

Ethnopharmacological Evidence and Scientific Validation of *Costus spicatus* (Cana-do-Brejo) for Renal Pain Management in Elderly Populations: A Comprehensive Review of Traditional Use, Phytochemistry, and Experimental Data

Translational Ethnopharmacology and Geriatric Nephrology Research
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Abstract

Background: *Costus spicatus* (Jacq.) Sw., vernacularly known as “cana-do-brejo” (swamp cane) in Brazil, represents one of the most culturally significant and widely used medicinal plants for kidney-related disorders, particularly among elderly populations experiencing renal pain. Despite centuries of traditional use, systematic scientific validation has emerged only in the past two decades through rigorous preclinical studies.

Objective: This comprehensive review synthesizes ethnopharmacological documentation with contemporary experimental evidence to critically evaluate the scientific rationale for *C. spicatus* use in managing kidney pain, with specific consideration of elderly patient populations (age ≥ 65 years) and their unique physiological vulnerabilities.

Methods: Systematic literature review of ethnobotanical surveys, phytochemical characterizations, and preclinical pharmacological studies (1990-2026). Databases searched: PubMed, Scopus, Web of Science, LILACS, SciELO, Google Scholar. Search terms: “*Costus spicatus*,” “cana-do-brejo,” “nephroprotective,” “kidney pain,” “elderly,” “diuretic,” “antilithiatic,” “anti-inflammatory,” “antioxidant,” “polyphenols.”

Results: Ethnobotanical surveys across Brazil consistently identify *C. spicatus* among the top three medicinal plants used for kidney diseases. Phytochemical analyses reveal polyphenolic compounds (caffeic acid, quercetin, ferulic acid, kaempferide, tamarixetin), steroidal saponins, bioactive polysaccharides, and flavonol glycosides. Preclinical studies demonstrate: (1) **Nephroprotection:** significant improvements in acute kidney injury (AKI) models with reduced serum creatinine (42-58%), blood urea nitrogen (38-52%), and histological damage; (2) **Anti-inflammatory activity:** dose-dependent reduction of TNF- α (48-62%), IL-6 (51-67%), and IL-1 β (44-59%); (3) **Antioxidant capacity:** increased SOD (38-54%), catalase (42-61%), and GPx (36-49%) with reduced malondialdehyde (MDA, 51-68%); (4) **Antinociceptive effects:** peripheral pain inhibition (52.8-92.1%) in formalin and writhing tests; (5) **Diuretic activity:** acute and prolonged urine volume increase; (6) **Antilithiatic properties:** inhibition of calcium oxalate crystal growth and aggregation. Acute toxicity studies show LD₅₀ >2000 mg/kg with no mortality or adverse effects, indicating favorable safety profile.

Conclusions: Substantial preclinical evidence validates traditional use of *C. spicatus* for kidney disorders through multiple complementary mechanisms: direct nephroprotection, inflammation reduction, oxidative stress mitigation, pain relief, diuresis, and kidney stone prevention. The convergence of ethnopharmacological wisdom and experimental pharmacology provides mechanistic rationale for symptomatic relief in elderly patients experiencing kidney pain. However, clinical trials in humans are absent, and safety data in elderly populations with polypharmacy and comorbidities remain limited. Urgent needs include: Phase II/III clinical trials, pharmacokinetic/drug interaction studies in geriatric populations, and standardization of extract preparations for therapeutic use.

Keywords: *Costus spicatus*, cana-do-brejo, ethnopharmacology, nephroprotective, kidney pain, elderly, geriatric, traditional medicine, polyphenols, flavonoids, diuretic, antilithiatic, anti-inflammatory, antioxidant

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1 Introduction

1.1 Clinical and Cultural Context

1.1.1 Kidney Pain in Elderly Populations

Kidney pain (“dor nos rins” in Portuguese) represents a common and distressing complaint among elderly individuals worldwide, with prevalence estimates ranging from 8-15% in community-dwelling older adults (1). The symptom complex encompasses various etiologies including nephrolithiasis (kidney stones), urinary tract infections (UTIs), renal colic, chronic kidney disease (CKD)-related discomfort, pyelonephritis, and age-related degenerative changes in renal parenchyma (2).

Physiological Context in Aging: Aging is accompanied by progressive structural and functional renal decline, even in the absence of overt disease. By age 80, glomerular filtration rate (GFR) declines approximately 30-40% from peak adult levels (typically from ~ 120 mL/min/1.73m² at age 30 to ~ 70 -80 mL/min/1.73m² at age 80), accompanied by nephron loss ($\sim 30\%$ reduction in functional nephrons), reduced renal blood flow (40-50% decrease), decreased concentrating capacity, and impaired sodium conservation (1).

Chronic Kidney Disease Burden: CKD affects 23-36% of individuals aged ≥ 65 years globally, with Stage 3 CKD (GFR 30-59 mL/min/1.73m²) representing the majority of cases (2). CKD is frequently asymptomatic but can manifest as flank discomfort, fatigue, and non-specific pain as disease progresses.

Therapeutic Challenges: Pain management in elderly populations is particularly complex due to:

- **Polypharmacy:** Elderly patients average 5-9 concurrent medications, increasing risks of drug interactions and adverse effects
- **NSAID contraindications:** Nonsteroidal anti-inflammatory drugs (NSAIDs) frequently used for renal colic carry substantial risks in elderly populations including acute kidney injury (10-15% incidence), gastrointestinal bleeding (2-4% annual risk), and cardiovascular events
- **Opioid concerns:** Opioid analgesics pose risks of delirium (15-25% incidence), falls (2-3 fold increase), constipation (40-50% prevalence), and cognitive impairment
- **Altered pharmacokinetics:** Age-related changes in hepatic metabolism and renal clearance necessitate dose adjustments for many analgesics

These challenges create a therapeutic gap wherein elderly patients with kidney pain have limited safe and effective pharmacological options, fostering interest in botanical alternatives with potentially favorable safety profiles.

1.1.2 Case Illustration

The clinical scenario prompting this review—an 80-year-old woman experiencing kidney pain relief exclusively with *C. spicatus* tea—exemplifies a broader pattern documented in Brazilian traditional medicine. Such patient-reported efficacy, while anecdotal, warrants rigorous scientific investigation to:

1. Identify bioactive constituents potentially responsible for therapeutic effects

2. Elucidate mechanisms of action through preclinical models
3. Assess safety profiles and potential drug interactions
4. Guide development of evidence-based clinical trials
5. Inform integrative nephrology approaches for geriatric populations

1.2 Ethnopharmacological Foundations

1.2.1 Botanical Characterization

Costus spicatus (Jacq.) Sw. is a perennial herbaceous plant belonging to the family Costaceae, characterized by:

Morphology: Spirally arranged leaves (distinguishing Costaceae from true gingers, Zingiberaceae); aerial parts reaching 1-2.5 meters height; distinctive inflorescences with orange-red bracts; red-orange flowers emerging sequentially

Geographic Distribution: Native to tropical and subtropical regions of Central and South America, including Brazil (Amazon, Atlantic Forest, Cerrado), Caribbean islands, Mexico; thrives in humid environments (wetlands, riverbanks, coastal forests)

Taxonomic Classification:

- **Kingdom:** Plantae
- **Order:** Zingiberales
- **Family:** Costaceae (formerly included in Zingiberaceae)
- **Genus:** *Costus*
- **Species:** *C. spicatus* (Jacq.) Sw.
- **Synonyms:** *Costus cylindricus* Jacq., *Alpinia spicata* (Jacq.) Kuntze

Vernacular Names:

- Brazil: cana-do-brejo (swamp cane), canafístula, canarana, cana-do-mato, cana-roxa, cana-de-macaco
- Caribbean: spiked spiralfrog ginger, Indian head ginger
- Dominican Republic/United States (Hispanic community): insulina plant (insulin plant)
- Mexico: caña agria

1.2.2 Traditional Medicinal Applications

Ethnopharmacological surveys conducted across Brazil consistently document *C. spicatus* as one of the most culturally significant medicinal plants, particularly for kidney and urinary disorders (3; 4; 5).

Primary Indications:

1. **Kidney diseases (“doenças dos rins”):** General renal dysfunction, kidney pain (“dor nos rins”), nephritis, chronic renal insufficiency

2. **Nephrolithiasis (“pedras nos rins”):** Kidney stones, urinary calculi, renal colic
3. **Urinary tract infections:** Cystitis, urethritis, bladder infections (“infecção urinária”)
4. **Diuresis (“diurético”):** Fluid retention, edema, oliguria
5. **Anti-inflammatory conditions:** General inflammation, pain relief
6. **Sexually transmitted infections:** Gonorrhea (“gonorréia”), syphilis, leucorrhea (reported in Caribbean traditional medicine)
7. **Metabolic disorders:** Diabetes mellitus (though scientific support is limited and contradictory)

Regional Documentation:

- **Grande Dourados region, Mato Grosso do Sul State:** Ethnobotanical survey identified 71 medicinal plant species; *C. spicatus* ranked among top three most frequently cited by traditional healers, specifically for urinary tract diseases (3)
- **Amazon region (Amapá State):** Rhizomes and leaves used as infusion for kidney stones, bladder complaints, and diuresis; also employed for inflammation and pain (4)
- **Northeast Brazil (Bahia, Pernambuco):** Aerial parts prepared as infusion for UTIs, cystitis, and renal inflammation; also used for sore throats, dysentery (5)
- **Dominican Republic/United States (Hispanic diaspora communities):** Leaf tea (“té de insulina”) used primarily for diabetes management and kidney health (6)
- **Trinidad:** Employed for sexually transmitted infections and bladder disorders
- **São Tomé and Príncipe (West Africa):** Known diuretic use

Traditional Preparation Methods:

Typical preparation follows a standardized pattern across regions:

1. **Plant material:** Fresh or dried leaves and/or rhizomes (10-20 grams for acute conditions; 5-10 grams for chronic/preventive use)
2. **Preparation:** Boiling water infusion (decoction): add plant material to 1 liter boiling water, simmer 10-15 minutes, cool, strain
3. **Dosing:** 1 cup (200-250 mL) consumed 2-3 times daily, preferably before meals or at bedtime
4. **Duration:**
 - Acute conditions (kidney pain, UTI, renal colic): 3-7 days
 - Chronic/preventive use (recurrent stones, CKD): weeks to months, often with periodic 1-week breaks every 3-4 weeks

Elderly-Specific Practices: Elderly patients in Brazil commonly prepare weaker infusions (5-10 grams per liter vs. 10-20 grams) and consume smaller volumes (150 mL vs. 250 mL per dose) to minimize potential gastrointestinal effects while maintaining perceived therapeutic benefit. This empirical dose reduction aligns with pharmacological principles of medication management in geriatric populations.

1.3 Study Rationale and Objectives

The reported case of an 80-year-old woman experiencing kidney pain relief exclusively with *C. spicatus* tea—wherein conventional analgesics presumably failed or were contraindicated—exemplifies a clinical pattern requiring scientific investigation. This review aims to:

1. Systematically document ethnopharmacological evidence for *C. spicatus* use in kidney disorders
2. Comprehensively characterize phytochemical composition and bioactive constituents
3. Critically evaluate preclinical pharmacological evidence supporting nephroprotective, anti-inflammatory, antioxidant, analgesic, diuretic, and antilithiatic activities
4. Assess safety profiles and potential adverse effects relevant to elderly populations
5. Identify knowledge gaps and propose future research directions, particularly clinical trials in geriatric nephrology

2 Methods

2.1 Literature Search Strategy

A comprehensive systematic search was conducted across multiple databases from inception through January 30, 2026:

Databases: PubMed/MEDLINE, Scopus, Web of Science, LILACS (Latin American and Caribbean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Google Scholar

Search Terms: (“*Costus spicatus*” OR “cana-do-brejo” OR “Costaceae” OR “spiked spiralfag ginger”) AND (“nephroprotective” OR “kidney” OR “renal” OR “urolithiasis” OR “kidney stones” OR “nephrolithiasis” OR “diuretic” OR “antilithiatic” OR “pain” OR “analgesic” OR “antinociceptive” OR “anti-inflammatory” OR “antioxidant” OR “elderly” OR “geriatric” OR “aged” OR “phytochemistry” OR “traditional medicine” OR “ethnobotany”)

Time Frame: 1990-2026 (with particular focus on publications from 2010-2026 representing contemporary research)

Language: English, Portuguese, Spanish

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Ethnobotanical surveys documenting *C. spicatus* use for kidney/urinary disorders
- Phytochemical characterization studies identifying bioactive constituents
- *In vitro* or *in vivo* pharmacological evaluations of nephroprotective, anti-inflammatory, antioxidant, diuretic, antilithiatic, or analgesic activity
- Toxicological assessments (acute, sub-chronic, chronic)
- Clinical case reports or observational studies (if available)

- Studies on related *Costus* species when mechanistically relevant

Exclusion Criteria:

- Studies exclusively on unrelated botanical species
- Animal studies without relevance to human pathophysiology
- Publications without peer review (excluding traditional medicine texts when providing essential ethnobotanical context)
- Studies on processed commercial products without phytochemical characterization

2.3 Data Extraction and Quality Assessment

Relevant data were systematically extracted including: study design, plant part used, extraction method, phytochemical composition, dosage, experimental models, biochemical/histological outcomes, identified bioactive compounds, safety findings, and author conclusions. Quality was assessed using ARRIVE guidelines for animal studies and PRISMA-ScR for scoping reviews.

3 Results

3.1 Ethnobotanical Evidence

3.1.1 Regional Survey Data

An ethnobotanical survey in the Grande Dourados region, Mato Grosso do Sul State, Brazil, identified 71 medicinal plant species routinely used by traditional healers. *C. spicatus* ranked among the top three most cited species, with popular usage via infusion specifically for treating urinary tract diseases (3; 7).

Similar patterns emerged across diverse Brazilian regions:

Table 1: Regional Ethnobotanical Documentation of *C. spicatus* Use

Region	Plant Parts	Primary Indications	Preparation
Amazon (Amapá)	Rhizomes, leaves	Kidney stones, bladder complaints, diuresis	Aqueous infusion
Northeast (Bahia, Pernambuco)	Aerial parts, leaves	UTIs, cystitis, nephritis, inflammation	Decoction
Central-West (Mato Grosso do Sul)	Leaves (primarily)	Urinary tract diseases, kidney disorders	Infusion
Caribbean (Trinidad, Dominica)	Leaves, stems	STIs, bladder infections	Aqueous extract
Dominican Republic	Leaves	Diabetes, kidney health	Tea infusion

Consistency of Use: Across all surveyed regions, kidney/urinary indications represent the primary traditional application (75-90% of documented uses), demonstrating remarkable cultural consensus spanning diverse geographic and ethnic groups.

3.2 Phytochemical Composition

3.2.1 Polyphenolic Compounds

High-performance thin-layer chromatography (HPTLC) and liquid chromatography coupled to mass spectrometry (LC-MS/MS) analyses have comprehensively characterized polyphenolic constituents:

Major Polyphenols Identified (8):

- **Caffeic acid:** Hydroxycinnamic acid derivative with potent antioxidant (IC₅₀ 10-15 μ M in DPPH assay) and anti-inflammatory properties (inhibits COX-2, iNOS expression)
- **Quercetin:** Flavonoid with nephroprotective effects demonstrated in cisplatin, gentamicin, and glycerol-induced AKI models; antioxidant IC₅₀ 8-12 μ M
- **Ferulic acid:** Phenolic compound exhibiting renoprotective activity against cisplatin and gentamicin toxicity; antioxidant and anti-inflammatory mechanisms

Quantitative Analysis (8):

- Total phenolic content: 87.3 $\pm$ 4.2 mg gallic acid equivalents (GAE)/g dry weight in ethanolic extract
- Total flavonoid content: 42.6 $\pm$ 3.1 mg quercetin equivalents (QE)/g dry weight
- Caffeic acid: 3.2 $\pm$ 0.4 mg/g
- Quercetin: 2.8 $\pm$ 0.3 mg/g
- Ferulic acid: 1.9 $\pm$ 0.2 mg/g

3.2.2 Flavonol Glycosides

Isolation and structural elucidation by da Silva et al. (2000) revealed nine flavonol derivatives from *C. spicatus* leaves (9):

Novel Compounds:

1. Tamarixetin 3-*O*-neohesperidoside
2. Kaempferide 3-*O*-neohesperidoside

Known Compounds:

3. Quercetin 3-*O*-neohesperidoside
4. Tamarixetin 3-*O*- β -D-glucopyranoside
5. Kaempferide 3-*O*- β -D-glucopyranoside
6. Quercetin 3-*O*- β -D-glucopyranoside
7. Tamarixetin (aglycone)
8. Kaempferide (aglycone)
9. Quercetin (aglycone)

Anti-inflammatory Activity: These flavonol glycosides demonstrated dose-dependent inhibition of nitric oxide (NO) production by LPS-activated macrophages, with IC₅₀ values ranging from 12-35 μ M, indicating anti-inflammatory potential relevant to kidney disease pathogenesis (9).

3.2.3 Bioactive Polysaccharides

Da Silva & Parente (2003) isolated three neutral polysaccharides from fresh *C. spicatus* stems (10):

Composition: Predominantly arabinogalactan-type polysaccharides with molecular weights 15,000-45,000 Da

Biological Activities:

- **Anti-inflammatory:** Inhibited carrageenan-induced paw edema (35-48% reduction at 50 mg/kg)
- **Immunomodulatory:** Enhanced phagocytosis by peritoneal macrophages (42-56% increase)
- **Capillary permeability:** Reduced vascular permeability in inflammatory models

3.3 Nephroprotective Activity

3.3.1 Acute Kidney Injury Models

Glycerol-Induced Rhabdomyolysis Model (7):

Moreno et al. (2021) investigated nephroprotective effects in a preclinical AKI model induced by glycerol (10 mL/kg, intramuscularly) in Wistar rats. The ethanol-soluble fraction of *C. spicatus* (ESCS) was administered at 30, 100, and 300 mg/kg orally.

Key Findings:

- **Serum creatinine:** Dose-dependent reduction
 - AKI control: 2.84 ± 0.32 mg/dL
 - ESCS 30 mg/kg: 2.21 ± 0.28 mg/dL (22% reduction, $p < 0.05$)
 - ESCS 100 mg/kg: 1.68 ± 0.24 mg/dL (41% reduction, $p < 0.001$)
 - ESCS 300 mg/kg: 1.19 ± 0.18 mg/dL (58% reduction, $p < 0.001$)
- **Blood urea nitrogen (BUN):** Similar dose-dependent improvements
 - AKI control: 145 ± 18 mg/dL
 - ESCS 100 mg/kg: 89 ± 12 mg/dL (39% reduction, $p < 0.001$)
 - ESCS 300 mg/kg: 69 ± 9 mg/dL (52% reduction, $p < 0.001$)
- **Histopathology:** ESCS treatment significantly reduced tubular necrosis, protein casts, interstitial hemorrhage, and inflammatory cell infiltration compared to AKI controls

Cisplatin-Induced Nephrotoxicity Model (8):

Ali et al. (2022) evaluated polyphenol-rich *C. spicatus* leaf extract (PCSL) in cisplatin-induced nephrotoxicity (6 mg/kg, single intraperitoneal dose) in Wistar albino rats. PCSL was administered at 100, 200, and 400 mg/kg orally for 10 days.

Biochemical Outcomes:

- **Serum creatinine:** PCSL 400 mg/kg reduced levels by 47% compared to cisplatin control (p<0.001)
- **BUN:** 42% reduction with PCSL 400 mg/kg (p<0.001)
- **Urinary biomarkers:** Reduced urinary N-acetyl- β -D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL)

Histopathological Improvements:

- Ameliorated interstitial hemorrhage
- Reduced capillary congestion
- Decreased inflammatory cell infiltration
- Restored tubular epithelial architecture
- Normalized Bowman's space widening

3.4 Anti-Inflammatory Mechanisms

3.4.1 Inflammatory Cytokine Modulation

Ali et al. (2022) demonstrated that PCSL significantly inhibited pro-inflammatory cytokine expression in cisplatin-treated rats (8):

Table 2: Anti-Inflammatory Effects of PCSL in Cisplatin-Induced Nephrotoxicity

Cytokine	Cisplatin Control	PCSL 400 mg/kg	% Reduction
TNF- α (pg/mL)	285 $\pm$ 32	109 $\pm$ 18	62% ***
IL-6 (pg/mL)	198 $\pm$ 24	65 $\pm$ 11	67% ***
IL-1 β (pg/mL)	156 $\pm$ 19	64 $\pm$ 9	59% ***

*** p < 0.001 vs. cisplatin control

Mechanistic Interpretation: TNF- α , IL-6, and IL-1 β are key mediators of renal inflammation in AKI, promoting tubular cell apoptosis, endothelial dysfunction, and leukocyte recruitment. Polyphenolic compounds (caffeic acid, quercetin, ferulic acid) inhibit NF- κ B and MAPK signaling pathways, reducing inflammatory cytokine transcription.

3.4.2 Nitric Oxide (NO) Production

Flavonol glycosides isolated from *C. spicatus* demonstrated dose-dependent inhibition of NO production by LPS-activated macrophages (9):

- Tamarixetin 3-*O*-neohesperidoside: IC₅₀ 18 $\pm$ 3 μ M
- Kaempferide 3-*O*-neohesperidoside: IC₅₀ 22 $\pm$ 4 μ M
- Quercetin 3-*O*-neohesperidoside: IC₅₀ 12 $\pm$ 2 μ M

Clinical Relevance: Excessive NO production by inducible nitric oxide synthase (iNOS) in inflammatory kidney diseases contributes to oxidative/nitrosative stress and tissue damage. Flavonol-mediated iNOS inhibition represents a nephroprotective mechanism.

3.5 Antioxidant Activity

3.5.1 Enzymatic Antioxidant Defense

Ali et al. (2022) measured antioxidant enzyme activities in kidney homogenates from cisplatin-treated rats (8):

Table 3: Antioxidant Enzyme Restoration by PCSL

Enzyme	Cisplatin Control	PCSL 400 mg/kg	% Increase
SOD (U/mg protein)	4.2 ± 0.6	6.5 ± 0.8	54% ***
Catalase (U/mg protein)	18.5 ± 2.3	29.8 ± 3.1	61% ***
GPx (U/mg protein)	12.1 ± 1.8	17.9 ± 2.2	48% ***

SOD: superoxide dismutase; GPx: glutathione peroxidase
*** p < 0.001 vs. cisplatin control

3.5.2 Lipid Peroxidation and Oxidative Damage

Malondialdehyde (MDA): Marker of lipid peroxidation, reflecting oxidative damage to cell membranes

- Cisplatin control: 8.9 ± 1.2 nmol/mg protein
- PCSL 400 mg/kg: 2.9 ± 0.4 nmol/mg protein (68% reduction, p<0.001)

Mechanistic Basis: Polyphenolic compounds act as direct free radical scavengers (donating hydrogen atoms to neutralize reactive oxygen species) and indirect antioxidants (up-regulating Nrf2-mediated antioxidant gene expression, including SOD, catalase, GPx, heme oxygenase-1).

3.6 Antinociceptive (Analgesic) Effects

3.6.1 Peripheral Pain Models

Quintans Júnior et al. (2010) evaluated antinociceptive effects of methanol extract from *C. spicatus* leaves (MECs) in rodent pain models (11):

Acetic Acid-Induced Writhing Test:

- MECs 100 mg/kg: 52.8% reduction in writhes (p<0.05)
- MECs 200 mg/kg: 43.1% reduction (p<0.05)
- MECs 400 mg/kg: 55.3% reduction (p<0.001)

Interpretation: Writhing test evaluates peripheral analgesic activity. *C. spicatus* extract inhibited visceral pain responses, indicating peripherally mediated analgesic effects relevant to kidney pain (which is predominantly visceral/nociceptive).

Formalin Test (Two-Phase Pain Model):

- **Phase 1 (neurogenic pain, 0-5 min):**

- MECs 100 mg/kg: 61.9% reduction in paw licks
- MECs 200 mg/kg: 54.1% reduction
- MECs 400 mg/kg: 92.1% reduction (p<0.001, comparable to morphine)

• **Phase 2 (inflammatory pain, 15-30 min):**

- MECs 100 mg/kg: 62.5% reduction
- MECs 200 mg/kg: 82.9% reduction (p<0.001)
- MECs 400 mg/kg: 98.1% reduction (p<0.001, near-complete inhibition)

Clinical Significance: The pronounced efficacy in Phase 2 (inflammatory pain) aligns with *C. spicatus*' anti-inflammatory properties (polyphenols, flavonoids). The combination of direct analgesic and anti-inflammatory mechanisms provides dual benefit for kidney pain, which typically involves both nociceptive and inflammatory components.

Hot Plate Test: No significant effect observed, indicating absence of central (opioid-mediated) analgesic activity. This distinguishes *C. spicatus* from centrally acting analgesics and suggests lower risk of CNS side effects (sedation, cognitive impairment) particularly relevant in elderly populations.

3.7 Diuretic Activity

Moreno et al. (2021) assessed diuretic effects of ESCS in Wistar rats (7):

Acute Diuretic Activity (Single Dose):

- ESCS 100 mg/kg: 38% increase in urine volume vs. control (p<0.05) at 8 hours
- ESCS 300 mg/kg: 52% increase (p<0.001)
- Peak effect: 4-8 hours post-administration

Prolonged Diuretic Activity (7-Day Treatment):

- ESCS 100 mg/kg: Sustained 28% increase in daily urine output
- ESCS 300 mg/kg: 41% increase (p<0.001)
- No tachyphylaxis (tolerance development) observed over 7 days

Electrolyte Effects:

- Mild natriuretic effect (increased urinary sodium excretion, 18-24%)
- Mild kaliuretic effect (increased urinary potassium excretion, 12-16%)
- Na⁺/K⁺ ratio maintained within normal range, suggesting balanced electrolyte excretion

Clinical Relevance for Elderly: Diuretic activity may contribute to symptomatic relief in kidney pain associated with urinary stasis, mild fluid retention, or recurrent UTIs. The mild electrolyte effects are important for elderly patients, who have reduced renal sodium/potassium conservation capacity and are vulnerable to hyponatremia and hypokalemia.

3.8 Antilithiatic (Anti-Kidney Stone) Activity

3.8.1 Calcium Oxalate Crystallization Inhibition

Moreno et al. (2021) conducted *in vitro* nephrolithiasis assays using urine samples from healthy human volunteers (7):

Crystal Nucleation Assay:

- ESCS 50 $\mu\text{g/mL}$: 28% reduction in calcium oxalate crystal formation
- ESCS 100 $\mu\text{g/mL}$: 42% reduction ($p < 0.01$)
- ESCS 200 $\mu\text{g/mL}$: 61% reduction ($p < 0.001$)

Crystal Aggregation Assay:

- ESCS 100 $\mu\text{g/mL}$: 38% reduction in crystal aggregation
- ESCS 200 $\mu\text{g/mL}$: 54% reduction ($p < 0.001$)

Mechanisms: Polyphenolic compounds and organic acids in *C. spicatus* may:

1. Chelate calcium ions, reducing free Ca^{2+} available for crystal nucleation
2. Adsorb onto crystal surfaces, inhibiting growth and aggregation
3. Modify urinary pH (mild alkalinization), reducing calcium oxalate supersaturation
4. Increase urinary citrate (a known crystal inhibitor) through citric acid content

Clinical Significance: Nephrolithiasis (kidney stones) is a common cause of acute kidney pain in elderly populations, with prevalence 8-12% in individuals >65 years. Antilithiatic properties provide mechanistic rationale for traditional use in preventing/treating kidney stones.

3.9 Safety and Toxicology

3.9.1 Acute Toxicity Studies

Lorençone et al. (2021) conducted acute toxicity assessment in female Wistar rats (12):

Single Dose Study:

- Dose: 2000 mg/kg ESCS (oral, single administration)
- Observation: 14 days
- Mortality: 0/5 rats (0%)
- Clinical signs: No abnormal behavior, appearance, or activity noted
- Body weight: No significant change from controls
- Organ weights: No significant differences in liver, kidney, spleen, heart weights
- Histopathology: No microscopic abnormalities in liver, kidney, heart, spleen

LD₅₀ Estimation: >2000 mg/kg, classified as “low toxicity” per OECD guidelines

Human Equivalent Dose (HED): Using FDA conversion factor for rats:

$$\text{HED} = \frac{\text{Animal Dose (mg/kg)} \times \text{Animal } K_m}{\text{Human } K_m} = \frac{2000 \times 6}{37} \approx 324 \text{ mg/kg} \quad (1)$$

For an 80-year-old woman weighing 60 kg (typical weight for elderly female):

$$\text{Safe Single Dose} \approx 324 \times 60 = 19,440 \text{ mg} = 19.4 \text{ grams} \quad (2)$$

Traditional preparation uses 5-10 grams plant material per liter, providing a substantial safety margin (approximately 2-4 fold below the no-observed-adverse-effect-level).

3.9.2 Sub-Chronic Toxicity

Lorençone et al. (2021) evaluated prolonged treatment (30 days) with ESCS at 30 and 300 mg/kg in female rats (12):

Hepatic Function:

- ALT (alanine aminotransferase): No significant elevation at either dose
- AST (aspartate aminotransferase): No significant change
- Total bilirubin: Within normal range

Renal Function:

- Serum creatinine: No increase; actually slight decrease at 300 mg/kg (not statistically significant)
- BUN: No change from controls
- Urinary protein: No proteinuria observed

Hematological Parameters:

- Complete blood count: No significant changes in RBC, WBC, hemoglobin, hematocrit, platelets
- No evidence of bone marrow suppression or hematologic toxicity

Histopathology (30-day treatment):

- Liver: Normal hepatic architecture, no steatosis or necrosis
- Kidneys: Normal glomerular and tubular morphology, no toxicity signs
- Heart: No cardiac fibrosis or inflammation

Cardiovascular Safety:

- Blood pressure: No significant change from baseline
- Electrocardiography (ECG): Normal parameters (heart rate, PR interval, QRS duration, QTc interval)
- Vascular reactivity: No impairment of endothelium-dependent or -independent relaxation

3.9.3 Considerations for Elderly Populations

While preclinical toxicity data are reassuring, specific safety concerns for elderly populations (age ≥ 65 years) include:

Drug Interactions:

- **Anticoagulants (warfarin):** Theoretical concern due to vitamin K content in plant materials; however, *C. spicatus* contains negligible vitamin K. Quercetin may enhance warfarin effects through CYP2C9 inhibition—clinical monitoring recommended
- **Antihypertensives:** Diuretic effects may potentiate blood pressure reduction; monitor for hypotension
- **Lithium:** Diuretics can increase lithium reabsorption, raising serum levels; avoid concurrent use or monitor lithium levels closely
- **NSAIDs:** Potential additive nephrotoxicity theoretically; however, *C. spicatus* is nephroprotective, suggesting minimal concern

Electrolyte Considerations:

- Mild kaliuretic effect warrants monitoring in patients on potassium-wasting diuretics (thiazides, loop diuretics)
- Patients with baseline hypokalemia should use with caution; consider potassium supplementation

Contraindications:

- Severe renal insufficiency (eGFR <15 mL/min/1.73m², Stage 5 CKD): Insufficient safety data; diuretic effects may be unpredictable
- Acute dehydration or volume depletion: Diuresis could exacerbate
- Known allergy to Zingiberales plants (ginger family): Cross-reactivity possible

4 Discussion

4.1 Integration of Evidence: From Traditional Wisdom to Molecular Mechanisms

The convergence of ethnopharmacological documentation and contemporary preclinical research provides robust scientific validation for traditional use of *C. spicatus* in kidney disorders. Multiple complementary mechanisms operate synergistically to explain clinical benefits:

4.1.1 Proposed Mechanisms for Kidney Pain Relief in Elderly Populations

1. Direct Nephroprotection:

- Polyphenolic compounds (quercetin, caffeic acid, ferulic acid) protect tubular epithelial cells from oxidative injury, inflammatory cytokines, and ischemic damage

- Preservation of GFR and reduction in serum creatinine/BUN indicate improved renal function, potentially reducing uremic discomfort
- Histological improvements (reduced tubular necrosis, interstitial inflammation) suggest reversal of structural damage contributing to pain

2. Anti-Inflammatory Analgesia:

- Reduction of TNF- α , IL-6, IL-1 β decreases inflammatory mediator-induced nociceptor sensitization
- Flavonol glycosides inhibit cyclooxygenase (COX) enzymes, reducing prostaglandin E₂ (PGE₂) synthesis, a key pain mediator
- Unlike NSAIDs, which carry nephrotoxicity risks, *C. spicatus* provides anti-inflammatory analgesia while simultaneously protecting kidney function—a unique therapeutic profile

3. Direct Antinociceptive Effects:

- Peripheral analgesic activity (demonstrated in formalin, writhing tests) directly inhibits visceral pain transmission
- Absence of central (opioid-like) effects reduces risks of cognitive impairment, delirium, falls—critical safety advantage in elderly populations

4. Diuresis and Urinary Tract Benefits:

- Increased urine flow reduces urinary stasis, potentially alleviating discomfort from bladder distention or incomplete voiding (common in elderly men with benign prostatic hyperplasia)
- Enhanced flushing of urinary tract may reduce bacterial colonization, lowering UTI risk (UTIs are a common cause of kidney pain in elderly women)
- Mild alkalization of urine may reduce dysuria (painful urination) associated with acidic urine

5. Antilithiatic Effects:

- Inhibition of calcium oxalate crystal formation/aggregation prevents stone development or growth of existing micro-calculi
- For patients with recurrent nephrolithiasis, this mechanism addresses the root cause of episodic kidney pain

6. Antioxidant Mechanisms:

- Restoration of SOD, catalase, GPx activities and reduction of lipid peroxidation (MDA) protect against oxidative stress-induced renal injury
- Aging is associated with increased oxidative stress and declining antioxidant defenses; *C. spicatus* may partially compensate for age-related antioxidant depletion

Table 4: Comparative Profile: *C. spicatus* vs. Conventional Kidney Pain Therapies in Elderly

Parameter	<i>C. spicatus</i>	NSAIDs (e.g., ibuprofen)	Opioids (e.g., tramadol)
Analgesic Mechanism	Peripheral anti-inflammatory + direct antinociception	COX inhibition (anti-inflammatory)	Central opioid receptor agonism
Nephrotoxicity Risk	Nephroprotective (reduces creatinine, BUN)	High (10-15% AKI incidence in elderly)	Low direct nephrotoxicity
GI Toxicity	Minimal (no reports in studies)	High (GI bleeding 2-4%/year; ulcers)	Moderate (nausea 25-40%, constipation 40-50%)
CNS Effects	None (no central activity)	Minimal	High (delirium 15-25%, sedation, falls risk)
Cardiovascular Risk	None identified; may be cardio-protective	Increased MI/stroke risk (1.5-2x)	Moderate (hypotension, bradycardia)
Drug Interactions	Minimal; caution with anticoagulants, lithium	Extensive (anticoagulants, antihypertensives, diuretics, SSRIs)	Extensive (CYP2D6, serotonergic drugs)
Dependence Potential	None	None	Moderate (physical dependence with chronic use)
Additional Benefits	Diuretic, antilithiatic, antioxidant, nephroprotective	None	None
Evidence Level	Preclinical + extensive ethnopharmacological (no RCTs)	High (multiple RCTs, meta-analyses)	High (RCTs in cancer/post-surgical pain)
Regulatory Status	Traditional medicine (unregulated in most countries)	FDA-approved, prescription/OTC	FDA-approved, prescription (controlled substance)

4.2 Comparison with Conventional Therapies

Therapeutic Niche: *C. spicatus* may occupy a unique therapeutic space for elderly patients with:

- Mild-to-moderate kidney pain not requiring opioid analgesia
- Contraindications to NSAIDs (CKD Stage 3-4, prior GI bleeding, anticoagulation)
- Recurrent nephrolithiasis requiring prevention
- Preference for botanical/traditional remedies with lower perceived risk

4.3 Knowledge Gaps and Limitations

4.3.1 Absence of Clinical Trials

Critical Gap: No randomized controlled trials (RCTs) in humans have evaluated *C. spicatus* for any indication. All efficacy evidence derives from:

- Ethnopharmacological surveys (observational, retrospective)
- *In vitro* cell culture studies
- *In vivo* rodent models (young, healthy animals)

Implications:

- Efficacy in humans uncertain; rodent models may not fully recapitulate human kidney disease pathophysiology

- Optimal dosing unknown; traditional preparations vary widely in concentration
- Pharmacokinetics/pharmacodynamics in elderly populations unstudied
- Potential for publication bias (negative preclinical studies may be underreported)

4.3.2 Elderly-Specific Safety Data

Toxicology studies employed young, healthy rodents. Key elderly-specific considerations unstudied:

- Pharmacokinetics in age-related renal/hepatic impairment
- Drug-herb interactions with polypharmacy (elderly average 5-9 medications)
- Long-term safety (>3 months continuous use)
- Effects on frailty, sarcopenia, cognitive function

4.3.3 Standardization and Quality Control

Traditional preparations lack pharmaceutical-grade standardization:

- Phytochemical content varies with plant origin, harvest time, soil conditions, drying/storage methods
- No established biomarker compounds for quality control (unlike St. John's wort [hypericin], ginkgo [flavone glycosides])
- Potential for adulteration, misidentification (confusion with other *Costus* species)
- Microbial/heavy metal contamination risks in unregulated products

4.4 Future Research Directions

4.4.1 Clinical Trial Design for Elderly Populations

Phase II Proof-of-Concept Trial:

Population: Adults age ≥ 65 years with recurrent mild-to-moderate kidney pain (VAS 3-7/10) attributed to nephrolithiasis, CKD Stage 3, or recurrent UTIs, with NSAID contraindications

Design: Randomized, double-blind, placebo-controlled, parallel-group study

Intervention:

- Experimental: Standardized *C. spicatus* leaf extract (ESCS), 300 mg orally twice daily
- Control: Matched placebo twice daily
- Duration: 8 weeks acute treatment + 16-week extension for responders

Primary Outcome: Change in weekly average kidney pain intensity (0-10 NRS) from baseline to Week 8

Secondary Outcomes:

- Rescue analgesic use (acetaminophen tablets/week)
- Patient Global Impression of Change (PGIC)
- eGFR, serum creatinine, BUN (renal function biomarkers)
- Urinary biomarkers (NAG, KIM-1, NGAL)
- Stone recurrence rate (in nephrolithiasis subgroup)
- Quality of life (SF-36, kidney-specific QOL)
- Safety: adverse events, hepatic/renal function, drug interactions

Sample Size: 120 participants (60 per arm) to detect 1.5-point NRS reduction with 80% power, $\alpha=0.05$, assuming 20% dropout

4.4.2 Pharmacokinetic/Pharmacodynamic Studies

Geriatric PK Study:

- Single-dose and multiple-dose PK in elderly (age ≥ 70 years) vs. young adults (age 20-40 years)
- Plasma/urine concentrations of key polyphenols (quercetin, caffeic acid, ferulic acid) by LC-MS/MS
- Assessment of age-related changes in absorption, distribution, metabolism (hepatic phase II conjugation), excretion
- Renal impairment sub-study (CKD Stage 3 vs. normal renal function)

Drug Interaction Studies:

- *In vitro* CYP450 enzyme inhibition/induction (CYP3A4, CYP2C9, CYP2D6, CYP1A2)
- *In vivo* interaction with warfarin (INR monitoring), antihypertensives (blood pressure effects), diuretics (electrolyte balance)

4.4.3 Mechanistic Clinical Studies

Biomarker Study in CKD Patients:

- *Population:* CKD Stage 3-4 patients, age ≥ 60 years
- *Intervention:* ESCS 300 mg twice daily $\times$ 12 weeks
- *Outcomes:*
 - Inflammatory biomarkers: serum TNF- α , IL-6, IL-1 β , CRP
 - Oxidative stress markers: plasma MDA, F₂-isoprostanes, protein carbonyls
 - Antioxidant capacity: total antioxidant capacity (TAC), erythrocyte SOD/catalase
 - Urinary biomarkers: albumin-to-creatinine ratio (ACR), NAG, KIM-1
 - Endothelial function: flow-mediated dilation (FMD), pulse wave velocity (PWV)

4.4.4 Product Development and Standardization

Pharmaceutical-Grade Extract Development:

- Establish standardized extraction protocols (solvent, temperature, time, plant-to-solvent ratio)
- Define biomarker compounds for quality control (e.g., total polyphenols ≥ 80 mg GAE/g; quercetin ≥ 2.5 mg/g)
- Stability testing (shelf-life determination, degradation kinetics)
- Good Manufacturing Practices (GMP) compliance

Comparative Effectiveness Research:

- Head-to-head trial: ESCS vs. low-dose acetaminophen vs. placebo in elderly with chronic kidney pain
- Cost-effectiveness analysis from healthcare system and patient perspectives

4.5 Regulatory and Translational Considerations

4.5.1 Pathway to Clinical Use

Traditional Medicine Frameworks:

- Brazil: *C. spicatus* included in RENISUS (National List of Medicinal Plants of Interest to the Unified Health System), facilitating research and potential incorporation into public health formularies
- WHO Traditional Medicine Strategy 2014-2023: Encourages integration of evidence-based traditional medicines into national health systems

Botanical Drug Development (U.S. FDA Guidance):

- Botanical drugs can be approved with less stringent requirements than synthetic drugs if supported by traditional use history and adequate safety/efficacy data
- Phase I safety + Phase II efficacy data may suffice for conditional approval, particularly for conditions with unmet medical needs in elderly populations

4.5.2 Patient Counseling and Clinical Use

For healthcare providers considering *C. spicatus* in elderly patients:

Appropriate Candidates:

- Mild-to-moderate kidney pain (VAS $\leq 6/10$) with identifiable etiology (stones, CKD, recurrent UTIs)
- NSAID contraindications (CKD Stage 3-4, prior GI bleeding, anticoagulation, CV disease)
- Opioid-averse or opioid-intolerant patients
- Preference for botanical/integrative approaches

Dosing Recommendations (Empirical, Based on Traditional Use):

- **Preparation:** 5-10 grams dried leaves per liter boiling water, simmer 10-15 minutes, strain
- **Dose:** 150-200 mL (approximately 2/3 - 1 cup) 2-3 times daily
- **Timing:** Before meals or at bedtime; consistent daily schedule
- **Duration:** Trial period 2-4 weeks for acute pain; may continue long-term for chronic conditions if effective and well-tolerated

Monitoring:

- Baseline and periodic (every 3-6 months) serum creatinine, BUN, electrolytes (Na^+ , K^+)
- Blood pressure monitoring (due to diuretic effects)
- For patients on warfarin: INR monitoring during first month of concurrent use
- Symptom diary: pain intensity (0-10 NRS), rescue medication use, adverse effects

Red Flags for Discontinuation:

- New or worsening renal function ($>20\%$ increase in serum creatinine)
- Electrolyte abnormalities (hypokalemia <3.5 mEq/L, hyponatremia <135 mEq/L)
- Hypotension (SBP <100 mmHg with symptoms)
- Allergic reactions (rash, pruritus, angioedema)
- Gastrointestinal intolerance (nausea, diarrhea persisting >1 week)

5 Conclusions

5.1 Summary of Key Findings

This comprehensive review establishes a robust scientific foundation validating traditional use of *Costus spicatus* for kidney pain management through multiple converging lines of evidence:

1. **Ethnopharmacological Consensus:** Across diverse Brazilian regions and ethnic groups, *C. spicatus* is consistently identified among the top three medicinal plants for kidney and urinary disorders, demonstrating remarkable cultural validation spanning centuries of empirical use.
2. **Rich Phytochemical Profile:** The plant contains a complex array of bioactive constituents including polyphenols (caffeic acid, quercetin, ferulic acid), flavonol glycosides (tamarixetin, kaempferide derivatives), steroidal saponins, and immunomodulatory polysaccharides, providing mechanistic diversity for therapeutic effects.
3. **Nephroprotective Efficacy:** Preclinical AKI models demonstrate dose-dependent improvements in serum creatinine (42-58% reduction), BUN (38-52% reduction), and histological architecture, with preservation of tubular integrity and glomerular function.

4. **Multi-Mechanistic Pain Relief:** Dual mechanisms of peripheral antinociception (52.8-98.1% pain inhibition in rodent models) and anti-inflammatory activity (62-67% reduction in TNF- α , IL-6, IL-1 β) provide synergistic analgesic effects relevant to kidney pain pathophysiology.
5. **Antioxidant Defense Restoration:** Significant increases in SOD (54%), catalase (61%), and GPx (48%) activities, combined with 68% reduction in lipid peroxidation (MDA), address age-related oxidative stress burden in elderly populations.
6. **Diuretic and Antilithiatic Properties:** Sustained urine volume increase (41-52%) without electrolyte imbalance, plus inhibition of calcium oxalate crystal formation/aggregation (54-61%), provide complementary mechanisms addressing urinary stasis and stone formation.
7. **Favorable Safety Profile:** LD₅₀ >2000 mg/kg, no adverse effects in sub-chronic (30-day) toxicity studies, and absence of hepatotoxicity, nephrotoxicity, hematologic toxicity, or cardiovascular impairment suggest excellent tolerability. Critically, the plant is nephroprotective rather than nephrotoxic, distinguishing it from NSAIDs.

5.2 Clinical Implications for Elderly Populations

The case of an 80-year-old woman experiencing kidney pain relief exclusively with *C. spicatus* tea is scientifically plausible based on convergent mechanisms:

- **Direct analgesic effects** reduce visceral pain transmission
- **Anti-inflammatory properties** address inflammatory components of kidney pain without NSAID-associated nephrotoxicity
- **Diuretic activity** relieves urinary stasis and distention discomfort
- **Antilithiatic effects** prevent stone formation/growth in patients with nephrolithiasis
- **Nephroprotective mechanisms** may slow CKD progression and reduce uremic symptoms
- **Antioxidant restoration** compensates for age-related oxidative stress

These mechanisms operate synergistically to provide multi-faceted therapeutic benefit unattainable with single-target conventional analgesics. The favorable safety profile—particularly absence of nephrotoxicity, cognitive impairment, and GI bleeding—addresses critical vulnerabilities in elderly populations with polypharmacy and comorbidities.

5.3 Evidence-to-Practice Gap and Research Imperatives

Despite compelling preclinical evidence and extensive ethnopharmacological validation, a critical gap remains: **absence of clinical trials in humans**. The transition from traditional wisdom and rodent models to evidence-based clinical practice requires:

Immediate Priorities:

1. **Phase II RCT in elderly patients** with kidney pain (nephrolithiasis, CKD Stage 3, recurrent UTIs) and NSAID contraindications

2. **Pharmacokinetic studies** in geriatric populations with renal impairment to establish optimal dosing and identify drug interactions
3. **Biomarker studies** measuring inflammatory cytokines, oxidative stress markers, and urinary kidney injury biomarkers to validate mechanisms in humans
4. **Standardized extract development** with pharmaceutical-grade quality control and stability testing

Long-Term Goals:

1. **Phase III efficacy trials** comparing *C. spicatus* vs. standard-of-care (acetaminophen) vs. placebo
2. **Comparative effectiveness research** evaluating cost-effectiveness and patient-reported outcomes
3. **Post-marketing surveillance** in real-world elderly populations with diverse comorbidities
4. **Integration into clinical guidelines** for integrative nephrology and geriatric pain management

5.4 Final Perspective

Costus spicatus represents a compelling example of ethnopharmacological knowledge awaiting rigorous clinical validation. The plant's traditional use for kidney pain—documented across centuries and diverse cultures—finds substantial support in contemporary preclinical pharmacology. For elderly patients like the 80-year-old woman described, who face limited safe and effective pharmacological options due to NSAID nephrotoxicity, opioid cognitive risks, and polypharmacy concerns, *C. spicatus* offers a biologically plausible, multi-mechanistic, and potentially safer alternative.

However, clinical adoption must be tempered by recognition of evidence limitations. Patients and healthcare providers should understand that while mechanistic rationale is strong, human efficacy remains unproven in controlled trials. Use should be considered adjunctive to standard care, not replacement, and requires monitoring for safety and efficacy.

The convergence of traditional wisdom, phytochemical characterization, and experimental pharmacology provides a robust foundation for translational research. Clinical trials are not merely desirable—they are ethically imperative to either validate or refute traditional claims, ensuring that elderly patients receive treatments supported by the highest quality evidence. Until such trials are conducted, *C. spicatus* remains a promising but unproven therapeutic option, best utilized within shared decision-making frameworks that honor patient preferences while acknowledging scientific uncertainty.

The journey from ethnopharmacological observation to evidence-based botanical medicine is long and resource-intensive, but for conditions like kidney pain in elderly populations—where therapeutic options are limited and risks are high—this investment is justified. *Costus spicatus* may ultimately prove to be a valuable addition to the geriatric nephrology therapeutic armamentarium, but only rigorous clinical science can determine if traditional wisdom translates to modern medical practice.

Acknowledgments

This review honors the traditional healers and indigenous communities across Brazil and Latin America who have preserved knowledge of *Costus spicatus* therapeutic uses for generations. We acknowledge the researchers who have conducted preclinical studies establishing the scientific foundation for this traditional knowledge. We dedicate this work to elderly patients worldwide seeking safe and effective relief from kidney pain.

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