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The effect of probiotic strains of lactic acid bacteria and bifidobacteria on the Th1 and Th2 type cytokines production in intravaginal staphylococcosis in mice

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The probiotic strains of Lactobacillus casei IMV B-7280, Bifidobacterium animalis VKL, B. animalis VKB (individually) or L. casei IMV B-7280 - B. animalis VKB - B. animalis VKL composition balanced the Th1/Th2 cytokines production at normal condition and in the cases of experimental intravaginal staphylococcosis in BALB/c mice in different periods of observation. L. casei IMV B-7280 and B. animalis VKB (individually) at normal condition increased the Th1 type cytokines interleukin (IL)-12 and interferon (IFN)-γ production. Instead, B. animalis VKL after injection into intact mice did not affect the IL-12 production but slightly increased the IFN-γ production. In the cases of experimental intravaginal staphylococcosis in mice the balancing of Th1/Th2 immune response under the influence of L. casei IMV B-7280 is due to increased production of IL-12 and IFN-γ, as well as decreased Th2 type cytokine IL-4 production. The IL-12 and IFN-γ production in staphylococcus-infected mice that received B. animalis VKL or B. animalis VKB (individually) was increased, but these probiotic bacteria had no significant effect on IL-4 production. Under the influence of L. casei IMV B-7280, B. animalis VKB, B. animalis VKL (individually) in the cases of experimental intravaginal staphylococcosis in mice the IL-4/IFN-γ ratio was significantly decreased. The shift from Th2 to Th1 type cytokines production was also observed in staphylococcus-infected mice that received L. casei IMV B-7280 - B. animalis VKB - B. animalis VKL composition. The IL-12 and IFN-γ production was increased, instead, IL-4 production as well as IL-4/IFN-γ ratio were decreased in mice that received this probiotic composition in different periods of observation.So, L. casei IMV B-7280, B. animalis VKB and B. animalis VKL (individually) and L. casei IMV B-7280 - B. animalis VKB - B. animalis VKL composition are promising to create highly effective immunobiotics with immunomodulatory effect that are able to balance Th1/Th2 type of immunity by shifting the cytokine profile with decreased the IL-4/IFN-γ ratio.
Key words: lactic acid bacteria; bifidobacteria; mice; intravaginal staphylococcosis; cytokines.

INTRODUCTION

The appearance of atypical forms of pathogens and pathogens with resistance to a wide range of antibiotics and other antibacterial drugs as a result of often unjustified use of them has determined the requirement of new highly effective methods of antibacterial therapy of patients with infectious and inflammatory diseases, including urinary tract infections. Lactic acid bacteria (LAB) and bifidobacteria that belong to the groups of microorganisms most frequently uses as probiotics due to their competitive inhibition of pathogenic bacteria colonization in the intestinal and urinary tracts; their ability to colonize the mucosal epithelial cells as well as their beneficial effects on the gut immune system can be used in complex therapy of patients with infectious diseases of urinary tract and other pathologies [1, 2, 3. 4, 5].

It has been established that an important mechanisms of immunomodulatory effect of many probiotic strains of LAB and bifidobacteria are the induction of regulatory cytokines

via the Toll-like receptor (TLR) pathway [6, 7, 8, 9, 10, 11], modulation of antigen presenting cells [11], induction of T regulatory cells [12, 13, 14], and influence on development and functions of epithelial cells [15]. Effect of probiotic bacteria on the production of Th1 (interleukin (IL)-2, IL-12, interferon (IFN)-γ etc.) and Th2 (IL-4, IL-5, IL-9 etc.) type cytokines, balancing of Th1/Th2 immune response and, as a result, determining the development of cellular or humoral immunity respectively play an important role in effective immune response ensuring in many pathological conditions. It should be noted that the Th1 and Th2 type cytokines production by immune cells in response to the effect of LAB and bifidobacteria is strain- and dose-dependent [9, 16, 17, 18, 19] and the level of IL-12 production is critical for determining the direction of the Th1 type immune response in mice, but the Th1 type immunity in the human depends on the IL-12 as well as IFN-γ production [20]. So, various strains of LAB and bifidobacteria can differently influence the production of Th1 or/and Th2 type cytokines; therefore this feature should be taken into account when creating a probiotics. Perhaps there are also differences in immunomodulatory effect of probiotic bacteria under normal and various pathological conditions. Therefore, in the selection of LAB and bifibobacteria strains for probiotics creation it is necessary to evaluate their immunomodulatory effect with obligatory definition of their influence on cytokines production simultaneously in various experimental and clinical studies.

Early we have screened our collection of LAB and bifidobacteria for their efficacy in modulating host immune response at normal condition and in the cases of experimental staphylococcosis in BALB/c mice. It was established that probiotic bacteria *Lactobacillus casei* IMV B-7280, *Bifidobacterium animalis* VKB and *B. animalis* VKL are promising for the creation of immunobiotics with antibacterial and immunomodulatory effects. Increase the functional activity of phagocytes and production of IFN in intact mice under the influence of these probiotic bacteria were observed [21]. *L. casei* IMV B-7280, *B. animalis* VKB and *B. animalis* VKL (individually) or *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition were able to inhibit *Staphylococcus aureus* growth in the vagina and influence the cellular immune response in the case of the experimental intravaginal staphylococcosis in BALB/c mice. These probiotic bacteria and probiotic composition normalized the CD4+/CD8+ ratio in staphylococcus-infected mice compared with infected mice that did not receive probiotic bacteria. An increase in the number of CD19+ B-lymphocytes in the spleens of these mice was also detected [22].

So, the aim of this work was to study the comparative effect of *L. casei* IMV B-7280, *B. animalis* VKB and *B. animalis* VKL (individually) or *L. casei* IMV B-7280 - B. animalis VKB - *B. animalis* VKL composition on the Th1 and Th2 type cytokines production in the case of the experimental intravaginal staphylococcosis in mice as well as under normal condition.

METHODS

Experimental studies were performed on six-week-old female BALB/c mice, synchronized in their estral cycle. Mice were kept in standard vivarium conditions at a temperature of 22 ± 1 °C, they were provided with the full mixed feed and had free access to automatic water bowls.

This study was carried out in strict accordance with the rules established by the Law of Ukraine № 3447-IV "On protection of animals from cruelty" and "European Convention for the Protection of vertebrate animals used for experimental and scientific purposes from 09.20.1985" (Strasbourg, 1986) and in accordance with the "General ethical animal experimentation" (First National Congress on bioethics, 2001). All surgery was performed under anesthesia, and all efforts were made to minimize suffering.

L. casei IMV B-7280, *B. animalis* VKL and *B. animalis* VKB from our collection of LAB and bifidobacteria were previously selected by us from gut content of healthy people and deposited

in the Ukrainian collection of microorganisms (D.K. Zabolotny Institute of Microbiology and Virology, NAS of Ukraine, Ukraine). The studies were performed using bacteria lyophilized in Cuddon Freeze Dryer FD1500 (New Zealand). Before each experiment the viability of the probiotic bacteria was tested by monitoring their growth on the Man-Rogosa-Sharpe (MRS) agar medium or Bifidum-agar at 37 °C for 24-48 h. *Staphylococcus aureus* strain 8325-4 (kindly provided to us by Professor V.S. Zuyeva, N.F. Gamaleya Institute of Epidemiology and Microbiology, Russian Federation) was grown on selective agar medium for staphylococci (BAIRD-PARKER-Agar, Merck, Germany), which contained gentamicin at a concentration of 15 mg/ml, at 37 °C for 24 h. This strain had plasmid-based resistance to gentamicin, allowing it to be separated from other vaginal *Staphylococcus* strains.

Staphylococcosis was modelled through single intravaginal administration of *S. aureus* strain 8325-4 daily culture to mice, in dose of 25 mcl of phosphate buffered saline (PBS) in the amount of 5 x 10^7 cells per animal. The following clinical manifestations of the infection process were observed in the infected mice: significant increase of whitish mucous secretions of the vagina, elevation of body temperature, inactivity, and loss of appetite.

One day after infection with *S. aureus* strain 8325-4 mice were given an intravaginal injection of lyophilized *L. casei* IMV B-7280, *B. animalis* VKL, *B. animalis* VKB (individually) or *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition in dose of 25 mcl of PBS in the amount of 1 x 10^6 cells per animal, once a day for 7 days. When three strains of proboitic bacteria were used as a composition, they were used at the concentration to reach this total amount of bacterial cells. *L. casei* IMV B-7280, *B. animalis* VKL, *B. animalis* VKB (individually) were also injected into the vagina of non infected (intact) mice using the same scheme. Two separate groups of comparison included staphylococcus-infected and intact mice, which did not receive probiotic strains, but received 25 mcl of PBS into vagina.

BALB/c mice were divided into 6 experimental groups (10 mice in each): 1) intact mice; 2) intact mice that received *L. casei* IMV B-7280; 3) intact mice that received *B. animalis* VKB; 4) intact mice that received *B. animalis* VKL; 5) control mice, infected with *S. aureus* 8325-4; 6) staphylococcus-infected mice that received *L. casei* IMV B-7280; 7) staphylococcus-infected mice that received *B. animalis* VKB; 8) staphylococcus-infected mice that received *B. animalis* VKL; 6) staphylococcus-infected mice that received *L. casei* IMV B-7280 - *B. animalis* VKL - *B. animalis* VKB composition.

On the 1st, 3rd and 6th days after probiotic bacteria or probiotic composition injection, peripheral blood were taken from the tail vein of each mouse of all groups. Blood serum samples were kept at -40 °C during one month. In the blood serum samples the concentration of IL-12, IFN-γ and IL-4 was determined by ELISA according to the manufacturer's instructions (Bender MedSystems GmbH Campus Vienna Biocenter 2 A-1030, Austria).

All received digital data were processed with the help of the Epi Info software (version 6.0) through analysis of variance. Numerical data were represented as arithmetic average and standard error. The null hypothesis for the control and experimental comparative groups was checked using Wilcoxon-Mann-Whitney (U) criterion. The differences between the groups were considered statistically meaningful at $P < 0.05$.

RESULTS AND DISCUSSION

Analysis of serum cytokines showed an increase level of Th1 type cytokines IL-12 and IFN-γ after injection of *L. casei* IMV B-7280 or *B. animalis* VKB (individually) into intact mice in different periods of observation (Table 1).

The IL-12 and IFN-γ levels in serum were increased on the 3rd and 6th days under influence of *L. casei* IMV B-7280. Intact mice that received *B. animalis* VKB had higher IL-12 level on the 1st and 3rd days. The IFN-γ level in the serum of mice of this probiotic bacteria

Table 1. The cytokines level in the serum of intact mice that received probiotic bacteria

Groups of mice	Observation period after injection of probiotic strains	Concentration of cytokines (pg/ml)		
		IL-12	IFN-γ	IL-4
Intact mice	-	613.8 ± 56.9	3.7 ± 0.5	1.23 ± 0.20
Intact mice that	1 day	736.0 ± 41.6	9.2 ± 0.6*	1.02 ± 0.10
received *L. casei* IMV	3 day	928.8 ± 56.6*	4.3 ± 0.9	1.96 ± 0.09
B-7280	6 day	904.4 ± 66.3*	7.0 ± 0.7*	0.98 ± 0.02
Intact mice that	1 day	811.8 ± 52.5*	14.7 ± 1.0*	1.43 ± 0.48
received *B. animalis*	3 day	831.4 ± 46.5*	19.3 ± 2.7*	1.59 ± 0.31
VKB	6 day	526.4 ± 31.7	18.7 ± 1.1*	0.46 ± 0.08*
Intact mice that	1 day	439.0 ± 94.8	7.0 ± 0.2	1.39 ± 0.43
received *B. animalis*	3 day	542.3 ± 23.8	5.7 ± 0.3	1.21 ± 0.12
VKL	6 day	482.0 ± 68.7	5.6 ± 0.9	0.70 ± 0.20

Significant difference with the intact mice is represented by * ($P < 0.05$).

group was increased throughout the observation period. Thus, *B. animalis* VKB more effectively enhanced the IFN-γ production in intact mice than *L. casei* IMV B-7280. Instead, *B. animalis* VKL did not affect the IL-12 production in intact mice (Table 1). However, treatment with these probiotic bacteria resulted in slightly increasing of the IFN-γ level in serum of intact mice on the 1st day.

As shown in Table 1, *L. casei* IMV B-7280 or *B. animalis* VKL (individually) did not affect the production of Th2 type cytokine IL-4 in intact mice. The IL-4 level in serum of intact mice after *B. animalis* VKB injection also did not change on the 1st and 3rd days, but on the 6th day was slightly decreased.

At the same time, we have found that the IL-12 and IFN-γ as well as IL-4 production after injection of *L. casei* IMV B-7280, *B. animalis* VKL or *B. animalis* VKB (individually) into staphylococcus-infected mice was different than in intact mice (Table 2). It should be noted that the IL-12 level in the serum of staphylococcus-infected mice that did not receive the probiotic bacteria (control group) was decreased but the IL-4 level was increased on the 1st day compared with intact mice. Also, the tendency to decrease of the IFN-γ production in these mice was detected throughout the observation period.

The IL-12 level in serum of staphylococcus-infected mice after injection of *L. casei* IMV B-7280 or *B. animalis* VKL (individually) was increased on the 1st and 6th days compared with control group. Staphylococcus-infected mice that received *B. animalis* VKB had higher IL-12 level in serum throughout the observation period. As shown in Table 2, the IFN-γ level in serum of staphylococcus-infected mice in different periods of observation after injection of *L. casei* IMV B-7280 (on the 1st and 3dr days) or *B. animalis* VKB (on the 1st and 6th days), or *B. animalis* VKL (on the 3rd and 6th days) was also increased compared with control group. The IL-12 and IFN-γ level in serum of mice of these three probiotic bacteria groups in most cases was even increased compared with intact mice.

Under the influence of *L. casei* IMV B-7280 the IL-4 level in serum of staphylococcus-infected mice was decreased on the 1st day compared with control group. Also, the tendency to decrease of IL-4 level in serum of staphylococcus-infected mice that received *B. animalis* VKB or *B. animalis* VKL on the 1st day was detected.

Treatment of staphylococcus-infected mice with *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition also resulted in increasing of the IL-12 and IFN-γ production in different periods of observation (Table 2).

Table 2. The cytokines level in the serum of staphylococcus-infected mice that received probiotic bacteria or probiotic composition

Groups of mice	Observation period after injection of probiotic strains	Concentration of cytokines (pg/ml)		
		IL-12	IFN-γ	IL-4
Intact mice	-	613.8 ± 56.9	3.7 ± 0.5	1.23 ± 0.20
Infected mice (control group)	1 day	346.8 ± 19.8*	2.3 ± 0.8	2.04 ± 0.01*
	3 day	686.2 ± 41.0	2.5 ± 0.9	1.19 ± 0.12
	6 day	598.3 ± 53.3	2.4 ± 0.1	1.09 ± 0.34
Infected mice that received *L. casei* IMV B-7280	1 day	615.0 ± 15.8•*	14.5 ± 1.9•*	1.03 ± 0.05•*
	3 day	701.0 ± 13.0	27.9 ± 1.8•*	1.20 ± 0.09
	6 day	831.0 ± 45.2•*	4.2 ± 1.0	1.39 ± 0.76
Infected mice that received *B. animalis* VKB	1 day	1118.5 ± 34.5•*	7.9 ± 0.4•*	1.52 ± 0.23
	3 day	1317.0 ± 26.0•*	4.7 ± 0.1	1.05 ± 0.37
	6 day	969.0 ± 24.9•*	7.0 ± 0.8•*	1.88 ± 0.76
Infected mice that received *B. animalis* VKL	1 day	863.3 ± 13.9•*	2.5 ± 0.8	1.58 ± 0.41
	3 day	633.3 ± 25.8	9.4 ± 1.0•*	1.24 ± 0.56
	6 day	1003.0 ± 19.3•*	16.5 ± 1.8•*	1.45 ± 0.09
Infected mice that received composition of probiotic strains	1 day	615.0 ± 28.0•*	30.3 ± 2.8•*	0.89 ± 0.04•*
	3 day	1378.2 ± 89.8•*	11.5 ± 1.9•*	1.23 ± 0.31
	6 day	537.2 ± 22.6	10.8 ± 1.1•*	1.10 ± 0.54

Significant differences with the intact mice are represented by * ($P < 0.05$), while differences with the indicators of the staphylococcus-infected mice who did not receive probiotic strains or probiotic composition (control group) are represented by * ($P < 0.05$).

Staphylococcus-infected mice that received *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition had higher level of IL-12 in serum on the 1st and 3rd days but the level of IFN-γ in serum was increased throughout the observation period compared with control group. The IL-4 level in serum of infected mice that obtained probiotic composition was decreased on the 1st day.

The ratio of IL-4/IFN-γ was significantly increased in the staphylococcus-infected mice on the 1st day (Fig. 1).

On the 3rd day, IL-4/IFN-γ ratio was decreased, but remained slightly increased compared with intact mice ($P < 0.05$). After injection of *L. casei* IMV B-7280, *B. animalis* VKB, *B. animalis* VKL (individually) or *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition into staphylococcus-infected mice the ratio of IL-4/IFN-γ was significantly decreased compared with control group throughout the observation period. So, these results suggested that infection with *S. aureus* 8325-4 change the immune response which manifested as a shift from Th1 to Th2 type of immunity. But *L. casei* IMV B-7280, *B. animalis* VKB, *B. animalis* VKL (individually) or *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition alter the development of immune response of staphylococcus-infected mice, which appears as a shift from Th2 to Th1 type of immunity.

We had previously shown [22] that *L. casei* IMV B-7280, *B. animalis* VKL and *B. animalis* VKB, (individually) or *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition after intravaginal injection once a day for 7 days, effectively delayed *S. aureus* 8325-4 growth in the vagina (during the observation period – up to 12 days) of staphylococcus-infected BALB/c mice and reduced the severity of disease. In this paper we established that the shift from Th2 to

Th1 type cytokines production may be one of the important mechanisms of protective effect of these probiotic bacteria and probiotic composition in the cases of experimental intravaginal staphylococcosis in BALB/c mice. *L. casei* IMV B-7280, *B. animalis* VKL and *B. animalis* VKB (individually) shifted cytokines production from Th2 to Th1 type also at normal condition. Thus probably these probiotic bacteria can be used prophylactically to prevent infection disease but more research is needed to confirm this.

The production of Th1 type cytokines IL-12 and IFN-γ after *L. casei* IMV B-7280 or *B. animalis* VKB (individually) injection into staphylococcus-infected mice as well as intact mice was increased at different periods of observation. The correlation between the IL-12 and IFN-γ production in mice of these two probiotic bacteria groups was found. Instead, *B. animalis* VKL increased the production of IL-12 and IFN-γ in different periods of observation in staphylococcus-infected mice, but did not affect the IL-12 production in intact mice. Among this three probiotic strains only *L. casei* IMV B-7280 reduced the increased production of IL-4 after injection to staphylococcus-infected mice. The results of our studies have shown that cytokine production in response to some probiotic bacteria, such as *B. animalis* VKL, may depend on the different levels of producing cells activity in the normal state and pathology.

So, in the cases of experimental intravaginal staphylococcosis in mice the Th1/Th2 balancing under the influence of *L. casei* IMV B-7280 can be indicated in increased production of IL-12 and IFN-γ as well as reduced production of IL-4. *B. animalis* VKL or *B. animalis* VKB in cases of intravaginal staphylococcal infection increased production of IL-12 and IFN-γ, but had no significant effect on IL-4 production. The ratio of IL-4/IFN-γ was significantly decreased after *L. casei* IMV B-7280, *B. animalis* VKB, *B. animalis* VKL (individually) injection into staphylococcus-infected mice that confirmed a shift from Th2 to Th1 immune response.

According to the literature data, LAB strains had different effect on the Th1/Th2 balance upward of Th1 type cytokines production [23, 24, 25]. *L. plantarum* NCU116 after injection into immunosuppressed mice enhanced the

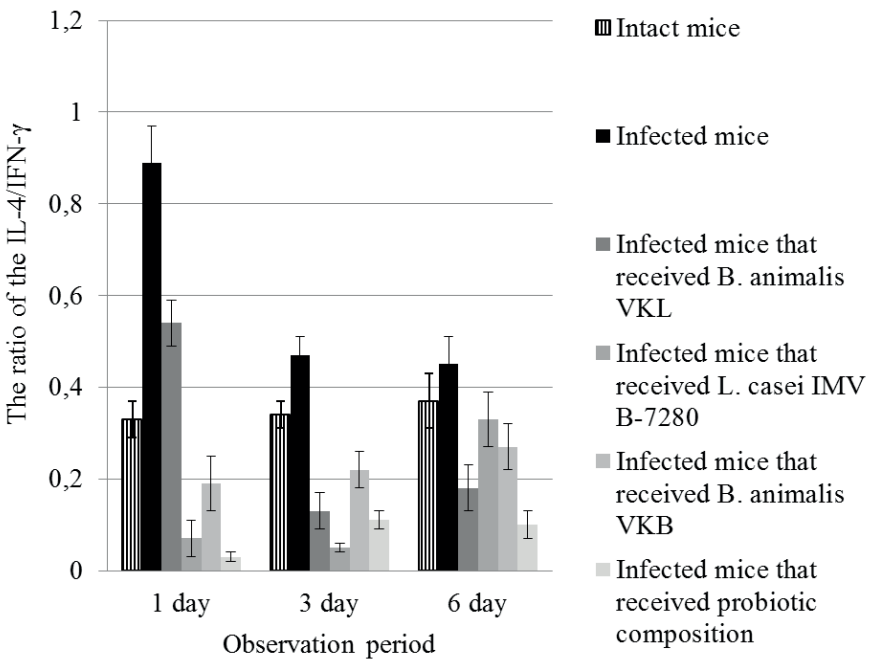

Fig. 1. The ratio of IL-4/IFN-γ in staphylococcus-infected mice that received *L. casei* IMV B-7280, *B. animalis* VKL and *B. animalis* VKB, (individually) or *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition

level of Th1 type cytokine IL-2 gene expression and significantly reduced the level of Th2-type cytokine IL-4 in the small intestine [26]. *L. rhamnosus* balanced Th1/Th2 profile of splenocytes by increasing IFN-γ and decreasing IL-4 as well as IL-10 production in aging mice that associated with enhanced resistance to *E. coli* infection [27]. Consumption of *L. rhamnosus* (MTCC: 5897) probiotic strain that contained in fermented milk, balanced Th1/Th2 immune response by shifting the cytokine profile (IFN-γ, IL-4 and IL-10) with increasing of IFN-γ/IL-4 ratio in newborn mice during the suckling-weaning transition [28]. Some of bifidobacteria strains also increase Th1-type cytokines production but other strains of bifidobacteria do not have effect on their production or increase it slightly [17, 29, 30]. Instead, *B. animalis* ssp. *lactis* CNCM-I2494 in the case of chronic dinitrobenzene sulfonic acid-induced low-grade inflammation model in mice balanced the Th1/Th2 ratio by increasing the production of Th2 type cytokines IL-4, IL-5, and IL-10 [31]. Therefore, comprehensive studies of probiotic bacteria immunomodulatory action under various pathologies are necessary.

Some strains of LAB and bifidobacteria are able to enhance the production of IFN-γ and IL-12 and also activate the production of other pro-inflammatory cytokines such as TNF-α [9]. This property is also strain-dependent. For example, *L. reuteri* BM36304 had a pro-inflammatory effect that confirmed by significantly stimulated production of TNF-α, but *L. reuteri* BM36301 was an anti-inflammatory strain [19]. *L. casei* IMV B-7280, *B. animalis* VKL and *B. animalis* VKB from our collection of probiotic bacteria increased the production of IFN-γ, whereas they did not affect the production of TNF-α *in vivo* [21], so it can be assumed that they will not cause the development of inflammation.

In our study the shift from Th2 to Th1 was also observed after injection of *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition to staphylococcus-infected mice. The IL-12 and IFN-γ production was increased, instead, IL-4 production as well as IL-4/IFN-γ ratio were decreased in mice of this probiotic composition group. It should be noted, that unlike the single probiotic bacteria, *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition in staphylococcus-infected mice caused activation of γ-interferonogenesis throughout the observation period. This probably causes the effective antistaphylococcal influence of the probiotic compositions in the cases of experimental intravaginal compared to each strain separately, as shown earlier [22].

So, *L. casei* IMV B-7280, *B. animalis* VKL or *B. animalis* VKB (individually) and *L. casei* IMV B-7280 - *B. animalis* VKB - *B. animalis* VKL composition are promising to create highly effective immunobiotics, that are able to balance Th1/Th2 type of immunity by shifting the cytokine profile (IL-12, IFN-γ and IL-4) with increased IFN-γ/IL-4 ratio and have antibacterial effect. However, additional clinical studies should be conducted to ensure that these probiotic strains and probiotic composition could be used in treatment or prevention of infection diseases.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ВЛИЯНИЕ ПРОБИОТИЧЕСКИХ ШТАММОВ ЛАКТОБАЦИЛЛ И БИФИДОБАКТЕРИЙ НА ПРОДУКЦИЮ ЦИТОКИНОВ ТИПА TH1 И TH2 ПРИ ИНТРАВАГИНАЛЬНОЙ СТАФИЛОКОККОВОЙ ИНФЕКЦИИ У МЫШЕЙ

Пробиотические штаммы *Lactobacillus casei* IMB B-7280, *Bifidobacterium animalis* VKL, *B. animalis* VKB (отдельно) или композиция *L. casei* IMB B-7280 - *B. animalis* VKB - *B. animalis* VKL балансировали продукцию цитокинов Th1/Th2 в условиях нормы и при экспериментальной интравагинальной стафилококковой инфекции у мышей линии

BALB/c в различные периоды наблюдения. *L. casei* IMB B-7280 и *B. animalis* VKB (отдельно) в условиях нормы увеличивали продукцию цитокинов Th1-типа – интерлейкина (ИЛ)-12 и интерферона (ИФН)-γ. Напротив *B. animalis* VKL после введения интактным мышам не влиял на продукцию ИЛ-12, но незначительно усиливал продукцию ИФН-γ. При экспериментальной интравагинальной стафилококковой инфекции балансирование Th1/Th2-ответа под влиянием *L. casei* IMB B-7280 происходило вследствие как повышения продукции ИЛ-12 и ИФН-γ, так и снижения продукции цитокина Th2-типа – ИЛ-4. Продукция ИЛ-12 и ИФН-γ повышалась у инфицированных стафилококком мышей, которым вводили *B. animalis* VKL или *B. animalis* VKB (отдельно), но эти пробиотические бактерии не имели существенного влияния на продукцию цитокина ИЛ-4. Под влиянием *L. casei* IMB B-7280, *B. animalis* VKB, *B. animalis* VKL (отдельно) при экспериментальной интравагинальной стафилококковой инфекции у мышей значительно уменьшалось соотношение содержание ИЛ-4/ИФН-γ. Сдвиг продукции цитокинов от типа Th2 к Th1 наблюдался также после введения инфицированным стафилококком мышам композиции *L. casei* IMB B-7280 - *B. animalis* VKB - *B. animalis* VKL. Продукция ИЛ-12 и ИФН-γ увеличивалась, а ИЛ-4 и соотношение содержания ИЛ-4/ИФН-γ, наоборот, снижались в разные периоды наблюдения в группе мышей, получавших эту пробиотическую композицию. Таким образом, *L. casei* IMB B-7280, *B. animalis* VKB, *B. animalis* VKL (отдельно) и композиция *L. casei* IMB B-7280 - *B. animalis* VKB - *B. animalis* VKL являются перспективными для создания высокоэффективных иммунобиотиков с иммуномодулирующим действием, которые способны балансировать Th1/Th2-иммунный ответ, изменяя цитокиновый профиль со снижением соотношения ИЛ-4/ ИФН-γ.

Ключевые слова: лактобациллы; бифидобактерии; мыши; интравагинальная стафилококковая инфекция; цитокины.

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ВПЛИВ ПРОБІОТИЧНИХ ШТАМІВ ЛАКТОБАЦИЛ І БІФІДОБАКТЕРІЙ НА ПРОДУКЦІЮ ЦИТОКІНІВ ТИПУ TH1 ТА TH2 ЗА ІНТРАВАГІНАЛЬНОЇ СТАФІЛОКОКОВОЇ ІНФЕКЦІЇ У МИШЕЙ

Пробіотичні штами *Lactobacillus casei* IMB B-7280, *Bifidobacterium animalis* VKL, *B. animalis* VKB (окремо) або композиція *L. casei* IMB B-7280 - *B. animalis* VKB - *B. animalis* VKL балансували продукцію цитокінів Th1/Th2 у нормі та за експериментальної інтравагінальної стафілококової інфекції у мишей лінії BALB/c у різні періоди спостереження. *L. casei* IMB B-7280 і *B. animalis* VKB (окремо) в нормі підвищували продукцію цитокінів Th1 типу – інтерлейкіну (ІЛ) -12 та інтерферону (ІФН)-γ. Навпаки *B. animalis* VKL після введення інтактним мишам не впливав на продукцію ІЛ-12, але незначно посилював продукцію ІФН-γ. За експериментальної інтравагінальної стафілококової інфекції у мишей балансування Th1/Th2-відповіді під впливом *L. casei* IMB B-7280 відбувалося внаслідок як підвищення продукції ІЛ-12 і ІФН-γ, так і зниження продукції цитокіну Th2-типу – ІЛ-4. Продукція ІЛ-12 і ІФН-γ підвищувалась в інфікованих стафілококом мишей, яким вводили *B. animalis* VKL або *B. animalis* VKB (окремо), але ці пробіотичні бактерії не мали суттєвого впливу на продукцію ІЛ-4. Під впливом *L. casei* IMB B-7280, *B. animalis* VKB, *B. animalis* VKL (окремо) за експериментальної інтравагінальної стафілококової інфекції у мишей значно зменшувалося співвідношення вмісту ІЛ-4/ІФН-γ. Зрушення продукції цитокінів від типу Th2 до Th1 спостерігалося також після введення інфікованим стафілококом мишам композиції *L. casei* IMB B-7280 - *B. animalis* VKB - *B. animalis* VKL. Продукція ІЛ-12 і ІФН-γ збільшувалася, а ІЛ-4 та співвідношення вмісту ІЛ-4/ІФН-γ, навпаки, знижувались у різні періоди спостереження в групі інфікованих стафілококом мишей, які отримували цю пробіотичну композицію. Таким чином, *L. casei* IMB B-7280, *B. animalis* VKB, *B. animalis* VKL (окремо) і композиція *L. casei* IMB B-7280 - *B. animalis* VKB - *B. animalis* VKL є перспективними для створення високоефективних імунобіотиків з імуномодулювальною дією, які здатні балансувати Th1/Th2 імунну відповідь, змінюючи цитокіновий профіль зі зниженням співвідношення ІЛ-4/ІФН-γ.

Ключові слова: лактобацили; біфідобактерії; миші; інтравагінальна стафілококова інфекція; цитокіни.

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