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Original article

IMMUNOMODULATORY FEED ADDITIVES FOR FARM ANIMALS AND FISH

D.V. Rudoy, E.N. Ponomareva, D.S. Mangasaryan, T.A. Maltseva

Abstract

Background. Modern applied biotechnology is focused on the development and implementation of fundamentally new multifunctional feed additives in a complex form. Currently, new approaches to the maintenance of farm animals and aquaculture objects under the influence of environmental factors are being sought, based on the use of biologically active additives. Intensive antibiotic therapy has become one of the reasons for the disruption of normal bacteriocenosis and a decrease in the immunobiological reactivity of animals and fish, the emergence of resistant strains of pathogens, which reduces the therapeutic effect of antibacterial drugs. The use of antibiotics leads to the accumulation of microorganisms with complex antibiotic resistance in the environment, their entry into natural water bodies is almost impossible. One of the promising ways to solve these problems is the use of feed additives with immunomodulatory action. The article examines existing feed additives with biological activity, provides generalized literature data on the use of biological additives in animal husbandry and aquaculture.

Purpose. The objective of the present study is to investigate impact of immunomodulatory feed additives on farm animals and fish.

Materials and methods. Feeds play a crucial role in the diet of farm animals and fish, as they must contain all the necessary nutrients, vitamins and minerals to ensure healthy growth and development of animals and aquaculture objects. Such preparations as probiotics (including symbiotics and metabiotics), prebiotics, and synbiotics, which are actively used in feed production, meet these requirements. In 1995, Gibson and Robertfroy introduced the concepts that should be classified as prebiotics and found that these components should be: 1) a selective component that promotes the metabolic activity or growth of one or more beneficial bacteria; 2) capable of altering the microbiota towards a healthy state; 3) capable of exerting a systemic or luminal beneficial effect on the host organism; 4) not absorbed and not hydrolyzed in the upper part of the stomach.

Results. Current research shows the positive impact of prebiotic use on performance, including improved weight gain, improved feed conversion and reduced disease. Prebiotics promote the growth of beneficial microorganisms such as bifidobacteria and lactobacilli in the intestines of animals. This reduces the concentration of pathogens such as salmonella and coliform bacteria, which reduces the risk of disease and improves the overall health of animals and fish. Research confirms the possibility of reducing the use of antibiotics in feed through the use of prebiotics, which is important in the context of the problem of antibiotic resistance. Prebiotics can be used to improve the environmental sustainability of livestock and aquaculture, as they help to reduce the release of harmful substances into the environment.

Conclusion. Numerous scientific studies confirm the beneficial effects of immunomodulatory additives on the health of animals, poultry and aquaculture objects, especially in terms of protection against pathogens, stimulation of the immune response and increased productivity. Prebiotics can be used as an alternative or enhance the effect of probiotics. The use of a combination of these components, demonstrating a synergistic effect, can be even more effective in stimulating the intestinal microbiota and protecting animal health. One promising area of research is the use of wheat grain heap as an immunomodulatory additive, which has high prebiotic properties.

In the future, it is necessary to pay attention to studies of the thermal treatment of grain in the production of feed and feed additives. It should be emphasized that the use of feed additives such as probiotics, prebiotics and synbiotics is safe, does not have a negative impact on the natural environment and reduces the demand for antibiotic-based growth promoters. However, the mechanisms of action of probiotic organisms, prebiotics, and their combinations in synbiotics require further research. In the technology of compound feed production, plant raw materials, including wheat, are subjected to the extrusion process in order to increase the nutritional value, during which, during heat treatment, pathogenic microorganisms are killed. Presumably, wheat grain of early ripeness phases may lose its beneficial properties during heat treatment (extrusion). In this regard, it is advisable to conduct research on the effect of grain processing on its prebiotic properties.

Keywords: probiotic; prebiotic; symbiotic; compound feed; grain

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Научная статья

ИММУНОМОДУЛИРУЮЩИЕ КОРМОВЫЕ ДОБАВКИ ДЛЯ СЕЛЬСКОХОЗЯЙСТВЕННЫХ ЖИВОТНЫХ И РЫБ

Д.В. Рудой, Е.Н. Пономарева, Д.С. Мангасарян, Т.А. Мальцева

Аннотация

Обоснование. Современная прикладная биотехнология ориентирована на разработку и внедрение принципиально новых многофункциональных кормовых добавок в комплексной форме. В настоящее время ведется поиск новых подходов к содержанию сельскохозяйственных животных и объектов аквакультуры в условиях воздействия факторов окружающей среды, основанных на использовании биологически активных добавок. Интенсивная антибиотикотерапия стала одной из причин нарушения нормального бактериоценоза и снижения иммунобиологической реактивности животных и рыб, появления устойчивых штаммов патогенных микроорганизмов, что снижает терапевтический эффект антибактериальных препаратов. Применение антибиотиков приводит к накоплению в окружающей среде микроорганизмов с комплексной антибиотикорезистентностью, их попадание в природные водоемы практически невозможно. Одним из перспективных путей решения этих проблем является использование кормовых добавок с иммуномодулирующим действием. В статье рассмотрены существующие кормовые добавки с биологической активностью, приведены обобщенные литературные данные по использованию биологических добавок в животноводстве и аквакультуре.

Цель. Цель исследования – изучить влияние иммуномодулирующих кормовых добавок на сельскохозяйственных животных и рыб.

Материалы и методы. Корма играют важнейшую роль в рационе сельскохозяйственных животных и рыб, поскольку должны содержать все необходимые питательные вещества, витамины и минералы для обеспечения здорового роста и развития животных и объектов аквакультуры. Этим требованиям отвечают такие препараты, как пробиотики (включая синбиотики и метабиотики), пребиотики и синбиотики, которые активно используются в кормопроизводстве. В 1995 году Гибсон и Роберфруа представили понятия, которые следует относить к пребиотикам, и пришли к выводу, что эти компоненты должны быть: 1) селективным компонентом, способствующим метаболической актив-

ности или росту одной или нескольких полезных бактерий; 2) способным изменять микробиоту в сторону здорового состояния; 3) способным оказывать системное или люминальное благоприятное воздействие на организм хозяина; 4) не всасывается и не гидролизуется в верхнем отделе желудка.

Результаты. Современные исследования показывают положительное влияние применения пребиотиков на продуктивность, в том числе на увеличение веса, повышение конверсии корма и снижение заболеваемости. Пребиотики способствуют росту полезных микроорганизмов, таких как бифидобактерии и лактобактерии, в кишечнике животных. Это снижает концентрацию патогенных микроорганизмов, таких как сальмонелла и колиформные бактерии, что уменьшает риск заболеваний и улучшает общее состояние здоровья животных и рыб. Исследования подтверждают возможность снижения использования антибиотиков в кормах за счет применения пребиотиков, что важно в контексте проблемы устойчивости к антибиотикам. Пребиотики можно использовать для повышения экологической устойчивости животноводства и аквакультуры, поскольку они помогают сократить выброс вредных веществ в окружающую среду.

Заключение. Многочисленные научные исследования подтверждают благотворное влияние иммуномодулирующих добавок на здоровье животных, птицы и объектов аквакультуры, особенно в плане защиты от патогенов, стимуляции иммунного ответа и повышения продуктивности. Пребиотики могут использоваться в качестве альтернативы или усиливать действие пробиотиков. Использование комбинации этих компонентов, демонстрирующей синергетический эффект, может быть еще более эффективным в стимулировании кишечной микробиоты и защите здоровья животных. Одним из перспективных направлений исследований является использование в качестве иммуномодулирующей добавки зернового вороха пшеницы, который обладает высокими пребиотическими свойствами. В дальнейшем необходимо уделить внимание исследованиям термической обработки зерна при производстве кормов и кормовых добавок. Следует подчеркнуть, что использование таких кормовых добавок, как пробиотики, пребиотики и синбиотики, является безопасным, не оказывает негативного влияния на окружающую среду и снижает потребность в стимуляторах роста на основе антибиотиков. Однако механизмы действия пробиотических организмов, пребиотиков и их комбинаций в синбиотиках требуют дальнейшего изучения. В технологии производства комбикормов растительное сырье, в том числе пшеница, для повышения питательной ценности подвергается процессу экструзии, в ходе которого при термической обработке уничтожаются патогенные микроорганизмы. Предположительно, зерно пше-

ницы ранних фаз спелости может потерять свои полезные свойства в процессе тепловой обработки (экструзии). В связи с этим целесообразно провести исследование влияния обработки зерна на его пребиотические свойства.

Ключевые слова: пробиотики; пребиотики; синбиотики; комбикорм; зерно

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Introduction

The agribusiness is a dynamically developing sector with significant potential in relation to the strategy of ensuring food security of any country. However, technological problems arise on the way to a stable increase in production volumes in the country and providing the population with high-quality, diverse and affordable agricultural products. First of all, these include:

– diseases of cultivated objects that reduce productivity and marketability of goods;

– lack of effective systems for monitoring and rapid diagnostics of pathogens;

– environmental issues related to the quality of the environment for growing aquatic organisms;

– lack of sufficient assortment and high cost of specialized domestically produced compound feeds, etc.

The problem of ensuring food security for the population is becoming increasingly important. One of the important aspects in this matter is providing livestock with high-quality and balanced compound feed. The global volume of compound feed products is growing every year. Compared to 2023, global production of compound feed increased by 1% and amounted to 1187.7 million tons (FAO Cereal Supply and Demand Brief, 2024) (Fig. 1) [1]. This is primarily due to the increase in the world's population and the increase in demand for animal and plant products. Along with the increase in the volume of feed production, their prices are also rising [2]. In this regard, increasing the volume of feed raw materials is an urgent task.

Feeds play a crucial role in the diet of farm animals and fish, as they must contain all the necessary nutrients, vitamins and minerals to ensure healthy growth and development of animals and aquaculture objects. Such preparations as probiotics (including symbiotics and metabiotics), prebiotics, and synbiotics, which are actively used in feed production, meet these requirements. In 1995,

Gibson and Robertfroy introduced the concepts that should be classified as prebiotics and found that these components should be:

1) a selective component that promotes the metabolic activity or growth of one or more beneficial bacteria;

2) capable of altering the microbiota towards a healthy state;

3) capable of exerting a systemic or luminal beneficial effect on the host organism;

4) not absorbed and not hydrolyzed in the upper part of the stomach [3].

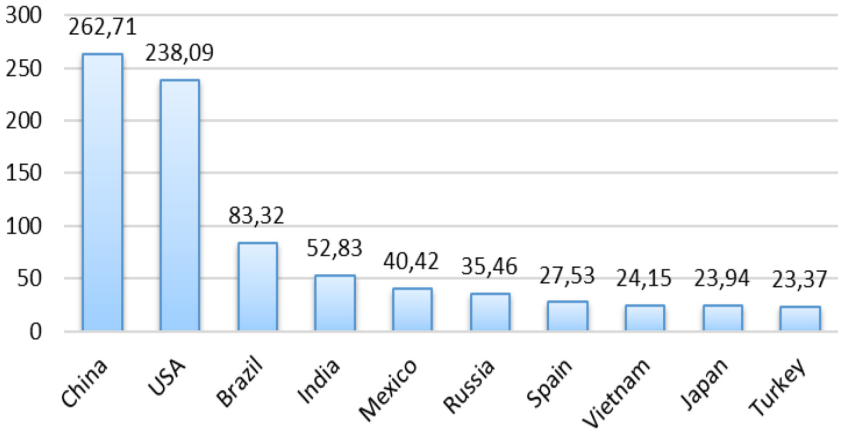

Fig. 1. TOP 10 countries by feed production volume, million tons

Currently, immunotropic drugs of different groups are offered for practical animal husbandry, and there is a need for their extensive industrial testing. For this purpose, a review of existing additives and their impact on the body of animals, birds and aquaculture objects has been conducted.

The use of prebiotic additives in agriculture helps to normalize the microbiocenosis of the organism of farm animals and fish, as well as their resistance to pathogenic microflora, which ultimately affects the increase in productivity and quality of goods.

Prebiotics are carbohydrates that are not broken down in the upper gastrointestinal tract, and other products that are a source of nutrition for normal intestinal microflora. Prebiotics include fructose- and galactose-oligosaccharides, inulin, lactulose, lactiol, dietary fiber, etc. [4].

Prebiotics are insoluble food ingredients that help stimulate the growth and activity of beneficial microorganisms in the intestines of animals and fish. These

feed additives play an important role in regulating the microbiota and metabolism of animals and fish, which affects their health and productivity.

Current research shows the positive impact of prebiotic use on performance, including improved weight gain, improved feed conversion and reduced disease. Prebiotics promote the growth of beneficial microorganisms such as bifidobacteria and lactobacilli in the intestines of animals. This reduces the concentration of pathogens such as salmonella and coliform bacteria, which reduces the risk of disease and improves the overall health of animals and fish. Research confirms the possibility of reducing the use of antibiotics in feed through the use of prebiotics, which is important in the context of the problem of antibiotic resistance. Prebiotics can be used to improve the environmental sustainability of livestock and aquaculture, as they help to reduce the release of harmful substances into the environment.

Purpose. The objective of the present study is to investigate impact of immunomodulatory feed additives on farm animals and fish.

Materials and methods

For a substance to be classified as a prebiotic, a detailed specification of its parameters – including origin, purity, and structural characteristics – is an essential prerequisite. Regulatory acceptance mandates adherence to global safety protocols, requiring not only a recognized safety status but also a thorough assessment of its toxicological profile, dosage efficacy, and the absence of adulterants. A fundamental requirement is its confirmed role in promoting the ecological equilibrium of the gut microbiome [5].

As delineated by Wang [6], the classification of a nutritional component as a prebiotic is contingent upon satisfying five key criteria (Fig. 2, 3):

1. Resilience to gastric acidity, hydrolysis by mammalian enzymes, and gastrointestinal absorption.
2. Serving as a selective substrate for colonic microbiota fermentation.
3. Eliciting a beneficial physiological effect on the host's well-being.
4. Selectively enriching for populations of health-promoting bacteria.
5. Maintaining chemical stability throughout industrial processing and storage.

The fundamental criteria for prebiotic compounds begin with their resilience to enzymatic digestion and absorption in the upper gastrointestinal tract. This indigestibility ensures their intact passage to the colon, where they serve as substrates for selective fermentation by beneficial commensal bacteria–constituting the second criterion. The subsequent fermentation metabolites, notably short-chain fatty acids, mediate the third criterion by induc-

ing beneficial shifts in host metabolism and enhancing immunomodulatory functions. Furthermore, a definitive prebiotic must demonstrate a selective stimulation of probiotic bacterial growth (criterion four) and retain stability through food processing technologies to remain bioavailable within the gut lumen (criterion five).

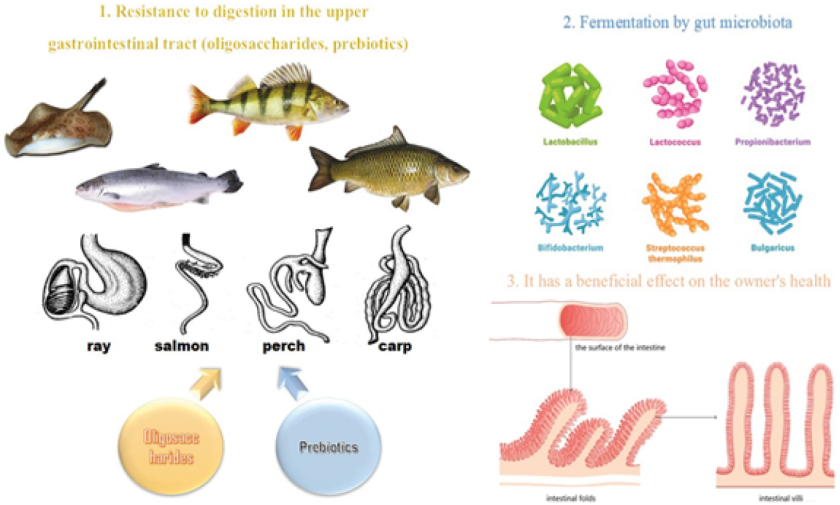

Fig. 2. The main criteria for classifying feed components as prebiotics

Fig. 3. The main criteria for classifying feed components as prebiotics (continued)

The technological process of feed production involves an extrusion process, as a result of which the digestibility of feed and its organoleptic properties are increased. In addition, pathogenic microorganisms die during heat treatment, which ensures the safety of compound feeds. The extrusion process takes place at temperatures from 120 to 200 °C, so it is important to select such probiotics that will be resistant to high temperatures [7].

Results

Research on feed additives and poultry health

Most studies related to poultry microbiota and/or prebiotic potential have focused mainly on the cecum microbiota. The cecum is the most densely populated and microbiologically diverse region of the poultry gastrointestinal tract, with a digestion time of 12 to 24 hours and a major site for bacterial anaerobic fermentation and pathogen colonization [8]. Lignin from sugarcane bagasse has been found to have potential as an animal feed additive when added to feed rations. It promotes the growth of bifidobacteria, a well-known beneficial bacteria, inhabiting the gut microbiota, whose activity, among other things, inhibits the growth of pathogenic bacteria (e.g. Enterobacteriaceae), which is an important factor for animal husbandry.

The study showed that the inclusion of lignin in broiler diets improved the population of lactobacilli and bifidobacteria in the cecum. This indicates that the inclusion of lignin in poultry feed can potentially promote the growth of bifidobacteria in the cecum of broilers, thus acting as a prebiotic ingredient in poultry nutrition.

Another study determined the effect of plant feed supplement and prebiotic on plant protein diet in broiler chickens. A total of 90 chickens (Cobb-500) were weighed and randomly assigned to three treatment groups supplemented with either plant feed supplement or prebiotic and raised for 28 days [9]. The results showed that significant increase in body weight of broiler chickens was observed in both plant feed supplement and prebiotic groups compared to the control group at 4 weeks of age. No significant differences were found in body weight gain between treatment groups at weekly intervals throughout the experimental period. However, significant differences were evident in cumulative weight gain at 3 and 4 weeks of age. The addition of plant protein with a plant feed additive or a prebiotic showed a positive effect of the additive on feed efficiency throughout the entire experimental period compared to the control diet without additives. The authors of the article recommended the use of plant protein as an important source of protein in broiler diets [10].

On the other hand, studies [11] by scientists from the Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences showed

that fructooligosaccharides (organophosphorus compounds) administered to commercial male turkeys for 8 weeks did not affect the productivity of the animals. The organophosphorus compounds used were assessed in terms of their effectiveness in terms of productivity and physiological response of the digestive tract. Particular attention was paid to the metabolism of the cecum. The following levels were used in the diet: 0.5, 1 and 2%. After 8 weeks of experimental feeding, diet intake, body weight and feed efficiency were the same in all examined groups. The pH of the ileum and cecum contents was reduced as a result of dietary procedures, especially when using 2% dietary organophosphorus compounds. The experimental treatment did not statistically affect the activity of bacterial enzymes; However, after taking the organophosphorus compounds preparation, a slight beneficial decrease in the activity of β-glucosidase and β-glucuronidase was observed. Addition of organophosphorus compounds to the diet did not affect the growth and productivity of animals.

Another example of a beneficial effect on the intestinal microflora of broilers is a study by scientists from the Institute of Bacteriology and Mycology, Veterinary Faculty of the University of Leipzig [13]. The team conducted a field trial to evaluate the effect of a fructan-containing syrup (0.5%) diluted in drinking water on bacterial activity levels, endotoxin values, as well as body weight and relative organ weights. Fructan resulted in a significant reduction in total aerobes, Enterobacteriaceae and C. perfringens counts, as well as in lower blood endotoxin levels compared to control birds. An increase in body weight as a result of consumption was observed on day 35 of the study period ($P < 0.05$). These results indicate that drinking water containing fructan has a beneficial effect on growth performance, reduces bacterial endotoxin levels and suppresses potential pathogens in the intestine of broilers.

Sims M.D. and co-authors [14] fed crossbred male turkeys to 18 weeks of age for a subsequent comparison of growth promoters. Four dietary treatments were used in the study: negative control (CON), bacitracin methylene disalicylate (BMD) at 55 mg/kg up to 6 weeks and 27.5 mg/kg thereafter, mannan oligosaccharide (MOS) at 0.1% up to 6 weeks and 0.05% thereafter, and BMD and MOS at the concentrations listed above.

Research on feed additives on pig health

Various feed additives are used in studies of the effects of prebiotics on the gastrointestinal microbiota and overall health of pigs.

M.R. Smiricky-Tjardes and co-authors evaluated the effect of galactooligosaccharides (GALOS) supplementation in pig diets on nutrient digestibility, ileal and fecal bacterial populations, and ileal short-chain fatty acid (SCFA)

production and determined their effect on ileal enzymatic performance in vitro. The galactooligosaccharides used in this study were prebiotics that increased in vivo beneficial bacteria and SCFA concentrations both in vivo and in vitro. Pigs were fed 35 g/kg TOS for 6 weeks. A significant increase in fecal bifidobacteria and lactobacilli was found compared to the control group.

Studies of feed additives on the health status of aquaculture objects. In addition to the production of animal feed, there is also a need to increase the volume of food fish products, which in turn requires an increase in the growth of feed production for aquaculture facilities. The growth of aquaculture is hampered by a growing number of problems, primarily infectious diseases and improper or irrational fish nutrition. Therefore, it is essential to develop new prevention strategies to minimize infectious diseases and pharmaceutical interventions. Nutritional problems and health of fish can be improved by regulating their gut microbiota. Microbiomes can play a critical role in fish physiology, especially in digestion, by metabolizing largely indigestible components of feed for the host or synthesizing essential micronutrients. In addition to their nutritional role, microbiomes are considered the first line of defense against pathogens [17].

Scientists from the Don State Technical University, together with the Astrakhan State Technical University, the Southern Scientific Center of the Russian Academy of Sciences, and the Agricultural Research Center "Donskoy", conducted research on the effect of feed with probiotics B-1895 and Subtilis-S on the growth and physiological state of sterlet producers [24-26]. Experiments with B-1895 and Subtilis-S based on Bacillus subtilis on sterlet producers grown in a recirculating aquaculture system revealed their positive effect on the studied fish. Compared to the control, the body weight gain in the first experimental group ("B-1895") was 13.3% higher, and in the second group ("Subtilis-S") - by 53.3%. At the same time, an improvement in the physiological state of the experimental fish was recorded, expressed in stabilization and moderate reduction of physiological and biochemical parameters of the blood, in contrast to the control group of fish, in which they either remained unchanged or remained unchanged. increased slightly. In the protein system, the most positive changes were noted in the second group of experimental fish with the greatest weight gain. From the obtained results of the conducted studies, it follows that the most positive effect of the studied probiotics in feeding fish was provided by the drug "Subtilis-S".

The researchers tested a new prebiotic mixture (Selectovit) consisting of

1,3/1,6-beta-glucans, mannan oligosaccharides, nucleic acids, nucleotides, mediumchain fatty acids and single-chain fatty acids at different inclusion levels (0.0; 0.5; 1.0; 2.0 g/kg) in the diet of Atlantic salmon (Salmo salar). Using experimental

feed trials and microbiome profiling with 16 S rRNA, the effects of the prebiotic mixture on fish growth and the microbial community in both the gastrointestinal tract and skin were assessed. Overall, the supplementation did not significantly affect growth. However, the prebiotic could significantly affect the number of microorganisms in the distal gut and skin. Several potentially beneficial bacteria, such as Bacillus and Mycoplasma spp. were significantly more numerous in the prebiotic-fed groups compared to the control. In contrast, putative pathogenic bacteria were less numerous in salmon fed the prebiotic mixture. The supplement caused more changes in the skin than in the intestine. In fish, there is increasing evidence of very complex interactions between microorganisms in the digestive system and the external mucosa, as well as with the immune system. Further research in this area may lead to the development of new bacterial biomarkers and new non-invasive strategies for monitoring the health of the fish digestive system [18].

Manufacturers of herbal supplements: Delacon Biotechnik, Biomin Phytogenics, Phytobiotics Futterzusatzstoffe, Pancosma, EW Nutrition, Dostofarm, Nutriad International, Ropapharm International, Himalaya Drug Company, Tanin Sevnica and others [22].

Conclusion

Numerous scientific studies confirm the beneficial effects of immunomodulatory additives on the health of animals, poultry and aquaculture objects, especially in terms of protection against pathogens, stimulation of the immune response and increased productivity. Prebiotics can be used as an alternative or enhance the effect of probiotics. The use of a combination of these components, demonstrating a synergistic effect, can be even more effective in stimulating the intestinal microbiota and protecting animal health. One promising area of research is the use of wheat grain heap as an immunomodulatory additive, which has high prebiotic properties. In the future, it is necessary to pay attention to studies of the thermal treatment of grain in the production of feed and feed additives. It should be emphasized that the use of feed additives such as probiotics, prebiotics and synbiotics is safe, does not have a negative impact on the natural environment and reduces the demand for antibiotic-based growth promoters. However, the mechanisms of action of probiotic organisms, prebiotics, and their combinations in synbiotics require further research. In the technology of compound feed production, plant raw materials, including wheat, are subjected to the extrusion process in order to increase the nutritional value, during which, during heat treatment, pathogenic microorganisms are killed. Presumably, wheat grain of early ripeness phases may lose its beneficial prop-

erties during heat treatment (extrusion). In this regard, it is advisable to conduct research on the effect of grain processing on its prebiotic properties.

Conflict of interest information. The authors declare that they have no conflict of interest.

Sponsorship information. The work is carried out as part of the project "Development of personalized feeds of a new generation with plant and probiotic additives to increase the survival rate and improve the health of fish" (FZNE-2023-0003).

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