

Adaptogenic humic agent

Abstract

FIELD: pharmaceuticals.

SUBSTANCE: invention relates to the pharmaceutical industry, namely, to an agent exhibiting adaptogenic activity. Agent exhibiting adaptogenic activity, constituting a colloidal solution containing water, humic substances constituting humic and fulvic acids and salts thereof, hydroquinone and chrysin, wherein the size of colloidal particles is in the range from 30 nm to 10 mcm, the mass of humic substances is from 1 to 20 wt.%, hydroquinone is contained in an amount not exceeding 3 wt.% of the humic substances, and chrysin in an amount not exceeding 2% of the weight of humic substances.

EFFECT: above agent has a pronounced adaptogenic activity, contains a broad range of humic substances, and does not have any chemical impurities.

1 cl, 5 tbl, 3 ex

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Claims (1)

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translated from Russian

An agent with adaptogenic activity, which is a colloidal solution containing water, humic substances, which are humic and fulvic acids and their salts, hydroquinone and chrysin, and the size of colloidal particles is in the range from 30 nm to 10 µm, the mass of humic substances is from 1 up to 20 wt.%, hydroquinone is contained in an amount not exceeding 3 wt.% by weight of humic substances, and chrysin - in an amount not exceeding 2% by weight of humic substances.

Description

translated from Russian

The invention relates to the field of medicine and pharmaceuticals, namely to humic preparations, and can be used to increase physical activity, endurance, accelerate recovery after physical activity of athletes and the performance of people leading an active lifestyle, as well as in rehabilitation after illnesses and surgical interventions.

Adaptogens are drugs that increase the body's nonspecific resistance to adverse environmental influences. Adaptogens increase the nonspecific reactivity of the body, increase the activity of antioxidant defense mechanisms, stabilize biological membranes, protect them from disintegration during overloads, promote the processes of synthesis, metabolism, improve oxygen transport to the muscles, to the nervous system, increasing the formation of red blood cells and preventing the action of hypoxic stress. In the prior art, there are many drugs that have adaptogenic activity of various nature - both synthetic and natural (E.P. Studentsov et al. Adaptogens and related groups of drugs - 50 years of research. Reviews of clinical pharmacology and drug therapy, 2013, t 11, No. 4, pp. 3-43). However, synthetic drug compounds have a negative side effect and a narrowly targeted effect. Also known means containing natural products of plant origin.

In the prior art, various preparations based on natural raw materials with an adaptogenic effect are known. In particular, from the patent RU 2423888, 07/20/2011, a drink is known that has an adaptogenic effect, containing citric acid, carbonated or non-carbonated water, a flavoring additive, sodium benzoate and an adaptogenic agent consisting of a mixture of natural honey, water-soluble mummy extract and rosehip syrup. The disadvantage of this drink is that it cannot be used in people allergic to honey. In addition, said beverage includes chemicals such as sodium benzoate and flavoring.

From patent RU 2155059, 27.08.2000, an agent with adaptogenic activity is known, which contains oak acorns as a base, amaranth, viburnum, burdock, mistletoe and wild rose seeds as reinforcing agents, and bee honey as a corrective additive. The disadvantage of the known tool is that it is multicomponent, many of the components are difficult to access.

It is known that humic acids, fulvic acids have a powerful effect on any living organism due to their rich composition. They contain a complete set of amino acids, macro- and microelements, minerals, as well as polysaccharides of natural origin, vitamins, peptides, fatty acids, polyphenols, ketones, catechins, etc. There are more than 70 useful components in total. Such a rich composition explains the positive biological effects of humic acid (see <https://fb.ru/article/288472/guminovyye-kisloty-i-cto-etotakoe-i-kak-oni-vliyayut-na-organizm>).

Humic acids are able to stimulate some functions of human neutrophils. For preparations based on humic and humic-like substances, antiviral activity was detected, for example, for the herpes simplex virus - HSV. Humic compounds can be used as microbiocides, prophylactic agents against the spread of HIV/AIDS. The cytotoxic and antiviral properties of humic acids and fulvic acids isolated from coal and peat were studied. Studies have shown that all the studied compounds were of low toxicity and had a fairly high inhibitory effect on HIV infection (A.I. POPOV et al. Biological activity and biochemistry of humic substances. Part 2. Medico-biological aspect (literature review). Bulletin of the Russian Academy of Sciences, 2016/5, pp. 9-15). It has been shown that Oxyhumate increases the activity of Th-1 cells and reduces the production of cytokines by Th-2 cells [Mariette et al., 2002]. The observed stimulation of human lymphocyte proliferation has been associated with increased production of IL-2 and expression of IL-2 receptors, together with a decrease in the amount of IL-10 under the action of Oxyhumate [Joone et al., 2003]. It has been shown in vivo that oral administration of humic substances improves the parameters of innate immunity in experimental animals: there is an increase in the antibacterial activity of blood serum, phagocytic activity, lysozyme activity, and bacterial agglutination [Sanmiguel et al., 2016]. Research in the development of new biologically active compounds has shown that humic substances of various origins have immunomodulatory and anti-inflammatory effects, which allows them to be used for the prevention and treatment of chronic dermatosis, atopic dermatitis, allergic rhinitis and other diseases accompanied by inflammatory and allergic reactions. Promising is the use of humic substances as antifungal, antiviral agents. The anti-inflammatory activity of humic acids has been studied in models of acute and chronic inflammation. A possible

mechanism of anti-inflammatory action is explained by the ability of humic acids to reduce the generation of oxygen radicals and reduce oxygen consumption by activated phagocytes (I.A. SAVCHENKO et al. Biological activity of humic substances: prospects and problems of their use in medicine (review). Journal Medial, No. 1 (23) April, 2019, pp. 54-60, DOI: <http://dx.doi.org/10.21145/2225-0026-2019-1-54-60>).

The objective of the present invention is to obtain a humic agent containing a wide range of humic substances and having adaptogenic activity, not containing synthetic chemicals.

The technical result of the claimed invention is to obtain an adaptogenic humic agent containing a wide range of humic substances and not having chemical impurities, which can be used in the field of medicine and pharmaceuticals.

This technical result is achieved due to the fact that the claimed humic agent with adaptogenic activity is a colloidal solution containing water, humic substances, which are humic and fulvic acids and their salts, hydroquinone and chrysin, and the size of colloidal particles is in the range from 30 nm to 10 μ m, the mass of humic substances is from 1 to 20 wt.%, hydroquinone is contained in an amount not exceeding 3 wt.% by weight of humic substances, and chrysin - in an amount not exceeding 2% by weight of humic substances.

It is also proposed to use the resulting humic agent as an adaptogen.

Examples

Example 1. Obtaining the claimed adaptogenic agent

To obtain the claimed agent, pre-crushed humic-containing raw materials were used in a mixture with water, which was placed in an ultrasonic unit. The mixture of humic raw materials with water placed in the ultrasonic unit was heated to 30-80°C, and upon reaching the required temperature, sonication was performed at a pressure of 0.05-0.8 MPa. After sonication, the solution was cooled to room temperature and filtered to separate particles larger than 10 μ m. The resulting agent was diluted with water to the content of humic substances, which is from 1 to 20 wt.%, while the amount of hydroquinone in the composition of the agent does not exceed 3 wt.% of the mass of humic substances and chrysin does not exceed 2 wt.% of the mass of humic substances. The size of colloidal particles is in the range of 30 nm-10 μ m.

The study of the composition of the obtained agent was carried out by GC-MS on the analyzer "Khromatek", consisting of a gas chromatograph "Khromatek-Crystal 5000" and a liquid dispenser DAZH-2M. The derivatives were identified using the NIST17 MS Library automatic database for searching and identifying chromatography-mass spectrometry data.

Research conditions:

Капиллярная колонка	Phenomenex ZB-DRUG-1 30 м*0.25 мм*0.25 мкм, (или аналогичная);
Условия МС-детектора:	Деление потока 5,0. Температура источника ионов = 200 °С. Температура переходной линии = 290 °С. Диапазон сканирования = 50-550 а.е.м., длительность скана = 0.3.
Объем пробы	1 мкл;
Условия ПИД-детектора	Температура, 270 °С. Расход водорода, мл/мин 20,0. Расход воздуха, мл/мин 200,0. Температура инжектора, °С 280,0 Колонка Agilent 5ms 30м*0,25мм*0,25мкм
Детектор	МС или ПИД;

Капиллярная колонка	Phenomenex ZB-DRUG-1 30 м*0.25 мм*0.25 мкм, (или аналогичная);
Условия МС-детектора:	Деление потока 5,0. Температура источника ионов = 200 °С. Температура переходной линии = 290 °С. Диапазон сканирования = 50-550 а.е.м., длительность скана = 0.3.
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Условия ПИД-детектора	Температура, 270 °С. Расход водорода, мл/мин 20,0. Расход воздуха, мл/мин 200,0. Температура инжектора, °С 280,0 Колонка Agilent 5ms 30м*0,25мм*0,25мкм
Детектор	МС или ПИД;

The results of the study are given in table. one

Табл.1

**Перечень надёжно идентифицированных соединений в составе
препарата гуминового напитка методом ГХ-МС**

Название	Вре мя	Высота	Площадь	Площа дь, %	Вероятно сть	Matc h	R.Mat ch
Oxalic acid, 2TMS derivative	10.6 2	41756018 .01	75477275 .30	58.40	81.54	825	938
Propanedioic acid, 2TMS derivative	11.9 0	11728138 .47	21050841 .43	16.29	83.53	890	917
Octanoic acid, TMS derivative	12.8 2	229615.8 6	486664.9 8	0.38	72.55	672	786
Benzoic Acid, TMS derivative	13.4 3	608462.6 4	1014714. 07	0.79	82.5	832	854
Butanedioic acid, 2TMS derivative	14.1 2	3406595. 08	6833765. 55	5.29	69.77	851	880
2-Butenedioic acid, (E)-, 2TMS derivative	14.5 0	126856.2 9	129195.5 4	0.10	52.71	589	747
Nonanoic acid, TMS derivative	14.7 3	213604.3 1	280904.7 1	0.22	85.17	732	799

Табл.1

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Nonanoic acid, TMS derivative	14.7 3	213604.3 1	280904.7 1	0.22	85.17	732	799

Methylmaleic acid, 2TMS derivative	15.51	309845.22	715036.39	0.55	65.56	606	910
Pentanedioic acid, 2TMS derivative	15.87	447922.11	887009.07	0.69	81.75	730	807
Decanoic acid, TMS derivative	16.54	117241.98	169249.45	0.13	51.7	600	766
Hexanedioic acid, 2TMS derivative	17.77	150364.36	230696.13	0.18	78.78	665	768
Undecanoic acid, TMS derivative	18.26	37835.19	24699.79	0.02	17.02	492	618
Dodecanoic acid, 1-methylethyl ester	19.96	65527.21	132130.63	0.10	42.75	541	685
4-Hydroxybenzoic acid, 2TMS derivative	20.11	120423.53	216000.55	0.17	74.89	714	774
Suberic acid, 2TMS derivative	21.32	82365.63	206289.69	0.16	56.5	542	769
Phthalic acid, 2TMS derivative	22.06	669813.68	1639401.99	1.27	96.52	877	916
Isophthalic acid, 2TMS derivative	23.05	208118.73	508161.57	0.39	89.98	795	872
Phthalic acid, 2TMS derivative	23.47	226871.03	553823.23	0.43	61.17	642	808
Palmitic Acid, TMS derivative	28.50	458588.18	1253716.69	0.97	93.57	822	844
Stearic acid, TMS derivative	32.42	340967.87	837880.68	0.65	88.01	697	759
Nonadecanoic acid, TMS derivative	33.96	61947.42	105976.86	0.08	64.98	572	731
Arachidic acid, TMS derivative	35.37	155566.96	309909.97	0.24	34.83	478	600
Lignoceric acid, TMS derivative	40.06	75749.44	134757.72	0.10	23.12	480	695
3-Methylsalicylic acid, 2TMS derivative	19.49	205157.78	339556.30	0.26	14.58	557	659

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3-Methylsalicylic acid, 2TMS derivative	19.67	205018.47	545772.26	0.42	34.89	809	857
Aspirin, TMS derivative	15.43	156868.92	273560.52	0.21	65.54	662	722
Salicylic acid, 2TMS derivative	18.05	1479568.33	2487460.30	1.92	68.27	837	886
Chrysin, 2TMS derivative	27.78	898312.04	2813053.44	2.18	40.97	655	659
{Sulfanediylbis(4,6-dichlorobenzene-2,1-diyl)oxy}bis(trimethylsilane)	33.29	189131.42	417511.42	0.32	25.5	479	495
{Sulfanediylbis(4,6-dichlorobenzene-2,1-diyl)oxy}bis(trimethylsilane)	33.51	217405.45	546563.44	0.42	12.11	474	482
Hydroquinone, 2TMS derivative	11.72	894863.99	3817475.25	2.95	61.48	807	813
Benzaldehyde, 2,5-dimethyl-	14.43	113845.60	114932.74	0.09	41.7	712	833
2,6-Dihydroxyacetophenone, 2TMS derivative	19.40	54077.75	91889.63	0.07	10.64	444	584
2-Hydroxyphenethyl alcohol, 2TBDMS derivative	24.30	178719.73	364271.15	0.28	15.2	623	667
1-(2-Thienyl(2-((trimethylsilyl)oxy)-1-naphthyl)methyl)piperidine	25.99	70043.12	267004.05	0.21	11.72	525	576
1-Phenyl-1,2-ethanediol, 2TBDMS derivative	26.87	54016.05	139548.81	0.11	20.12	498	713
Trimethylsilyl O,O'-bis(trimethylsilyl)vanilpyruvate	31.31	1126005.84	2801566.68	2.17	33.03	554	724
4-Hydroxy-3-ethoxyphenylpyruvic	32.27	114537.34	361005.20	0.28	16.11	481	748

3-Methylsalicylic acid, 2TMS derivative	19.6 7	205018.4 7	545772.2 6	0.42	34.89	809	857
Aspirin, TMS derivative	15.4 3	156868.9 2	273560.5 2	0.21	65.54	662	722
Salicylic acid, 2TMS derivative	18.0 5	1479568. 33	2487460. 30	1.92	68.27	837	886
Chrysin, 2TMS derivative	27.7 8	898312.0 4	2813053. 44	2.18	40.97	655	659
{Sulfanediylbis(4,6-dichlorobenzene-2,1-diyl)oxy}bis(trimethylsilane)	33.2 9	189131.4 2	417511.4 2	0.32	25.5	479	495
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2-Hydroxyphenethyl alcohol, 2TBDMS derivative	24.3 0	178719.7 3	364271.1 5	0.28	15.2	623	667
1-(2-Thienyl(2-((trimethylsilyl)oxy)-1-naphthyl)methyl)piperidine	25.9 9	70043.12	267004.0 5	0.21	11.72	525	576
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4-Hydroxy-3-ethoxyphenylpyruvic	32.2 7	114537.3 4	361005.2 0	0.28	16.11	481	748

acid, tri-TMS							
9,10-Anthracenedione, 2-methyl-1,6-bis(trimethylsilyl)oxy-	27.1 0	203564.3 5	664701.5 4	0.51	24.61	669	884

acid, tri-TMS							
9,10-Anthracenedione, 2-methyl-1,6-bis(trimethylsilyl)oxy-	27.1 0	203564.3 5	664701.5 4	0.51	24.61	669	884

According to the given data, in addition to humic and fulvic acids, the composition of the claimed agent also includes phenolic derivatives, in particular hydroquinone, flavanoids (chrysin) and other active substances. Therefore, the claimed tool is characterized by a wide range of active substances.

Example 2 Toxicity Test

Determination of acute toxicity indicators included experiments on mice. Animals were distributed into groups randomly by randomization. The criteria for acceptability of randomization were the absence of external signs of diseases and the homogeneity of groups by body weight ($\pm 10\%$). The introduction of the drug was carried out intragastrically in increasing doses according to Litchfield-Wilcoxon. The highest dose was limited by the maximum possible volume of drug administration. For the study of each dose of the drug, groups of 10 animals of different sexes were used. The observation period was 14 days. With the introduction of the drug in doses of 4000-8000 mg / kg (for humic acid) in animals, a change in the reaction to picking up, a change in breathing, motor activity, and muscle tone was revealed, in some animals a change in the consistency of feces was observed. With the introduction of the drug at a dose of up to 4000 mg/kg (for humic acid), all animals survived, with the introduction of the drug at a concentration of 6000 mg/kg (for humic acid), 5 out of 10 animals died, and with the introduction of the drug at a dose of 8000 mg/kg (for humic acid) 8 out of 10 animals died. The surviving animals satisfactorily endured intoxication and after the end of the drug effect for 14 days of observation, no signs of a delayed effect were noted. There were no signs of prolonged clinical intoxication. The dynamics of the body weight of the experimental animals did not differ from the

control. At the end of the observation period - on day 14, the surviving animals were slaughtered in order to determine possible pathological changes after a single dose of the drug. Examination of the experimental and control groups showed that all animals in them were normally well-fed, had the correct physique, smooth and shiny hairline, shiny, normal-colored mucous membranes, clean and tidy natural openings. Macroscopic examination of the internal organs did not reveal any features. Analysis of the values of mass coefficients did not reveal any significant differences between groups of animals that received different doses of the drug. Thus, the obtained results suggest that the obtained drug can be attributed to class V, i.e. practically non-toxic drugs.

Example 3. Study of the adaptogenic activity of the claimed agent

The effect of an adaptogenic agent on the overall physical endurance of mice

The experiments were carried out on CBA mice of both sexes, weighing 18–20 g. Animals of the experimental group were intragastrically injected with the claimed adaptogenic agent once in a volume of 2.5, 5 and 10 ml/kg, 1 hour before testing (Table 2); and also repeatedly - in the same volume of an aqueous solution, within 7 days before testing (1 time per day 30 minutes before feeding) (Table 3). Animals in the control group received an equivolume of distilled water. Eleutherococcus extract was used as a reference drug in the form of an aqueous solution in a volume of 5 ml/kg. 1 hour after the administration of the test agent, the general physical endurance was determined by swimming the animals with a load of 5% of the body weight of the mouse until complete fatigue, the criterion of which was the 10-second immersion of the animal under water.

Statistical processing of the obtained data was carried out by the generally accepted method using the Wilcoxon-Mann-Whitney U-test (Sergienko, Bondareva, 2000). Differences were considered significant at a probability of 95% ($P < 0.05$). The data obtained are shown in tables 2-3.

Табл.2 Влияние лекарственного средства на общую физическую выносливость при однократном введении

№п/п	Группа животных	Объем средства, мл/кг	Количество животных	Продолжительность плавания, мин.
1	Контроль	.	10	4,5±0,32
2	Заявленное гуминовое адаптогенное средство	2,5	10	4,9±0,34
3	Заявленное гуминовое адаптогенное средство	5	10	6,3±0,41
4	Заявленное гуминовое адаптогенное средство	10	10	6,6±0,36
5	Экстракт элеутерококка	5	10	6,4±0,39

Табл.2 Влияние лекарственного средства на общую физическую выносливость при однократном введении

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1	Контроль	.	10	4,5±0,32
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3	Заявленное гуминовое адаптогенное средство	5	10	6,3±0,41
4	Заявленное гуминовое адаптогенное средство	10	10	6,6±0,36
5	Экстракт элеутерококка	5	10	6,4±0,39

Based on the data given in table. 2, it can be concluded that a single administration of the claimed adaptogenic agent in a volume of 2.5 ml/kg has an insignificant effect on the duration of swimming in mice, while its administration in a volume of 5.0 ml/kg was accompanied by an increase in the overall physical endurance of animals by an average of 40 % compared with the data of mice in the control group. An increase in the volume of the test agent to 10.0 ml/kg had a similar effect: the duration of swimming increased by 47% compared to the control. At the same time, the effectiveness of the claimed adaptogenic agent in volumes of 5.0 and 10.0 ml/kg was close to that of the Eleutherococcus extract.

Табл.3 Влияние лекарственного средства на общую физическую выносливость при многократном введении

№п/п	Группа животных	Объем средства, мл/кг	Количество животных	Продолжительность плавания, мин.
1	Контроль	5	10	5,1±0,36
2	Заявленное гуминовое адаптогенное средство	5	10	10,5±0,29
3	Экстракт элеутерококка	5	10	9,7±0,32

Табл.3 Влияние лекарственного средства на общую физическую выносливость при многократном введении

№п/п	Группа животных	Объем средства, мл/кг	Количество животных	Продолжительность плавания, мин.
1	Контроль	5	10	5,1±0,36
2	Заявленное гуминовое адаптогенное средство	5	10	10,5±0,29
3	Экстракт элеутерококка	5	10	9,7±0,32

Based on the data shown in table 3, the adaptogenic activity of the claimed agent increases with its repeated administration, as evidenced by an increase in the swimming duration of mice in the experimental group by 106% compared with the data of animals in the control group. At the same time, the effectiveness of the adaptogenic agent exceeded that of the Eleutherococcus extract.

Study of the antihypoxant activity of a humic agent.

The aim of the study was to study the antihypoxic properties of the claimed humic agent in conditions of oxygen deficiency in normobaric hypercapnic hypoxia.

The study was carried out on 120 male white outbred mice weighing 18.5±2.5 g; 6 experimental groups for three doses of humate in two series of experiments, differing in the scheme of administration, 2 control groups, 10 mice each. The animals of the experimental groups were injected with the claimed agent once intramuscularly in

doses of 1; 10 and 100 mg/kg. Control animals were injected with the appropriate volume of sterile 0.9% sodium chloride solution. Two series of experiments were carried out, differing in time from the moment of introduction of the humic agent to the functional load. In two series of experiments (the introduction of a humic agent 1 and 6 hours before the start of the experiment), the animals were subjected to exercise three times, repeated loads were performed 6 and 24 hours after the first. Each animal was placed separately in a glass container with a hermetically ground lid. Observations were carried out for 15 min, the endurance of animals to hypoxia was determined as the time elapsed from the beginning of the experiment until the development of the clinical picture of asphyxia (saccaded breathing or absence of respiratory movements, clonic convulsions, supine position). The criterion for evaluating the effectiveness was the duration of tolerance to hypoxia until the first signs of hypoxic coma (endurance to hypoxia) and the calculated values of the degree of change in endurance (SIV), the time was recorded using a stopwatch.

Scheme 1 - loading 1 hour after the introduction of the humic agent. It has been established that at the first load, the humic agent administered 1 hour before the extreme exposure in all doses does not have a significant effect on the development of endurance to hypoxia in the animals of the experimental groups in relation to the control. With repeated loading, the humic agent at doses of 1 and 10 mg/kg did not contribute to an increase in hypoxia tolerance. The humic agent at a dose of 100 mg/kg significantly ($P<0.001$) increased the endurance of animals both in relation to the control and in comparison with the initial endurance in this group. At the third load, the humic agent showed only a tendency to increase the tolerance of hypoxia (at doses of 1 and 10 mg/kg) when compared with the initial values.

Табл.4. Влияние гуминового средства на переносимость гипоксии
(нагрузка через 1 ч после введения)

Группа	Время переносимости гипоксии, сек.	СИБ, % к контролю	СИБ п/1 , % к исходному
Первая нагрузка – через 1 ч после введения гуминового средства (ГС)			
Контроль	714,5±18,7	100	100
ГС – 1 мг/кг	697,6±12,5	97,6	100
ГС - 10 мг/кг	698,1±25,0	97,7	100
ГС – 100 мг/кг	717,4±18,6	100,4	100
Вторая нагрузка – через 6 ч после первой			
Контроль	750,1±15,3	100	104,9
ГС – 1 мг/кг	743,2±22,4	99	106,5
ГС - 10 мг/кг	719,1±21,6	95,8	103
ГС – 100 мг/кг	883,7±22,2	117,8	123,1
Третья нагрузка – через 24 ч после первой			
Контроль	811,1±26,5	100	113,5
ГС – 1 мг/кг	801,7±22,0	98,8	114,9
ГС - 10 мг/кг	808,7±24,6	99,7	115,8
ГС – 100 мг/кг	771,1±22,0	95,1	107,4

Примечание: СИБ – степень изменения выносливости в опытной группе по отношению к контрольной; СИБп/1 – степень изменения выносливости при каждой последующей нагрузке по отношению к исходной первой нагрузке в опытных или контрольной группах.

Табл.4. Влияние гуминового средства на переносимость гипоксии
(нагрузка через 1 ч после введения)

Группа	Время переносимости гипоксии, сек.	СИБ, % к контролю	СИБ п/1 , % к исходному
Первая нагрузка – через 1 ч после введения гуминового средства (ГС)			
Контроль	714,5±18,7	100	100
ГС – 1 мг/кг	697,6±12,5	97,6	100
ГС - 10 мг/кг	698,1±25,0	97,7	100
ГС – 100 мг/кг	717,4±18,6	100,4	100
Вторая нагрузка – через 6 ч после первой			
Контроль	750,1±15,3	100	104,9
ГС – 1 мг/кг	743,2±22,4	99	106,5
ГС - 10 мг/кг	719,1±21,6	95,8	103
ГС – 100 мг/кг	883,7±22,2	117,8	123,1
Третья нагрузка – через 24 ч после первой			
Контроль	811,1±26,5	100	113,5
ГС – 1 мг/кг	801,7±22,0	98,8	114,9
ГС - 10 мг/кг	808,7±24,6	99,7	115,8
ГС – 100 мг/кг	771,1±22,0	95,1	107,4

Примечание: СИБ – степень изменения выносливости в опытной группе по отношению к контрольной; СИБп/1 – степень изменения выносливости при каждой последующей нагрузке по отношению к исходной первой нагрузке в опытных или контрольной группах.

Scheme 2 - loading 6 hours after the introduction of the humic agent.

At the first load, the humic agent at doses of 1 and 10 mg/kg does not have a positive effect on the endurance of mice to hypoxia. The humic agent at a dose of 100 mg/kg significantly ($P<0.001$) increases the time of tolerance to hypoxia (Table 5). With a repeated load, the humic agent at doses of 1 and 10 mg/kg does not significantly affect endurance, as compared with the control, when compared with the initial values. With the introduction of a humic agent at a dose of 100 mg/kg, a significant ($P<0.01$) increase in endurance was revealed compared to the control. At the third load, an increase in endurance was found with the use of a humic agent at doses of 1 and 10 mg/kg compared with the baseline. The humic agent at a dose of 100 mg/kg slightly increased the endurance of animals compared to the control.

Табл.5. Влияние гуминового средства на переносимость гипоксии
(нагрузка через 6 ч после введения)

Группа	Время переносимости гипоксии, сек.	СИБ, % к контролю	СИБ п/1 , % к исходному
Первая нагрузка – через 6 ч после введения гуминового средства (ГС)			
Контроль	690,0±21,4	100	100
ГС – 1 мг/кг	689,6±28,2	99,9	100
ГС - 10 мг/кг	649,6±24,0	94,1	100
ГС – 100 мг/кг	855,2±30,1	123,9	100
Вторая нагрузка – через 6 ч после первой			
Контроль	727,2±24,0	100	105,4
ГС – 1 мг/кг	751,4±25,5	103,3	108,9
ГС - 10 мг/кг	706,7±27,2	97,1	108,8
ГС – 100 мг/кг	840,7±25,7	115,6	98,3
Третья нагрузка – через 24 ч после первой			
Контроль	767,4±24,2	100	111,2
ГС – 1 мг/кг	794,2±29,2	103,4	115,2
ГС - 10 мг/кг	794,8±27,4	103,6	122,3
ГС – 100 мг/кг	789,1±21,3	102,8	92,2

Примечание: СИБ – степень изменения выносливости в опытной группе по отношению к контрольной; СИБп/1 – степень изменения выносливости при каждой последующей нагрузке по отношению к исходной первой нагрузке в опытных или контрольной группах.

Табл.5. Влияние гуминового средства на переносимость гипоксии
(нагрузка через 6 ч после введения)

Группа	Время переносимости гипоксии, сек.	СИБ, % к контролю	СИБ п/1 , % к исходному
Первая нагрузка – через 6 ч после введения гуминового средства (ГС)			
Контроль	690,0±21,4	100	100
ГС – 1 мг/кг	689,6±28,2	99,9	100
ГС - 10 мг/кг	649,6±24,0	94,1	100
ГС – 100 мг/кг	855,2±30,1	123,9	100
Вторая нагрузка – через 6 ч после первой			
Контроль	727,2±24,0	100	105,4
ГС – 1 мг/кг	751,4±25,5	103,3	108,9
ГС - 10 мг/кг	706,7±27,2	97,1	108,8
ГС – 100 мг/кг	840,7±25,7	115,6	98,3
Третья нагрузка – через 24 ч после первой			
Контроль	767,4±24,2	100	111,2
ГС – 1 мг/кг	794,2±29,2	103,4	115,2
ГС - 10 мг/кг	794,8±27,4	103,6	122,3
ГС – 100 мг/кг	789,1±21,3	102,8	92,2

Примечание: СИБ – степень изменения выносливости в опытной группе по отношению к контрольной; СИБп/1 – степень изменения выносливости при каждой последующей нагрузке по отношению к исходной первой нагрузке в опытных или контрольной группах.

Non-Patent Citations (1) increases the endurance of animals during hypercapnic hypoxia. The effectiveness of the humic agent begins to appear 6 hours after administration.

Title	Thus, the claimed humic agent has a high biological activity, which manifests itself in an increase in endurance. Therefore, the claimed agent can be used as an adaptogenic agent.
Publication number	OLGA KOSAKOWSKA et all. Chemical variability of common skullcap (Scutellaria galericulata L.) wild growing in the area of eastern Poland // Herba Pol 2016; 62(3): 7-19. *

* Cited by examiner, † Cited by third party

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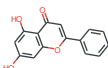
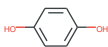

Publication	Publication Date	Title
US9238024B2	2016-01-19	Methods for improving health in canines
Dhanalakshmi et al.	2007	Protective effect of Triphala on cold stress-induced behavioral and biochemical abnormalities in rats
RU2775079C1	2022-06-28	Adaptogenic humic agent
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KR20180067685A	2018-06-20	Agents having anti-stress, anti-anxiety, and antidepressant activity and compositions based thereon
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RU2654713C1	2018-05-22	Pharmaceutical composition containing the combination of memantine and melatonin
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TWI745609B	2021-11-11	Composition for promoting antioxidative activity
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RU2559647C1	2015-08-10	Biologically active feed concentrate "azoflor"
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benzohydroquinone		claims,abstract,description	16	0.000
humic acid		claims,abstract,description	14	0.000
chrysin		claims,abstract,description	8	0.000
chrysin		claims,abstract,description	8	0.000
water		claims,abstract,description	8	0.000
fulvic acid		claims,abstract,description	6	0.000
particle		claims,abstract,description	5	0.000
sodium chloride		claims,abstract,description	4	0.000
salts		claims,abstract,description	3	0.000
drug		abstract,description	20	0.000
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