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ANTIHERPETIC EFFICACY OF LACTOBACILLI AND BIFIDOBACTERIA PROBIOTIC STRAINS IN EXPERIMENTAL GENITAL HERPES IN GUINEA PIGS

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Aim*. The aim was to determine the antiherpetic effectiveness of the Lactobacillus casei IMV B-7280 probiotic strain and L. casei IMV B-7280 – Bifidobacterium animalis VKL – B. animalis VKB (B-7280 – VKL – VKB) composition on the experimental model of genital herpes in guinea pigs induced by herpes simplex virus type 2 (HSV-2).*

Materials and methods*. Genital herpetic infection was modeled using HSV-2 (strain BH) on female non-breeding guinea pigs. The criteria for assessing the severity of the course of the infectious process were: the area and the degree of specific lesions, as well as the presence of edema, hyperemia and ulcers. HSV-2 titer was determined in blood serum by using common virological methods of research. The spectrum of microbiota in the vagina of animals was determined using generally accepted microbiological methods. The effectiveness of the probiotic bacteria was evaluated during the maximum development of the pathological process: the decrease in the severity of clinical manifestations of the disease and TCD ID_{50} infectious titer of HSV-2, as well as the reduction of terms of the disease and therapeutic index (TI).*

Results and discussion. *It was established that in cases of experimental genital herpes in guinea pigs, treatment with L. casei IMV B-7280 probiotic strain or B-7280 – VKL – VKB composition reduced: the severity of clinical symptoms of the disease, the duration of its course, and the infectious titer of HSV-2, though TI did not exceed 50 %. Under the influence of L. casei IMV B-7280 and the composition, there was a decrease in the TCD ID_{50} infectious titer of HSV-2, which indicates the anti-herpetic efficacy of these probiotic strains, whose mechanisms may involve the change of vaginal microbiome. The microbiological parameters of the vagina at the maximum severity of clinical symptoms of genital herpes were characterized by a decrease in the number of staphylococci in the vagina of infected guinea pigs treated with L. casei IMV B-7280 with a high level of these bacteria after treating of guinea pigs with B-7280 – VKL – VKB composition, as well as lactobacilli (LAB) appearance in individual animals. It should be noted that LAB detected by us at the end of the experiment, differed from the lactobacilli used in the experiment by morphological characteristics. So, we can assume that there has been a restoration of the normal vagina microbiota specific for guinea pigs.*

Conclusions. *L. casei IMV B-7280 strain and B-7280 – VKL – VKB composition are promising for the development of target probiotics for the prevention and treatment of infectious-inflammatory diseases of the genitourinary system.*

Key words: *herpes simplex virus type 2; lactobacilli; bifidobacteria; genital herpes; guinea pigs.*

Genital herpes (GH) ranks second after trichomoniasis among sexually transmitted diseases (STDs) [1]. It is possible that GH is much wider than expected, since only symptomatic forms of the disease that afflicts about 86 millions people in the world can be counted [2]. The etiological factor of GH in 80 % of cases is herpes simplex virus type 2 (HSV-2), in 20 % – HSV-1 [6-3]. Antibodies to HSV-1 or HSV-2 in Western Europe show a frequency of more than 80 cases per 100,000 people, and in the United States – about 200 per 100,000. The prevalence of HSV-2 is significantly higher than other viral STDs, such as human papillomavirus (HPV), hepatitis B and human immunodeficiency virus (HIV) [4]. Antibodies to HSV-2 are detected in 20-50 % of cases among adult patients who consult a venereologist, although many people have never had clinical symptoms of herpes infection [3].

GH differs from other STDs by the lifelong carriers of the pathogen (latent period), which determines the high level of its relapse [5]. Diseases caused by HSV, occupy one of the first places in the structure of people mortality. Among the causes of death due to viral infections (excluding

AIDS), they are in the 2nd place (15.8 % of cases) after the flu [6]. In addition, it should be noted that HSV-1 and HSV-2 are a risk factor for HPV-induced cervical cancer, the second one for detecting tumor pathology in women [7].

For normal functioning of the immune system, the infection with herpes viruses usually leads to the formation of a powerful long-term, and in many cases, life-long immunity against a specific type of virus. Relapse of the disease is most often due to the various factors that can cause disorders in the immune system (decrease in functional activity of T- and B-lymphocytes, systems of phagocytosis, complement, etc.) [6, 8]. At the same time, herpes viruses, especially HSV, have immunosuppressive properties: they produce a number of proteins that block the expression of class I and II receptors of the main histocompatibility complex, which leads to the destruction of the cascade of proliferation and differentiation signaling throughout the system of specific immune response, including productions of antibodies, interferon-γ (IFN-γ) and the development of antigen-specific CD8+ T-lymphocytes [3].

The relapse of infection and remission reduces the production of immunoglobulins and changes occur in the ratio of T-lymphocytes: T-suppressors begin to prevail over T-killers [8]. Therefore, relapsing herpetic infection is a marker of immunodeficiency state. The presence of clinical symptoms of immunopathology and changes in the parameters of the immunity or herpetic infection justify the expediency of immunocorrection in the complex personified treatment of the majority of patients in this category, along with etiotropic therapy.

An active search for anti-herpetic preparations has led to the development of drugs with different mechanisms of action: abnormal nucleosides: Aciclovir and its group drugs – Valacyclovir, Ganciclovir, Penciclovir, Famciclovir, suppressing the DNA polymerase enzyme; Valtrex®, Vectavir®, Famvir®, Cymevene®, suppressing the synthesis of viral DNA and replication of herpes viruses by competitive inhibition of viral DNA polymerase; synthetic non-nucleoside analogs of pyrophosphates (for example, Foscarnet), selectively suppressing viral DNA polymerase and reverse transcriptase [9-10].

In the complex treatment of patients with herpetic infections immunomodulators are used: Alpisarin, Immunofanum, Licopid®, Polyoxidonium®, IFN inducers (Amixin, Neovir®, Cycloferon®, etc.), preparations based on flavonoids (Proteflazid®), as well as probiotics (Biosporin, Subalin®, Bifidumbacterin Forte®, etc.) [11-13]. Probiotic therapy of herpetic infections is carried out to restore microbiota of various biotops of the organism [14] and to correct the immune system. It has been established that the change of the genitourinary microbiota is a risk factor for HSV-2 and HPV [17–20]. It has been shown that probiotic strains of LAB prevent the penetration of HSV-2 into cells in the initial stages of infection [21], and their metabolites have virucidal action [22].

Previously, we have shown that the sequenced original probiotic strain *Lactobacillus casei* IMV B-7280 and the composition *L. casei* IMV B-7280 – *Bifidobacterium animalis* VKL – *B. animalis* VKB (B-7280 – VKL – VKB) in cases of experimental infectious-inflammatory diseases of the genitourinary system of bacterial and fungal genesis in mice had effective antibacterial, anti-inflammatory, as well as immunomodulatory effect, aimed at activating the phagocytosis system and balancing Th1/Th2 immune response by induction of various cytokines [23]. Therefore, *L. casei* IMV B-7280 in monoculture and this probiotic composition are promising for the creation of highly effective probiotics (immunobiotics) for target use.

In connection with the foregoing, the purpose of the study was to determine the anti-herpetic efficacy of the *L. casei* IMV B-7280 probiotic strain and the B-7280 – VKL – VKB composition in experimental genital herpes in guinea pigs induced by HSV-2.

Materials and methods

The anti-herpetic efficacy of probiotic strains of bacteria was determined on the model of genital herpes in female non-breeding guinea pigs (250-300 g), obtained from the «Glevakha» vivarium. Animals were kept under standard vivarium conditions at a temperature of (22±1) °C, they were provided with high-quality feed and had free access to automatic drinking bowls. Keeping animals and conducting research involving animals complied with the «European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes» (Strasbourg, 1986) and «General Ethical Principles of Animal Experiments» [24].

Lyophilized original probiotic bacteria *L. casei* IMV B-7280, *B. animalis* VKL and *B. animalis* VKB were used in this work. Before the experimental studies, the viability of the lyophilized probiotic strains of lactobacilli and bifidobacteria was checked by controlling their growth on selective agar medium MRS (Man-Rogosa-Sharpe, HiMedia, India) or Bifidum (HiMedia, India), respectively.

Genital herpetic infection was modeled using HSV-2 (strain BH), isolated from the patient with genital herpes (rinsing from the affected surface), which was maintained by serial passages in a Vero cells culture. Before the experiments, the virus was stored at -70 °C. The model of genital herpetic infection was reproduced by infecting the genital organs of guinea pigs with a virus-containing liquid with an infectious titer of 5.0-5.5 lg TCD_{50} / ml by the method of Marennikova S.S. et al. [25], which was applied to the pre-scarified skin of the labia. Scarification was performed using a surgical lancet after the animals were anesthetized with ether. The size of

the scarification area was 4-7 mm^2. The virus-containing liquid was applied by pipette immediately after scarification with following careful rubbing.

Clinical symptoms of genital herpes were recorded daily and traced throughout the period of the disease. The criteria for assessing the severity of the infectious process course were: the area and the degree of specific lesions, as well as the presence of edema, hyperemia and ulcers. The maximum score on this scale was 4. Based on the clinical signs of genital herpes, a scale was constructed and the type of the course of the disease was graphically reflected – from the onset of the first signs of the disease to their complete disappearance. The duration of the observations was 21 days.

The infected guinea pigs obtained into vagina suspension of *L. casei* IMV B-7280 probiotic strain or B-7280 – VKL – VKB composition (1:1:1) in 0.15 M NaCl once a day for 10 days in a volume of 300 µL and quantity of 1x10^9 cells/animal. Three groups of animals (3 animals per each) were formed: 1) animals infected with HSV-2, which were injected with *L. casei* IMV B-7280; 2) animals infected with HSV-2, which obtained B-7280 – VKL – VKB composition into vagina; 3) animals infected with HSV-2, which obtained 0.15 M NaCl into vagina (control group of animals).

Prior to infection, on the 3rd and 7th days after infection, as well as after the disappearance of clinical signs of the disease (on the 10th day), the peripheral blood was obtained from the alive guinea pigs, from which the serum was isolated and stored at -70 °C before investigation. Titers of HSV-2 in blood serum were determined by commonly used virological methods in Vero cell culture [25].

Vaginal discharges were obtained from vagina of animals using sterile unified tampons and put into transport test tubes with Amies medium (F.L. Medical, Italia). Samples from each test tube were plated on Petri dishes with Yolk-salt agar (Salini staphilococcus agar), Enterococcus agar, Endo agar, Sabouraud agar («Pharmactiv» Ltd, Ukraine), Lactobacagar and Bifidum (FBIS SRCAMB, Russian Federation) using Gold-Rhodoman method. Petri dishes were incubated at (37±1) °C for 24 hours. Morphology of the colonies on agar was studied, and the number of them was counted. Subsequently, the removal of individual colonies was carried out on Olkenitsky agar – nutrient agar for cultivation and primary identification of microorganisms (GMP agar, FBIS SRCAMB, Russian Federation), and beveled blood agar («Pharmactiv» Ltd., Ukraine). Biochemical identification of bacteria was carried out on the 3rd day, using pure cultures of microorganisms grown on a beveled agar, selective nutrient media and biochemical tests according to generally accepted microbiological research methods [26].

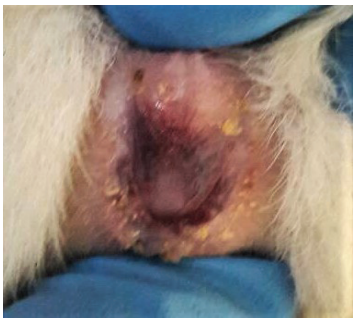
The effectiveness of the probiotic bacteria was evaluated during the maximum development of the pathological process: the decrease in the severity of clinical manifestations of the disease and TCD ID_{50} infectious titer of HSV-2, as well as the reduction of terms of the disease and therapeutic index (TI) in the experimental groups compared to the control.

TI was calculated using the formula:

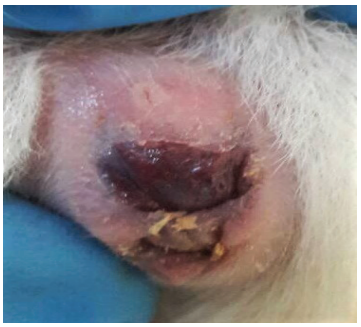
$$TI\ (in\ \%) = \frac{\text{The amount of points in the control – amount of points in the group of animals receiving probiotic strains}}{\text{The amount of points in the control}}$$

Results and discussion

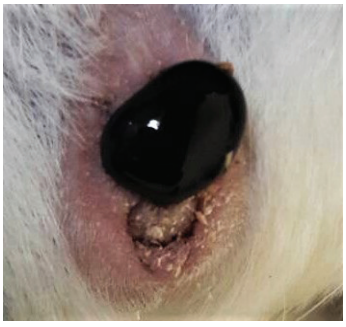
Infection of the guinea pigs with HSV-2 resulted in specific clinical symptoms of genital herpes in different periods of observations, such as swelling, hyperemia, numerous bright pink blisters and ulcers (Figure 1).



Hyperemia, swelling, ulcers



Swelling, ulcers, blisters, hyperemia



Swelling, ulcers, blisters, hyperemia, hemorrhagic bladder

Figure 1. Development of clinical symptoms of genital herpes in female guinea pigs, infected with HSV-2.

Thus, insignificant swelling and hyperemia on the genitals of guinea pigs appeared already on the 4th day after infection. On the 5th and 6th days, the maximum manifestation of clinical symptoms of genital herpes was observed: the degree of severity of edema, hyperemia and blisters was stronger, and ulcers had 2-3 points. On the 7th day after infection, the severity of edema on the genitalia of guinea pigs remained at the same level, but the intensity of the manifestation of hyperemia, blisters and ulcers diminished. On the 9th day after infection, these symptoms were much weaker, which indicates a gradual attenuation of the infectious process, on the 10th day symptoms completely disappeared.

Table 1 presents the results of the study of the *L. casei* IMV B-7280 probiotic strain and the composition B-7280 – VKL – VKB therapeutic effect for genital herpes in guinea pigs, which was evaluated by decreasing the severity of clinical manifestations of the disease, reducing of its duration and TI.

Table 1

Influence of probiotic bacteria on the manifestation of clinical signs of genital herpes and TI in guinea pigs

Term of observation	Group of animals	Clinical symptoms / points				Number of points	TI, %
		Swelling	Hyperemia	Blisters	Ulcers		
4th day	1	3.0	3.0	-	-	6.0	
	2	3.0	3.0	-	-	6.0	
	3	2.0	2.0	-	-	4.0	
5th day	1	4.0	4.0	3.0	-	11.0	21.4
	2	4.0	4.0	3.0	-	11.0	21.4
	3	4.0	4.0	4.0	2.0	14.0	
6th day	1	4.0	4.0	4.0	1.0	13.0	13.3
	2	4.0	4.0	4.0	2.0	14.0	6.6
	3	4.0	4.0	4.0	3.0	15.0	
7th day	1	3.0	2.0	2.0	1.0	8.0	27.2
	2	3.0	2.0	1.0	1.0	7.0	36.3
	3	4.0	3.0	2.0	2.0	11.0	
9th day	1	0	0	0	0	0	9.0
	2	0	0	0	0	0	9.0
	3	1.0	1.0	1.0	1.0	4.0	
11th day	1	0	0	0	0	0	
	2	0	0	0	0	0	
	3	0	0	0	0	0	

Notes: 1) Group 1 – infected animals that obtained *L. casei* IMV B-7280; 2) Group 2 – infected animals that obtained probiotic composition; 3) Group 3 – infected animals that did not obtain probiotic bacteria (control).

The degree of severity of the clinical signs of the disease in infected guinea pigs, which were treated with *L. casei* IMV B-7280 or B-7280 – VKL – VKB composition was lower than in infected animals in the control group (Table 1). It should be noted that in case of therapeutic use of these probiotic strains of bacteria, ulcers on the genitals of infected guinea pigs appeared later – on the 6th day, and the intensity of their manifestation in the subsequent observation period was significantly less than that in the control. So, clinical signs of genital herpes in infected guinea pigs, which were treated with *L. casei* IMV B-7280 or B-7280 – VKL – VKB composition, disappeared 3 days earlier than that of control animals. It has been established that TI for these probiotic strains did not exceed 50 % for experimental genital herpes (Table 1), but under their influence we observed a change in the infectious titre of HSV-2 in the blood serum of infected animals (Table 2).

Table 2

Influence of probiotic strains of lactobacilli and bifidobacteria on the infectious titre of HSV-2 in serum

Group of animals	Infectious titer TCD ID_{50}	Inhibiting of infectious titer in lg ID_{50}
Infected animals treated with *L. casei* IMV B-7280	2.1+/-0.1	3.4+/-0.3
Infected animals treated with B-7280 – VKL – VKB composition	2.5+/-0.5	3.0+/-0.2
Infected animals that did not obtain probiotic bacteria	5.5+/-0.5	

HSV-2 was detected in blood serum of infected guinea pigs of the control group during the maximal development of clinical symptoms of the disease (on the 5^{th}-6^{th} days); the infectious titre of the virus was 5.5 lg ID_{50} (Table 2). HSV-2 was also detected in the blood serum of infected animals treated with *L. casei* IMV B-7280 or B-7280 – VKL – VKB composition at the maximize development of clinical symptoms of genital herpes, but its infectious titer decreased compared with control. It should be noted that the degree of suppression of the TCD ID_{50} infectious titer of HSV-2 under the influence of *L. casei* IMV B-7280 and the probiotic composition was the same.

The microbiota of the vagina has been investigated in the infected guinea pigs of all groups of comparison, since the influence of probiotic strains of bacteria on the composition and the number of vaginal microorganisms can be involved in the mechanisms of their therapeutic effect in experimental genital herpes in guinea pigs. The vaginal microbiota of intact guinea pigs was represented by coagulase-negative staphylococci, enterococci, *Proteus*; LAB were not detected (Table 3).

Table 3

Microbiota of the vagina of intact guinea pigs

Detected microorganism	CFU/ml							
	1	2	3	4	5	6	7	8
Coagulase-negative *Staphylococcus spp.*	1.2×10^8	1.2×10^8	2.3×10^9	1.1×10^9	1.2×10^8	1.3×10^8	2.4×10^9	1.1×10^9
Enterococcus spp.	5.8×10^9	6.3×10^9	2.6×10^9	3.3×10^9	5.3×10^9	2.3×10^9	6.3×10^9	2.6×10^9
Proteus mirabilis	-	5.1×10^7	-	-	1.2×10^8	-	5.6×10^5	5.3×10^7
LAB	-	-	-	-	-	-		

The composition of vaginal microbiota of infected guinea pigs of the control group on the 3^{rd} day of observation did not significantly change compared with indicators before infection (Table 4).

Table 4

Microbiota of the vagina of guinea pigs on the 3^{rd} day after infection with HSV-2

Detected microorganism	CFU/ml							
	1	2	3	4	5	6	7	8
Coagulase-negative *Staphylococcus* spp.	3.2×10^9	3.7×10^9	1.0×10^9	1.1×10^9	1.2×10^9	1.3×10^9	3.2×10^9	3.7×10^9
Enterococcus spp.	5.7×10^9	6.1×10^9	2.6×10^9	3.4×10^9	3.2×10^9	2.2×10^9	5.7×10^9	6.1×10^9
Proteus mirabilis	5.1×10^6	-	-	-	1.3×10^8	-	5.1×10^6	-
LAB	-	-	-	-	-	-	-	-

On the 3rd day the number of coagulase-negative staphylococci increased by an order in the vagina of infected guinea pigs that were treated with *L. casei* IMV B-7280. However, the number of coagulase-negative staphylococci increased by an order also in the control group.

The number of enterococci in the vagina of infected guinea pigs of all three groups of comparison on the 3rd day of observation was kept at 10^9 CFU / ml. *Proteus* was isolated only from one HSV-2 infected animal, which was treated with *L. casei* IMV B-7280, as well as in from animal in control. On the 3rd day of observation LAB were not detected in the vagina of infected animals treated with *L. casei* IMV B-7280or a probiotic composition.

On the 7th day after infection, the number of enterococci, staphylococci and enterococci was reduced in the vagina of control group of animals; LAB were absent (Table 5).

Table 5

Microbiota of the vagina of guinea pigs on the 7th day after infection with HSV-2

Detected microorganism	Group of animals / CFU/ml					
	Infected animals treated with *L. casei* IMV B-7280		Infected animals treated with B-7280 – VKL – VKB composition		Infected animals that did not obtain probiotic bacteria	
	1	2	3	4	5	6
Coagulase-negative *Staphylococcus* spp.	1.3×10^8	5.6×10^5	2.0×10^9	1.2×10^9	1.2×10^8	3.2×10^3
Enterococcus spp.	0	1.4×10^3	2.6×10^9	1.2×10^7	1.3×10^5	1.2×10^9
Proteus mirabilis	-	5.2×10^7	-	6.7×10^7	7.0×10^7	3.0×10^5
LAB	1.1×10^{10}	-	-	2.2×10^3	-	-

The change in the vaginal microbiota composition of the infected guinea pigs, treated with *L. casei* IMV B-7280, or a probiotic composition, was more significant on the 7th day of observation. Thus, the number of enterococci and staphylococci decreased in the vagina of infected animals treated with *L. casei* IMV B-7280; LAB was also detected in the vagina of one animal of this group. It was observed a slight decrease in the number of enterococci in the vagina of one infected guinea pig that obtained B-7280 – VKL – VKB composition, LAB was also detected in the vagina of this animal.

Restoration of vaginal microbiota of infected guinea pigs of all groups of comparison occurred only at the end of the experiment – on the 10th day (Table 6).

Table 6

Microbiota of the vagina of guinea pigs on the 10th day after infection with HSV-2

Detected microorganism	Group of animals / CFU/ml					
	Infected animals treated with *L. casei* IMV B-7280		Infected animals treated with B-7280 – VKL – VKB composition		Infected animals that did not obtain probiotic bacteria	
	1	2	3	4	5	6
Coagulase-negative *Staphylococcus* spp.	1.5×10^5	1.3×10^8	1.5×10^3	1.5×10^3	$1.1\times\cdot10^3$	1.2×10^3
Enterococcus spp.	2.0×10^{10}	2.1×10^{10}	2.2×10^{10}	2.2×10^{10}	2.0×10^{10}	2.1×10^{10}
Proteus mirabilis	-	6.0×10^5	-	5.1×10^5	5.0×10^5	-
LAB	1.5×10^3	2.5×10^5	1.5×10^3	-	-	2.5×10^5

The number of coagulase-negative staphylococci remained low in infected guinea pigs treated with probiotic composition and in control. In infected guinea pigs that obtained *L. casei* IMV B-7280, the amount of coagulase-negative staphylococci was 10^5 CFU and 10^8 CFU in 1 ml of washouts from vagina. LAB were isolated on the 10th day of observation from the vaginal infected guinea pigs after therapeutic use of *L. casei* IMV B-7280 or probiotic composition. It should be noted that LAB were also isolated from the vagina of one animal of the control group.

Consequently, as a result of our research, it was found that the use of *L. casei* IMV B-7280 probiotic strains or B-7280 – VKL – VKB composition on the model of experimental genital herpes in guinea pigs reduced the severity of the clinical symptoms of the disease, the duration of its course, as well as infectious titer of HSV-2, although the TI of these probiotic strains of bacteria did not exceed 50 %. The decrease of the infectious titer of HSV-2 on 3.0-3.4 lg ID_{50} in infected guinea pigs under the influence of probiotic strains indicates the anti-herpetic efficacy of these bacteria, mechanisms of which may involve the change of vaginal microbiota.

The microbiological parameters of the vagina at the maximum severity of clinical symptoms of genital herpes were characterized by a decrease in the number of staphylococci in the vagina of infected guinea pigs treated with *L. casei* IMV B-7280 with a high level of these bacteria after treating of guinea pigs with B-7280 – VKL – VKB composition, as well as LAB appearance in individual animals.

At the end of the experiment, LAB were also detected in the vagina of infected animals of the control group. It is known that vaginal LAB inactivates pathogens due to antimicrobial action of products of their metabolism (lactic acid, H_2O_2, bacteriocins), competition for sites for attachment of pathogens to epithelial cells, and also the preservation of mucin in the mucous membranes of the vagina and cervix through inhibition of glucosidase anaerobes and activation of the immune response [27, 28]. It should be noted that LAB detected by us at the end of the experiment, differed from the lactobacilli used in the experiment by morphological characteristics. So, we can assume that there has been a restoration of the vaginal microbiota specific for guinea pigs.

Anti-herpetic efficacy *in vivo* and *in vitro* was also found in other probiotic strains of bacteria. In particular, it was shown that under the influence of *L. plantarum* 200D and *S. thermophilus* Sm and Sn strains the cytopathic effect of HSV-1 and -2 was suppressed and the severity of clinical symptoms of herpesvirus meningoencephalitis in white non-breeding mice was reduced [29]. Strains *L. brevis* CD2, *L. salivarius* FV2, *L. plantarum* FV9 suppressed the propagation of HSV-2 in Vero cells culture. The inhibitory effect of these probiotic bacteria in the early stages of the viral infection is due to their adhesive potential, presumably due to blocking the receptors for HSV-2 on the cell surface.

However, all these strains with the same efficacy inhibited intracellular reproduction of the virus. Such metabolites of *Lactobacillus* with known antimicrobial activity as purified lactic acid and H_2O_2 had dose-dependent virucidal action [22]. The *L. crispatus* strain also suppressed the intrusion of HSV-2 into the HeLa and Vero cells cultures at the initial stages of infection, due to the formation of microcolony on the cells surface that blocked the receptors for HSV-2 and prevents the virus penetrating into the cells at the initial stages of infection. At the same time, under the influence of this *Lactobacillus* strain, there was no inhibition of HPV proliferation in cells [21].

It was shown that *L. gasseri* CMUL57, *L. acidophilus* CMUL67 and *L. plantarum* CMUL140 strains reduced the cytopathic effect of HSV-2 in Vero cells culture if they were cultured with the virus before infection of the cells. The presence of DNA of HSV-2 in bacteria indicates that they are likely to capture viral particles [19]. The strain *L. rhamnosus* reduced the cytopathic effect of HSV-1 in the J774 line macrophage cells culture by blocking the viral receptors on their surface and enhancing the production of tumor necrosis factor alpha (TNF-α), IFN-γ and nitric oxide [17]. It was found in studies with *L. brevis* strain, that the mediated anti-herpetic effect of LAB corresponds to cellular components that are resistant to high temperature and are digested with proteases having a molecular weight greater than 10 kD. Instead, DNA, RNA, and lipids isolated from *L. brevis* did not have an antiviral effect [30]. The *L. brevis* strain in the vaginal probiotic demonstrated high therapeutic efficacy in treating patients with genital herpes [31].

In the mechanisms of antiviral effectiveness of different strains of LAB *in vivo*, activation of the immune response can be involved – increased activity of macrophages, natural killer cells, Th1 cytokine production, etc. The therapeutic or prophylactic efficacy of *L. casei* YIT 9018 [32, 33] and *L. plantarum* 06CC2 [18] strains has been proved on various experimental models of herpetic infection. Oral administration of *L. plantarum* 06CC2 strain to mice with HSV-1-induced skin lesions, a decrease in the incidence of HSV-2 appearance in the brain (on the 4th after infection) was observed against the backdrop of an enhanced Th1 immune response that correlated with activation of natural killer cells and increased expression of genes of β2 interleukin-12 (IL-12) receptor, IFN-γ in Peyer's patches, and IFN-γ in the culture of splenocytes.

The *L. casei* IMV B-7280 strain that we studied also have effective immunomodulatory properties [23, 34], which are confirmed by its ability to activate the phagocytic system cells and balance the Th1/Th2 immune response on the model of experimental infectious-inflammatory processes of the bacterial-fungal genesis. Therefore, the anti-herpetic efficacy of *L. casei* IMV B-7280 and the composition of B-7280 – VKL – VKB in cases of experimental genital herpes in guinea pigs can be mediated by the activation of congenital and acquired immunity factors, but further research is needed.

Conclusion

Thus, the data obtained by us showed that the strain *L. casei* IMV B-7280 and composition B-7280 – VKL – VKB

are promising for the development of target probiotics for prevention and treatment of infectious-inflammatory diseases of the genitourinary system.

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АНТИГЕРПЕТИЧНА ЕФЕКТИВНІСТЬ ПРОБІОТИЧНИХ ШТАМІВ ЛАКТО- ТА БІФІДОБАКТЕРІЙ ЗА ЕКСПЕРИМЕНТАЛЬНОГО ГЕНІТАЛЬНОГО ГЕРПЕСУ У МУРЧАКІВ

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РЕЗЮМЕ. Метою було визначення антигерпетичної ефективності пробіотичного штаму Lactobacillus casei IMB B-7280 та композиції L. casei IMB B-7280 – Bifidobacterium animalis VKL – B. animalis VKB (B-7280 – VKL – VKB) за експериментального генітального герпесу в мурчаків, індукованого вірусом простого герпесу 2-го типу (ВПГ-2).

Матеріали і методи. *Генітальну герпетичну інфекцію моделювали за допомогою ВПГ-2 (штам ВН) у самиць безпородних мурчаків. Критеріями оцінки ступеня тяжкості інфекційного процесу були: площа і ступінь специфічних уражень, а також наявність набряку, гіперемії й виразок. У сироватці крові тварин визначали титр ВПГ-2 за допомогою загальноприйнятих вірусологічних методів дослідження. Спектр мікробіоти піхви тварин визначали за допомогою загальноприйнятих мікробіологічних методів дослідження. Ефективність дії пробіотичних бактерій оцінювали за максимального розвитку патологічного процесу: за згасанням клінічних проявів захворювання та інфекційного титру ТЦД ID_{50} ВПГ-2, а також скороченням термінів захворювання та індексом лікувальної дії (ІЛД).*

Результати досліджень та їх обговорення. *Встановлено, що за експериментального генітального герпесу у мурчаків при застосуванні пробіотичного штаму L. casei IMB B-7280 та композиції B-7280 – VKL – VKB зменшувались: ступінь клінічних симптомів захворювання, його тривалість, а також інфекційний титр ВПГ-2, хоч ІЛД не перевищував 50 %. Під впливом L. casei IMB B-7280 та композиції відбувалось зменшення інфекційного титру ТЦД ID_{50} ВПГ-2, що свідчить про антигерпетичну ефективність цих пробіотичних штамів бактерій, у механізми якої може залучатись зміна мікробіоти піхви. Мікробіологічний пейзаж піхви за максимальної яскравості клінічних симптомів генітального герпесу характеризувався зниженням кількості стафілококів у піхві інфікованих мурчаків, яким вводили L. casei IMB B-7280, при високому рівні цих бактерій за умови застосування композиції B-7280 – VKL – VKB, а також появою в окремих тварин лактобацил (ЛАБ). Зауважимо, що виділені нами в кінці експерименту ЛАБ за своєю морфологією від-*

різнялися від лактобактерій, використаних в експерименті. Тобто можна припустити, що відбулося відновлення характерної для мурчаків нормальної мікробіоти піхви.

Висновок. *Штам L. casei IMB B-7280 та композиція B-7280 – VKL – VKB є перспективними для розробки цільових пробіотиків для профілактики й лікування інфекційно-запальних хвороб сечостатевої системи.*

Ключові слова: *віруси простого герпесу 2-го типу, лактобактерії, біфідобактерії, генітальний герпес, мурчаки.*

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