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Effect of Probiotic Preparations on the Intestinal Microbiome

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Abstract: The inclusion of probiotics in the technology of growing young animals is the latest way of preventing gastrointestinal diseases based on environmentally friendly mechanisms of maintaining a high level of colonization resistance of the intestine. The aim of the research was to study the effect of probiotic preparations of different composition on the dynamics of normoflora and opportunistic pathogenic microflora of newborn calve's and weaning age piglet's intestinal microbiome. To achieve this goal, four groups of newborn calves were formed which received a synbiotic based on medicinal plant raw material and lactobacilli, "Sporovit" and "Enzymsporin" and four groups of 45 days old piglets that also received the above preparations. Prior to the beginning of the experiment then on the 10-30th days from the beginning of the experiment, feces were taken for microbiological studies. The use of the synbiotic based on medicinal plant raw material and lactobacilli, probiotics "Sporovit" and "Enzymsporin" in newborn calves and piglets at weaning increased the activity of bifid and lactoflora by 1.8 and 2.4 times; Inhibited the content of *E. coli* by 1.2 and 1.8 times, Enterococci by 1.4 and 1.5 times, Staphylococci by 1.4 and 1.9 times, yeast-like fungi of Candida by 1.7 and 1. 9 times, Clostridia by 1.4 and 1.5 times.

Key words: Microbiome, gastrointestinal tract, probiotic preparation, lactobacilli, bifid bacteria, inhibited

INTRODUCTION

At present, the normal biocenosis of the organism is considered to be a part of a complex ecosystem "environment its microflora animal" or a separate "metabolic body" for performing most of the various functions. At a young age, physiological dysbacteriosis is observed that is often combined with immune deficiency that makes this age group particularly vulnerable to gastrointestinal diseases (Afanasyev and Elenshleger, 2017; Ozdemirov, 2017; Abraham and Elenshleger, 2017; Givans, 2018).

The unbalanced qualitative and quantitative composition of the intestinal microflora becomes incapable of preventing the colonization of the intestine by pathogenic and opportunistic microorganisms which in the course of their activity, produce a large number of toxins that are unsafe for a newborn's life (Andreeva and Nikolaeva, 2016; Belousova and Chkhenkeli, 2017). It was at that particular time and these were the main reasons for the occurrence of diseases of the digestive tract of newborn calves and pigs in the early postpartum period of development. If the optimal homeostasis of the intestinal microbiocenosis of the newborn young cattle and pigs is maintained, its high level resists colonization adsorption of pathogenic and opportunistic microorganisms that plays an important role in the formation of immune reactivity of the organism (Andreeva and Nikolaeva, 2016; Rinald *et al*., 2018).

However, in modern ecological conditions with the increasing production of livestock products and medicinal impact there is a tendency for the growth of pathological disorders which are accompanied by a violation of the microbiome balance of various cavities of the macroorganism (Kovalyonok and Kurdeko, 2017; Park, 2018).

It is well known that the use of antibiotics for the prevention and treatment of the diseases of young cattle and swine becomes less effective and unsafe as the result of the onset of antibiotic-resistant mutated microorganisms, their accumulation in the gastrointestinal tract and the manifestation of allergic reactions of the animal organism because of that. Antibiotics along with the causative agents of intestinal infections suppress that

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part of the microflora which normally performs protective functions and does not allow potential pathogens to colonize the intestine massively. Antibiotics reduce the amount of both gram-negative and positive microflora (*Clostridium perfringens*, Fusobacterium, Prevotella, Bifidobacteria). Their extensive use leads to the formation of the antibiotic-resistant part of the population of opportunistic microorganisms with the increased pathogenic properties and promotes the development of the intestinal dysbacteriosis of the Proteus, Staphylococcal, Candida and Clostridia Character and the lengthening of their presence in the intestine (Givans, 2018; Deoabov, 2012).

In these cases, an additional method of fighting infections is the use of drugs based on living microorganisms that act as antagonists of pathogens and tools that suppress antagonistic microflora, all this should contribute to the balance of the natural intestinal microflora or prevent its derangement (Lyusin, 2017; Heath *et al*., 2018).

Drugs that exist today and actively affect the microbiome of animals can be roughly divided into three groups: probiotics drugs of microbial origin showing positive properties for the macroorganism through the regulation of intestinal microflora, prebiotics preparations of non-microbial origin capable of giving a positive effect on the host body by stimulating the choice of growth or activity of normal intestinal microflora and synbiotics drugs obtained as a result of the rational combination of probiotics and prebiotics (Gryazneva *et al*., 2018; Sugyan and Zakharova, 2017).

An important arsenal of perfection of probiotics towards the antagonistic activity expansion against opportunistic and pathogenic bacteria is the bacterium Bacillus a representative of normal microflora. In the 1990's it was shown that aerobic spore-bearing bacteria of this species are able to synthesize about 200 different antibiotics, *B. subtilis* type around 70. Unlike antibiotics, pathogenic microorganisms do not develop resistance to sporous probiotics, since, bacilli do not produce individual antibiotics but a whole pool of them, similar in structure. Their antibiotic effects are different and the development of resistant variants of microorganisms does not occur (Andreeva and Nikolaeva, 2016; Trushkin *et al*., 2018).

The use of probiotic preparations by calves and pigs since birth is also important because normal intestinal microflora in newborn animals acts as the first and safe stimulant of the immune system.

For the foregoing reasons it is clear that the search for effective probiotic drugs for the normalization of the qualitative and quantitative structure of the microbiome of the digestive tract is a topical issue in biological and veterinary science.

The aim of the study is to investigate the influence of the synbiotic based on medicinal plant raw material and lactobacteria, probiotics "Sporovit" and "Enzymsporin" on the dynamics of the opportunistic and obligate microflora of the intestinal microbiome of newborn calves and pigs of weaning age.

MATERIALS AND METHODS

The study was carried out on the basis of the Department of Infectious Diseases, Zoohygiene and Veterinary-sanitary expertise of the FSBEE of HE Bashkir State Agrarian University in cattle-breeding and pig-breeding complexes of Sharansky, Ufimsky and Karmaskalinsky Districts of Bashkortostan. The object of the research was presented by 60 new-born calves of black-motley breed and 60 piglets of the large white breed of 45 days weaning. The animals for experiments were selected by the principle of paired analogues.

The work used: synbiotics based on medicinal plant raw material and lactobacilli microbial live weight of lactobacilli (*L. plantarum* 8P-A3) grown on whey-milk medium with the addition of large celandine herb (*Chlidonium majus* L.) water extracts and fruits of common barberry (*Berberis vulgaris*) with the viable cell content of $7.4\text{-}9.3\times10^9$ CFU/mL.

Probiotic "Sporovit" contains a suspension of live *Bacillus subtilis* 12 B strain bacteria and auxiliary components.

Probiotic "Enzymsporin" contains spore-forming bacteria *Bacillus subtilis* BKM B-2998D, *Bacillus licheniformis* BKM D-2999D, *Bacillus subtilis* BKM B-3057D in equal proportions, milk dry whey, maltodextrin, cornmeal.

The research was carried out in two stages. At the first stage, the effects of the synbiotic based on medicinal plant raw material and lactobacilli, probiotic based on *Bacillus subtilis* 12 B strain and the probiotic "Enzymsporin" on the dynamics of the intestinal microbiome indices of newborn calves (Table 1) were studied.

At the second stage, a study was made of the effect of the synbiotic based on medicinal plant raw material and lactobacteria, the probiotic based on *Bacillus subtilis* 12B strain and the probiotic "Enzymsporin" on the composition of the intestinal microbiome of piglets of weaning age (Table 1).

Table 1: Scheme of scientific and industrial experiments on studying the effect of probiotics of various composition on the intestinal microbiome

Groups	Composition
Group of animals (n = 15)	The drugs used
	The study of the effect of probiotics of various composition on the intestinal microbiocenosis of newborn calves
1 control	Basal Diet (BD)
2	BD+peroral synbiotic based on medicinal plant raw material and lactobacilli (20 mL per animal) since birth daily for 10 days in two stages with 10 days apart
3	BD+peroral "Sporovit" (20 mL per animal) since birth daily for 10 days in two stages with 10 days apart
4	BD+peroral "Enzymsporin" (20 mL per animal) since birth daily for 10 days in two stages with 10 days apart
	The study of the effect of probiotics of various composition on the intestinal microbiocenosis of piglets of weaning age
Group (n = 10)	Drugs administration regimen
1 control	Basic Diet (BD)
2	BD+synbiotic based on medicinal plant raw material and lactobacilli, for 10 days, 1 mL/10 kg of the animal's body weight
3	BD+peroral probiotic "Sporovit", for 10 days, 1 mL/10 kg of the animal's body weight
4	BD+peroral probiotic "Enzymsporin", for 10 days, 1 mL/10 kg of the animal's body weight

For studying the composition of the intestinal microbiome samples of feces were collected prior to the beginning of the experiment, then on the 10-30th days from the start of the study. The microbiological study of feces included the determination of the composition of the intestinal microbiome and the typing of microorganisms (lacto and bifid bacteria, opportunistic bacteria). The level of the population of each group of microorganisms was expressed in decimal logarithms.

The statistical processing of the results of the study was assessed using Student's t-test. Differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The results of bacteriological studies showed that the background level of bifid bacteria in the intestines of newborn calves ranged from 4.85±0.2-5.65±0.1 Lg CFU/g. The background value of the amount of lactobacilli was 3.5±0.06-4.1±0.04 Lg CFU/g.

The use of the synbiotic based on medicinal plant raw material and lactobacilli and of the probiotic based on *Bacillus subtilis* 12 B strain made it possible to correct the calve's microbiome toward the predominance of bifid and lactic acid bacteria. By the end of the experiment, the level of bifid and lactoflora exceeded the values of control animals by 2.9 and by 4.18 Lg CFU/g, respectively. In the calves that received "Enzymsporin", the number of bifidobacteria relative to the control and background values was higher, respectively: On the 10th day by 1.8 and 2.2 Lg CFU/g; On the 20th day by 3.7 and by 4.1 Lg CFU/g; On the 30th day by 4.2 and by 7.1 Lg CFU/g. The maximum values of the amount of lactobacilli were observed in the intestine of calves that received the probiotic "Enzymsporin" exceeding the control parameters: on the 10th day by 2.3 Lg CFU/g, on the 20th day by 4.45 Lg CFU/g; On the 30th day by 3.15 Lg CFU/g.

When studying the composition of the opportunistic microflora of the intestine the following has been established. The background level of *E. coli* varied from 10.15±0.2-10.6±0.2 Lg CFU/g; Enterococci from 4.4±0.2-4.8±0.01 Lg CFU/g; Staphylococci from 3.5±0.04-4.1± 0.03 Lg CFU/g; Clostridia 4.6±0.12-5.2±0.03 Lg CFU/g, yeast-like Candida genus fungi from 4.2±0.11-4.8±0.021 Lg CFU/g.

By the end of the trial period in groups where the synbiotic based on medicinal raw plant material and lactobacilli and a probiotic based on *Bacillus subtilis* 12 B strain was used, the amount of *Staphylococcus aureus* decreased by 1.32 and 1.6 times with respect to the control values; Enterococci by 1.26 and 1.3 times; Clostridia by 1.25 and 1.34 times; fungi of the Candida genus by 1.8 and 2.1 times.

In calves of the fourth group who received "Enzymsporin", the level of *E. coli* decreased with respect to control and background: on the 10th day by 2.3 and 2.5 Lg CFU/g, on the 20th day by 4.5 and by 4.2 Lg CFU/g, on the 30th day by 4.3 and by 4.6 Lg CFU/g. When studying the dynamics of enterococci, a tendency for their decrease with respect to control and background from the 10th day of studies was found by 1.2 Lg CFU/g, on the 20th day by 1.5 and by 1.2 Lg CFU/g, on the 30th day by 1.6 and 1.4 Lg CFU/g. Also, in that group, the number of staphylococci decreased at most with respect to background and control: on the 10th day by 1.3 and by 0.7 Lg CFU/g, on the 20th day by 2.2 and by 1.2 Lg CFU/g, on the 30th day by 2.1 and by 1.4 Lg CFU/g. The dynamics of decrease in yeast-like fungi was also more pronounced in the calves of the fourth group with respect to control and background: On the 10th day by 1.04 and 0.8 Lg CFU/g, on the 30th day by 1.5 Lg CFU/g. In addition, in the calves of the fourth group, clostridium decreased relative to control and background, respectively: on the 30th day by 1.8 and 1.18 Lg CFU/g.

In the study of the intestinal microbiome of the piglets of the control and experimental groups, changes in microbial equilibrium caused by weaning were established.

With the use in pig's diet of the synbiotic based on medicinal plant raw material and lactobacilli the amount of bifid bacteria was higher than the control values by 0.85 Lg CFU/g on the 10th day of the experiment, on the 20th day by 1.10 Lg CFU/g, on the 30th day by t 1.60 Lg CFU/g. The use of the probiotic based on *Bacillus subtilis* 12 B strain and of the probiotic "Enzymsporin" increased the amount of bifid bacteria in the intestines of piglets by the terms of the experiment. So, on the 10th day of studies, the amount of bifid bacteria was higher than the control values, respectively by 0.3 Lg CFU/g, on the 20th day by 0.35 and 1.4 Lg CFU/g, on the 30th day by 1.4 and 1.6 Lg CFU/g.

The number of lactobacilli in the intestines of the control and test group pigs was found at 3.4±0.05-4.1±0.05 Lg CFU/g. In piglets of the second group, the number of lactobacilli was higher than in the control group on the 10th day of studies by 1.1 Lg CFU/g; on the 20th day by 1.5 Lg CFU/g, on the 30th day by 2.9 Lg CFU/g, respectively. The use of the probiotic based on *Bacillus subtilis* 12 B strain and probiotic "Enzymsporin" promoted a pronounced increase in lactobacilli in enterobiocenosis. Thus, in the third and fourth groups, the amount of lactobacilli increased in comparison with the evidence from experimental animals on the 10th day of studies by 1.4 and 2.1 Lg CFU/g, on the 20th day by 2.3 and 2.62 Lg CFU/g, on the 30th day by 3.2 and 4.6 Lg CFU/g.

The background level of *E. coli* in the intestines of the piglets of the control and test groups ranged from 8.8 -9.4 Lg CFU/g; Staphylococci from 3.14-2.65 Lg CFU/g, the number of Enterococci was at the level of 3.65-3.54 Lg CFU/g; Clostridia from the intestines of piglets were sown in the amount of 3.45-3.57 Lg CFU/g, the content of yeast-like fungi ranged from 3.3-3.12 Lg CFU/g.

In all experimental groups of pigs who received the synbiotic based on medicinal plant raw material and lactobacilli, probiotic based on *Bacillus subtilis* strain 12B and "Enzymsporin", a decrease in the opportunistic microflora was observed.

Changes in the content of *E. coli* were observed in the microbiocenosis of the animals of the second and fourth groups, they were expressed by its decrease in the value by 0.15 and 0.95 Lg CFU/g in comparison with the control values on the 10th day of the study by 1.6 and 1.75 Lg CFU/g, on the 20th day and by 1.45 and 1.66 Lg CFU/g, on the 30th day, respectively.

The level of Staphylococci decreased in the intestines of the piglets of the second group. On the 10th day of the study, this indicator was below the control figures by 0.51 Lg CFU/g, on the 20th day by 0.61 Lg CFU/g, on the 30th day by 0.74 Lg CFU/g. The maximum decrease in Staphylococci was observed in the intestines of piglets of the third and fourth experimental groups. On the 10th day of the experiment, this indicator was below the control values by 0.4 and 0.06 Lg CFU/g by the 20th day by 0.6 5 and 0.7 Lg CFU/g, on the 30th day by 0.85 and 1.12 Lg CFU/g.

A low level of enterococci in the intestine was recorded in the second group, it was lower than the control values on the 10th day by 0.65 Lg CFU/g, on the 20th day by 0.87 Lg CFU/g, on the 30th day by 1.28 Lg CFU/g. Piglets of the third and fourth experimental groups also showed a dynamic decrease of the studied index where their content decreased relative to the control level on the 10th day of the experiment by 0.25 Lg CFU/g and 0.87 Lg CFU/g, on the 20th day by 0.56 and 0.55 Lg CFU/g, on the 30th day by 0.88 and 0.91 Lg CFU/g.

In pigs that received probiotics based on *Bacillus subtilis* strain 12B and "Enzymsporin", a decrease in the number of clostridia was observed. Thus, on the 10th day of the experiment, their number was below the control values by 0.15 and 0.34 Lg CFU/g, on the 30th day by 0.89 and 0.77 Lg CFU/g, on the 60th day by 1.2 and 1.8 Lg CFU/g.

There was also a decrease in yeast-like fungi in the intestines of the piglets of the experimental groups. Thus, the amount of yeast-like fungi was lower than the background values on the 10th day of the experiment in the third and fourth groups by 0.25 and 0.56 Lg CFU/g, on the 20th day by 0.78 and 1.22 Lg CFU/g, on the 30th day by 1.45 and 1.21 Lg CFU/g, respectively. The maximum reduction in the number of yeast-like fungi was observed in the intestines of piglets that received the synbiotic based on medicinal plant raw material and lactobacilli. So, on the 10th day of the experiment, their level in that group was below the control values by 0.74 Lg CFU/g, on the 20th day by 1.13 Lg CFU/g, on the 30th day by 1.41 Lg/g.

The dynamics of the microbiome development of the calves of the control and experimental groups as a whole differed by the composition of the intestinal biocoenosis. It was established that in the experimental calves there was a tendency for more intensive intestine colonization by representatives of normal microflora. With age, they regularly increased the number of populations of useful microflora (lacto and bifid bacterium flora) and decreased the number of pathogenic and opportunistic pathogens. In the control calves, the opposite trend was observed. The results obtained by us are confirmed in the studies of Gryazneva *et al*. (2018), Kovalenko *et al*. (2017), Lyusin (2017).

Thus, according to the results of bacteriological studies, it can be concluded that the use of the synbiotic based on medicinal plant raw material and Lactobacilli and probiotics based on *Bacillus subtilis* 12 B strain and "Enzysporin" optimizes the microecological status of the gastrointestinal tract of newborn calves showing high antagonistic activity against pathogenic and potentially pathogenic microorganisms (bacteria of the genus *Staphylococcus, Enterococcus, E. coli, Clostridium*, yeast-like fungi of the genus *Candida*), creates favorable conditions for the development of beneficial microflora (lactobacilli, bifid bacteria) which in turn, enhances the immune status of the animals and prevents the development of diseases.

In the study of the microbiocoenosis of the intestine of pigs-weaners of control and experimental groups, dysbiotic disorders were identified which can be described as a dysbacteriosis. Thus, the lactobacillus titer was reduced (6.22-6.81 Lg CFU/g), the amount of *E. coli* increased (8.95-9.5 and 6.19-6.34 CFU/g), moreover, hemolytic *E. coli* was sown from the feces.

Contemporary ideas about intestinal dysbacteriosis suggest the consistent development of two processes a decrease in the number of gram-positive intestinal flora and an increase in the n umber of opportunistic gram-negative microorganisms. In this case, variants with altered ecological characteristics are accumulated in the populations of normal and opportunistic microorganisms. In representatives of normal microflora, antagonistic, adhesive and biochemical activity decreases and virulent properties increase in gram-negative bacteria. Violations of anatomical, physiological and immunological defense mechanisms create conditions for the development of an infectious process caused by its own, in normal conditions, non-pathogenic microflora or saprophytic microorganisms from the environment as shown by Belousova and Chkhenkeli (2017), Abraham and Quigley (2017) and Barco *et al.* (2018) and others. It has been established that if the synbiotic based on medicinal plant raw material and lactobacilli and probiotics based on *Bacillus subtilis* 12 B strain and "Enzymsporin" is used from the 10th day of the experiment, a significant increase in the level of lacto and bifid bacterium flora is observed. Under these circumstances, the number of lactobacilli and bifid bacteria in piglets weaned on the 45th day by the end of the test period in the second, third and fourth test groups was higher than the control values by 2.9, 3.2 and 4.6 Lg CFU/g, respectively. A significant increase in the population level of representatives of normal microflora in piglets of the experimental groups can be regarded as a positive factor of the influence of the synbiotic and probiotic drugs.

CONCLUSION

Thus, the use of the synbiotic based on medicinal plant raw material and lactobacilli, of probiotics based on *Bacillus subtilis* 12 B strain and of "Enzymsporin" helps to restore the intestinal microbiome.

In neonatal calves, the amount of lacto and bifid bacterium flora increases by 1.5, 1.9 and 2.3 times, the amount of *E. coli* is inhibited by 1.9 times of enterococci by 1.36, 1.4 and 1.5 times, staphylococci by 1.4, 1.8 and 1.9 times, Clostridii by 1.2, 1.4 and 1.5 times; yeast-like Candida fungi by 1.9, 2.2 and 1.5 times.

In pigs of weaning age, the activity of lacto and bifid bacteria increased by 1.6, 1.8 and 2.2 times as compared with the control animals; the amount of *E. coli* decreased by 1.2 and 1.26 times, respectively; Staphylococci by 1.39, 1.6 and 1.4 times; Enterococci by 1.48, 1.3 and 1.4 times; Clostridia by 1.4 and 1.3 times; yeast-like fungi by 1.7, 1.8 and 1.7 times.

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