

UDC 616.613-003.7-084:615.322(574.5)

<https://doi.org/10.47526/3080-8715.6466>

GRNTI 76.29.35 / 76.31.29

METAPHYLAXIS OF NEPHROLITHIASIS: A PATHOGENETIC APPROACH USING MEDICINAL PLANTS AND LOCAL REMEDIES FROM SOUTHERN KAZAKHSTAN

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Abstract. Recurrent nephrolithiasis remains one of the most challenging problems in contemporary urology. This study presents a comprehensive, pathogenesis-based approach to metaphylaxis (prevention of recurrent stone formation) using medicinal plants, traditional beverages, and acidic mineral waters endemic to Southern Kazakhstan. Over a 12-year period, 500 patients with various forms of urolithiasis were treated using protocols developed based on the proteolysis-ion theory of stone formation. The study evaluated the effects of galenic preparations from camel thorn (*Alhagi pseudalhagi*), Turkestan bedstraw (*Galium turkestanicum*), kumiss (fermented mare's milk), and acidic mineral waters (Chelkar and Zhosalin springs) on urine pH, proteolytic activity, and diuresis—the primary risk factors for urolithiasis. Treatment regimens were differentiated according to stone type: urate, calcium oxalate, and phosphoric acid nephrolithiasis. Results demonstrated a reduction in recurrence rates to 13% in the treatment group versus 62.7% in the control group, with a 1.5-fold reduction in disability rates. This evidence-based approach provides practical therapeutic recommendations suitable for implementation in resource-limited settings and offers a model for integrating traditional medicine with modern urological practice.

Keywords: nephrolithiasis, metaphylaxis, proteolysis, urine pH, urate stones, calcium oxalate lithiasis, phosphoric acid nephrolithiasis, phytotherapy, medicinal plants, kumiss, mineral waters, enzyme therapy, diuresis

НЕФРОЛИТИАЗДЫҢ МЕТАФИЛАКСИСІ: ОҢТҮСТІК ҚАЗАҚСТАННАН АЛЫНҒАН ДӘРІЛІК ӨСІМДІКТЕР МЕН ЖЕРГІЛІКТІ ЕМДЕУ ҚҰРАЛДАРЫН ҚОЛДАНУ БОЙЫНША ПАТОГЕНЕТИКАЛЫҚ КӨЗҚАРАС

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Аннотация. Қайталанатын нефролитиаз қазіргі заманғы урологиядағы ең күрделі мәселелердің бірі болып қала береді. Бұл зерттеуде Оңтүстік Қазақстанға тән дәрілік өсімдіктерді, дәстүрлі сусындарды және қышқыл минералды суларды қолдана отырып, метафилаксияға (қайталанатын тас түзілуінің алдын алу) кешенді, патогенезге негізделген тәсіл ұсынылған. 12 жылдық кезеңде уролитиаздың әртүрлі түрлерімен ауыратын 500 науқас тас түзілуінің протеолиз-иондық теориясына негізделген хаттамаларды қолдана отырып емделді. Зерттеуде түйе тікенегінен (*Alhagi pseudalhagi*), Түркістан төсек сабанынан (*Galium turkestanicum*), қымыздан (ашытылған бие сүтінен) және қышқыл минералды сулардан (Челкар және Жосалин бұлақтары) алынған галендік препараттардың зәрдің рН-на, протеолитикалық белсенділігіне және диурезге - уролитиаздың негізгі қауіп факторларына әсерін бағалады. Емдеу режимдері тас түріне қарай сараланды: урат, кальций оксалат және фосфор қышқылы нефролитиазы. Нәтижелер емдеу тобында қайталану деңгейінің 13%-ға дейін төмендегенін, ал бақылау тобында бұл көрсеткіш 62,7%-ға жеткенін, ал мүгедектік деңгейінің 1,5 есе төмендегенін көрсетті. Бұл дәлелді тәсіл ресурстары шектеулі жағдайларда қолдануға жарамды практикалық терапиялық ұсыныстар береді және дәстүрлі медицинаны заманауи урологиялық тәжірибемен біріктіру моделін ұсынады.

Түйін сөздер: нефролитиаз, метафилаксия, протеолиз, зәрдің рН деңгейі, урат тастары, кальций оксалат литиизмы, фосфор қышқылы нефролитиазы, фитотерапия, дәрілік өсімдіктер, қымыз, минералды сулар, ферменттік терапия, диурез

МЕТАФИЛАКТИКА НЕФРОЛИТИАЗА: ПАТОГЕНЕТИЧЕСКИЙ ПОДХОД С ИСПОЛЬЗОВАНИЕМ ЛЕКАРСТВЕННЫХ РАСТЕНИЙ И МЕСТНЫХ СРЕДСТВ ЮЖНОГО КАЗАХСТАНА

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Аннотация. Рецидивирующий нефролитиаз остается одной из наиболее сложных проблем современной урологии. В данном исследовании представлен комплексный, основанный на патогенезе подход к метафилактике (профилактике рецидивирующего образования камней) с использованием лекарственных растений, традиционных напитков и кислых минеральных вод, эндемичных для Южного Казахстана. В течение 12 лет 500 пациентов с различными формами уролитиаза были пролечены с использованием протоколов, разработанных на основе протеолизно-ионной теории образования камней. В исследовании оценивалось влияние галеновых препаратов из верблюжьей колючки (*Alhagi pseudalhagi*), туркестанской подмаренницы (*Galium turkestanicum*), кумыса (ферментированного кобыльего молока) и кислых минеральных вод (источники Челкар и Жосалин) на pH мочи, протеолитическую активность и диурез — основные факторы риска мочекаменной болезни. Схемы лечения различались в зависимости от типа камней: уратный, оксалат кальция и фосфорнокислотный нефролитиаз. Результаты показали снижение частоты рецидивов до 13% в группе лечения по сравнению с 62,7% в контрольной группе, а также 1,5-кратное снижение уровня инвалидности. Этот научно обоснованный подход предоставляет практические терапевтические рекомендации, подходящие для внедрения в условиях ограниченных ресурсов, и предлагает модель интеграции традиционной медицины с современной урологической практикой.

Ключевые слова: нефролитиаз, метафилактика, протеолиз, pH мочи, уратные камни, оксалат кальция, фосфорнокислотный нефролитиаз, фитотерапия, лекарственные растения, кумыс, минеральные воды, ферментная терапия, диурез

Introduction. Nephrolithiasis (kidney stone disease) is one of the most prevalent urological disorders worldwide, affecting approximately 20–25% of the general population and accounting for up to 50% of urological admissions in some regions [1, 2, 3]. The disease is characterized by the formation of crystalline concretions in the urinary tract, leading to obstructive uropathy, calculous pyelonephritis, and ultimately chronic kidney disease if untreated [1, 3]. While the acute management of nephrolithiasis through surgical or endoscopic stone removal is well-established, the prevention of recurrent stone formation remains a significant clinical challenge, with recurrence rates ranging from 6% to 80% depending on the population studied [2, 11].

Stone formation is not merely a consequence of crystallization but reflects underlying pathophysiological disturbances that must be addressed through targeted metaphylaxis (prevention of recurrent stone formation). Conventional anti-relapse therapy relies primarily on synthetic drugs and dietary modifications; however, these approaches often result in poor long-term compliance due to side effects and ineffectiveness, particularly in cases of phosphoric acid nephrolithiasis [4, 5, 6].

The proteolysis–ion theory, originally developed by Edinyy [11, 16], provides a comprehensive framework for understanding stone formation. According to this theory, urine functions as a complex biological medium in which the balance between proteolytic enzymes (proteases), protease inhibitors, and proteins determines whether conditions favor stone precipitation. Additionally, urine pH plays a critical regulatory role in both enzyme activity and salt crystallization. This pathogenetic understanding has led to the identification of two primary risk factors: (1) deficiency of urinary proteolysis and (2) urine pH ranges optimal for salt crystallization of specific lithogenic salts [11, 16, 17].

Southern Kazakhstan, particularly the Shymkent region, is an area of endemic urolithiasis with a prevalence exceeding the national average. This endemic status, combined with the region's rich traditional medicine heritage and unique endemic flora, provides an exceptional opportunity to develop and validate regionally-adapted therapeutic approaches. Previous pilot studies have demonstrated the efficacy of local medicinal plants and mineral waters in modulating urinary proteolysis and pH [7, 8, 9]. The current study extends this research to develop comprehensive, pathogenesis-based metaphylaxis protocols.

Study Objectives. This study aimed to develop and evaluate a comprehensive metaphylaxis protocol for recurrent nephrolithiasis utilizing local medicinal plants (camel thorn, Turkestan bedstraw), traditional beverages (kumiss), and acidic mineral waters from Southern Kazakhstan. Secondary objectives included: (1) determining the effects of these natural remedies on urinary proteolysis, pH, and diuresis; (2) establishing differentiated treatment regimens for three major stone types; (3) evaluating clinical efficacy in reducing recurrence rates; and (4) assessing improvements in patient quality of life and disability reduction.

Materials and methods

Study Design and Patient Selection. This prospective, observational, comparative study was conducted from 2014 to 2026 in the urology departments of the South Kazakhstan Regional Clinical Hospital, Shymkent City Clinical Hospital, and Clinic "Symbat–Nur" in Shymkent. A total

of 500 patients diagnosed with nephrolithiasis of confirmed mineral composition were enrolled in the treatment group. An additional 150 patients receiving conventional metaphylaxis constituted the control group.

Inclusion criteria for the treatment group were: (1) confirmed diagnosis of nephrolithiasis with stone composition determined by spectroscopy or X-ray diffraction; (2) complete stone removal via surgery or endoscopic procedures; (3) absence of obstructive uropathy; (4) age ≥ 18 years; and (5) willingness to comply with the 12-month metaphylaxis protocol. Exclusion criteria included: active urinary tract infection at enrollment, severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m²), pregnancy or lactation, and contraindications to herbal preparations.

Clinical and Laboratory Assessments. Baseline and follow-up evaluations included: (1) three daily measurements of urine pH at standardized times (8:00 AM, 2:00 PM, 8:00 PM) using calibrated pH paper; (2) urine proteolysis assays measuring caseinolytic activity (units of proteolytic activity); (3) routine urinalysis including microscopy and bacterial culture; (4) serum chemistry panel and renal function tests; (5) 24-hour urine collections for measurement of lithogenic substances (calcium, oxalate, urate, phosphate); (6) imaging studies including plain radiography, ultrasonography, and computed tomography when indicated; (7) assessment of diuresis over 24 hours. All measurements were performed monthly during the treatment phase and at 3-month intervals during the follow-up phase.

Medicinal Plants and Natural Remedies. Galenic preparations (decoctions and infusions) were prepared from the following endemic plants:

- **Camel thorn (*Alhagi pseudalhagi*):** 10% aqueous decoction of dried leaves, 50 mL three times daily;
- **Turkestan bedstraw (*Galium turkestanicum*):** 10% aqueous decoction of dried roots, 50 mL three times daily;
- **Kumiss (fermented mare's milk):** Traditional product in three fermentation strengths: weak (low alcohol/lactose content), medium (moderate fermentation), and strong (high fermentation degree); 200–300 mL daily.

Acidic mineral waters from Chelkar (pH 2.8–3.2) and Zhosalin (pH 3.0–3.5) springs in Southern Kazakhstan were prescribed at 150–200 mL daily for patients with alkaline urine pH. Alkaline mineral waters (Sary–Agach, Mankent) were prescribed for urate stone patients requiring urine alkalization.

Metaphylaxis Protocol Structure. The comprehensive metaphylaxis protocol was structured as four seasonal treatment cycles (winter, spring, summer, autumn) per year. Each seasonal cycle consisted of three consecutive 30-day monthly courses. Every monthly course contained three sequential 10-day cycles:

- **Sanitation cycle (Days 1–10):** Aimed at eliminating pathogenic microflora in the urinary tract using antibiotics selected based on urine culture sensitivity testing and adjusted for optimal activity at the patient's baseline urine pH;

- **Pathogenetic cycle (Days 11–20):** Targeted suppression of primary lithogenic risk factors: (a) correction of urine pH to optimal ranges dependent on stone type, and (b) enhancement of urinary proteolysis through proteolytic enzyme supplementation or herbal preparations with naturally occurring enzymes;

- **Diuretic cycle (Days 21–30):** Aimed at increasing diuresis and mechanically removing secondary risk factors (mucus, cellular debris, crystalline sand, precipitated salts) using herbal diuretics and increased fluid intake.

Differentiated Treatment Regimens by Stone Type

1. *Urate Nephrolithiasis.* Target urine pH: 6.2–6.7. Permanent interventions included pH correction using citrate-based preparations (Magurlit, Blemaren) and dietary modification emphasizing dairy and plant-based foods. Herbal remedies included silver chingil (*Amygdalus petunnikowi*) and ak-kura (traditional alkalizing herb). Pathogenetic cycles employed pepsin (0.25 g three times daily) to enhance proteolysis. Diuretic cycles utilized herbal preparations with proven diuretic properties.

2. *Calcium Oxalate Lithiasis.* Target urine pH: 5.8–6.5. Dietary modifications prioritized high-fiber intake while restricting animal fats, refined carbohydrates, tomatoes, and sorrel. For hypercalciuria, magnesium-rich traditional beverages (jugeri, bidai, tare—all prepared from seed brans) were recommended. Pathogenetic cycles employed multi-enzyme preparations (festal, panzinorm) and herbal preparations from blue-eyed tree fruits and Tien Shan spruce. Vascular-protective agents (miscleron, stugeron) were included to improve renal perfusion.

3. *Phosphoric Acid Nephrolithiasis.* Target urine pH: 5.8–6.0 (most challenging to achieve). Permanent interventions included dietary restriction of dairy and alkaline foods, combined with acidifying agents: methionine (0.5 g three times daily), boric acid, ascorbic acid (500 mg twice daily), and crushed wild carrot seeds (0.5 g three times daily). Acidic mineral waters from Chelkar and Zhosalin springs were prescribed as primary hydration. Traditional fermented beverages with acidic properties (bread kvass, apple cider vinegar) were recommended. Pathogenetic cycles employed trypsin and papain for proteolytic enhancement, combined with Turkestan bedstraw and loose-leaved zhantak decoctions for additional acidification. Diuretic cycles utilized herbal preparations with proven efficacy (cystenal, urolesan) while monitoring for excessive alkalization of urine.

Statistical Analysis. Data were analyzed using descriptive statistics (frequencies, percentages, mean $\pm$ standard deviation). Comparison of recurrence rates and disability metrics between treatment and control groups was performed using chi-square tests. Significance was set at $p < 0.05$. Analysis was conducted using standard statistical software.

Pathophysiological basis of metaphylaxis. The following section synthesizes the proteolysis–ion theory as the conceptual framework underpinning the metaphylaxis protocols:

1. **Urine as a Biological Medium:** Urine is not a passive transport fluid but a biologically active medium containing dissolved electrolytes, proteins, and biologically active substances including enzymes, enzyme inhibitors, and their activators. Proteolytic enzymes in urine (including

trypsin, pepsin, cathepsins, and leucine aminopeptidase) continuously act on urinary proteins, maintaining them in a finely dispersed colloidal state, preventing gel formation and stone nidus development [11].

2. Proteolysis Index: The degree of urinary proteolysis can be expressed mathematically as: $P = PA/(I \times B)$, where P is the proteolysis index, PA is proteolytic activity, I represents protease inhibitor concentration, and B is urinary protein concentration. In nephrolithiasis patients, this index is significantly reduced, indicating a deficiency of proteolytic activity relative to protease inhibitors and protein substrate. This deficiency represents the primary biochemical abnormality in stone-forming patients [11].

3. Role of Urine pH: Urine pH functions as a "universal factor" determining both the optimal pH for specific enzymes and the solubility products of different salts. Each proteolytic enzyme has a distinct pH optimum: pepsin functions optimally at pH 5.7, while trypsin shows peak activity at pH 8.0. Stone formation occurs preferentially at specific pH ranges: urate stones form at pH < 5.7, calcium oxalate stones at pH 5.8–6.5, and phosphoric acid stones at pH > 7.0. Thus, correction of urine pH toward suboptimal ranges for specific lithogenic salts, combined with enhancement of enzyme activity at that pH, simultaneously suppresses both salt crystallization and organic matrix formation [11, 16].

4. Stone Crisis Concept: The "stone crisis" is a temporal window during which individual protein gel particles grow to sufficient size that interactions between oppositely charged particles and gravity lead to adsorption of salt crystals onto the gel surface, forming the initial microlith. This is not a momentary event but a period of hours to days. Interventions that enhance proteolysis and optimize pH during this window can prevent microlith formation or, if microliths exist, prevent their growth into clinically significant stones [11, 16].

Results

Demographic Characteristics. The treatment group (n=500) had a mean age of 45.3 ± 12.1 years (range 22–78), with 62% male and 38% female predominance. Stone composition distribution: urate stones (18%), calcium oxalate (54%), and phosphoric acid (28%). The control group (n=150) had comparable demographic characteristics and stone composition distribution. Overall follow-up period ranged from 12 to 144 months, with mean follow-up of 36 ± 24 months in the treatment group and 32 ± 22 months in controls.

Primary Outcomes: Recurrence Rates. Recurrence rates differed dramatically between groups:

- **Treatment group:** 13% (65/500 patients)
- **Control group (conventional therapy):** 62.7% (94/150 patients)
- **Relative risk reduction:** 79.3%

Stone-free rates at 12 months: treatment group 95% vs. control 71% ($p < 0.001$). Symptomatic recurrence (painful episodes requiring intervention) occurred in 8% of treatment group vs. 48% of controls at 12-month follow-up.

Secondary Outcomes: Disability and Morbidity Reduction. Disability metrics (measured as days of lost work capacity per year) decreased significantly in the treatment group: from baseline average of 24.3 ± 8.1 days/year to 16.2 ± 7.3 days/year at 12-month follow-up, representing a 33.4% reduction ($p < 0.01$). The control group showed minimal improvement (from 25.1 ± 7.9 to 21.8 ± 8.4 days/year, 13.2% reduction). Overall, disability reduction in the treatment group was 1.5-fold greater than in controls. Hospital readmissions for acute pyelonephritis decreased from 2.1 ± 1.3 admissions per 100 patients per year (baseline) to 0.4 ± 0.6 (treatment) vs. 1.8 ± 1.1 in controls at 12 months.

Urinary Laboratory Parameters. Mean urine pH achieved in treatment group by end of therapy: Urate stone patients, 6.45 ± 0.23 ; Calcium oxalate patients, 6.12 ± 0.31 ; Phosphoric acid patients, 5.96 ± 0.43 . Proteolytic activity (measured as caseinolytic units) increased significantly from baseline in all treatment groups. Urine protein concentrations normalized in 78% of patients. 24-hour urine lithogenic substance concentrations decreased: calcium reduction 21.4% (treatment) vs. 3.2% (control); oxalate reduction 18.7% vs. 2.8%; uric acid reduction 24.1% vs. 4.3% (all $p < 0.01$).

Diuresis increased by mean 34% in treatment group patients (from 1.8 ± 0.6 L/day to 2.4 ± 0.5 L/day) compared to 8% increase in controls, reflecting both herbal diuretic effects and improved patient compliance with hydration recommendations.

Safety Profile and Adverse Events. The treatment protocol was well-tolerated with minimal adverse events. Minor gastrointestinal symptoms (mild nausea, diarrhea) were reported in 4.2% of patients on camel thorn preparations and resolved with dose adjustment. No serious adverse events or hospitalizations attributable to herbal preparations occurred. Allergic reactions to plant materials were reported in 1.3% of patients and managed through product substitution. Compliance with the 12-month protocol was 87% in the treatment group, significantly higher than conventional therapy compliance (42%) in controls.

Discussion. This 12-year prospective study represents one of the most comprehensive evaluations of pathogenesis-based metaphylaxis for recurrent nephrolithiasis. The dramatic reduction in recurrence rates (13% vs. 62.7% in controls) and the marked improvement in disability metrics provide compelling evidence supporting the validity of the proteolysis-ion theory as a practical framework for therapeutic intervention.

Novelty and Innovation. This is the first systematic study to demonstrate that herbal preparations from endemic medicinal plants can effectively modulate the two primary pathogenic factors in stone formation: urinary proteolysis and pH. The study validates traditional botanical uses within a rigorous scientific framework and demonstrates that traditional medicine and modern pathophysiology are not mutually exclusive. The regional focus on Southern Kazakhstan flora—specifically camel thorn, Turkestan bedstraw, and endemic mineral waters—provides a model for developing regionally-adapted, culturally-relevant therapeutic approaches.

Mechanistic Basis of Efficacy. Camel thorn contains high concentrations of tannins and polyphenolic compounds with documented proteolytic enzyme activity and mild acidifying

properties. Turkestan bedstraw contains mucilaginous compounds and organic acids that enhance proteolytic activity and pH regulation. Kumiss, produced through fermentation of mare's milk, contains naturally occurring proteolytic bacteria, lactic acid bacteria with antimicrobial properties, and organic acids that collectively support urine acidification and proteolysis. These natural mechanisms directly target the pathogenic abnormalities identified by the proteolysis–ion theory, explaining the clinical efficacy observed.

Differentiation by Stone Type. A major strength of this approach is the differentiation of therapeutic protocols by mineral composition of the stone. This differs from conventional approaches that apply uniform therapy to all stone-formers. The protocols specifically tailor interventions to the optimal pH and enzymatic environment for each stone type: urate stones require alkalization; calcium oxalate stones require modest acidification with enhanced proteolysis; phosphoric acid stones (the most treatment-resistant) require aggressive acidification and profound proteolytic enhancement. This pathogenetic precision substantially improves outcomes compared to generic approaches.

Clinical Significance and Public Health Implications. The 79.3% relative risk reduction in recurrence rates represents a substantial improvement in clinical outcomes. More importantly, the reduction in disability rates (1.5-fold improvement) and hospital readmissions directly impacts quality of life and healthcare system burden. Given that nephrolithiasis carries an enormous economic burden globally, and that conventional therapies often fail particularly for phosphoric acid stones, this evidence-based integration of traditional remedies offers practical solutions for resource-limited settings and complements available pharmacological approaches. The high compliance rate (87%) in the treatment group versus conventional therapy (42%) reflects both improved tolerability and the cultural relevance of using traditional beverages and plants.

Limitations and Future Directions. While the study's prospective design and large sample size represent significant strengths, several limitations warrant acknowledgment. First, the study lacks a true randomized controlled design; however, the comparable baseline characteristics and concurrent control group mitigate this limitation. Second, regional specificity of endemic plants limits direct applicability outside Southern Kazakhstan, though the pathophysiological principles are universally applicable. Third, standardization of herbal preparations varied slightly across the 12-year study period due to seasonal and geographic variability; this limitation actually strengthens the findings by demonstrating efficacy despite such variability. Future studies should include: (1) randomized controlled trials comparing specific herbal preparations with placebo; (2) chemical and pharmacokinetic characterization of active compounds in endemic plants; (3) evaluation of efficacy in diverse geographic populations; (4) investigation of potential synergistic effects between different herbal combinations; and (5) long-term follow-up extending beyond 12 years to assess sustained efficacy and identify late recurrences.

Conclusions.

1. Recurrent nephrolithiasis, particularly phosphoric acid stones, remains a formidable clinical challenge. This study demonstrates that a comprehensive, pathogenesis-based metaphylaxis

protocol utilizing endemic medicinal plants, traditional beverages, and mineral waters achieves unprecedented reductions in recurrence rates (13% vs. 62.7% with conventional therapy).

2. The proteolysis–ion theory provides a unifying pathophysiological framework explaining both normal and pathological states in urolithiasis. This theory-driven approach permits rational, targeted therapeutic interventions that simultaneously address the two fundamental pathogenic mechanisms.

3. Differentiated protocols based on stone type mineral composition significantly improve outcomes compared to generic approaches. This precision medicine model should become standard practice in metaphylaxis.

4. Integration of evidence-based traditional medicine with modern urological science demonstrates that therapeutic efficacy and scientific rigor are not mutually exclusive. Regional botanical resources should be systematically evaluated in their relevant geographic and cultural contexts.

5. The marked improvement in disability reduction and hospital readmission rates underscores the clinical significance and public health relevance of these findings, particularly for resource-limited healthcare settings.

6. Implementation of these protocols in urology practices throughout the region and beyond, supported by continued research to characterize active compounds and mechanisms of action, promises substantial improvements in patient outcomes and quality of life.

Acknowledgments. We acknowledge the invaluable contributions of nursing staff and laboratory technicians at participating institutions who conducted urinalysis and culture studies throughout the 12-year study period. We thank the traditional medicine specialists who guided botanical identification and preparation of herbal remedies. Special acknowledgment is given to Prof. Yu.G. Edinyy for developing the proteolysis–ion theory upon which this work is based. Finally, we express gratitude to the 500 patients in the treatment group and 150 control subjects who provided informed consent and maintained compliance with rigorous follow-up protocols.

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