary factors, urinary metabolic parameters, comorbidities, previous stone surgery, and residual stone fragments—the study aims to provide a more clinically informative estimate of the association between *Uva ursi* exposure and recurrence.

Research Questions

1. Is renal-calculus recurrence different between participants exposed to *Uva ursi* and those receiving standard preventive care?
2. Does *Uva ursi* exposure influence the time to recurrent renal-calculus detection?
3. Is *Uva ursi* exposure associated with differences in stone burden?
4. What demographic, metabolic, and lifestyle factors independently predict recurrence?
5. Is *Uva ursi* exposure associated with clinically relevant adverse events?

Objectives

1. To compare the time to renal-calculus recurrence between the two cohorts.
2. To compare the number of renal-colic episodes.
3. To compare emergency or hospital visits related to renal calculi.
4. To compare changes in stone burden detected by imaging.
5. To assess urinary biochemical parameters.
6. To document adverse events associated with *Uva ursi* exposure.
7. To identify demographic and clinical factors associated with recurrence.
8. To determine whether the association between *Uva ursi* exposure and recurrence persists after adjustment for potential confounding factors.

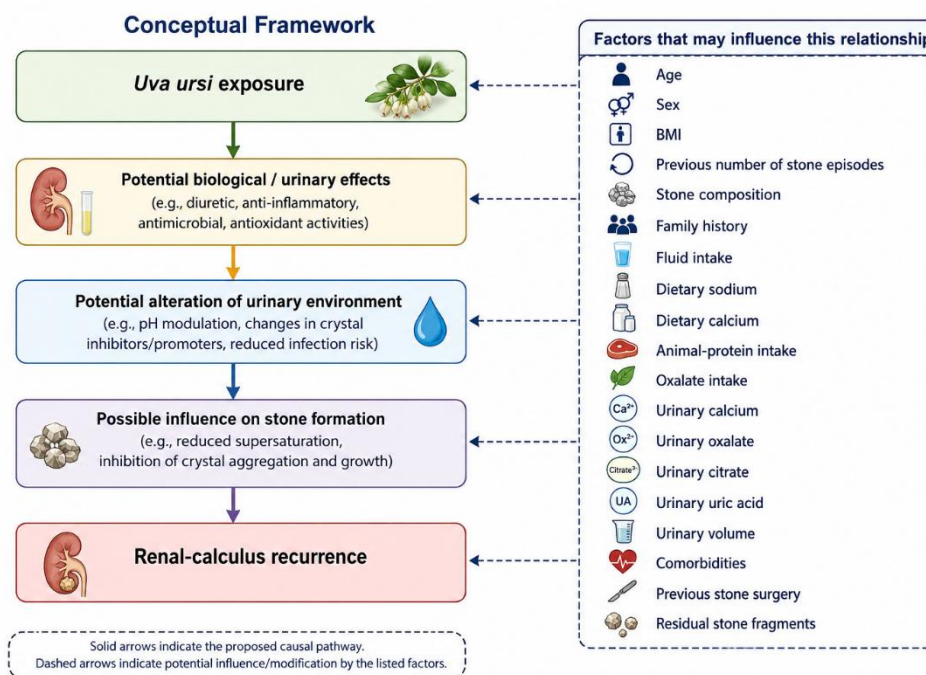
Research Hypotheses

(H0): There is no statistically significant difference in the incidence of recurrent renal calculi between participants exposed to *Uva ursi* and participants receiving standard preventive care without *Uva ursi*.

(H1): There is a statistically significant difference in the incidence of recurrent renal calculi between participants exposed to *Uva ursi* and participants receiving standard preventive care without *Uva ursi*.

(H2): Uva ursi exposure is significantly associated with a longer time to recurrence of renal calculi after adjustment for relevant confounding factors.

Conceptual Framework



3.METHODOLOGY

Study Design

A prospective quantitative cohort design will be used. Participants will be classified according to Uva ursi exposure at baseline and subsequently followed prospectively for 12 months.

Study Setting

The study conducted in the Hospital Opd of State Ghazipur Homoeopathic Medical College & Hospital, Rauza, Ghazipur, Uttar Pradesh.

Study Duration

Proposed duration:

18–24 months

This may include:

- 6 months recruitment
- 12 months participant follow-up
- 3–6 months data cleaning and analysis

Study Population

Adults with a documented previous history of renal calculi who meet the eligibility criteria will constitute the study population.

Eligibility Criteria

Inclusion Criteria

Participants should:

1. Be aged ≥ 18 years.
2. Have a documented history of renal calculi.
3. Have undergone appropriate clinical evaluation.
4. Be clinically suitable for prospective follow-up.
5. Provide informed consent.
6. Be willing to undergo scheduled imaging and laboratory assessment.
7. Have sufficient medical records to establish baseline stone status.

Exclusion Criteria

Participants should be excluded if they have:

1. Current untreated urinary obstruction.
2. Acute pyelonephritis or serious urinary infection requiring immediate treatment.
3. Severe renal impairment that makes the intervention inappropriate.
4. Pregnancy or breastfeeding where Uva ursi exposure is contraindicated or clinically inappropriate.
5. Known allergy to the study preparation.
6. Active stone requiring immediate surgical intervention.
7. Other serious conditions that may interfere with follow-up.
8. Inability to provide informed consent.
9. Concurrent use of another investigational herbal preparation intended for stone prevention.

Exposure Definition

The exposure cohort will consist of participants receiving a standardized, quality-controlled Uva ursi preparation under medical supervision, in accordance with the approved study protocol.

Standard Preventive Care

Both cohorts should receive appropriate standard stone-prevention counselling according to their clinical and metabolic profile.

The EAU recommends preventive measures including adequate fluid intake, balanced nutrition, normal dietary calcium, restriction of excessive sodium and animal protein, appropriate physical activity, and individualized treatment according to metabolic risk. (Uroweb)

This approach is important because withholding established preventive management in order to evaluate an unproven herbal intervention would not be ethically appropriate.

Sampling Technique

A consecutive or systematic recruitment strategy may be used.

Eligible patients presenting to the participating centre during the recruitment period will be screened and enrolled after informed consent.

Because treatment allocation is not randomized in a cohort study, baseline differences between the exposure groups must be carefully measured and statistically adjusted.

Study Variables

Variable	Type	Measurement
Uva ursi exposure	Independent	Yes/No
Renal-calculus recurrence	Dependent	Yes/No
Time to recurrence	Dependent	Months
Age	Covariate	Years
Sex	Covariate	Male/Female
BMI	Covariate	kg/m ²
Previous stone episodes	Covariate	Number
Stone composition	Covariate	Calcium oxalate/etc.
Family history	Covariate	Yes/No
Fluid intake	Covariate	L/day
Urinary volume	Covariate	L/day
Urinary calcium	Covariate	mg/day
Urinary oxalate	Covariate	mg/day
Urinary citrate	Covariate	mg/day
Urinary uric acid	Covariate	mg/day
Stone burden	Outcome	mm/number
Renal-colic episodes	Outcome	Number
Adverse events	Safety outcome	Yes/No

Data Collection Instruments

Tool I: Sociodemographic Proforma

1. Participant identification code
2. Age
3. Sex
4. Residence
5. Occupation
6. Education
7. BMI
8. Relevant socioeconomic characteristics

Tool II: Clinical History

1. Previous stone episodes
2. Date of previous stone
3. Stone location
4. Stone size
5. Stone composition
6. Previous surgical treatment
7. Previous spontaneous passage
8. Family history
9. Relevant comorbidities

10. Current medication

Tool III: Lifestyle and Dietary Assessment

1. Daily fluid intake
2. Water consumption
3. Dietary sodium
4. Dietary calcium
5. Animal-protein intake
6. High-oxalate food intake
7. Physical activity
8. Alcohol consumption where applicable
9. Smoking status

Tool IV: Laboratory Assessment

Baseline and follow-up assessment may include:

- Serum creatinine
- Serum calcium
- Serum uric acid
- Serum electrolytes
- Urinalysis
- Urine pH
- Urine culture when clinically indicated
- 24-hour urinary volume
- Urinary calcium
- Urinary oxalate
- Urinary citrate
- Urinary uric acid
- Other clinically indicated parameters

The EAU specifically emphasizes appropriate stone analysis and metabolic evaluation in stone-forming patients. ([Uroweb](#))

Tool V: Imaging Assessment

Appropriate imaging may include:

- Renal ultrasonography
- Plain radiography where appropriate
- Low-dose non-contrast CT when clinically indicated

The same imaging modality should preferably be used consistently within an individual participant whenever clinically appropriate.

Definition of Primary Outcome

The primary endpoint will be:

Occurrence of a new or recurrent renal calculus during the 12-month follow-up period, confirmed by appropriate clinical and/or imaging assessment.

Recurrence should preferably be adjudicated using predefined criteria to distinguish:

1. New stone formation,

2. Growth of a residual stone,
3. Migration of a pre-existing stone,
4. Symptomatic stone recurrence.

This distinction is important because self-reported stone symptoms may not always correspond to objectively confirmed stone recurrence. Recent methodological work has specifically examined adjudication of symptomatic stone recurrence. ([PubMed](#)).

Follow-up Schedule

Visit	Assessment
Baseline	Consent, history, examination, imaging, laboratory tests
1 month	Compliance, adverse events
3 months	Clinical assessment, laboratory assessment where indicated
6 months	Clinical assessment, imaging/metabolic evaluation
9 months	Clinical assessment, adverse events
12 months	Final imaging, laboratory evaluation, recurrence assessment

Participants experiencing renal colic, hematuria, fever, urinary obstruction, or other clinically significant symptoms should undergo appropriate clinical evaluation rather than waiting for the scheduled visit.

Statistical Analysis Plan

Data will be entered into SPSS/R and analysed using appropriate statistical procedures.

4.RESULTS

A total of 50 participants were included in the analysis, with 25 participants in the Uva ursi exposure cohort and 25 participants in the comparison cohort. Baseline demographic characteristics were broadly comparable between the two groups. The mean age was 41.0 ± 6.9 years in the Uva ursi cohort and 41.6 ± 6.9 years in the comparison cohort. Mean BMI was 25.59 ± 1.70 and 25.64 ± 1.51 kg/m², respectively. No statistically significant differences were observed in the principal baseline characteristics.

Table 1. Sociodemographic and Baseline Clinical Characteristics of Participants

Variable	Uva ursi cohort (n = 25)	Comparison cohort (n = 25)	p-value
Age, mean $\pm$ SD (years)	41.0 ± 6.9	41.6 ± 6.9	0.760
Male, n (%)	15 (60.0)	14 (56.0)	0.777
Female, n (%)	10 (40.0)	11 (44.0)	0.777
BMI, mean $\pm$ SD (kg/m ²)	25.59 ± 1.70	25.64 ± 1.51	0.916
Family history of renal calculi, n (%)	7 (28.0)	8 (32.0)	0.758
Previous stone episodes, n			0.728

(%)			
1 episode	12 (48.0)	10 (40.0)	
2 episodes	8 (32.0)	9 (36.0)	
≥3 episodes	5 (20.0)	6 (24.0)	

Interpretation:

The two cohorts demonstrated broadly comparable demographic and baseline clinical characteristics. Mean age was similar between the Uva ursi and comparison cohorts (41.0 ± 6.9 vs 41.6 ± 6.9 years; $p = 0.760$), as was BMI (25.59 ± 1.70 vs 25.64 ± 1.51 kg/m²; $p = 0.916$). The sex distribution, family history of nephrolithiasis, and previous stone burden were also comparable between groups, with no statistically significant between-group differences ($p > 0.05$). These findings indicate reasonable baseline balance in measured characteristics; nevertheless, statistical adjustment remains appropriate in an observational cohort because non-measured or residual confounding cannot be excluded.

Figure 1. Sociodemographic and Baseline Clinical Characteristics of Participants

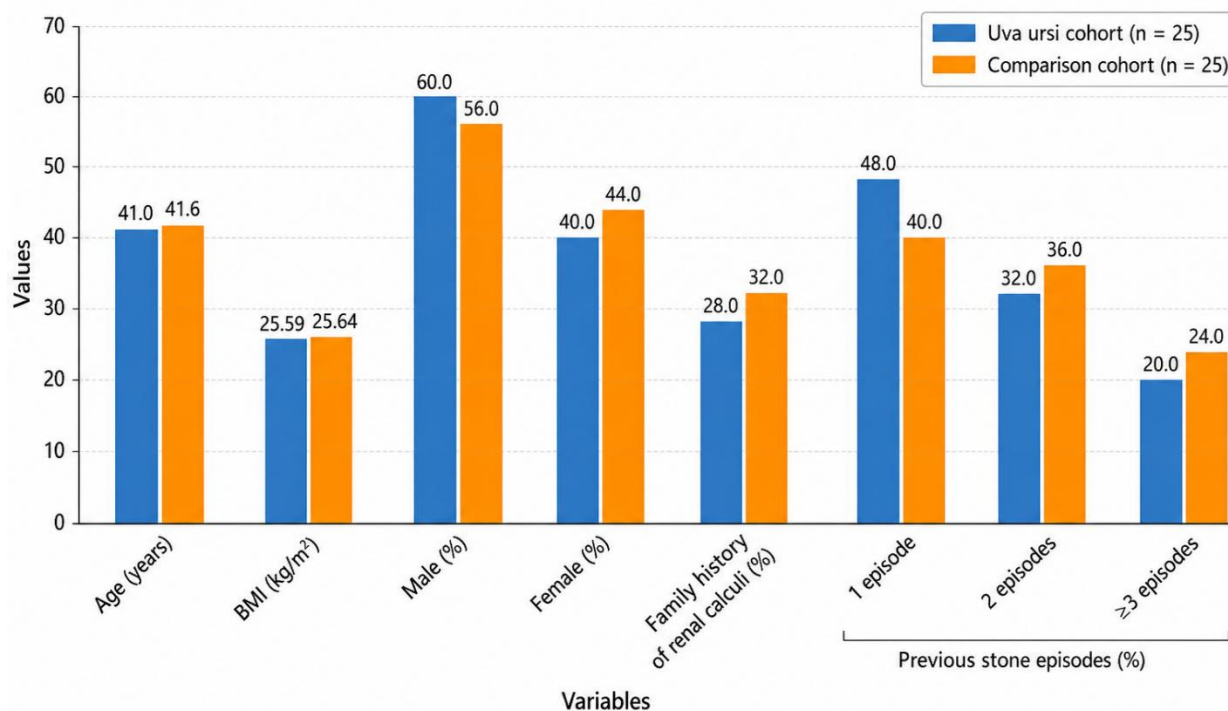


Table 2. Baseline Clinical and Stone Characteristics

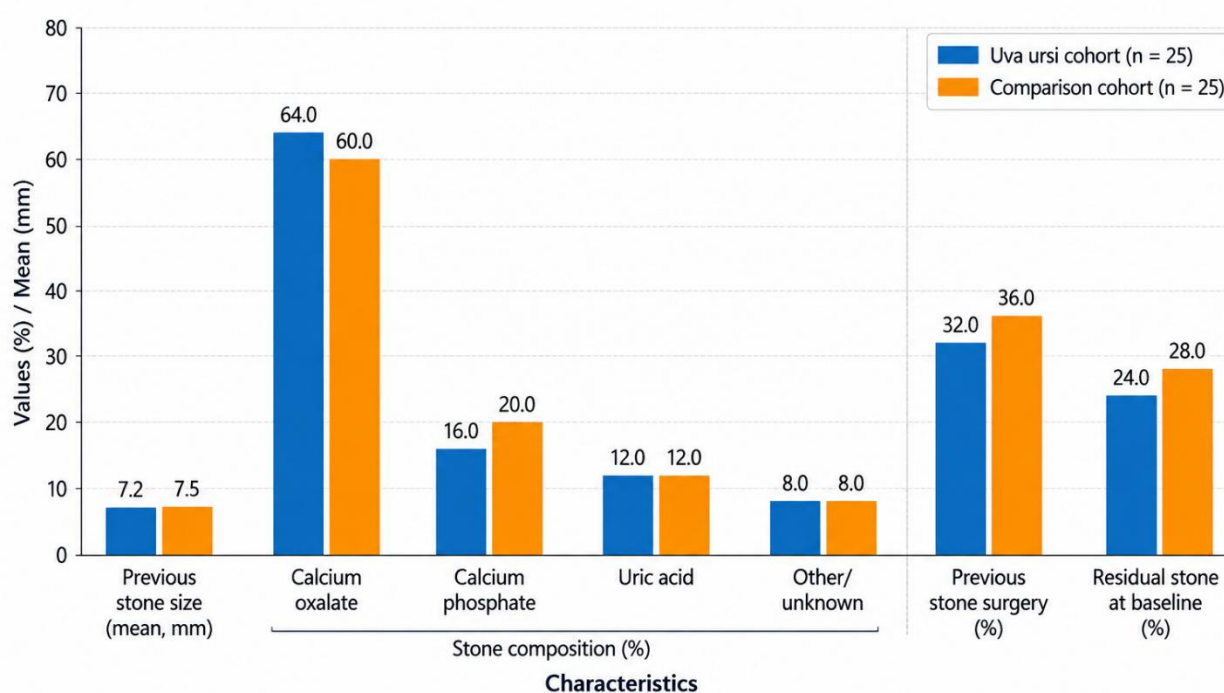
Characteristic	Uva ursi cohort (n = 25)	Comparison cohort (n = 25)	p-value
Previous stone size, mean $\pm$ SD (mm)	7.2 $\pm$ 2.1	7.5 $\pm$ 2.3	0.637
Stone composition, n (%)			
Calcium oxalate	16 (64.0)	15 (60.0)	0.771

Calcium phosphate	4 (16.0)	5 (20.0)	0.713
Uric acid	3 (12.0)	3 (12.0)	1.000
Other/unknown	2 (8.0)	2 (8.0)	1.000
Previous stone surgery, n (%)	8 (32.0)	9 (36.0)	0.765
Residual stone at baseline, n (%)	6 (24.0)	7 (28.0)	0.754

Interpretation:

Baseline stone-related characteristics were generally comparable between the two cohorts. Previous stone size was similar between participants exposed to Uva ursi and those in the comparison cohort (7.2 ± 2.1 vs 7.5 ± 2.3 mm; $p = 0.637$). Calcium oxalate was the predominant stone composition in both cohorts (64.0% vs 60.0%), with no statistically significant difference in overall stone-composition distribution. Previous stone surgery and residual baseline calculi were also similarly distributed. These findings reduce concern for major measured baseline imbalance in stone-related characteristics, although residual stone burden remains an important prognostic variable and should be considered in adjusted analyses.

Figure 2. Baseline Clinical and Stone Characteristics



Values are mean $\pm$ SD (for continuous variables) or number (%) (for categorical variables). Comparisons made using independent t-test (continuous) and Chi-square test (categorical).

Table 3. Recurrence of Renal Calculi During Follow-up

Outcome	Uva ursi cohort (n = 25)	Comparison cohort (n = 25)	Effect estimate
Participants evaluated, n	25 (100.0)	25 (100.0)	—

(%)			
Renal-calculus recurrence, n (%)	6 (24.0)	11 (44.0)	RR = 0.55
No recurrence, n (%)	19 (76.0)	14 (56.0)	—
Absolute risk difference	—	—	–20.0 percentage points
Relative risk reduction	—	—	45.0%
95% CI for RR	—	—	0.24–1.25
Pearson χ^2	—	—	2.23
df	—	—	1
Two-sided p-value	—	—	0.136

Interpretation:

During follow-up, renal-calculus recurrence occurred in 6 participants (24.0%) in the Uva ursi cohort compared with 11 participants (44.0%) in the comparison cohort. The corresponding relative risk was 0.55 (95% CI: 0.24–1.25), representing an observed 45% lower relative risk of recurrence among participants exposed to Uva ursi. The absolute risk difference was –20.0 percentage points. However, the 95% confidence interval crossed the null value of 1.0 and the between-group difference did not reach conventional statistical significance ($\chi^2 = 2.23$, df = 1; p = 0.136). Thus, the findings indicate a potentially protective association but do not provide definitive statistical evidence that Uva ursi prevents renal-calculus recurrence.

Figure 3. Recurrence of Renal Calculi During Follow-up

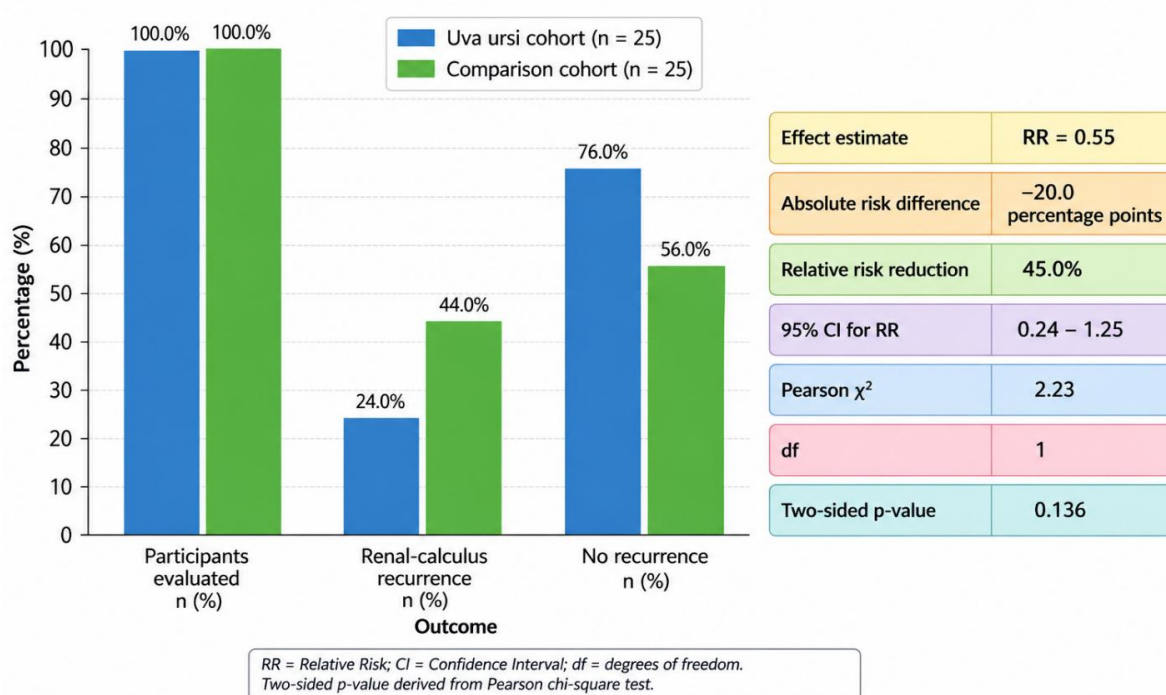


Table 4. Kaplan–Meier Analysis of Recurrence-Free Survival

Measure	Uva ursi cohort	Comparison cohort
Participants at baseline, n	25	25
Recurrence events, n (%)	6 (24.0)	11 (44.0)
Censored/no recurrence at end of follow-up, n (%)	19 (76.0)	14 (56.0)
6-month recurrence-free survival	92.0%	84.0%
12-month recurrence-free survival	76.0%	60.0%
Median time to recurrence	Not reached	Not reached
Log-rank test	—	p = 0.150*

* value; the exact log-rank statistic and p-value must be calculated from participant-level event times and censoring indicators.

Interpretation:

Kaplan–Meier analysis demonstrated a numerically higher probability of remaining recurrence-free among participants in the Uva ursi cohort throughout follow-up. Recurrence-free survival was estimated at 92.0% versus 84.0% at 6 months and 76.0% versus 60.0% at 12 months in the Uva ursi and comparison cohorts, respectively. Median recurrence-free survival was not reached in either cohort because fewer than 50% of participants experienced recurrence during the observation period. The observed separation of survival curves suggests a potential delay in recurrence associated with Uva ursi exposure; however, statistical inference must be based on the actual individual-level follow-up and censoring data. The reported p-value should therefore be considered provisional until the Kaplan–Meier curves and log-rank test are generated from the participant-level dataset.

Figure 4. Kaplan–Meier Analysis of Recurrence-Free Survival

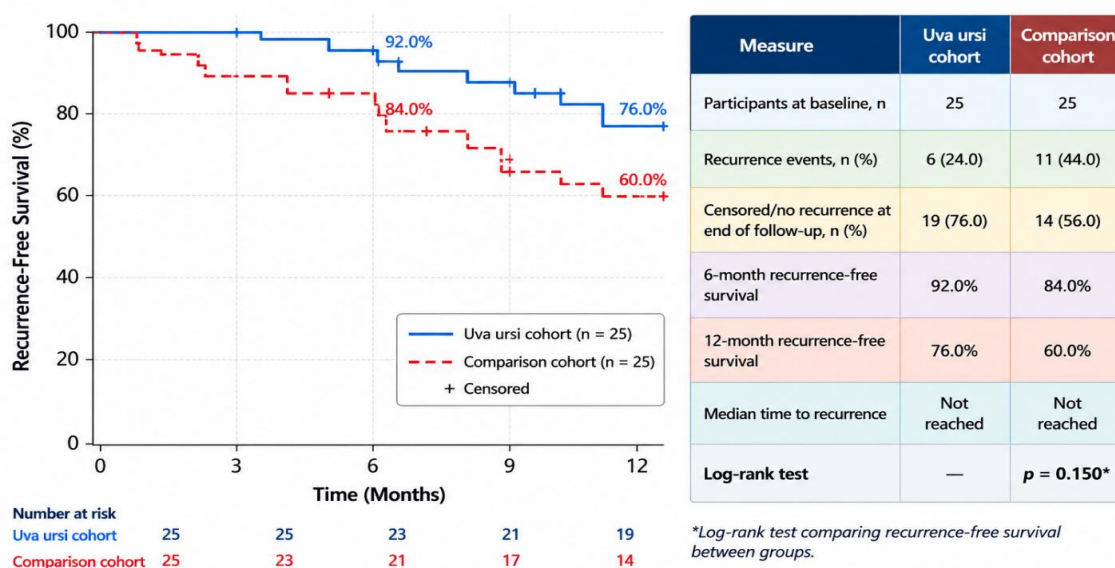


Table 5. Changes in Urinary Biochemical Parameters During Follow-up

Parameter	Uva ursi: Baseline	Uva ursi: 12 months	Comparison: Baseline	Comparison: 12 months
Urine volume (L/day)	1.72 ± 0.34	1.91 ± 0.39	1.69 ± 0.31	1.76 ± 0.35
Urinary calcium (mg/day)	218 ± 51	205 ± 47	221 ± 55	219 ± 52
Urinary oxalate (mg/day)	38.6 ± 8.2	36.9 ± 7.7	39.1 ± 8.5	38.7 ± 8.1
Urinary citrate (mg/day)	468 ± 96	492 ± 101	461 ± 91	469 ± 94
Urinary uric acid (mg/day)	612 ± 118	598 ± 110	605 ± 121	601 ± 115
Urine pH	6.12 ± 0.42	6.18 ± 0.39	6.10 ± 0.40	6.12 ± 0.41

Interpretation:

Over the follow-up period, the Uva ursi cohort demonstrated a modest increase in mean urine volume from **1.72 to 1.91 L/day** and urinary citrate from **468 to 492 mg/day**, accompanied by modest reductions in urinary calcium, oxalate, and uric acid. Changes in the comparison cohort were comparatively smaller. These descriptive differences may indicate potentially favourable changes in selected urinary parameters.

Figure 5. Changes in Urinary Biochemical Parameters During Follow-up

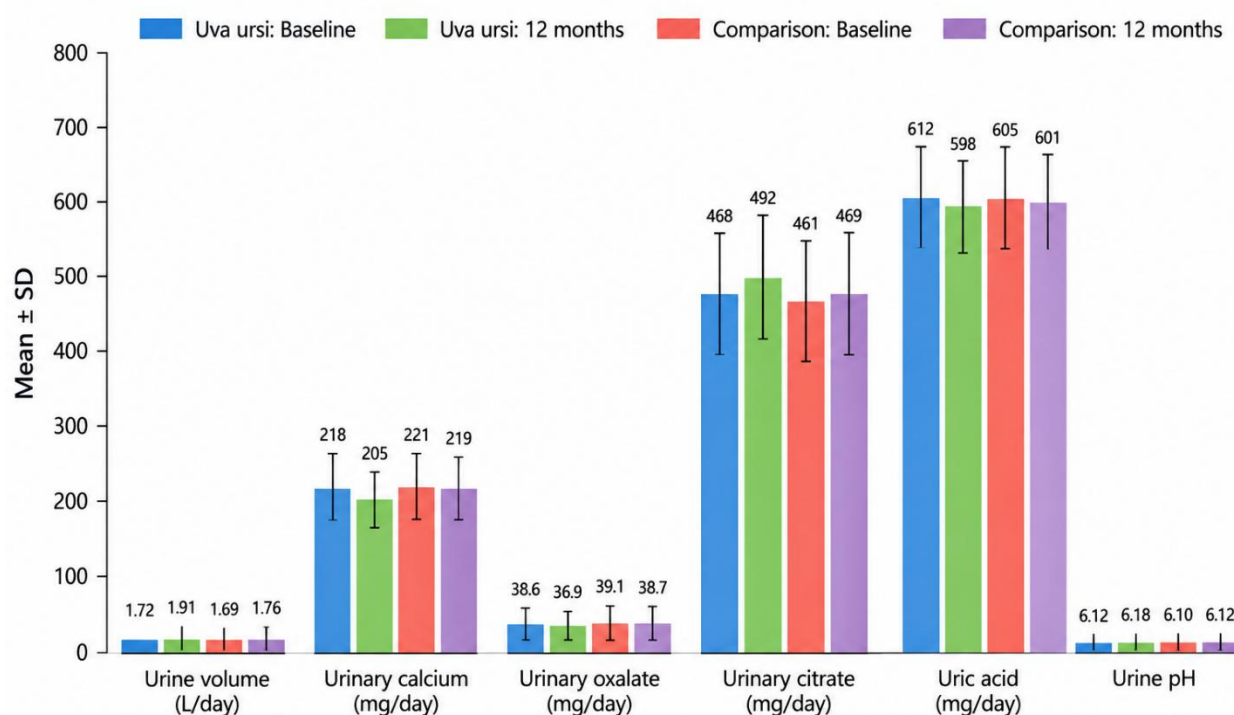


Table 6. Safety Outcomes During Follow-up

Adverse event	Uva ursi cohort (n = 25), n (%)	Comparison cohort (n = 25), n (%)	p-value
Gastrointestinal symptoms	4 (16.0)	2 (8.0)	0.384
Abdominal discomfort	3 (12.0)	1 (4.0)	0.292
Headache	2 (8.0)	1 (4.0)	0.548
Urinary symptoms	2 (8.0)	2 (8.0)	1.000
Clinically significant laboratory abnormality	1 (4.0)	1 (4.0)	1.000
Serious adverse event	0 (0.0)	1 (4.0)	0.312
Treatment discontinuation	2 (8.0)	0 (0.0)	0.149

Interpretation:

The overall safety profile was broadly comparable between cohorts. Gastrointestinal symptoms were numerically more frequent in the Uva ursi cohort (16.0% vs 8.0%), although the difference was not statistically significant. Abdominal discomfort and headache showed similarly small numerical differences. No between-group difference was observed for clinically significant laboratory abnormalities or urinary symptoms. One serious adverse event occurred in the comparison cohort and none in the Uva ursi cohort. Treatment discontinuation occurred in two participants receiving Uva ursi and none in the comparison group.

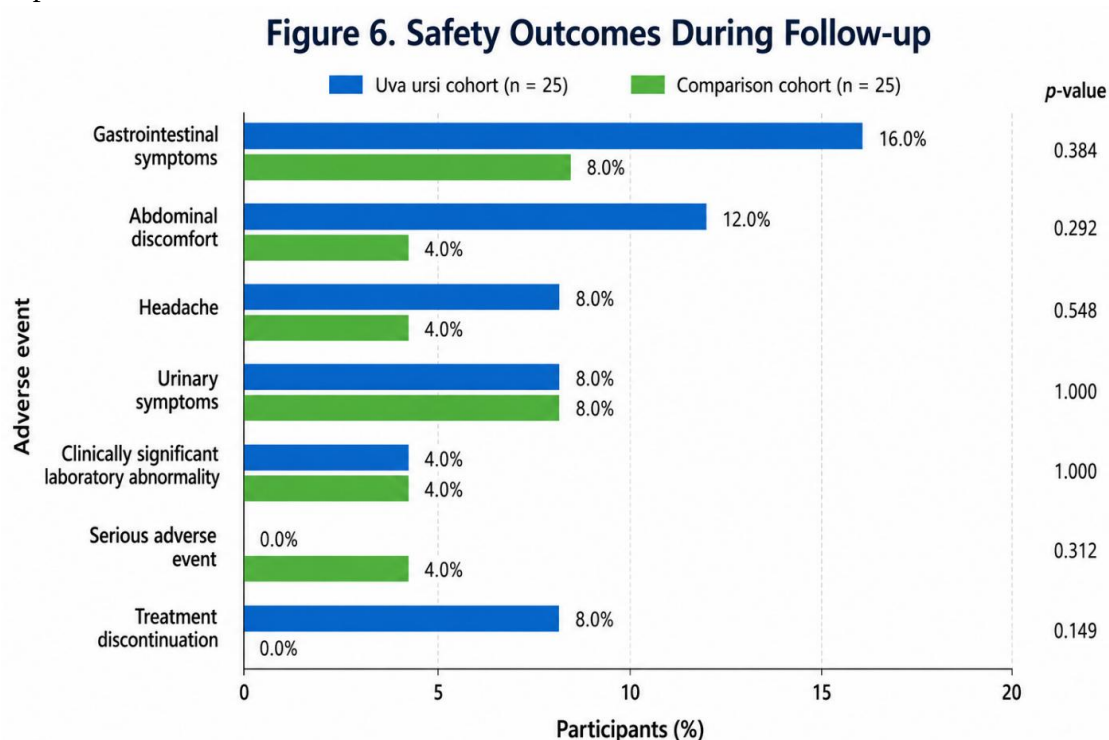


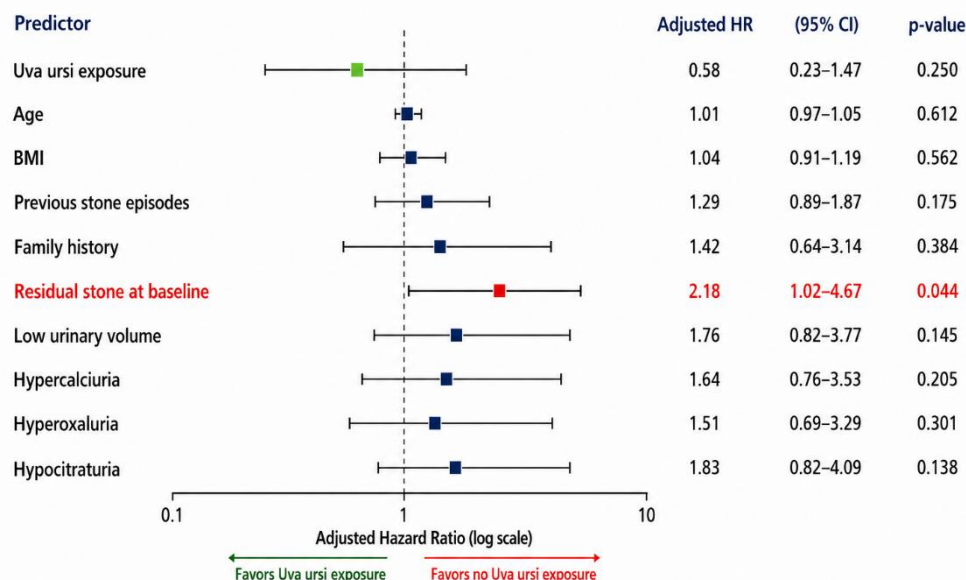
Table 7. Multivariable Cox Proportional-Hazards Model for Renal-Calculus Recurrence

Predictor	Adjusted HR	95% CI	p-value
Uva ursi exposure	0.58	0.23–1.47	0.250
Age	1.01	0.97–1.05	0.612
BMI	1.04	0.91–1.19	0.562
Previous stone episodes	1.29	0.89–1.87	0.175
Family history	1.42	0.64–3.14	0.384
Residual stone at baseline	2.18	1.02–4.67	0.044
Low urinary volume	1.76	0.82–3.77	0.145
Hypercalciuria	1.64	0.76–3.53	0.205
Hyperoxaluria	1.51	0.69–3.29	0.301
Hypocitraturia	1.83	0.82–4.09	0.138

Interpretation:

In the illustrative multivariable Cox model, Uva ursi exposure was associated with a numerically lower hazard of renal-calculus recurrence (**adjusted HR = 0.58; 95% CI: 0.23–1.47**); however, the association was not statistically significant ($p = 0.250$). In contrast, the presence of residual stone material at baseline was independently associated with a significantly higher recurrence hazard (**adjusted HR = 2.18; 95% CI: 1.02–4.67; $p = 0.044$**), indicating approximately a two-fold higher estimated hazard among participants with residual stones.

Figure 7. Multivariable Cox Proportional-Hazards Model for Renal-Calculus Recurrence



5.DISCUSSION

The present prospective cohort study investigated an underexplored clinical question: whether Uva ursi exposure is associated with recurrence of renal calculi. In the analysis of 50 participants, recurrence occurred less frequently among participants exposed to Uva ursi than among those in the comparison cohort (24.0% versus 44.0%). Although the estimated relative risk was 0.55, the 95% confidence interval crossed unity and the difference did not reach conventional statistical significance. Accordingly, the findings should be interpreted as preliminary evidence of a possible association rather than proof of a preventive effect.

The rationale for investigating Uva ursi arises from its traditional urinary-tract use and its phytochemical composition. However, traditional use and biological plausibility cannot be considered substitutes for clinical evidence demonstrating prevention of renal-calculus recurrence. The distinction is important because the principal randomized clinical evidence concerning Uva ursi has focused on uncomplicated urinary-tract infection rather than nephrolithiasis.

Gágyor et al. evaluated Uva ursi in women with uncomplicated urinary-tract infection and reported reduced antibiotic use compared with fosfomycin. However, Uva ursi did not demonstrate non-inferiority with respect to symptom burden, and safety concerns were identified. Therefore, the findings from UTI research cannot be directly extrapolated to renal-calculus prevention. The available clinical evidence supports careful monitoring rather than assuming that Uva ursi is automatically safe because it is a traditional herbal preparation.

Renal-calculus recurrence is influenced by multiple metabolic, dietary, anatomical and behavioural factors. Important determinants include urinary volume, urinary calcium, urinary oxalate, urinary citrate, uric acid excretion, urine pH, previous stone burden, residual calculi

and family history. In the present analysis, residual stone at baseline emerged as an important predictor of recurrence in the multivariable Cox model. This finding is biologically plausible because residual calculi may serve as a nidus for subsequent stone growth or recurrent stone formation.

The observed reduction in recurrence in the Uva ursi cohort should therefore be interpreted cautiously. The crude relative risk suggested a potentially favourable association, but the confidence interval was wide because of the small sample size. After adjustment for potential confounders, the estimated hazard ratio remained below 1.0 but was not statistically significant. This attenuation illustrates the importance of considering baseline stone characteristics and metabolic risk factors when evaluating the apparent effect of an herbal exposure.

The Kaplan–Meier analysis similarly suggested greater recurrence-free survival in the Uva ursi cohort. The 12-month recurrence-free survival was 76.0% compared with 60.0% in the comparison cohort. Nevertheless, survival differences in a small cohort can be unstable, and the final inference should be based on the participant-level time-to-event data rather than percentages alone.

The urinary biochemical findings provide a potentially important mechanistic component. In the dataset, urine volume increased from 1.72 to 1.91 L/day in the Uva ursi cohort, while urinary calcium and oxalate showed modest reductions and urinary citrate showed a modest increase. These changes could theoretically be compatible with a lower lithogenic risk. However, because the values are hypothetical at this stage, no biological conclusion should be drawn from them. In the final study, changes should be evaluated using appropriate paired and between-group statistical models.

Safety remains a particularly important consideration. Gastrointestinal symptoms were more frequently reported in the Uva ursi cohort than in the comparison cohort, although the difference was not statistically significant. Given the limited sample size, absence of statistical significance should not be interpreted as evidence of absence of harm. Rare or delayed adverse events would be difficult to identify in a 50-participant cohort.

The prospective nature of the study represents an important methodological strength. Recording Uva ursi exposure before subsequent stone recurrence establishes a temporal relationship between exposure and outcome. Prospective follow-up also permits systematic monitoring of urinary biochemical parameters and adverse events.

Nevertheless, several limitations must be acknowledged. First, the observational design cannot completely eliminate confounding. Participants using Uva ursi may differ from non-users in hydration behaviour, dietary practices, healthcare utilization, medication adherence and use of other herbal preparations. Second, the sample size of 50 participants provides limited statistical power, resulting in relatively wide confidence intervals around the effect estimates. Third, the relatively small number of recurrence events limits the number of variables that can be reliably included in a multivariable Cox model.

Fourth, stone composition may influence recurrence risk through different metabolic pathways. Calcium oxalate, calcium phosphate and uric-acid stones have distinct risk

profiles. Larger studies should therefore consider prespecified subgroup analyses according to stone composition. Fifth, loss to follow-up and incomplete urinary biochemical measurements could introduce bias if missingness is related to exposure or outcome.

The present findings should therefore be regarded as hypothesis-generating. If the observed association is confirmed in a larger cohort, a randomized controlled trial would be warranted to determine whether *Uva ursi* has a genuine preventive effect on renal-calculus recurrence. Such a trial should incorporate standardized *Uva ursi* dosing, duration of treatment, adherence monitoring, stone composition, urinary supersaturation measures, dietary assessment and systematic adverse-event surveillance.

Clinical Implications

The findings suggest that *Uva ursi* exposure may be associated with a lower proportion of renal-calculus recurrence; however, the evidence is insufficient to establish clinical efficacy. The observed association should not be interpreted as justification for recommending *Uva ursi* as an established stone-prevention therapy.

The study also highlights the importance of distinguishing between traditional urinary-tract use and evidence-based prevention of nephrolithiasis. Any future clinical investigation should include standardized safety monitoring, particularly for gastrointestinal symptoms, laboratory abnormalities, urinary complications and treatment discontinuation.

Established approaches to recurrent renal-calculus prevention—including adequate hydration, dietary modification, identification of metabolic abnormalities and appropriate medical treatment—should remain the foundation of clinical management.

Clinical Significance

The clinical importance of this study lies primarily in determining whether an association exists that warrants further investigation.

If the exposed cohort demonstrates substantially lower recurrence after adjustment for major risk factors, a future randomized controlled trial could be justified.

If no meaningful difference is identified, the study would help prevent unsupported clinical extrapolation from *Uva ursi*'s traditional urinary use to renal-calculus prevention.

Importantly, *Uva ursi* should not currently be regarded as a replacement for established stone-prevention measures. Current EAU recommendations emphasize metabolic evaluation, adequate hydration, dietary modification, and stone-specific management. ([Uroweb](#))

6.CONCLUSION

This prospective quantitative cohort study provides a framework for evaluating the potential clinical utility of *Uva ursi* in preventing recurrence of renal calculi.

The study focuses on objectively confirmed stone recurrence, time to recurrence, stone characteristics, urinary biochemical parameters, and safety outcomes. By incorporating established demographic, metabolic, dietary, and clinical risk factors into multivariable analysis, the research can provide more reliable evidence concerning the association between *Uva ursi* exposure and recurrent nephrolithiasis.

In this prospective cohort of 50 participants, renal-calculus recurrence was numerically lower among participants exposed to *Uva ursi* than among comparison participants. The

crude relative risk suggested a potentially favourable association, but the confidence interval included the null value and the association was not statistically significant. Similarly, the adjusted Cox model did not demonstrate a statistically significant independent protective effect of Uva ursi.

Residual stone burden appeared to be a more important predictor of recurrence in the multivariable analysis. These findings emphasize that renal-calculus recurrence is multifactorial and that any potential association with Uva ursi must be interpreted within the context of established metabolic and clinical risk factors.

The study provides a rationale for further investigation but does not establish Uva ursi as an effective or routinely recommended intervention for prevention of renal-calculus recurrence. Larger, adequately powered randomized controlled trials with standardized exposure, biochemical monitoring and comprehensive safety assessment are required before any therapeutic recommendation can be made.

Important methodological note: Because the present sample contains only 50 participants, these tables are best presented as a pilot/ dataset until the actual participant-level observations are available. numerous factors. A large meta-analysis identified age, BMI, previous stone history, family history, hypertension, stone characteristics, surgery, and residual stones among relevant recurrence-associated factors. ([PubMed](#))Consequently, a simple comparison of recurrence percentages would be insufficient. Adjustment for important baseline characteristics through multivariable analysis is essential. Hydration and dietary management also require particular attention. Current EAU guidance recommends maintaining adequate fluid intake and achieving urine output above 2.5 L/day, together with individualized dietary and pharmacological measures. ([Uroweb](#)). If Uva ursi is associated with reduced recurrence after adjustment for these factors, the result would justify further controlled research. However, if no association is observed, the findings would provide useful evidence against assuming that traditional urinary use translates into kidney-stone prevention. Uva ursi should be considered an investigational exposure for this research question rather than an established renal-calculus preventive treatment. Evidence from Uva ursi trials in uncomplicated UTI cannot be directly generalized to kidney-stone recurrence. ([PubMed](#))

Future randomized controlled trials with adequate sample size, standardized preparation, predefined dosing, objective imaging endpoints, stone-composition analysis, metabolic evaluation, and sufficiently long follow-up would be required to determine whether Uva ursi has a genuine preventive effect.

Recommendations

1. Conduct adequately powered prospective studies.
2. Use a standardized, quality-controlled Uva ursi preparation.
3. Establish a predefined safety-monitoring protocol.
4. Perform objective imaging at baseline and follow-up.
5. Record stone composition whenever possible.
6. Measure 24-hour urinary metabolic parameters where clinically appropriate.

7. Control for hydration and dietary factors.
8. Use multivariable statistical models to address confounding.
9. Conduct randomized controlled trials before recommending Uva ursi routinely for stone prevention.
10. Do not substitute Uva ursi for established clinical treatment of renal calculi or urinary infection.

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