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FEATURES OF THE EFFECT OF THE DIETARY SUPPLEMENT "NEPHROBIOTIC" ON INFLAMMATORY MARKERS, NITROGENOUS UREMIC TOXINS, AND THE CONDITION OF THE GASTROINTESTINAL TRACT IN PATIENTS WITH CHRONIC KIDNEY FAILURE

Summary. *The article is dedicated to the study of methods for effectively removing uremic toxins in patients with chronic kidney failure and the development of a probiotic that influences this process.*

The study aimed to develop the dietary supplement "NEPHROBIOTIC" and determine its effect on inflammatory markers, nitrogenous uremic toxins, and the condition of the gastrointestinal tract in patients with chronic kidney failure.

Materials and methods. During the development and study of the dietary supplement "NEPHROBIOTIC," a combination of lacto- and bifidobacteria was used, including three probiotic strains of beneficial bacteria: Streptococcus thermophilus (IMB B-8116), Lactobacillus acidophilus (IMB B-8117), and Bifidobacterium longum (IMB B-8118).

*Results and discussion. It has been demonstrated that chronic kidney disease may be accompanied by the development of intestinal inflammation and disruption of the epithelial barrier, leading to accelerated systemic translocation of bacterial-origin uremic toxins. These discoveries have provided new therapeutic opportunities for treating uremia, including prebiotics, probiotics, and synbiotics. The study showed that the developed dietary supplement "NEPHROBIOTIC" could metabolise urea in human urine from 41.56% to 80.38%. "NEPHROBIOTIC" contains three live probiotic cultures: Bifidobacterium longum IMB B-8118, Lactobacillus acidophilus IMB B-8117, and Streptococcus thermophilus IMB B-8116. It was established that individual pure live cultures (monocultures) exhibited a limited ability to metabolise urea: 80.38% (*Bifidobacterium longum *IMB B-8118), 51.24% (*Streptococcus thermophilus *IMB B-8116), and 49.0% (*Lactobacillus acidophilus *IMB B-8117). The mixture of three pure cultures demonstrated a lower ability to metabolise urea – 41.56%.*

Conclusion. The dietary supplement "NEPHROBIOTIC" may be recommended as part of the diet as an additional source of biologically active substances to support the beneficial effects of probiotics on inflammatory markers, protein-bound nitrogenous uremic toxins, and gastrointestinal symptoms in patients with chronic kidney failure.

Key words: *nephrology, urea metabolism, probiotic, microflora, development, treatment.*

Introduction. Kidney transplantation and dialysis are currently the only available treatments for end-stage renal disease [1]. These procedures significantly increase the concentration of uremic toxins in plasma, including creatinine, urea, and uric acid. These invasive procedures impose high social costs, making it difficult for many low-income countries to adequately treat patients suffering from

kidney failure [1; 2; 3; 4].

Among the key cells involved in toxin filtration are renal tubular cells and glomerular cells. Notably, renal tubular cells are at the forefront of exposure to uremic toxins, making them key targets for research due to their vital role in kidney function and susceptibility to toxin-induced damage [5; 6]. Over the years, numerous studies have been published on removing uremic toxins through the intestinal lumen [1; 2; 3]. This accumulation is believed to be associated with increased toxin formation from a dysbiotic microbiome, accompanied by reduced renal excretion due to impaired kidney function.

The gut microbiota plays a crucial role in accumulating uremic toxins, as numerous uremic solutes are produced during the fermentation of protein by colonic microbiota. Certain diseases, including chronic kidney disease (CKD), are associated with dysbiosis, which can be defined as an "imbalance in the gut microbial community with quantitative and qualitative changes in composition and metabolic activity" [5; 7].

More recently, various research groups have conducted microencapsulation of probiotic bacteria. These findings have provided a new perspective on the therapeutic modification of gut bacterial flora in the context of kidney disease. Probiotic supplements have been proposed as an adjunct therapy to improve gut microbiota balance, promoting intestinal barrier integrity and metabolic control in these patients.

Probiotics are "natural or genetically modified microorganisms that express specific exogenous enzymes capable of surviving stomach acid and bile, increasing the concentration of symbionts in the colon, and providing health benefits." The mechanisms by which probiotics exert their effects include changes in intestinal pH, pathogen antagonism through the production of antibacterial components, competition for available nutrients, binding to mutagens and carcinogens to prevent

their effects, and enhancement of intestinal barrier functions [8].

More than 2000 commensal bacteria inhabit the human body, most of which are found in the intestines, which exist in a natural balance known as symbiosis. Among the probiotic bacteria that belong to the gut ecosystem, bifidobacteria (Gram-positive, anaerobic, and irregularly shaped rods) are the most widespread and have the potential to enhance humoral and cellular immune responses to antigens. The population of probiotics in the gut decreases with antibiotic use and ageing while pathogenic flora increases. Additionally, such changes occur in various chronic diseases [9; 10].

Bifidobacterium and *Lactobacillus acidophilus* levels were significantly lower in CKD patients compared to healthy controls, whereas *Escherichia coli* and *Enterococcus faecalis levels* were significantly higher in CKD patients compared to healthy controls [11].

Streptococcus thermophilus is a type of probiotic bacteria from the *Streptococcus* genus. It is one of the most valuable lactic acid bacteria and has long been used as a starter culture for producing fermented dairy products. These "friendly" bacteria naturally reside in the digestive, urinary, and reproductive systems. *S. thermophilus* is most commonly taken orally to treat and prevent diarrhea, constipation, diabetes, and many other conditions associated with dysbiosis. It is known that *S. thermophilus* strains have reduced the risk of diarrhea caused by antibiotic use.

Lactobacillus acidophilus is a bacterium from the *Lactobacillus* genus. It is primarily found in the human intestine and other parts of the body, aiding the digestive system in breaking down sugars and breaking lactose into lactic acid. *L. acidophilus* is also used in dietary supplements as a probiotic, which numerous studies have supported. Specifically, several studies have shown that probiotics containing *L. acidophilus* can help prevent and reduce diarrhea associated with

various diseases in adults and children. Likewise, taking *L. acidophilus* for four months reduced nasal swelling and other symptoms in children with perennial allergic rhinitis, which causes symptoms similar to hay fever year-round. It has been established that a combined supplement containing *L. acidophilus* increases the number of lactobacilli and bifidobacteria in the gut, as well as branched-chain fatty acids, which are an important component of a healthy gut.

Bifidobacterium longum is a species of actinobacteria from the *Bifidobacterium* genus, naturally found in the oral cavity and gastrointestinal tract, helping to maintain normal gut function. *Bifidobacterium longum* is among the first bacteria to colonise the human intestine, alongside *Bifidobacterium infantis*. It is included in various dietary supplements as a probiotic due to its beneficial effects on human health. In patients with active ulcerative colitis who consumed a dietary supplement containing *Bifidobacterium longum*, an improvement in clinical progression was observed. Additionally, existing *Bifidobacterium longum* strains have effectively alleviated gastrointestinal, immunological, and infectious diseases [7].

During chronic kidney disease (CKD), protein-bound uremic toxins progressively accumulate, including indoxyl sulfate, p-cresyl glucuronide, p-cresyl sulfate, and indole-3-acetic acid. Chronic kidney disease may be accompanied by intestinal inflammation and disruption of the epithelial barrier, leading to accelerated systemic translocation of uremic toxins of bacterial origin and subsequent oxidative stress damage to the kidneys, cardiovascular system, and endocrine system. These findings suggest new therapeutic possibilities for treating uremia, inflammation, and the progression of kidney disease, as well as preventing adverse outcomes in CKD patients. Dietary interventions incorporating prebiotics, probiotics, and synbiotics appear promising strategies for managing uremic toxins in CKD [5; 11].

This study aims to develop the dietary supplement "NEFROBIOTIC" and determine its effects on inflammatory markers, nitrogenous uremic toxins, and the condition of the gastrointestinal tract in patients with chronic kidney failure.

Materials and methods of research. During the development of the dietary supplement "NEPHROBIOTIC," a combination of lacto- and bifidobacteria was used, including three probiotic strains of beneficial bacteria: *Streptococcus thermophilus* (IMB B-8116), *Lactobacillus acidophilus* (IMB B-8117), and *Bifidobacterium longum* (IMB B-8118). Their combination is assumed to contribute to removing toxic nitrogenous uremic toxins from the intestines.

To research the ability of the provided probiotic strains to metabolise urea, it was necessary to revive the dried cultures and determine whether they were present in monoculture or whether other bacteria were also present in the given preparations. For this purpose, the following media were used: MRS-agar and MRS-broth (*Merk*), with the following composition: Chemical composition (g/L): Casein peptone – 10.0; Meat extract – 10.0; Yeast extract – 4.0; D (+)-glucose – 20.0; Dipotassium phosphate – 2.0; Tween 80 – 1.0; Diammonium citrate – 2.0; Sodium acetate – 5.0; Magnesium sulfate – 0.2; Manganese sulfate – 0.04; Agar-agar – 14.0.

Cultures were grown under both aerobic and anaerobic conditions. To accumulate live cultures necessary for the study, probiotic strains were cultivated under anaerobic conditions using an anaerostat, in which GENbox anaer (*BIOMERIEUX*) packets were placed.

The study of the ability of probiotic cultures to metabolise urea was conducted according to the following scheme:

1. 10 ml of urine + 230 mg of urea + 0.99 ml of live probiotic culture suspension in 3 different concentrations: 200 units, 40 units, and 20 units of turbidity.
2. 10 ml of urine + 230 mg of urea + 0.99 ml of live probiotic culture suspension in 3 different concentrations: 200 units, 40 units, and 20 units of turbidity.

3. 10 ml of urine + 230 mg of urea + 0.99 ml of live probiotic culture suspension in 3 different concentrations: 200 units, 40 units, and 20 units of turbidity.

Cultures were prepared according to turbidity control: a) 200 units, b) 40 units, c) 20 units.

For *Bifidobacterium longum* IMB B-8118 and *Lactobacillus acidophilus* IMB B-8117: 200 units of turbidity correspond to 10 million CFU, 40 units – 2 million CFU, 20 units – 1 million CFU. For *Streptococcus thermophilus* IMB B-8116: 200 turbidity units correspond to 2 million CFU, 40 – 400 thousand CFU, and 20 units – 200 thousand CFU.

The ability of monocultures of live bacteria to metabolise urea was studied. To do this, probiotic strains were isolated as monocultures, and studies were conducted on the ability of pure probiotic strains to metabolise urea.

Urine from a 3-year-old child was used as a medium. Since the experimental method was not described in the literature, different urea contents (50 mg and 100 mg) were taken.

Conditions for the experiment on the ability of monocultures of live bacteria to metabolise urea: Control (C). 115 mg of urea + 5 ml of urine. Experiment: 1. 115 mg of urea + 5 ml of urine + 1 ml of *Bifidobacterium longum* IMB B-8118 suspension at 40 turbidity units. 2. 115 mg of urea + 5 ml of urine + 1 ml of *Lactobacillus acidophilus* IMB B-8117 suspension at 40 units of turbidity. 3. 115 mg of urea + 5 ml of urine + 1 ml of *Streptococcus thermophilus* IMB B-8116 suspension at 40 units of turbidity. 4. 115 mg of urea + 5 ml of urine + 1 ml of *Lactobacillus acidophilus* IMB B-7216 suspension at 40 units of turbidity. 5. 115 mg of urea + 5 ml of urine + 1 ml of a mixture of 3 pure cultures at 40 turbidity units.

Results and discussion.

Clinical justification.

In recent years, numerous clinical studies have been conducted on

administering probiotics to alleviate uraemia. These studies aim to assess the effectiveness of natural probiotics or identify genetically modified bacteria in the pathology of uraemia that develops in patients suffering from CKD [5; 7; 8]. For instance, eight patients on haemodialysis who received treatment with *Lactobacillus acidophilus* (NCFM TM) showed a significant reduction in dimethylamine and nitroso-dimethylamine, two gut-derived uraemic toxins.

A subsequent study evaluated the effectiveness of 27.9 mg of Lebenin® (one capsule = *Bifidobacterium infantis* 1×10^8, *Lactobacillus acidophilus* 1×10^8, and *Enterococcus faecalis* 1×10^8) administered to 20 patients twice daily for one month. After two weeks, faecal levels of p-cresol and indican, but not phenol, were reduced. After four weeks, plasma indican levels significantly decreased from 212 ± 40 to 147 ± 25 nmol/ml, whereas p-cresol levels decreased only slightly, despite its accumulation in the faeces leading to Lebenin inhibition.

The therapeutic efficacy of a five-week administration of *Bifidobacterium longum* in gastro-resistant capsules (3×10^9 CFU; Bifina) compared to bifidobacteria in powder form (2×10^7 CFU; Lac B) on indoxyl sulphate levels was also examined in 22 patients on haemodialysis. In this study, 11 patients received Bifina capsules. In comparison, the remaining 11 patients were given Lac B. Serum indoxyl sulphate levels were significantly reduced in patients who received Bifina before dialysis (from 4.5 to 3.8 mg/dl) but not in those who received Lac B treatment [12].

Another study involved the administration of *Bifidobacterium longum* (Bifidus HD) - enteric-coated capsules, to 27 patients with CKD for six months [1]. Although there were no significant differences in the studied group, biochemical parameters revealed that CKD patients with an initial serum creatinine concentration of ≥4.0 mg/dl or inorganic phosphate concentration of >4.0 mg/dl experienced changes. In 2010, Majors et al. conducted a study to assess the efficacy of a four-week dose-escalation regimen of inulin enriched with oligofructose for 22

haemodialysis patients (Orafti Synergy 1 = a mixture of oligofructose and Raftiline HP; 10 g per sachet; Orafti, Tienen, Belgium). The administration of probiotics significantly reduced the formation rate of p-cresyl sulphate and its serum concentration in all haemodialysis patients [11; 12].

A randomised, double-masked, placebo-controlled, multinational crossover study evaluating the efficacy of Renadyl, containing *Lactobacillus acidophilus*, *Streptococcus thermophilus*, and *Bifidobacterium longum*, in patients with stage 3 and 4 CKD also found that six months of treatment was associated with a significant reduction in blood urea levels and an improvement in quality of life [13].

Nakabayashi and colleagues conducted another study to evaluate the effectiveness of a synbiotic formulation (two weeks, three times daily; SYN) containing *Lactobacillus casei Shirota*, *Bifidobacterium breve Yakult*, and galactooligosaccharides on p-cresol levels in nine haemodialysis patients. Patients with high serum p-cresol levels often experience difficulties with defecation. After SYN treatment, the frequency of bowel movements significantly increased, while solid, cloudy, or soft stools were generally replaced with normal stools. Serum p-cresol levels also significantly decreased [14].

The dietary supplement "NEPHROBIOTIC" contains a combination of lacto- and bifidobacteria, including three probiotic strains of beneficial bacteria: *Streptococcus thermophilus* IMB B-8116 (Fig. 1), *Lactobacillus acidophilus* IMB B-8117 (Fig. 2), and *Bifidobacterium longum* IMB B-8118 (Fig. 3).

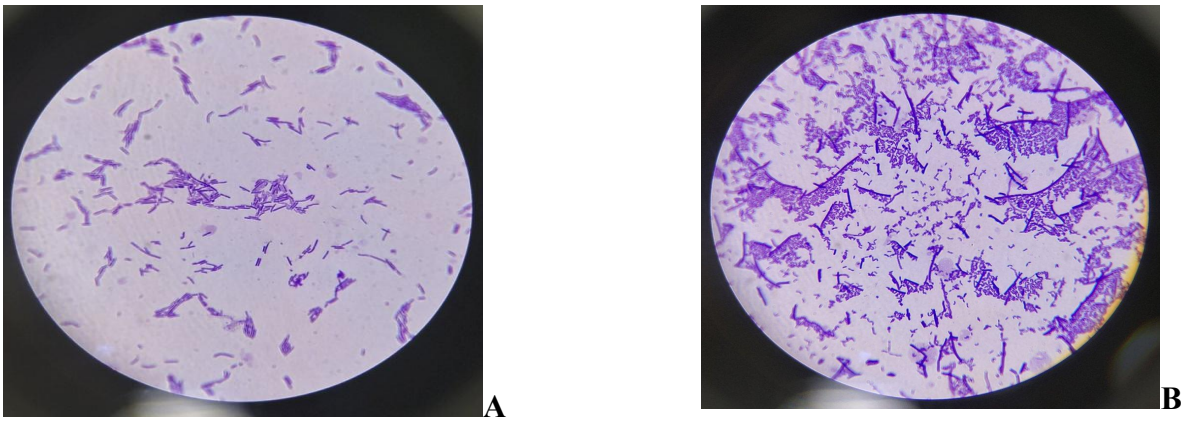

Fig. 1. Streptococcus thermophilus IMB B-8116 (A - anaerobic; B - aerobic)

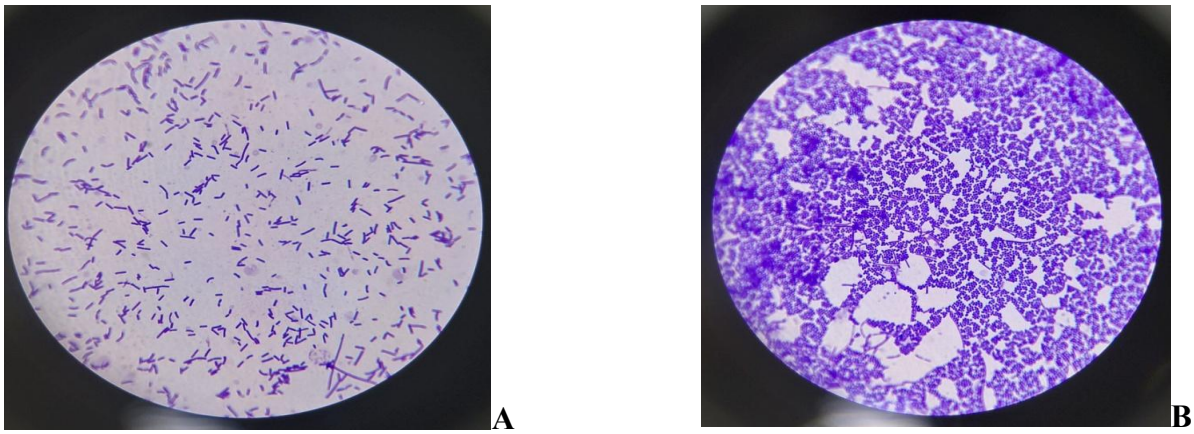

Fig. 2. Lactobacillus acidophilus IMB B-8117 (A - anaerobic; B - aerobic)

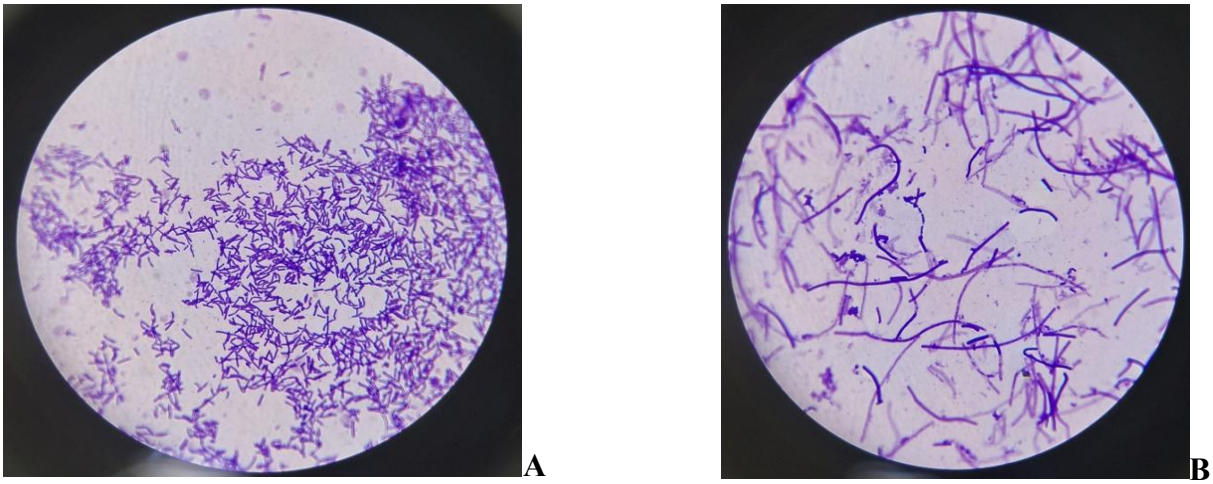

Fig. 3. Bifidobacterium longum IMB B-8118 (A - anaerobic; B - aerobic)

Microscopic examination results indicate that none of the cultures are monocultures, as all contained impurities from other bacterial cultures. For further studies, monocultures of *Bifidobacterium longum* IMB B-8118, *Lactobacillus acidophilus* IMB B-8117, and *Streptococcus thermophilus* IMB B-8116 were obtained from dry preparations that contained impurities of other bacteria.

During the study, it was established that the ability of probiotic cultures to metabolise urea depends on its source. Research conducted using the urine of a three-year-old child, with urea content in the reaction mixture at 50 mg and 100 mg in the medium, showed a positive result when using all three concentrations of probiotic cultures (Table 1).

Table 1

Ability of probiotic bacterial strains to metabolise urea, *%*

Research option	Δ	Mmol	Ability of pro-biotic strains to metabolise urea (%)
	50 mg of urea		
Quantity	0.0925	8.3	
Control 1	0.41	1471.56	
***Bifidobacterium longum* IMB B-8118**	0.14	502.48	**68.5**
Control 2	0.33	1184.43	
***Lactobacillus acidophilus* IMB B-8117**	0.138	495.31	**58.18**
***Streptococcus thermoplilus* IMB B-8116**	0.135	484.54	**59.01**
100 mg of urea			
Control 1	0.52	3732.75	
***Bifidobacterium longum* IMB B-8118**	0.102	732.19	**80.38**
Control 2	0.2	1435.67	
***Lactobacillus acidophilus* IMB B-8117**	0.102	732.19	**49.0**
***Streptococcus thermoplilus* IMB B-8116**	0.975	699.89	**51.24**

Note: Δ is average urea content at A_{560}

The ability to metabolise urea in an environment containing 50 mg was 68.5%, 58.18%, and 59.01%. Meanwhile, the ability of probiotic cultures to metabolise urea in a reaction medium containing 100 mg of urea was 80.38%, 49.0%, and 51.24%.

Thus, the ability of three probiotic cultures—*Bifidobacterium longum* IMB B-8118, *Lactobacillus acidophilus* IMB B-8117, *and Streptococcus thermophilus* IMB B-8116—which were not presented as monocultures but contained traces of other bacterial strains to metabolise urea in human urine ranged from 49.0% to 80.38%.

Since the probiotic strains were also isolated as monocultures, studies were conducted to assess the ability of pure probiotic strains to metabolise urea (Table 2). The test medium used was a child's urine (3 years old).

Table 2

Ability of probiotic bacterial strains to metabolise urea

	Δ	Mmol	Ability of pro-biotic strains to metabolise urea (%)
	50 mg of urea		
Quantity	0.1	8.3	
Control	0.33	576.63	
3 pure cultures (*Bifidobacterium longum* IMB B-8118, *Lactobacillus acidophilus* IMB B-8117, *Streptococcus thermoplilus* IMB B-8116)	0.22	366.94	**41.56**

The results of the study indicate that all three separate pure live cultures of probiotic strains *Bifidobacterium longum* IMB B-8118, *Streptococcus thermophilus* IMB B-8116, and *Lactobacillus acidophilus* IMB B-8117 are quite effective in metabolising urea in a child's urine model (3 years old). The most effective culture was *Bifidobacterium longum* IMB B-8118 (80.38%), while the other two cultures, *Streptococcus thermophilus* IMB B-8116 (51.24%) and *Lactobacillus acidophilus* IMB B-8117 (49.0%), metabolised urea with almost the same efficiency. The

mixture of three pure cultures exhibited a lower but still significant ability to metabolise urea—41.56%.

The combination of *Streptococcus thermophilus* (IMB B-8116), *Lactobacillus acidophilus* (IMB B-8117), and *Bifidobacterium longum* (IMB B-8118) aids in the elimination of toxic nitrogenous uraemic toxins from the intestine. The use of probiotics in patients with chronic kidney failure has been studied in both experimental and clinical settings. Recently, a deeper understanding has been gained regarding the positive impact of probiotics on the progression of kidney disease—possible mechanisms (elimination of dysbiosis imbalance, including intestinal anti-inflammatory and antioxidant effects). Furthermore, several promising studies have linked intestinal dysbiosis with chronic kidney failure, known as the gut-kidney axis [5; 7; 15].

During chronic kidney failure, the gut microbiome produces many toxins, such as indoxyl sulfate, para-cresyl sulfate (PCS), and trimethylamine N-oxide (TMA), thereby increasing the burden on the kidneys [1; 6]. At the same time, uraemia affects the composition and metabolism of the gut microbiota. This creates a closed loop called the gut-kidney axis [7; 15; 16]. Based on a meta-analysis that included seven clinical trials with 842 patients with CKD, a potential beneficial effect of probiotics on inflammation markers, protein-bound nitrogenous uraemic toxins, and gastrointestinal symptoms in CKD patients was established [11]. Moreover, lactobacilli and bifidobacteria are used in various disorders caused by dysbiosis (diarrhoea, constipation, and irritable bowel syndrome). They also prevent colds, flu, and many other diseases.

The study assessed the biochemical and clinical effects of probiotics in a dietary supplement containing probiotic strains *Streptococcus thermophilus* (IMB B-8116), *Lactobacillus acidophilus* (IMB B-8117), and *Bifidobacterium longum* (IMB B-8118) in patients with CKD (stages 3 and 4). A number of promising

clinical findings were obtained. A significant reduction in blood urea nitrogen and improved well-being were observed, supporting the validity of the selected probiotic composition for eliminating toxic nitrogenous uraemic toxins from the intestine.

Thus, various clinical studies on CKD stage 3 patients suggest that the administration of a single probiotic or a combination of bacterial strains improves biochemical indicators in these patients.

Conclusion. During the study, the ability of the developed dietary supplement "NEPHROBIOTIC" to metabolise urea in human urine was demonstrated, ranging from 41.56% to 80.38%. "Nephrobiotic" contains three live probiotic cultures: *Bifidobacterium longum* IMB B-8118, *Lactobacillus acidophilus* IMB B-8117, *Streptococcus thermophilus* IMB B-8116. It was found that individual pure live cultures (monocultures) exhibited a moderate ability to metabolise urea: 80.38% (*Bifidobacterium longum* IMB B-8118), 51.24% (*Streptococcus thermophilus* IMB B-8116), and 49.0% (*Lactobacillus acidophilus* IMB B-8117). The mixture of the three pure cultures demonstrated a lower but practical ability to metabolise urea—41.56%.

Given the above data, "NEPHROBIOTIC" can be recommended as a dietary supplement and an additional source of biologically active substances to provide a beneficial probiotic impact on inflammatory markers, protein-bound nitrogenous uraemic toxins, and gastrointestinal symptoms in patients with chronic kidney failure.

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