A blood parameters comprehensive study in pigs with the microencapsulated probiotic preparation Antispin with the enzyme use

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Abstract. The article presents the haematological and biochemical blood parameters studies data obtained during the production test of the microencapsulated probiotic preparation Enzimsporin with an enzyme (crystalline trypsin) on Genesus genetics pigs in the fattening process. Data from three groups were analyzed: experimental group (microencapsulated Enzimsporin with enzyme), control group No. 1 (commercial non-encapsulated Enzimsporin) and control group No. 2 (without adding Enzimsporin to the feed). A general blood test showed that in animals receiving microencapsulated Enzimsporin with an enzyme, the erythrocytes and haemoglobin content reaches the upper physiological limit, which is significantly higher than in the control groups. When determining the blood biochemical parameters, a significant increase in the total protein and albumin amount in experimental animals was revealed by the 148th day of life. Reliably high glucose levels, within the physiological norm, were observed in animals receiving Enzimsporin, while in animals receiving the microencapsulated drug, the glucose level was significantly higher than in those receiving its unencapsulated form. The change in the trace elements level in the experimental animals’ blood showed regularities associated with an increase in the calcium amount and a decrease in phosphorus and magnesium. At the same time, an increase in the level of AST and ALT in the animals’ blood receiving Enzimsporin with an enzyme was noted by the 148th day of life. The observed immunoglobulins reliably high level throughout the experiment in experimental animals in comparison with control indicates a high resistance and pigs immune status.

1. Introduction
One of the main factors in the pigs’ productivity is their genetic potential, which realization, in turn, is ensured by balanced feeding, animals properly organized keeping, and preventive veterinary measures. All this together has a significant impact on the animals’ productivity. However, in the large modern livestock complexes conditions, the genetic potential cannot be fully realized because an increase in the feed caloric content leads to an increase in the production cost and a decrease in profitability. One of the
effective ways to correct the physiological status, increase metabolism and metabolism, and therefore, increase productivity, is the probiotics' use.

Microbiota is a key factor in maintaining the body's homeostasis. It performs significant functions in number: energy metabolism, the immune system maturation and maintenance, vitamins synthesis, bile acids reabsorption regulation in the intestine, and much more [1]. Probiotics are live microorganisms that benefit the host when administered in adequate amounts [2]. The following basic requirements are imposed on probiotics: they must be pheno- and genotypically classified, must not be pathogenic, must be kept alive, must be acid-resistant or must be enclosed in an acid-resistant capsule, capable of adhesion to the intestinal epithelium, capable of colonizing the intestine, must be safe [3, 4].

Most often, probiotic preparations are used in the traditional form - powder or suspension. In medicine, sorbed preparations are used to correct dysbacteriosis.

To be effective, probiotics must be in such a form and dosage to reach the intestines and maintain their activity, passing through the stomach acidic environment and the duodenum created alkaline environment by bile [5]. Therefore, in recent years, probiotics microencapsulated forms have begun to appear, possessing specified physical parameters and biological properties, passing capable through the stomach acidic environment without loss and activating their activity in the intestine.

The organism vital activity as a whole is largely carried out at the blood expense and its components. The blood composition study gives an animal state assessment and an adaptability general idea to environmental conditions and also allows observing various changes occurring in the animal's body under the feeding and maintenance influence, which makes it possible to assess the general physiological state.

Even though the homeostasis state is the animal organism characteristic, the probiotic preparations testing, and subsequently their use, causes changes in physiological parameters, including the blood general picture and its biochemical parameters.

For example, the probiotic Vitafort use in the lambs' diets from 10 to 120 days of age at a dose of 0.1 ml per 10 kg of live weight contributed to an increase in average daily gains by 8.8%. Within the physiological norm, when using the probiotic Vitafort in a dose of 0.1 ml per 10 kg of live weight, an increase was observed in such indicators as haemoglobin, total protein, calcium, inorganic phosphorus. And when analyzing blood serum, a protein fractions redistribution was revealed, namely, a decrease in albumin and an increase in gamma globulins, which is consistent with the lambs' intensive growth. The same changes were observed when comparing with the group where the probiotic Vetom was added to the main diet [6].

When applied to piglets from the weaning moment at 2 months of age, liquid probiotic preparations Sitexflor No. 1 and No. 5, which include genus Lactobacillus acidophilus strains and bifidobacteria and thermophilic streptococci symbiotic cultures (in doses of 30 ml per head), the blood picture in piglets significantly changed by 6 months of age. At the same time, the erythrocytes and haemoglobin number increased from 3.3% and 10% concerning the control, respectively. In these animals blood serum biochemical study, an increase in the total protein level was found, which amounted to an increase of 6%, while in the control it was only 1.4%. The calcium content increased by 7.1%, phosphorus by 6% and glucose by 11.2%. The authors also observed some changes in the protein fractions content in blood serum. So the gamma globulins amount was higher in piglets from sows receiving probiotic preparations, however, by the age of 6 months, the gamma globulins amount in general decreases, but retains a stable tendency to increase concerning control [7]. At the same time, when feeding these probiotics, their positive effect on the sows milk production and the piglets' safety was established. [8].

In animal husbandry, probiotic preparations are used on various animal species, including rabbits, seeing in this animal species the potential for the alternative animal husbandry development. When using the probiotic preparation Biogumitel, it was found that the experimental groups' rabbits at the experiment end had erythrocytes and leukocytes higher concentration, as well as a haemoglobin higher level, which indicates a metabolism higher level in the body, an increase in live weight and increased resistance. Thus, the experimental groups' rabbits who received drugs in various doses exceeded their peers in the
control group in erythrocytes content terms in the blood by 10.54% -19.53%). The haemoglobin content was higher than that of the peers of the 1st control group, by 6.81% -10.08%) [9].

Interesting data is given by A. Syrtsev, who conducted experiments on cows. During the milking period, the animals were fed the probiotic preparation enzymesporin at a dose of 15 g per head for 120, 200 and 305 days of lactation. At the same time, the scientist found that with the total protein content at the same level in all animals groups, the albumin-globulin index significantly increased in comparison with the control by 14, 11 and 11%, respectively. The author explains this by the fact that Bacillus subtilis, multiplying, produce enzymes, including proteases, thereby accelerating the protein molecules breakdown. In this case, albumins provide for anions and cations dissolution and transportation, metabolic products from one tissue to another; after preliminary hydrolysis, amino acids used for the synthesis of specific proteins are released. With a high blood glucose level before the experiment, after using the drug, the blood glucose level in cows from the experimental groups decreased to normal values (3.28-3.77 mmol / l) and significantly differed from the control in all three groups. The author concludes that the symbiotic microflora contributed to the pathogenic microorganisms displacement and reduced the mycotoxins' toxic effect on the pancreas. The insulin production returned to normal, the glucose absorption from the blood improved, along with an increase in protein metabolism, this increased milk yield. At the same time, it was noted that the calcium content in the animals' blood in all experimental groups significantly increased: in group 1 - by 0.31 mmol/l, in group 2 - by 0.32, in group 3 - by 0.25 mmol/l. The researcher associates this with the fact that organic acids synthesized by microorganisms contributed to the intestine secretory function enhancement, improving the macro-and microelements resorption. The general conclusion was that in cows fed with enzymesporin, the protein metabolism processes were more intensive. The mycotoxins negative impact decreased - the glucose and calcium absorption improved. As a result, cows milk productivity increased during the milking period [10].

The Enzimsporin inclusion in the lactating cows' diet in the first 120 days of lactation had a positive effect on the average daily milk yield in 1, 2 and 3 experimental groups: they increased by 3.99, respectively; 4.79 and 3.63% [11].

Changes in the blood composition when using probiotics, within the physiological norm, are also observed in calves used in the experiment from the life first days to 10 days of age. So the researchers injected, the calves the first group orally daily, probiotic bacteria associations based on the strains Bifidobacterium bifidum DSM 20456, ATCC 29521 and Enterococcus faecalis H22 at a dose of 5 cm, the second group animals - similarly to the probiotic bacteria association based on strains DSM bifidobac ATCC 29521 and Enterococcus faecium UDS 86 at a dose of 5 cm3, the third group animals did not receive probiotics and served as control. The authors obtained the following results in calves on day 10: the erythrocytes number increased by 6.4 and 7.9%, respectively than in the control group; the leukocytes number increased by 11.9 and 13.1%; the haemoglobin level increased by 2.1 and 1.8%; due to this, the hematocrit value increased by 6.7 and 9.2% than in the control group [12].

Changes in the blood picture when using the probiotic drug Sakhabactisubtil is also observed in animals living in Russia far north. In the blood morphological parameters study, it was found that in the experimental groups' deer, in comparison with the control, the erythrocytes content was higher on average by 13.6%, haemoglobin - by 22.3%, total protein - by 9.09%, albumin - by 5, 5%, γ-globulins - by 11.7%, lymphocytes - by 31.6%, blood serum lysozyme activity by 33% [13].

Earlier, when studying the microencapsulated probiotic drug Enzimsporin with an enzyme effect on the Genesus genetics pigs physiological status, we found that when using the drug from 48 days of life achieved an increase reliable results in live weight and average daily weight gain at 98 and 148 days of life. At the same time the average daily weight gain in the control group No. 1 (intact) was 0.61 kg, in the control group No. 2 with Enzimsporin it was 0.656 kg, and when fed with the microencapsulated probiotic drug Enzimsporin with the enzyme 0.712 kg, which is reliable higher (p<0.05) values of control groups. From 98 to 148 days, the average daily body weight gain in the group with the drug Enzimsporin with enzyme was 0.824 kg, which is significantly higher (p <0.05) than in the intact control group No. 1 - 0.736 kg and control groups No. 2 - 0.802 kg respectively. By qualitative caprological
analysis, it was found that the drug enhances the digestive ability in the pigs' intestines more intensively than its unencapsulated form without a proteolytic enzyme.

Thus, due to the blood picture study after the probiotic preparations use, it is possible to reveal the changes patterns, to find out which metabolic processes prevail, and therefore to predict the animals' productivity.

In this regard, we under the Kursk State Agricultural Academy biochemical laboratory conditions developed a methodology for the Enzimsporin with an enzyme probiotic preparation and microencapsulation.

The Enzimsporin original probiotic preparation included bacterial strains: Bacillus subtilis VKPM B-314, Bacillus licheniformis VKPM B-8054, Bacillus subtilis (Bacillus natto) VKPM V-12079 and crystalline trypsin in an amount of 5%. According to the regulatory documents, the CFU level varied within $5.0 \times 10^9 - 6.3 \times 10^9$ per 1 g of the drug. [14] We included the crystalline trypsin enzyme in the preparation in the amount of 5%. Microencapsulation was carried out by dispersion in sodium alginate according to the method described in the RF patent No. 2689164 [15], improving it according to the method described in the RF patent No. 2736377 dated November 16, 2020. [16].

The finished microcapsules yield was 85-90%. Microcapsules were grey-yellow oval particles 80-150 μm in size. The viable probiotic bacteria number in the prepared microencapsulated preparation was $5.5 \times 10^9$ cells per 1 g.

In vitro studies simulating the exposure degree to the stomach and bile in the intestine acidic environment have shown the developed method effectiveness due to the drug probiotic microflora 100% survival under conditions close to physiological.

The microencapsulated preparation Enzimsporin with the enzyme manufactured laboratory sample bacteriological test was carried out in the Kursk Regional Veterinary Laboratory bacteriological department conditions.

Further, the drug was tested on laboratory animals for mutagenic activity, acute and chronic toxicity and showed the absence of those [17, 18].

The microencapsulated drug Enzimsporin with enzyme biological efficacy was tested by studying the effect on average daily body weight gain of pigs of Genesus genetics used in industrial pig breeding, in comparison with drug Enzimsporin and microencapsulated drug Enzimsporin, made by the method patent for invention No. 2689164 [15]. It was shown that average daily body weight gain in the group with Enzimsporin with enzyme was consistently higher than in the control groups. Safety in all groups was 100%.

In this regard, the new microencapsulated drug Enzimsporin with enzyme further study, namely the general blood analysis and its biochemical composition in animals study, seems relevant.

2. Material and research methods

Experiments to study a microencapsulated probiotic preparation Enzimsporin with trypsin laboratory sample effect made according to the method described in the RF patent No. 2736377 dated 16.11.2020 [16] on blood parameters in pigs were performed at the OTKRITIE LLC pig-breeding complex in the Russian Federation Kursk region, specializing in the Genesus genetics pigs cultivation. Blood samples study in the Veterinary Medicine, the Kursk State Agricultural Academy the Department of Physiology and Chemistry, Faculty laboratory. The original non-microencapsulated preparation Enzimsporin was produced by the LLC Fermlab (Moscow). The probiotic drug Enzimsporin with trypsin 1 gram composition includes sodium alginate - 750 mg, Enzimsporin (spore-forming bacteria Bacillus subtilis VKM B-2998D (VKPM B-314), Bacillus licheniformis VKM B-2999D (VKPM B-8054), Bacillus subtilis VKM B-3057D (VKPM B-12079) in equal proportions and fillers - whey powder, maltodextrin, corn flour) - 237.5 mg and 12.5 mg of crystalline trypsin.

The experiments were carried out on Genesus genetics pigs at the age of 48 days and weighing 16.2 kg. Healthy animals were taken for the study. They were kept under standard conditions.

All experimental animals received specialized food and filtered tap water. The manipulations were carried out at the same time in the afternoon.
The drugs were added to the feed, once a day.

The experiment total duration was 100 days in the period (from 48 to 148 days of life). During the experiment, the experimental animals were observed. The blood sampling control points were 48 days, 98 days, 148 days.

To study haematological parameters, 10 ml of blood was taken from all groups' animals for laboratory analysis. General haematological parameters (ESR, hematocrit, erythrocytes, leukocytes, haemoglobin) were determined in the blood. The biochemical blood test included the determination of total protein, albumin, total immunoglobulins, urea, creatinine, bilirubin, ALT, AST, cholesterol, glucose, total calcium, inorganic phosphorus, total magnesium and iron.

The experimental animals were divided into the following groups:

- experimental group (microencapsulated drug Enzimsporin with enzyme introduction into complementary foods at a dose of 3.0 g per day per head, n=10).
- control No. 1 (without introducing probiotic preparations into complementary foods, n=10);
- control No. 2 (the drug Enzimsporin introduction into complementary foods at a dose of 3.0 g per day per head, n=10).

3. Research results

To assess the microencapsulated probiotic preparation Enzimsporin with the enzyme effect on the body internal environment, we determined haematological parameters in the study group pigs in comparison with two control groups. The results are presented in tables.

In the studies course, it was found that in all groups pigs included in the experiment, the general haematological parameters were within the physiological boundaries (table 1).

The erythrocyte sedimentation rate was 2.5±0.08 - 3.1±0.09 mm/hour. The hematocrit value ranged from 39.8±2.0 to 41.9±2.5. At the same time, with increasing animals age, it increased.

The erythrocytes and haemoglobin content in all groups pigs during set up for the experiment was at the minimum level (6.8±0.34 - 7.0±0.26 x10 12/l; 97.9±3.8 – 98.8±3.0 g/l). However, in animals with enzymesporin in their diet, their content increased by the experiment end. At the same time, in pigs that received a microencapsulated probiotic with an enzyme (experiment), this increase was significant (p<0.05). In the control group No. 1 and No. 2 pigs, changes in the erythrocytes and haemoglobin content were statistically insignificant.

During the leukocytes study in their content, no significant differences were found. These blood cells number was within physiological norms.

When studying the blood biochemical components, reflecting most of the metabolic processes occurring in the experimental groups' animals body, we found that some indicators had a general tendency to increase, others decreased, and some indicators changed within unreliable limits (table 1).

The indicators group demonstrating a noticeable increase in values in our experiment included total protein, as well as albumin. These components contained in the pigs' blood receiving microencapsulated probiotic with Fe, gradually increased with the animals' age, reaching a maximum value at 148 days of age (total protein - 78.7±2.0 g/l; albumin - 44.5±2.0%). In the 2nd control group pigs, these blood parameters also increased by the experiment end, however, this increase was unreliable (p>0.05). In the 1st control group pigs, the total protein and albumin content, relative to the experimental groups animals, changed insignificantly. So, if before the experiment starts the total protein content was 68.0±2.1 g/l, and albumin - 38.5±2.0%, then at 153 days of age their content, respectively, reached 68.7±1.5 g/l and 39.1±1.8 %.
Table 1. Blood test parameters and biochemical parameters average values in pigs that received microencapsulated enzyme-containing enzyme (experimental group), non-encapsulated enzymesporin (control group No. 2) and did not receive drugs (control group No. 1).

| Indicators                        | Analyzes days |                     |                     |                     |                     |                     |                     |                     |                     |                     |
|-----------------------------------|---------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                                   | 48            | 98                  | 148                 |                     |                     |                     |                     |                     |                     |                     |
|                                   | Experiment    | Control № 2         | Control № 1         | Experiment          | Control № 2         | Control № 1         | Experiment          | Control № 2         | Control № 1         |                     |
| Blood test parameters average values |               |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| ESR, mm/hour                      | 3.0±          | 2.8±                | 3.1±                | 2.5±                | 2.9±                | 2.7±                | 2.8±                | 3.1±                | 3.0±                |                     |
| Hematocrit, %                     | 39.8±         | 40.0±               | 40.2±               | 41.0±               | 40.0±               | 40.0±               | 41.9±               | 41.0±               | 40.4±               |                     |
| Erythrocytes, x10, x10¹²/l        | 6.8±          | 6.9±                | 7.0±                | 6.9±                | 6.9±                | 7.0±                | 7.4±                | 7.3±                | 6.9±                |                     |
| Leukocytes, x10⁹/l               | 9.4±          | 9.7±                | 9.5±                | 9.8±                | 9.5±                | 9.3±                | 9.9±                | 9.6±                | 9.8±                |                     |
| Hemoglobin, g/l                   | 98.8±         | 97.9±               | 98.8±               | 99.5±               | 99.0±               | 99.0±               | 108.5±              | 104.5±              | 99.4±               |                     |
| Biochemical parameters            |               |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| Total protein, g/l                | 67.5±         | 67.8±               | 68.0±               | 68.4±               | 68.1±               | 68.1±               | 78.7±               | 69.8±               | 68.7±               |                     |
| Albumins, %                       | 38.5±         | 38.7±               | 38.5±               | 39.4±               | 39.0±               | 38.8±               | 44.5±               | 43.0±               | 39.1±               |                     |
| Immunoglobulins, mg/ml            | 11.7±         | 12.1±               | 11.9±               | 12.0±               | 12.3±               | 11.7±               | 19.9±               | 15.5±               | 12.4±               |                     |
| Urea, mmol/l                      | 3.6±          | 3.8±                | 3.5±                | 3.8±                | 3.7±                | 3.7±                | 3.7±                | 3.9±                | 4.1±                |                     |
| Creatinine, mmol/l                | 0.11±         | 0.10±               | 0.11±               | 0.10±               | 0.12±               | 0.13±               | 0.11±               | 0.10±               | 0.10±               |                     |
| Bilirubin, μmol/l                 | 1.12±         | 1.09±               | 1.10±               | 1.23±               | 1.18±               | 1.15±               | 1.27±               | 1.10±               | 1.20±               |                     |
| ALT, U/l                          | 12.0±         | 11.7±               | 11.7±               | 12.9±               | 12.5±               | 11.6±               | 14.7±               | 15.4±               | 12.0±               |                     |
| AST, Units/l                      | 26.7±         | 27.1±               | 26.3±               | 27.4±               | 28.8±               | 27.5±               | 28.8±               | 29.9±               | 26.5±               |                     |
| ALF, U/l                          | 51.5±         | 50.7±               | 50.9±               | 50.3±               | 51.8±               | 51.7±               | 52.2±               | 52.0±               | 51.8±               |                     |
| Cholesterol, mmol/l               | 3.8           | 4.4                 | 4.3                 | 4.7                 | 3.3                 | 3.7                 | 4.9                 | 3.0                 | 3.5                 |                     |
| Glucose, mmol/l                   | 2.47±         | 2.51±               | 2.50±               | 2.68±               | 2.61±               | 2.53±               | 3.11±               | 3.04±               | 2.60±               |                     |
In pigs that received a microencapsulated probiotic with an enzyme during the experiment, the total immunoglobulins content in the blood was significantly higher (p<0.05) (12.0±0.37 - 19.9±0.26 mg/ml) compared with the second control animals (12.3±0.38 - 15.5±0.20 mg/ml) and the first control (11.7±0.44 - 12.4±0.23 mg/ml) groups. This indicates that a microencapsulated probiotic in combination with an enzyme increases the body's protective status against infectious agents.

In the experimental group of pigs blood, there was an increase in glucose (2.68±0.15 - 3.11±0.17 mmol/L). This biochemical component is an energy material and provides many metabolic reactions in the body with energy. An increase in blood glucose in pigs receiving a microencapsulated probiotic with an enzyme indicates the intensity of metabolic processes occurring in the body. The second experimental group (enzysporin) results showed a significant increase in blood glucose (2.61±0.15 - 3.04±0.19 mmol/l). At the same time, its value was slightly reduced compared to the first experimental group data. No significant changes were found in the first control group's pigs in glucose content (2.53±0.09 - 2.60±0.11 mmol/l).

The mineral elements quantitative content analysis in the different animal groups experimental samples blood revealed significant changes in the quantitative content of total calcium, inorganic phosphorus, and magnesium. If the calcium level reliably (p<0.05) was increased in pigs receiving microencapsulated probiotic with enzyme (2.93±0.14 - 3.14±0.11 mmol/l), then phosphorus content (1.50±0.09 - 1.72±0.14 mmol/l) and magnesium (1.11±0.10 - 1.30±0.10 mmol/l), on the contrary, (p<0.05). To a certain extent, the identified changes on the part of these minerals can be explained by their active participation in the exchange processes occurring in the experimental groups' pigs. This assumption confirms the fact that in the control group pigs change in the inorganic phosphorus, calcium and magnesium content had a less pronounced character.

The ALT and ACT definition showed that in pigs receiving microencapsulated enzymesporin, their enzymatic activity increased by the experiment end and was reliably (p<0.05) higher (ALT - 15.4±0.53 U/l; ACT - 29.9±0.46 Ed/l) than control animals (ALT - 12.0±0.68 U/l; ACT - 26.5±0.60 U/l). In the experimental group pigs, which were fed microencapsulated enzymesporin with an enzyme, there were no reliable differences with the control animals. The findings in the aminotransferase study indicate that the load on liver function in animals receiving microencapsulated drugs was less than that of pigs receiving simply capped enzymesporin.

As for the animals' biochemical indicators that were part of the control group and did not receive the probiotic, there were no significant changes in their content. So, urea level (3.6±0.23 - 4.0±0.19 mmol/l), creatinine (0.10±0.02 (0.04) - 0.12±0.05 mmol/l), bilirubin (1.09±0.16 - 1.23±0.17 microns cholesterol (1.67±0.20 - 1.86±0.24 mmol/l), alkaline phosphate (50.3±4.7 - 52.2±4.9 U/l the experimental group pigs and the second control group had no physical boundaries and no reliable differences (p>0.05) from the animals.
4. Conclusion
For the first time in the Kursk region, research was conducted and scientific justification was given for a microencapsulated probiotic with an enzyme effect on the young pig’s biochemical and haematological parameters. This drug effect on the body immunobiological status formation and the pigs’ function degree gastrointestinal tract has been studied.

Studies show that after the experiment staging on feeding the microencapsulated probiotic drug enzyme, negative changes in haematological and biochemical indicators of animal blood were not observed, but on the contrary, there was a positive noticeable shift, compared to other groups.

In determining the general haematological biochemical indicators, animals receiving microencapsulated probiotic drug with enzyme established a high content - at the level of the upper physiological limit - red blood cells, haemoglobin, general protein, albumin, glucose, general calcium, which indicates the metabolic processes intensity. At the same time, the immunoglobulins elevated level indicates an animal body immunity and higher resistance high level.

Thus, the study’s results show that microcapsules enzyme with an enzyme has a more pronounced effect on metabolism in pigs compared to an unencapsulated probiotic drug without an enzyme.

Taking into account the microencapsulated probiotic drug enzymsporin with an enzyme results can be recommended for widespread use in the modern pig farming practice.

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