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THE USE OF HERBAL MEDICINE FOR TREATING SMALL KIDNEY STONES

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Introduction. The proportion of urolithiasis in the structure of the incidence is 10-15% in the world and 5-9% in Europe. In the USA 13% of men and 7% of women suffer from urolithiasis [2]. In Ukraine, the incidence of urolithiasis in the structure of urological diseases is 27.4% to 32.7% [7, 8]. Every year the number of patients increases. Most working-age men and women (30–50 years) have a tendency to this disease.

Urolithiasis is endemic. Here is a list of regions where urolithiasis is most common: Asia Minor with Arabian Peninsula, southern and eastern regions of Asia, India, China (southern regions), Indonesia, North Australia, Northeastern Africa, southern regions of North America, east and west coasts of Southern America, Scandinavia , The Netherlands, Southeastern France, the southern regions of Spain, Italy, the southern regions of Germany and Austria, Balkan Peninsula, the Altai Territory, Ukraine (Dnipropetrovsk and Donetsk regions). In each endemic region, there are localities where the incidence is highest (i.e. Solonyansky region of Dnipropetrovsk oblast) [3].

The composition of stones is different in different endemic regions. In India, more than 80% of the stones consist of calcium oxalate; in Sudan, oxalates are about 75% of the stones; in Iraq, calcium oxalates are only 2-3%; in Israel - 5%. Many countries (Norway, USA, Israel, Iraq, Austria, Sweden) have a large percentage of mixed calcium oxalate and calcium phosphate stones (50-60%). Struvites (magnesium phosphates - ammonium) are common in Belarus - 28%, England - 20%, Belgium - 15%, USA - 15%. Uric acid stones are more common in Iraq - 40%, Belarus - 30%, Jordan - 30%, Israel - 28%, Austria, France - 23%. Cystic stones are rarely found, 1-2% of all stones (Belgium, USA). Pure phosphates were most common in Belgium - 21%, England, Austria, Sudan - 8-9% (Fig. 1). But considering the different number of stones studied in different countries of the world (USA - 10,000 stones, Sudan - 32 stones), the incidence of different composition of stones may be different [3].

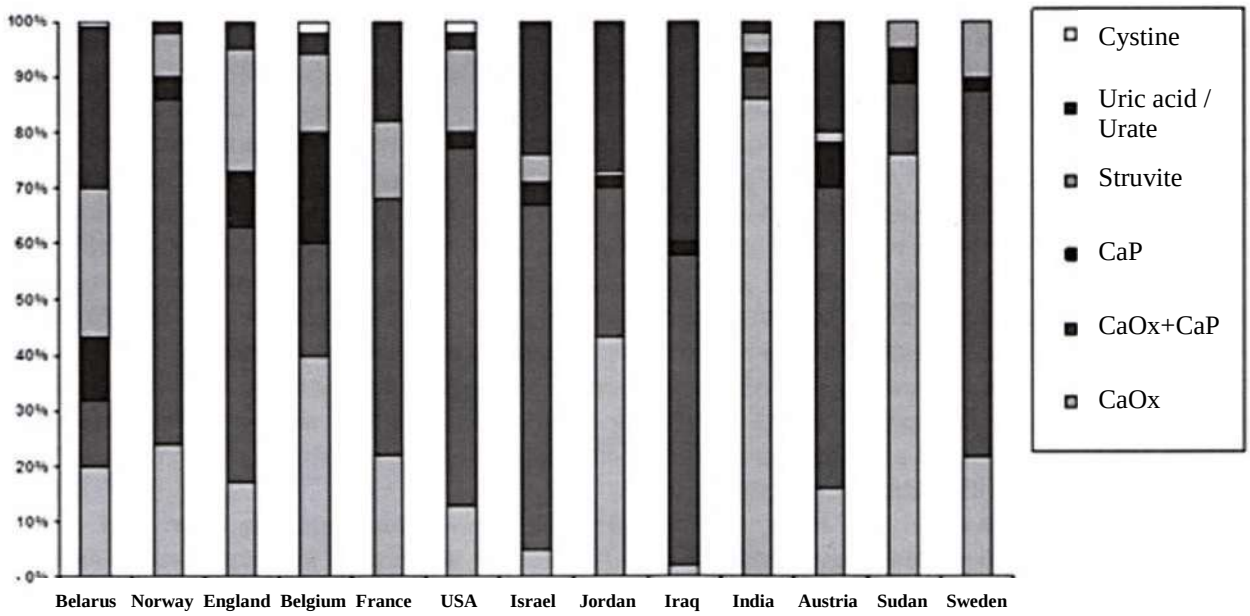

Fig. 1. Composition of stones in different countries

The diagram is based on the results of kidney stones analysis obtained after stone elimination in patients with urolithiasis; Belarus (151 stones), Norway (500 stones), England (243 stones), Belgium (239 stones), France (322 stones), USA (10 000 stones), Israel (1000 stones), Jordan (128 stones), Iraq (146 stones), India (431 stones), Austria (226 stones), Sudan (32 stones), Sweden (623 stones). All these stones were distributed according to the chemical composition in the following categories: Ca-Ox – pure calcium oxalate, Ca-Ox+CaP - mixed oxalate and phosphate calcium stones, CaP - pure calcium phosphate, struvite stones, uric acid stones and urate stones, and cystine stones.

Among the numerous etiological factors of urolithiasis, the main ones can be distinguished [4, 14]:

1. Impairment of urine outflow at any level of the urinary tract.
2. Metabolic disorders.
3. Infection.

The presence of more than one factor in a patient is likely to lead to stone formation. Stone is not formed overnight. A matrix is necessary for its formation. This matrix may be located in the collecting tubules and on the papilla of the kidney (most likely). The deposits of salt in the papilla and the collecting tubules, described by Randall, are likely the site of stone formation. According to the observations of Spanish urologists, such as Sabete Arrouya. H.A., Peras Ayala et all. (2018) the papillae damages may be in the form of deposits of Rendal plaques, tubular calcifications and papillary craters. Tubular calcifications are the most common injuries in patients with renal urolithiasis. Tubular calcifications were determined in patients with the increased urine calcium concentration. In patients with Rendal's plaque, hypocitraturia was observed. Hypoxaluria was observed more frequently in patients with papillary craters [11].

Currently, urolithiasis is not difficult to diagnose. After renal ultrasound examination, native computed tomography is performed. In 99–100% of cases it answers the following questions: whether stones are available, its localization, size and density, and whether urine outflow is impaired. In rare cases there may be the doubts regarding the localization of a small stone in the pelvic ureter and the absence of urine stasis. However, the presence of an appropriate clinic in a patient and ureteroscopy, which can be a diagnostic and, likely, a therapeutic measure, will give answer to question whether it is a stone or phlebolith [14].

Currently, the treatment of urolithiasis is rarely pathogenetic and not timely. We must honestly admit that unfortunately urologists are not able to treat urolithiasis, but they know well how to remove stones. The stones that have already “freed” from fixation on the papilla and are freely located in the pyelocus-pelvis system or ureter, can be removed. But removing is not a cure for urolithiasis [1].

In stone formation, urine pH plays an important role (its norm is 6.2–6.4). We all know the recommendations for its (pH) measurement for dissolving stones. But determining urine pH using litmus strips is not an accurate method. It is necessary to use pH-metry. Maybe this is the reason for the failed conservative therapy?

In practice the role of urine stabilizing protein – uromodulin is not yet used.

Attempts to dissolve stones are successful only in the presence of urate stones, and only in 55-60% of patients [1, 10]. In our practice, we have one (but proven) case of dissolving a urate stone sized of 2 cm (reception of blemaren within five months). It was proved by using computed tomography performed before and after blemaren treatment. However, both doctors and patients still want to dissolve stones by using modern therapeutical methods, but not only by eating eggshell with garlic [2, 5, 6].

Phytopreparations are used to treat various diseases, including kidney disease, but their use remains at the level of the Middle Ages or even worse. Only in rare studies we find attempts to scientifically explain a possible mechanism of action. For example, the study by N.G. Chaban et al., (2014), where the purpose of collecting herbs in two stages (immediately loosen, then dissolve) is experimentally proved [9,11].

In this study, we studied the effectiveness of phytocomplex Nokamen®, produced by the pharmaceutical company Ananta Medicare for patients with urolithiasis.

Since Nokamen contains mineral substances and 10 herbs most commonly used in urology, these results can also be interpolated to other phytopreparations containing these components (Table 1).

The purpose of this study: to study the effectiveness of Nokamen in patients with urolithiasis with stones sized of up to 55 mm.

Objectives:

1) to study the litholytic properties of Nokamen;
2) to study the lithokinetic properties of Nokamen;
3) to study the changes in the clinical and biochemical properties of blood and urine in the course of receiving Nokamen;
4) to study the antibacterial properties of Nokamen.

Materials and methods. The study was carried out on the clinical base of the Department of Urology of the State Institution “DMA of MoH of Ukraine” in “Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov". Clinical and biochemical studies were carried out in the certified laboratory of the State Institution "Dnipropetrovsk Medical Academy of MoH of Ukraine". In total, 32 patients with urolithiasis were involved in the study. The stones were localized in the kidneys. The maximum stone size did not exceed one centimetre, namely 69% in men and 31% in women. The age distribution was as follows: up to 20 years old –

4.5%; 20-39 years old – 4.5%; 30-39 years old – 13.7%; 50-69 years old – 27%.

In the left kidney, the stones were localized in 17 patients (53.1%), in the right kidney - in 4 (12.5%), in both kidneys - in 11 (34.4%). Some patients had a few stones.

The composition and properties of the components of Nokamen Table 1

Plant name	Active ingredients	Properties
Crataeva nurvala bark, 100 mg	Saponins (diosgenin), flavonoids, plant sterols (lupeol), tannins and glucosinolates (glucaparin)	• litholytic (oxalates) • anti-inflammatory • antispasmodic
Saxifraga ligulata rhizome, 60 mg	Furocoumarins (about 0.5% pimpineline, isopimpineline and isoberganten), isocoumarins (bergenin), 0.3-0.5% volatile oils and saponins	• litholytic (all types of stones due to the effect on the crystal-colloid ratio) • antibacterial • reduces irritation of the urinary tract
Butea frondosa flowers, 40 mg	Flavone glycosides (butein, butrin), chalcones, triterpenes and sterols	• anti-inflammatory • diuretic • litholytic (oxalates)
Dolichos biflorus seed, 40 mg	Phenolic compounds, flavonoids, unsaturated fatty acids, steroids and saponins	• antispasmodic • antioxidant • litholytic (oxalates, urates)
Sodium carbonate, 20 mg	Sodium hydrocarbonate	• litholytic (oxalates, urates)
Tribulus terrestris fruit, 100 mg	Steroid saponins, flavonoids, alkaloids and tannins	• litholytic (oxalates) • angiobacterial • improving the reproductive system tonus
Rosmarinus officinalis extract, 20 mg	Alkaloids (rosemarycin), tannins, flavonoids, resins, bitters	• antispasmodic • anti-inflammatory • natibacterial
Rubia cordifolia root extract, 20 mg	Anthraquinone glycosides (purpurin and munjistin), ruberitrinic acid	• litholytic (oxalates) • diuretic properties
Boerhavia diffusa root , 70 mg	Phytoecdysones, calcium salts and alkaloids, including punarnavin	• stimulation of metabolism • diuretic • litholytic (oxalates, urates)
Asphaltum, 70 mg	Oxidized alpha-pyrones, triterpenes, phenolic lipids, gum, albuminoids , gum and fatty acid traces, large amounts of benzoic and hippuric acids and their salts	• anti-inflammatory • immunostimulating • reparative

The native computed tomography was performed in patients for verification of the diagnosis. Ultrasound examination is not an absolutely reliable method for detecting stones. According to EAU clinical recommendations, ultrasound sensitivity is 32–70%, and specificity is 70–97%. Before the start of the study, the patients underwent urine and blood test, urine culture test and antibiotic sensitivity test, biochemical blood analysis (creatinine, urea, uric acid, calcium concentrations), urine biochemical analysis (calcium, uric acid concentrations). Patients took Nokamen 2

capsules twice a day for 6 months. It was recommended to take fluid, allowing to maintain diuresis at the level of 1.5-2 litres per day. After 6 months of taking Nokamen, complete blood and urine tests, urine culture test and antibiotic sensitivity test, biochemical blood analysis (creatinine, urea, uric acid, calcium concentrations), and urine biochemical analysis (calcium, uric acid concentrations) were repeated. Also, native computed tomography was re-performed for all patients.

After three months one patient stopped taking Nokamen on his own for domestic reasons.

Results and discussions.

In the course of the study, in 4 patients (12.5%) the calculi sized of 5-6 mm were discharged, independently. In 3 patients, the stones discharge was not accompanied by pain sensations. In one patient, the stones discharge was accompanied by renal colic, which required additional prescription of antispasmodics (baralgin).

According to the results of computed tomography, it was found that due to Nokamen activity, the growth of kidney stones was suspended.

Urine culture test has shown that out of 32 patients, bacteriuria was initially found in 7 patients. *Enterococcus faecalis* was found in 4 patients (in 2 patients – a concentration of $5x10^5$ mt/ml, in 2 patients – $5x10^3$ mt/ml). In 3 patients, *Escherichia coli* was found (in one patient – concentration of $5x10^6$ mt/ml, in 2 – $5x10^3$ mt/ml), in addition, one of them had associated with *Enterococcus faecalis* – $5x10^3$ mt/ml. *Pseudomonas aeroginosa* $5x10^6$ mt/ml was found in 1 patient. After treatment, the concentration of *Escherichia coli* $5x10^6$ mt/ml was decreased to $5x10^4$ mt/ml. There was no increase of *Escherichia coli* after 6 months of taking Nokamen in a patient with an initial concentration of *Escherichia coli* $5x10^3$ mt/ml. In one patient with a concentration of *Enterococcus faecalis* $5x10^5$ mt/ml, bacteriuria was not detected after treatment. In a patient with the original association of *Escherichia coli* and *Enterococcus faecalis*, *Ecinetobacter baumanti* $5x10^3$ mt/ml was found after treatment. In the patient who stopped treatment after 3 months (initially *Enterococcus faecalis* $5x10^8$ mt/ml), the type and concentration of the pathogen remained the same. In patients with *Pseudomonas aeruginosa*, the type and concentration of the pathogen is not changed after treatment (Table 2).

In 28.6% of patients in the general urine test, crystalluria (mainly oxaluria) was determined before taking Nokamen.

Effect of Nokamen on bacteriuria **Table 2**

Sr.No	Type of pathogen	Before treatment	After treatment
1.	Enterococcus faecalls	$5xl0^5$	No growth
2.	Enterococcus faecalls	$5x10^5$	Growth (2^{nd} patient stopped treatment after 3 months)
3.	Enterococcus faecalls	$5x10^3$	No growth
4	Escherichia coli	$5x10^6$	$5x10^4$
5.	Escherichia coli	$5x10^3$	No growth
6.	Enterococcus faecalis + Escherichia coli	$5x10^3$	Ecinetobacter baumanti $5x10^3$
7.	Ps. aeruginosa	$5x10^6$	$5x10^6$ Ps. aeruginosa

After 6 months of taking Nokamen, only one patient had salt crystals in the urine (oxalates) (Table 3), that attests to the litholytic properties of Nokamen.

The blood calcium concentration in the patients before Nokamen treatment was about 2.44 mmol/L. After 6 months, the calcium concentration decreased to 2.34 mmol/L (the change is statistically significant $p < 0.05$).

The blood uric acid concentration was also decreased from 268.0 mmol/L to 311.1 mmol/L (the change is statistically significant $p < 0.05$).

The blood creatinine concentration was not changed significantly in the course of the study in patients taking Nokamen® (104.3 mmol/L before treatment and 98.4 mmol/L after treatment) (Table 4).

The urine uric acid concentration before the start of the study was about 2.56 ± 0.12 mmol/L. After 6 months, the excretion of uric acid in the urine was

increased to 3.02 ± 0.14 mmol/L (the change is statistically significant p <0.05).

The urine calcium concentration was initially 3.66 + 0.05 mmol/L. After 6 months of taking Nokamen, the urinary calcium concentration was increased to 4.79 + 0.15 mmol/L (the change is statistically significant p <0.05) (Table 5).

Crystalluria severity **Table 3**

Parameters	Before treatment	After treatment
Crystalluria (Oxaluria)	28.6 %	3%

Effect of Nokamen on blood calcium, uric acid, creatinine concentrations **Table 4**

Parameters	Before treatment	After treatment
Ca	2.44 ± 0.15 mmol/L	2.34 ± 0.17 mmol/L
Uric acid	268.0 ± 49.2 mmol/L	311.1 ±58.1 mmol/L
Creatinine	104.4 ± 18.1 mmol/L	98.4 ± 16.5 mmol/L

Effect of Nokamen on urine calcium, uric acid concentrations **Table 5**

Parameters	Before treatment	After treatment
Ca	3.66 ± 0.15 mmol/L	4.79 + 0.15
Uric acid	2.56 ± 0.12 mmol/L	3.02 + 0.14

Conclusions

1. Nokamen® has a litokinetic effect. In 12% of patients, stones discharge has occurred, independently. In addition, in 3 patients the stones excreted without any pain (according to CT results the amount of kidney stones has decreased).
2. Nokamen® has a bactericidal effect. Bacteriuria has decreased from 22% to 12.5%.
3. Nokamen® effects on the blood and urine calcium, uric acid concentrations. This may contribute to the dissolution of calculi (Rendal plaques, etc.) or contribute to the prevention of stone formation.

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