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DESIGN OF THE TREATMENT AND PREVENTIVE MEAT PRODUCT «DINORMIN»

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Introduction. The scientific concept of innate immunity origin confirms the fact that survival possibility of any species including humans under the environment abundant in potentially pathogenic microorganisms is evolutionary process ofmechanisms development ensuring resistance to infections [7]. Resistance (immunity) is divided into the general and local, innate and adaptive one. Reactions providing resistance are divided into antibacterial and antitoxic [12].

Under the modern living conditions, the environmental, technological, climatic, human-induced impacts and other stress factors contributes to deterioration of adaptive and protective responses in organism and induce of immunodeficient conditions. First of all, it concerns young species especially during the first month of the postnatal development.

Therefore, many efforts have been recently made to develop immunostimulants and immunomodulators divided into microorganisms-, vegetable- and animal- generatedsubstances according its origin (polysaccharides, membrane phospholipids, glycopeptides, modified toxins, DNAs and RNAs of microorganisms, vaccines etc.) [5]. Endogenous peptide-likeimmunostimulants (preparations of thymus, spleen, marrow, interleukins etc.) [1, 6] and synthetic immunostimulants (levamisole, leacadin, thymogen) [17], stimulants for metabolic processes (anabolic hormones, riboxinum, plasmol, vitamins etc.) have been isolated.

Common synthetic and gene-engineering immunostimulants and isolated bio-factors (e.g. cytotoxicants) induce depletion of immune systemorgans and its other parts. Substancesextracted fromanimal organs and tissues (tissue-specific proteins) acting as immunostimulants have mild activation action on various immune reactions, and this process has a gradual and consistent character. An immunomodulating tissue-specific proteins is not a sharp activators, rather it is an agent to recover a deteriorated immune system. While having an immunecorrecting impact, tissue-specific proteins do not cause depletion of the immune system [14].

Recently, a stable interest in the field of animal origin materials implementation (including products of livestock slaughter) have been appeared [8, 15].

Immunemodulating bio-active substances extracting fromendocrine glands, thymus and spleen of reindeers featuringhave been shown to possess a strong stimulating impact on main characteristics of the immune system [3, 9, 11, 18]. The action of medicine spleen and thymus origin are influenced on the immune system and bloodvessels. Recovery the leucocytes number was shown tooccur in the peripheral blood with stable increase in the activity and intensity of spontaneous and induced neutrophilphagocytosis [2]. Based on collected data, raw animal materials are considered for production of products having an immunecorrecting effect [16].

The purpose of this work is to study immunebiological active components of the treatment and preventive product “Dinormin” produced from immunecompetent pork organs and tissues and its therapeutical effect *in vivo* based on secondary immunodeficiency simulation.

Materials and methods. Objects of the study included: the “Dinormin” complex product (no. 1); spleen extract (no. 2); thymus extract (no. 3); extract of mesenteric lymph nodes (no. 3); laboratory animals with simulated immunodeficiency.

“Dinormin” is a mixture of lyophilicdriedwater-salt extracts of swine tissues and immunecompetent organs obtained after anindustrial slaughter: thymus, spleen and mesenteric lymph nodes [10].

*The study of the amino acid composition*has been carried out on“BiotronikLC-2000” aminoacidanalyser (Germany). Separation of amino acids inanalytical column has been performed under the automatic mode in the three buffer system of sodium citrate buffers: buffer A – 0.18 M, pH 3,25; buffer B – 0.3 M, pH 3.9; buffer C – 1.6 M, pH 4.75. The ion exchange resin “DC-6A” (USA). The height of the resin in the column is 22 cm, the flow speed of the buffer solution is 32 ml/h. To detect amino acids, the method of post-column modification with the use of a ninhydrin reagent was applied. The speed of the reagent supply was 20 ml/h.

*The study by the electrophoresis method*was carried out in 12.5 % and 15 %polyacrylamide gel at the presence of 0,1 % sodiumdodecylsulfate (SDS).

*The study on laboratory animals*was carried out according to the International Rules for Humane Care of Animals. Animals were kept under similar conditions: temperature(22 ± 2) °C, moisture (50 ± 5) %, lighting

(day-night mode: from 7.00 a.m. to 7.00 p.m.), access to feed and water *ad libitum*.

The experiment was carried out on *Wistar* male rats, with the average weight of (220 ± 5) g. (n=38). Secondary immunodeficiency was simulated in the animals during the first 14 days using the following factors:

- high noise (80-90 Db),
- compulsory swimming (with a load of 10% of the animal weight up to its fatigue);
- intraperitoneal injection of Cyclophosphan®» (LANS-Farm, Russia) dosed as 75 mg/kg, three times every 72 hours.

On the 12th day the animals were dividedby pair analogues into 4 groups. Animals of 1st group were treated *per os* with "Dinormin" in dose 5 mg/kg of BW, 2nd – 50 mg/kg of BW, 3rd– 500 mg/kg of BW, 4th group was treated distilled water in equal portions.

Animals were euthanized on 28 days for blood sampling. Biochemical investigations were carried out on semiautomatic analyzer BioChem SA (HTI, USA); hematologic investigations were carried out on automatic analyzer Abacus Junior Vet (Diatron, Austria). The immunoassay was carried out on Immunochem 2100 reader (USA) based on the sandwich method using sets of ELISA species-specific agents (rat).

Blood parameters were compared with the parameters normal for this species and age [4] and with parameters of the 4th group animals.

The statistical analysis of the data obtained was carried out with the use of STATISTICA 6.0 Software Package, by application of the Student's t-test (differences at $p<0.05$ were considered statistically reliable). The mathematical treatment of the data including calculation of averages with standard errors (M ± m) was carried out.

Results and discussion. The analysis of the amino acid composition (**Figure 1**) shown the highest content of amino acids in spleen extract (about 40.85 % in sample). Amino acid content in thymus and mesenteric lymph extracts was considerably lower and averaged 24.38% and 24.26 %,respectively. The general content of amino acids in "Dinormin"was 37.46%. The amino acid composition analysis revealed a high content of acidic amino acids (22.68 %) in"Dinormin" such asAspartic acid Glutamic acid (9.13 % and 13.55 %, respectively). The content of basic amino acids (lysine – 9.71 %, histidine – 3.16 % and arginine – 6.82 %) wasapproximately19.7%. Concerning neutral amino acids,leucinecontent was 8.34 %, other neutral amino acid concentrations variedfrom 4.63 % for isoleucine to 5.81 % for tyrosine. The content of sulphur-containing amino acids was low and averaged2.8 % formethionine. The total content of neuromodulatory amino acids (Asp, Glu, Gly) in "Dinormin" was high and averaged32.49 % (**Figure 1**).

The protein profile of individual extracts and "Dinormin"is shown in the **Figure 2.**

Protein profile of individual extracts includes substances with the molecular weight (MW) from 10 to 95 kDa. Profiles of spleen and mesenteric lymph nodes extracts are quantitative and qualitative quite close. Protein bands corresponding toMWfrom 12 to 95 kDa appear in the tracks. The proximity of protein bands for these extracts can be explained byproximity of physiological functions of these immune system organs. Low-molecular fractions (MW<10kDa) were revealed in thymus extract.It

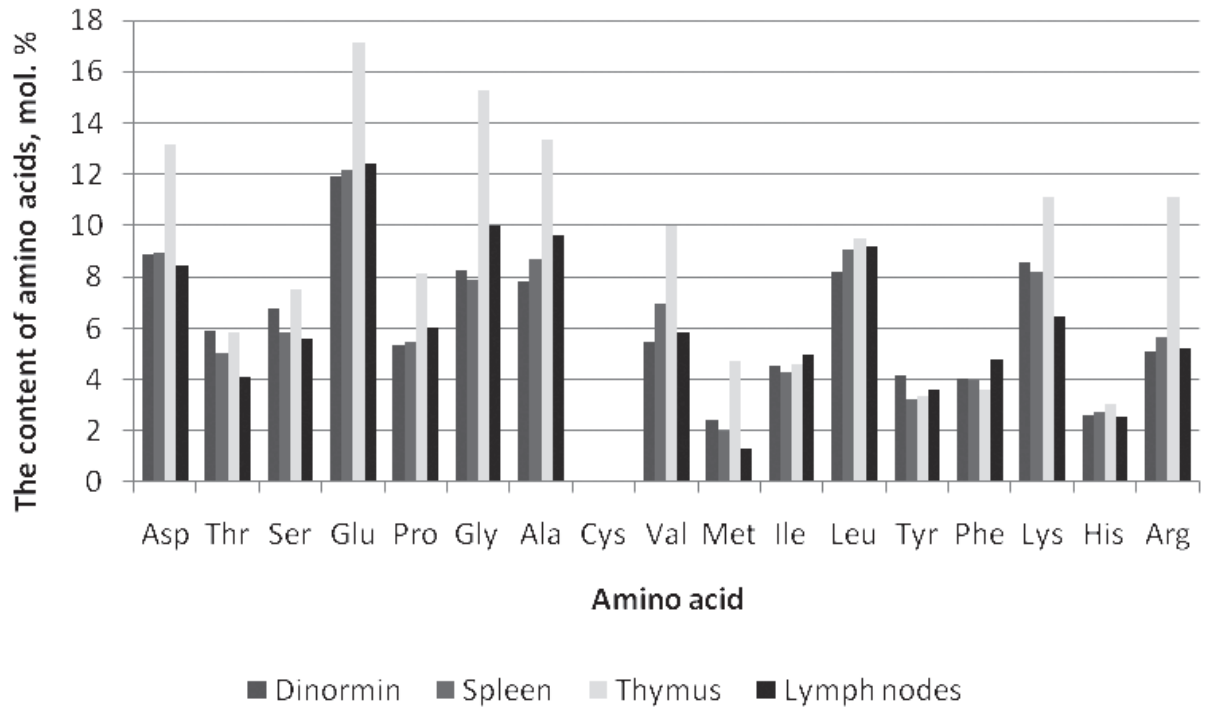

Figure 1.The content of amino acids, mol %.

Figure "1" indicates significant difference at $p<0.05$ between experimental and control groups, figure "2" indicatessignificant difference at $p<0.01$ between experimental and control groups, figure "3" indicatessignificant difference at $p<0.001$ between experimental and control groups.

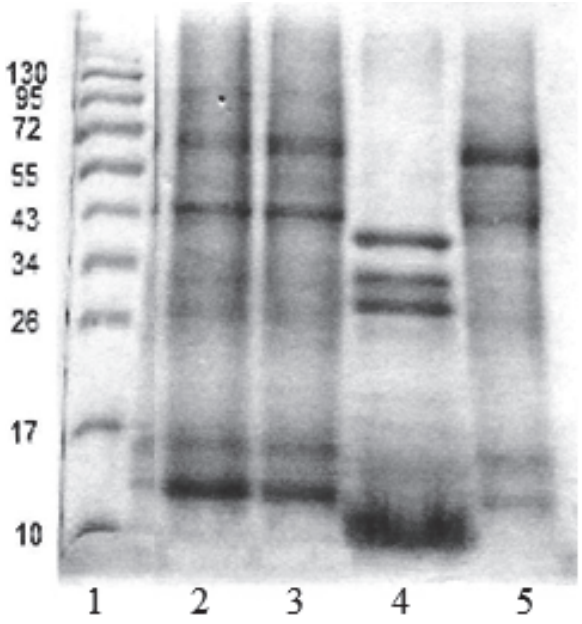

Figure 2. SDS-electrophoresis of the samples (12.5% polyacrylamide gel).

Legend:
Molecular mass standard (130 kDa – 10 kDa).
Spleen extract.
Mesenteric lymph node extract.
Thymus extract.
"Dinormin".

has been noted that all components detected in individual extracts tracks were also detected in "Dinormin".

We can suppose that the composition of the detected fractions includes certain known proteins, e.g. interleukin 17-A (17312 Da), 12-B (36829 Da), 7 (20161 Da), tyrosine – protein kinase (71620 Da), lysozyme C-1 (14668 Da) and others [13]. These functional proteins are responsible for receptors of the immune system contributing both incidentally and directly to the synthesis of molecules responsible for protection functions of the organism.Harsh reduction of physical activity, changes in the coat and mucous membranes were detected in animals with immunodeficiency simulation. Feed and water consumption were also reduced.

The haematology analysis data shown a reduction in the number of lymphocyte and monocytesand increase in the number of granulocytes and thrombocytes for groups 1 and 2, their number decreased for group 4 with an increase of thrombocytes. The content of leucocytes was normal for groups 1, 2 and 3, for group 4 this level was much lower. The animals of group 4 shown changes typical for secondary immunodeficiency: leukopaenia (decrease in the number of leucocytes up to 40% compared with the lower border of the normal level), monocytopenia (decrease in the number of monocytes up to 40% as compared with the lower border of the normal level), agranulocytosis (decrease in the content of granulocytes more than 50 %).

Table

Clinical analysis

Parameters	Normal level	Animal group			
		1 Dose 0,5 mg/100 g	2 Dose 5 mg/100 g	3 Dose 50 mg/100 g	4 Distilled water
Haematological parameters					
Leucocytes, 109/l	6.6-12.6	6.32±0.98[1]	8.39±4.11[2]	6.75±1.32[2]	4.87±2.41
Lymphocytes, 109/l	4.78-9.12	2.30±0.12[2]	3.16±0.18[2]	2.89±1.07[2]	4.99±0.01
Mixture: monocytes, eosinophils, basophiles, immature cells, 109/l	0.02-0.15	0.10±0.10[2]	0.14±0.06[3]	0.13±0.14[1]	0.07±0.04
Granulocytes, 109/l	1.77-3.38	4.05±0.88[1]	5.90±0.06[3]	3.69±0.14[2]	1.51±0.06
Thrombocytes, 109/l	631-719	799.8±94.4[1]	755.7±75.3[2]	696.75±34.7[3]	768.0±25.4
Biochemical parameters					
Glucose, ммоль/l	7.77-12.21	11.75±2.53[1]	9.11±0.95[3]	8.50±0.92[3]	8.41±1.19
Bilirubin (gen.), mcM /l	0-8.5	2.66±0.19[3]	2.43±0.21[3]	2.83±0.23[3]	2.45±0.21
Creatinine, mcM /l	9-70	59.08±4.41[1]	48.63±1.02[3]	62.83±2.56[2]	65.4±1.41
Urea, mcM /l	4.28-8.57	7.10±0.67[1]	5.98±0.36[2]	6.02±0.19[3]	6.21±0.11
LDH, E/l	50-700	307.42±27.68[2]	203.85±36.86[1]	173.55±11.85[3]	279.65±11.77
AST, E/l	20-100	114.30±13.56[2]	97.58±13.30[2]	103.33±16.89[1]	118.10±8.20
AST, E/l	10-80	35.07±4.04[3]	31.63±2.25[2]	31.50±2.86[2]	40.20±3.82
Alkalinephosphatase, E/l	70-450	105.40±7.72[1]	166.58±11.98[2]	137.60±12.21[2]	169.5±16.87
GGT, E/l	0-4	2.78±0.45[1]	5.67±0.12[2]	3.70±0.54[1]	3.51±0.08
Immunoenzymometric parameters					
IgM, mg/l	411±137	538.9±87.1[1]	582.8±55.1[1]	462.9±58.3[1]	380.9±17.1
IgG, g/l	4.98±1.37	4.1±1.1[1]	3.7±1.1[1]	3.4±0.3[2]	3.5±0.1
IFN A, pg/ml	-	29.6±8.4[3]	25.6±5.1[1]	21.6±7.9[2]	40.0±9.1
IFN B, pg/ml	-	23.7±11.2[2]	57.9±5.4[1]	30.0±2.5[1]	69.1±13.2

Normalization of the number of leucocytes, lymphopenia, monocytopenia (reduction of the number of monocytes by almost 2.5 times as compared with the lower border of the normal level), granulocytosis (increase in the content of granulocytes by more than 50%) were observed in blood of 1group animals treated with "Dinormin" *per os* in dose 0.5 mg/100 g. Lymphopenia, monocytopenia and even more considerable increase in the content of granulocytes (more than by 3 times as compared with the normal level) were observed in blood ofanimals ofgroup 2. The changes typical for progress of immunodeficiency conditions were less evident in blood of animals of groups 1, 2 and 3, with the most evident improvement of parameters for groups 1 and 2 (**table**).

The results of the biochemical study of serum (**table**) shown that total bilirubin concentration was close to the lower border of the normal level, creatinine concentration was close to the upper border, decrease in the activity of gamma-glutamyltransferase was also noticed in all the groups,.For groups 1 and 2, the glucose level was observed to be close to the upper border of the normal level, an increase of aspartate aminotransferase activity were detected in 1, 3 and 4. Urea level increase was revealed in animals of group 1 in comparison with groups 2, 3 and 4. LDH activityin group 1 considerably increased, ALP activity decreased in comparison with groups 2, 3 and 4.

Analysis of serum immune parameters of animals treated with"Dinormin" shown an increase in the number of immunoglobulins M for groups 1, 2 and 3, increase in the number immunoglobulins G for groups 1 and 2, and a considerable decrease in interferones A and B in comparison with group 4 (**table**).

Conclusion. The results have shown that use of the treatement and preventive product 'Dinormin'in dose 0.5 mg/100 g and 5 mg/100 g allowed to eliminateof immunedeficiencysigns,generate the activation of specific immunity in the animals according to general (remaining after the simulation) reduction of the number of immune blood cells with simultaneous increase of immunoglobulins M and G and decrease in interferons A and B. It should be noticed that despite of low content of leucocytes in the blood, including lymphocytes, the level of immunoglobulins in the blood increased and the level of interfeorns decreased for the animals treated with"Dinormin"in dose 0.5 mg/100 g and 5 mg/100 g/ This fact indicates the mobilization of the systematic immunity. The therapeutic dose of this product is in range from 0.5 mg/100 g to 5 mg/100 g. These data shown that "Dinormin" proved immune-protective action by increasing generation of humoral factors of the antiinfective protection for organism with deteriorated immunity functions as well as under persistent exposure to various pathogenic factors (as provided for conventional livestock management).

Prospects for further research. The positive impact of "Dinormin" on reparative processes in young pigs has been proved by many experiments. Probably, at the first stage this effect is provided by a consolidated action of oligapeptides and proteins of the innate immune system and proteins of the adaptive immune system. Probably, the process is also contributed by free amino acids having aneuromodulatory action. Then, upon deeper digestion of the tissue-specific proteins, individual amino acids and low-molecular peptides are able to have an neuroimmunologic impact on animal organisms by delivering from the zymohydrolysis in digestive tract to the bloodflow. Further research will be directed to the detailed study of product's activating properties.

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ВИКОРИСТАННЯ ПРИРОДНО-ТКАНИННОГО ПРЕПАРАТУ «ДІНОРМІН» В ЛІКУВАЛЬНО-ПРОФІЛАКТИЧНИХ ЦІЛЯХ

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Резюме. Природний тканинний препарат «Дінормін» є сумішшю ліофільно висушених водно-сольових екстрактів імунокомпетентних органів свиней: тимуса, селезінки і мезентеральних лімфатичних вузлів. Представлені результати дослідження амінокислотного і білкового складу препарату і компонентів, що входять до його складу. У комплексному препараті зберігається увесь амінокислотний спектр індивідуальних екстрактів. У «Дінормині» відмічена значна кількість високого вмісту аспаргінової, глутамінової амінокислот, лізину, аргініну і лейцину. При цьому третину загального вмісту амінокислот (32,5 %) складають нейромедіаторні амінокислоти (аспаргінова, глутамінова кислоти, гліцин).

Ці амінокислоти мають імунологічну активність і покращують адаптивні здібності тварин при стресах. Електрофоретичне дослідження показало високу гетерогенність екстрактів внутрішніх органів, присутність білкових з’єднань широкого діапазону молекулярних мас (високомолекулярні білки з молекулярними масами від 130 кДа до 43 кДа; низькомолекулярні білки – 34 кДа, 26 кДа, від 15 до 12 кДа). Зміст білкових з’єднань в комплексному препараті відповідає даним аналізу індивідуальних екстрактів. Представлені дані дозволяють зробити висновок, що «Дінормін» як комплексний препарат зберігає амінокислоти і активні речовини білкової природи, що містяться в окремих екстрактах імунокомпетентних органів, здатні впливати на імунні реакції організму. В експериментах in vivo була показана висока імунопротекторн активність. «Дінормін» сприяє активації імунної системи у тварин: відбувається реорганізація клітинної складової імунітету зі збільшенням вмісту імуноглобулінів М (41%) і G (17%) і зниженням кількості інтерферонів А (26%) і В (65 %). Терапевтична доза цього засобу знаходиться в діапазоні від 5 мг/кг до 50 мг/кг

Ключові слова: природно-тканинний препарат, «Дінормін», імуномодулятори, тканинні специфічні білки.

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ИСПОЛЬЗОВАНИЕ ПРИРОДНО-ТКАНЕВОГО ПРЕПАРАТА «ДИНОРМИН» В ЛЕЧЕБНО-ПРОФИЛАКТИЧЕСКИХ ЦЕЛЯХ

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Резюме. Природный тканевой препарат «Динормин» представляет собой смесь лиофильно высушенных водно-солевых экстрактов иммунокомпетентных органов свиней: тимуса, селезенки и мезентеральных лимфатических узлов. Представлены результаты исследования аминокислотного и белкового состава препарата и компонентов, входящих в его состав. В комплексном препарате сохраняется весь аминокислотный спектр индивидуальных экстрактов. В «Динормине» отмечено значительное количество высокое содержание аспаргиновой, глутаминовой аминокислот, лизина, аргинина и лейцина. При этом треть общего содержания аминокислот (32,5 %) составляют нейромедиаторные аминокислоты (аспаргиновая, глутаминовая кислоты, глицин).

Данные аминокислоты обладают иммунологической активностью и улучшают адаптивные способности животных при стрессах. Электрофоретическое исследование показало высокую гетерогенность экстрактов внутренних органов, присутствие белковых соединений широкого диапазона молекулярных масс (высокомолекулярные белки с молекулярными массами от 130 кДа до 43 кДа; низкомолекулярные белки – 34 кДа, 26 кДа, от 15 до 12 кДа). Содержание белковых соединений в комплексном препарате соответствует данным анализа индивидуальных экстрактов. Представленные данные позволяют сделать вывод, что «Динормин» как комплексный препарат сохраняет аминокислоты и активные вещества белковой природы, содержащиеся в отдельных экстрактах иммунокомпетентных органов, способные влиять на иммунные реакции организма. В экспериментах in vivo была показана высокая иммунопротекторное активность. “Динормин” способствует активации иммунной системы у животных: происходит реорганизация клеточной составляющей иммунитета с увеличением содержания иммуноглобулинов М (41%) и G (17%) и снижением количества интерферонов А (26%) и В (65 %). Терапевтическая доза данного средства находится в диапазоне от 5 мг/кг до 50 мг/кг.

Ключевые слова: природно-тканевой препарат, «Динормин», иммуномодуляторы, тканевые специфические белки.

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DESIGN OF THE TREATMENT AND PREVENTIVE MEAT PRODUCT «DINORMIN»

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Abstract. The purpose of this work is to study immunebiological active components of the treatment and preventive product "Dinormin" produced from immunecompetent pork organs and tissues and its therapeutical effect *in vivo* based on secondary immunodeficiency simulation.

Materials and methods. Objects of the study included: the "Dinormin" complex product (no. 1); spleen extract (no. 2); thymus extract (no. 3); extract of mesenteric lymph nodes (no. 3); laboratory animals with simulated immunodeficiency.

The analysis of the amino acid composition shown the highest content of amino acids in spleen extract (about 40.85 % in sample). Amino acid content in thymus and mesenteric lymph extracts was considerably lower and averaged 24.38% and 24.26 %,respectively. The general content of amino acids in "Dinormin"was 37.46%. The amino acid composition analysis revealed a high content of acidic amino acids (22.68 %) in"Dinormin" such asAspartic acid Glutamic acid (9.13 % and 13.55 %, respectively). The content of basic amino acids (lysine – 9.71 %, histidine – 3.16 % and arginine – 6.82 %) wasapproximately19.7%. Concerning neutral amino acids,leucinecontent was 8.34 %, other neutral amino acid concentrations variedfrom 4.63 % for isoleucine to 5.81 % for tyrosine. The content of sulphur-containing amino acids was low and averaged2.8 % formethionine. The total content of neuromodulatory amino acids (Asp, Glu, Gly) in "Dinormin" was high and averaged32.49 %

"Dinormin" is a mixture of lyophilicdriedwater-salt extracts of swine tissues and immunecompetent organs obtained after anindustrial slaughter: thymus, spleen and mesenteric lymph nodes "Dinormin" is a mixture of immunocompetent swine organs: lyophilic dried water-salt extracts thymus, spleen and mesenteric lymph nodes. Preparation and ingredients in its composition were studied with amino acid and protein composition analyses. Full range of individual amino acid extracts revealed in the complex preparation. There are a high content aspartic, glutamic amino acids, lysine, arginine and leucine in «Dinormin». Neurotransmitter amino acids (aspartic, glutamic acid, glycine) were composing a one third of the total amino acid content (32.5%). These amino acids have immunological activity and improve the adaptive capacity of animals under stress. SDS-electrophoresis showed the high heterogeneity of the extracts of internal organs and presence of the proteins of a wide molecular weights range (high molecular weight proteins – 130 kDa and 43 kDa, proteins of low molecular weight – 34 kDa, 26 kDa, 15 to 12 kDa). «Dinormin» retains amino acids and active proteinaceous material, contained in the individual extracts of immune organs and affected the immune response, in complex drug. Immunopotentiating activity was revealed during *in vivo* experiments. "Dinormin" promoted specific immune system in the animals according to general reduction of the number of immune blood cells with simultaneous increase of immunoglobulins M (41 %) and G (17 %) and decrease in interferons A (26 %) and B (65 %).The therapeutic dose of this product is in range from 0.5 mg/100 g to 5 mg/100 g. Research work 013.15.03.

Key words: meat product, "Dinormin", immunomodulator, tissue-specific proteins.

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