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SELECTION OF CONDITIONS FOR OBTAINING ECOLOGICALLY PURE DRY PROBIOTIC AGAINST MIXED INTESTINAL INFECTION FOR FARM ANIMALS

Abstract

As a result of the study, the best viability of monocultures and associations under freeze drying has been determined. The best two protective media during storage and their composition are the following: media No.1 includes (%) sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0; and protective media No.2 containштп (%) sucrose 8.0; gelatin - 1.5; skim milk - 5.0. Thus the titer of bacteria equaled to values of $6.0x10^{10}$ and $4.2x10^{10}$ CFU / g, respectively.

When determining the stability of dried preparations during storage of probiotic bacteria and their association, the best protective medium is No. 2 (sucrose 8.0%; gelatin - 1.5%; skim milk - 5.0%).

The antagonistic activity of monocultures (lactic acid bacteria *Lactobacillus plantarum1, Streptococcus salivarius 20n, Lactobacillus fermentum 15,* propionic acid bacteria *Propionibacterium shermanii 34*) and associations based on these monocultures is preserved practically at the initial level upon freeze drying.

A probiotic based on lactic acid and propionic acid bacteria can be used as a therapeutic and prophylactic agent against dyspepsia for farm animals. At the same time, there is no need for the use of antibiotics and other antibacterial agents for the treatment of diseased animals.

Key words: *probiotics, bifidobacteria, lactobacilli, antagonism, immunostimulating effect, antibiotics, polyresistance, dysbiosis, intestinal infections, extra-intestinal infections.*

Introduction

Infectious diseases of animals are urgent problem for many countries of the world. This increases the risk of human infection through animals, as well as food contamination. In this situation, disease prevention with probiotics can play an important role. Currently, a large number of probiotics is known, consisting of lactic acid and bifidobacteria, which are the main protective group of intestinal microorganisms, harmless to humans and animals [1-7]. However, the known probiotics have not become an alternative to antibiotics, since they have an insufficiently broad antimicrobial spectrum of action and are used mainly to restore normal intestinal microflora. Often, the use of recommended medicines is not effective, since it does not take into account the nature of the infection.

The probiotic developed by us is based on lactic acid and propionic acid bacteria, it differs from the known ones in a wide spectrum of antimicrobial action against pathogenic and relatively pathogenic stirrers of intestinal diseases due to the targeted selection of strains of lactic acid bacteria in its composition - antagonists to the most common pathogens. The composition of the drug contains propionic acid bacteria, which stimulate the antagonistic activity of lactic acid bacteria, reduce their dependence on composition of the nutrient medium, and also enrich the drug with B- group vitamins. This ensures high preventive and therapeutic efficacy of the drug not only against colibacillosis and salmonellosis, but also against mixed intestinal infection, typical for most cases of diseases. The data presented indicate a wide range of biological activity of the developed drug and the prospects for research on the development of technology for its production.

The main task of producing dry preparations is use of effective methods of maintaining the viability of cultures during long-term storage. For this, it is necessary that the least number of cells die during the drying process. The most modern and reliable way of long-term storage of microorganisms is freeze-drying (or lyophilization). It is based on the fact that water at a reduced

atmospheric pressure evaporates from the frozen material which is to be dried, turning into vapor, bypassing the liquid state. At the same time, the temperature of the dehydrated material during the entire period of free moisture removal remains below the freezing point, as a result of which the proteins are not exposed to the denaturing action of increased concentrations of electrolytes. In addition, with the freeze drying method in vacuum, the temperature is not higher than 30 degrees, and moisture is removed after freezing, at a time when microorganisms are in a state of anabiosis and are most resistant to various adverse effects. The freeze dryer has excellent distinctive features: low temperature mode; long shelf life of the product (only cryogenic freezing is longer); the original product remains alive in the literal sense, while maintaining biological characteristics and structural integrity; the most important thing is that the moistened product, after drying, restores all its original properties [8].

The lyophilization of bacteria, requires protective media that contain sugars and protein compounds. Without the addition of such substances, bacteria usually do not withstand lyophilization. Bacteria die when water or saline solution are used for lyophilization of cell suspensions. It is known that the sugars in protective media, penetrate into the cell and create a high osmotic pressure there, preventing formation of ice crystals and cellular destruction during the freezing process. Protein components of the protective environment do not penetrate into the cell, but force the cell membrane to adhere more tightly to the cytoplasm, which is important during thawing [9].

The main criterion for the selection of media were: the availability of components; good survival of bacteria when dried; stability when freezing and drying; the appearance of the dried preparation (the formation of a dense "tablet"); good solubility (rehydration) of the lyophilisate. Skim milk has good protective properties. Microorganisms, when dried in milk, retain a high survival rate: *Staphylococcus* and *E. coli* - up to 70%, phytopathogenic bacteria - up to 60-80% *Past. pestis* - up to 60% [10,11].

Materials and methods

The objects of research were lactic acid bacteria *Lactobacillus plantarum1, Streptococcus salivarius 20n, Lactobacillus fermentum 15*, propionic acid bacteria *Propionibacterium shermanii* 34 and association: *L. plantarum 1+S. salivarius 20n+L. fermentum 15+P. shermanii* 34.

Cultivation of lactic acid and propionic acid bacteria, as well as associations, was carried out in MRS nutrient medium with the addition of 1 mg% cobalt chloride in a thermostat at a temperature of 30-32^{0}C for 20 hours.

The following protective media were used in freeze drying of cultures: 1) protective media No. 1, which includes (%): sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0; 2) protective media No. 2 (%), which includes (%): - sucrose 8.0, gelatin - 1.5, skim milk - 5.0; 3) separated skim milk - 5%; 4) serum - 5%; control (without protective components).

After adding these components, liquid cultures were poured into 5 ml penicillin vials and frozen for 6 hours at -30^{0}C and -60^{0}C. Drying was performed in a Liobeta-35 freeze dryer. Product drying temperature 30^{0}C for 6 hours. In the preparations before and after drying, the number of viable bacterial cells was determined by plating cultures from appropriate dilutions in Petri dishes on solid MRS culture medium. To determine the stability of dried preparations during storage, an accelerated method was used, in which dry preparations were heated at 60 ° C for 15 minutes, and then the number of surviving bacteria was determined.

The tables show the average results from at least three replicates.

Results and Discussion

It is known that the quality of freeze-dried microbial preparations depends to a large extent on protectors used for drying.

Studies have shown that *L. plantarum 1* culture (table 1) survives freeze-drying with all protective media taken into the study. At the same time, dry preparations contain from 1.8 to 3.4 billion viable cells / g, and in the case of using protective medium No. 2, the number of viable cells reaches 1.7x10^{10} CFU / g.

Table 1 - Freeze drying of lactic acid and propionic acid bacteria cultures with different protectors

Bacteria cultures	Liquid culture titer, CFU / ml	The content of bacterial cells in dry preparations with various protectors, CFU / g				
		1	2	3	4	5
L. plantarum 1	1,5x10^9	3,4x10^9	1,7 x10^{10}	2,0 x10^9	1,8x10^9	1,5 x10^9
S. salivarius 20n	1,4 x10^9	3,2x10^9	3,2 x10^{10}	2,2 x10^9	1,5x10^9	1,4 x10^9
L. fermentum 15	1,6 x10^9	4,6x10^9	1,7 x10^{10}	3,7 x10^9	1,7x10^9	1,3 x10^9
P. shermanii 34	2,4 x10^9	4,0x10^9	4,5 x10^9	2,5 x10^9	1,8x10^9	1,5 x10^9
Association	2,6 x10^9	6,0x10^{10}	4,2 x10^{10}	5,5 x10^9	2,7 x10^9	2,5 x10^9
Note: 1) protective media No. 1, which includes (%): sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0; 2) protective media No. 2 (%), which includes (%): sucrose 8.0; gelatin - 1.5; skim milk - 5.0; 3) saturated skim milk - 5%; 4) serum - 5%; 5) control (without protective components)						

The culture of *S. salivarius 20n* retained better its viability during drying also in the variant with protective medium No. 2 (3.2 x10^{10}), and with protective media No. 1, 3, 4 (from 1.5 to 3.2 x10^9 CFU / g). The culture of *L. fermentum 15* had a bacterial titer in dry preparations with protective media No. 1, 3, 4 (from 1.7 to 4.6 x 10^9 CFU / g), with protective medium No. — 1.7 x 10^{10} CFU / g. Similar results were obtained with the propionic acid bacteria *P. shermanii 34* (PCB). The titer of bacteria in the variants was 1.8-4.5 x10^9 CFU / g. The association, consisting of 4 cultures of microorganisms, retained viability during freeze drying better with protective media No. 1 and No. 2 (6.0x10^{10} and 4.2x10^{10} CFU / g, respectively). With protective media No. 3 and No. 4, the titer of microorganisms ranged from 2.5 to 5.5 x10^9 CFU / g.

The best viability of monocultures and associations under freeze drying is obtained with protective media No. 1, which includes (%) sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0 and No. 2, which contains (%) sucrose 8.0; gelatin - 1.5; skim milk - 5.0, with detected bacterial titer 6.0x10^{10} and 4.2x10^{10} CFU / g, respectively.

To determine the stability of dried preparations during storage, an accelerated method was used, in which dry preparations are heated at 60 ° C for 15 minutes, and then the number of surviving bacteria was determined. The results are shown in Table 2.

Table 2 - Content of viable cells in freeze-dried preparations after heating

Bacteria cultures	Liquid culture titer, CFU / ml	The content of bacterial cells in dry preparations with various protectors after heating, CFU / g				
		1	2	3	4	5
L. plantarum 1	1,5x10^9	2,6x10^7	1,2 x10^{10}	9,1 x10^8	5,7x10^6	5,5 x10^5
S. salivarius 20n	1,4 x10^9	5,1x10^7	1,4 x10^9	8,2 x10^8	3,3x10^6	1,8 x10^6
L. fermentum 15	1,6 x10^9	3,4x10^7	1,1 x10^{10}	9,5 x10^8	2,1x10^6	1,7 x10^6
P. shermanii 34	2,4 x10^9	5,1x10^7	5,8 x10^8	7,8 x10^7	2,3x10^6	5,6 x10^5
Association	2,6 x10^9	4,2x10^8	3,2 x10^{10}	9,1 x10^8	3,75x10^6	2,4 x10^6
Note: 1) protective media No. 1, which includes (%): sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0; 2) protective media No. 2 (%), which includes (%): sucrose 8.0; gelatin - 1.5; skim milk - 5.0; 3) saturated skim milk - 5%; 4) serum - 5%; 5) control (without protective components)						

When determining the stability of dried preparations during storage of probiotic bacteria and their association, the lowest result of the survival was revealed when serum was used as a protective medium. In this case, the titer of bacteria did not exceed n x10^6 CFU / g. Also, high result wasn't obtained when using protective medium No. 1 (sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0%), the titer was n x10^7, although the association titer was one degree higher and amounted to 4.2x10^8 CFU / g. An indicator of the viability of bacteria was obtained as a result of the use of a

protective medium No. 3 (saturated skim milk - 5%), represented by a titer of 8,2-9,x10^8 CFU / g, with the exception of the propionic acid bacteria dried strain tier (7.8x10^7 CFU / g).

During storage, bacteria survive better in preparations dried with protective medium No. 2, both monocultures and their association, the titer was for *L. plantarum 1* 1.2 x10^{10}, *S. salivarius 20n* - 1.4 x10^9, *L. fermentum 15* - 1.1 x10^{10}, *P. shermanii 34* - 5.8 x10^8, associations - 3.2 x10^{10} CFU / g.

When determining the stability of dried preparations during storage of probiotic bacteria and their association, the best protective medium is No. 2 (sucrose 8.0%; gelatin - 1.5%; skim milk - 5.0%).

To check antimicrobial activity preservation of monocultures and associations based on them, a comparison was made of the activity before and after drying, which was carried out with a protective medium No. 2. Antimicrobial activity of probiotic cultures and associations before drying is presented in Table 3.

As can be seen from table No. 3, the antagonistic activity of both monocultures and associations based on them is preserved during freeze-drying at practically the same level. So, the growth inhibition zone of *Salmonella typhimurium* test culture with strain *L. plantarum 1* before drying was 19.0 mm after drying 19.1 mm; test cultures of *Salmonella enteritidis* up to 17.0 mm, after 17.2 mm; test cultures of *Salmonella gallinarum* up to - 18.0 mm, after - 18.3 mm; test cultures - *Shigella flexneri* 11 up to - 10.0 mm, after - 10.2 mm; *Shigella sonnei* – up to 8.0 mm, after - 8.1 mm; test cultures - *Proteus vulgaris* up to - 8.0 mm, after - 8, 2 mm; test cultures - *Citrobacter sp*. before - 16.0 mm, after - 15.7 mm; test cultures - *Edwardsiella sp.* before - 14.0 mm, after - 13.9 mm; test cultures - up to 16.0 mm, after - 13.9 mm. The antagonistic activity of *L. plantarum 1* against *Yersinia sp.* and *Escherichia coli* remained at the same level before and after drying, the growth inhibition zones were 16.0 and 18.0 mm, respectively.

The antimicrobial activity of *S. salivarius 20n* strain remained at the same level before and after drying against the following test cultures - *Salmonella typhimurium, Salmonella gallinarum, Shigella sonnei, Proteus vulgaris, Edwardsiella sp., Yersinia sp*. and *Escherichia coli,* the diameter of the growth inhibition zones was 14.0; 10.0; 9.0; 9.0; 18.0; 17.0; 15.0 mm, respectively. Zones of growth inhibition of test cultures by this strain of lactic acid bacteria *Shigella flexneri 11* and *Citrobacter sp.* were 13.0-13.1 and 18.0-17.9 mm, respectively.

The antimicrobial activity of *L. fermentum 15* strain remained at the same level before and after drying against the following test cultures - *Salmonella typhimurium, Salmonella enteritidis, Salmonella gallinarum, Proteus vulgaris, Edwardsiella sp., Yersinia sp.* the diameter of the growth inhibition zones was 16.0; 20.0; 15.0; 11.0; 14.0; 18.0 mm, respectively. The zones of inhibition of the growth of test cultures by this strain of lactic acid bacteria *Shigella flexneri 11, Shigella sonnei, Citrobacter sp., Escherichia coli* were 10.0-10.3; 11.0-10.8; 18.0-17.8; 19.0-18.7 mm, respectively.

Strain of propionic acid bacteria *P. shermanii 34* did not show antagonistic activity before and after drying to six test cultures, namely *Shigella flexneri 11, Shigella sonnei, Proteus vulgaris, Citrobacter sp., Edwardsiella sp., Yersinia sp.* The antimicrobial activity of *P. shermanii 34* strain remained at the same level before and after drying in relation to the following test cultures - *Salmonella typhimurium, Salmonella enteritidis, Salmonella gallinarum, Escherichia coli,* the diameter of growth inhibition zones was 10.0; 11.0; 10.0; 11.0 mm, respectively.

The antimicrobial activity of the association remained at the same level before and after drying against eight of the following test cultures - *Salmonella typhimurium, Salmonella enteritidis, Salmonella gallinarum, Shigella sonnei, Citrobacter sp., Edwardsiella sp., Yersinia sp*. and *Escherichia coli*, the diameter of the growth inhibition zones was 22.0; 23.0; 19.0; 13.0; 20.0; 21.0; 20.0; 23.0 mm, respectively. The zones of growth inhibition of the test cultures of this association, *Shigella flexneri 11* and *Proteus vulgaris,* were 15.0-15.3 and 12.0-12.1 mm, respectively.

The antagonistic activity of both monocultures and associations based on them is retained during freeze drying almost at the initial level.

Table 3 - Antimicrobial activity of lactic acid and propionic acid bacteria and associations before and after freeze drying

Bacterial strains	Diameter of suppression zones of test cultures' growth, mm																					
	Before drying										After drying											
	Salmonella typhimurium	*Salmonella enteritidis*	*Salmonella gallinarum*	*Shigella flexneri 11*	*Shigella sonnei*	*Proteus vulgaris*	*Citrobacter sp.*	*Edwardsiella sp.*	*Yersinia sp.*	*Escherichia coli*	*Salmonella typhimurium*	*Salmonella enteritidis*	*Salmonella gallinarum*	*Shigella flexneri 11*	*Shigella sonnei*	*Proteus vulgaris*	*Citrobacter sp.*	*Edwardsiella sp.*	*Yersinia sp.*	*Escherichia coli*		
L. plantarum 1	19,0	17,0	18,0	10,0	8,0	8,0	16,0	14,0	16,0	18,0	19,1	17,2	18,3	10,2	8,1	8,2	15,7	13,9	16,0	18,0		
S. salivarius 20н	14,0	16,0	10,0	13,0	9,0	9,0	18,0	18,0	17,0	15,0	14,0	16,1	10,0	13,1	9,0	9,0	17,9	18,0	17,0	15,0		
L. fermentum 15	16,0	20,0	15,0	10,0	11,0	11,0	18,0	14,0	18,0	19,0	16,0	20,0	15,0	10,3	10,8	11,0	17,8	14,0	17,7	18,7		
P. shermanii 34	10,0	11,0	10,0	0	0	0	0	0	0	11,0	10,0	11,0	10,0	0	0	0	0	0	0	11,0		
Association	22,0	23,0	19,0	15,0	13,0	12,0	20,0	21,0	20,0	23,0	22,0	23,0	19,0	15,3	13,0	12,1	20,0	21,0	20,0	23,0		

Conclusions

As a result of the study, the best viability of monocultures and associations with freeze drying is obtained with protective media No. 1, which includes (%) sodium acetate - 2.5; sodium citrate - 2.5; sucrose - 10.0 and No. 2, which contains (%) sucrose 8.0; gelatin - 1.5; skim milk - 5.0, with detected bacterial titer $6.0x10^{10}$ and $4.2x10^{10}$ CFU / g, respectively.

When determining the stability of dried preparations during storage of probiotic bacteria and their association, the best protective medium is No. 2 (sucrose 8.0%; gelatin - 1.5%; skim milk - 5.0%).

The antagonistic activity of both monocultures (lactic acid bacteria *Lactobacillus plantarum1, Streptococcus salivarius 20n, Lactobacillus fermentum 15*, propionic acid bacteria *Propionibacterium shermanii 34*) and associations based on them is preserved practically at the initial level upon freeze drying.

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ПОДБОР УСЛОВИЙ ПОЛУЧЕНИЯ ЭКОЛОГИЧЕСКИ ЧИСТОГО СУХОГО ПРЕПАРАТА ПРОБИОТИКА ПРОТИВ СМЕШАННОЙ КИШЕЧНОЙ ИНФЕКЦИИ ДЛЯ СЕЛЬСКОХОЗЯЙСТВЕННЫХ ЖИВОТНЫХ

Аннотация

В результате исследования выявлена наилучшая жизнеспособность монокультур и ассоциации при лиофильном высушивании. Лучшими защитными средами при хранении

оказались №1, в состав которой входят (%) натрий уксуснокислый - 2,5; натрий лимоннокислый - 2,5; сахароза - 10,0 и №2, в состав которой входят (%) сахароза 8,0; желатин - 1,5; обезжиренное молоко - 5,0, при этом титр бактерий равнялся $6,0x10^{10}$ и $4,2x10^{10}$ КОЕ/г, соответственно. При определении устойчивости высушенных препаратов при хранении пробиотических бактерий и их ассоциации лучшей является защитная среда №2 (сахароза 8,0 %; желатин - 1,5%; обезжиренное молоко - 5,0%). Антагонистическая активность как монокультур (молочнокислые бактерии *Lactobacillus plantarum1, Streptococcus salivarius 20н, Lactobacillus fermentum 15*, пропионовокислые бактерии *Propionibacterium shermanii* 34), так и ассоциации на их основе сохраняется при лиофильном высушивании практически на исходном уровне.

Пробиотик на основе молочнокислых и пропионовокислых бактерий может быть использован в качестве лечебного и профилактического средства против диспепсии для сельскохозяйственных животных. При этом отпадает необходимость в применении антибиотиков и других антибактериальных средств для лечения заболевших животных.

Ключевые слова: Пробиотики, бифидобактерии, лактобактерии, антагонизм, иммуностимулирующее действие, антибиотики, полирезистентность, дисбактериоз, кишечные инфекции, внекишечные инфекции.

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АУЫЛ ШАРУАШЫЛЫҒЫ ЖАНУАРЛАРЫ ҮШІН АРАЛАС ІШЕК ИНФЕКЦИЯСЫНА ҚАРСЫ ЭКОЛОГИЯЛЫҚ ТАЗА ҚҰРҒАҚ ПРОБИОТИК ПРЕПАРАТЫН АЛУ ШАРТТАРЫН ТАҢДАУ

Аңдатпа

Зерттеу нәтижесінде лиофильді кептіру кезінде монокультуралар мен ассоциациялардың ең жақсы өміршеңдігі анықталды. Сақтау кезінде ең жақсы қоректік ортасы №1 болды, оның құрамына (%) сірке қышқылы натрий - 2,5; лимон қышқылы натрий - 2,5; сахароза-10,0 және №2, оның құрамына (%) сахароза 8,0; желатин-1,5; майсыз сүт-5,0,ал бактериялардың титрі $6,0x10^{10}$ тең болды және сәйкесінше 4, $2x10^{10}$ ШТБ – шоғыр түзу бірлігі. Пробиотикалық бактерияларды және олардың ассоциациясын сақтау кезінде кептірілген препараттардың тұрақтылығын анықтау кезінде №2 қорғаныс ортасы ең жақсы болып табылады (сахароза 8,0 %; желатин - 1,5%; майсыз сүт - 5,0%). Монокультуралардың антагонистік белсенділігі (сүт қышқылы бактериялары *Lactobacillus plantarum1, Streptococcus salivarius 20н, Lactobacillus fermentum* 15, пропион қышқылы бактериялары *Propionibacterium shermanii* 34) және олардың негізіндегі ассоциациялар лиофильді кептіру кезінде бастапқы деңгейде сақталады.

Сүт қышқылы және пропион қышқылы бактерияларына негізделген пробиотикті ауылшаруашылық жануарларына арналған диспепсияға қарсы емдік және сонымен қатар профилактикалық агент ретінде пайдалануға болады. Бұл жағдайда ауру жануарларды емдеу үшін антибиотиктер мен басқа бактерияға қарсы препараттарды қолдану қажеттілігі жоғалады.

Кілт сөздер: Пробиотиктер, бифидобактериялар, лактобактериялар, антагонизм, иммуностимуляторлық әсер, антибиотиктер, полирезистенттілік, дисбиоз, ішек инфекциялары, ішектен тыс инфекциялар.