8. RU0002783772 - DRUG OF HUMIC NATURE, WHICH HAS AN IMMUNOMODULATORY EFFECT

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[RU]
Writing

[1] The invention relates to medicine, specifically to pharmacology, the results of which can be used to correct disorders in the immune system in pathological conditions associated with the deficiency of the Th2-dependent immune response in chronization of infections caused by extracellular bacteria and parasites.

[2] Humic substances are a group of natural biopolymers contained mainly in plant origin (caustobioliths)-peat, brown coal, bottom sediments (sapropels, peloids), consist of 80-90% of humic and fulvic acids.Humic acids (HA) of peat-high-molecular nitrogen-containing compounds of cyclic structure, which are a mixture of dark-colored organic, high-molecular, mainly aromatic, methoxy-containing, hydroxy-and oxocarboxylic acids, united by the general type of structure, but having some differences determined by their origin [1].

[3] Humic substances are long and widely used in many branches of human activity: in the industry for oil and gas production, for remediation of territories contaminated with production wastes, in agriculture as veterinary preparations [2] and components of organo-mineral fertilizers [3].

[4] **When studying the pharmacological properties of HA, weight results are obtained confirming both their anti-tumor, hepatoprotective, wound healing properties, and the intended mechanisms of action [4,5,6, 7].**

[5] Humic and fulvic acids are used to increase the resistance of the human body to various adverse factors, including as an auxiliary therapy in HIV-infected patients [8]. It has been shown that HA of various etiologies and different physicochemical characteristics have a wide range of pleiotropic immunological effects-have an influence on the polarization of immunocompetent cells on the classical or alternative pathway due to selectiveSecretion of pro-and anti-inflammatory cytokines (IL -1 beta, IL -2, IL -6, TNF-alpha and IFN-gamma) [9, 10] have antiviral activity against herpes viruses 1 and 2 (HSV1, HSV2), human respiratory and cytomegalovirus (HCMV, RSV) in vitro [11] and immunocorrecting properties against the background of antibacterial therapy with a number of antibiotics (ampicillin, amikacin, doxycycline, rifampicin, rifamycin)as well as contributes to significant localization of inflammation and increased vasoconstriction in xenotransplantation [12]. Humic substances suppress the delayed-type hypersensitivity reaction, graft-versus-host reaction, reduce contact hypersensitivity and paw edema in rats, level of C-reactive protein in patients suffering from osteoarthrosis, reduced fever, and also have cardioprotective and pro-angiogenic properties [13].In this case, HA does not show toxic effects in a wide range of doses in experimental animals in oral or skin administration, and potassium humate is safe for humans at a daily dose of up to 1 g/kg [13, 14].

[6] It is known that the effective immune response depends on the coordinated functioning of various innate and/or adaptive immunity cells in which T helper (CD4) is in particular location [15]. A representation of the existence of two CD4 + lymphocyte subclasses with recitproic functions and a different set of secreted type 1 cytokines-T-helper (Th1) and type 2 T-helpers (Th2) was formed in the middle of the 80-year of the past eyelid [16].T-helpers of the 1 st and 2 nd types differ in the spectrum of cytokines produced by them. Thus, Th1 produces interferon gamma (IFN-gamma), which is a marker of this subpopulation of T-helper cells, as well as interleukin 2 (IL -2), tumor necrosis factor alpha (TNF-alpha). In contrast, Th2 produces IL -4 (a Th2 subpopulation marker), IL -5, IL -10 and IL -13.Th1 cells play an important role in the development of cellular immunity reactions directed against viral and intracellular pathogens, and are also involved in delayed-type hypersensitivity reactions. Th2 cells provide for the reactions of humoral immunity, supporting proliferation and differentiation of IB lymphocytes, elimination of extracellular pathogens, participate in the development of immediate-type allergic reactions and protect the body from glidants [17].Excessive inflammatory reactions caused by T 1 activation can lead to uncontrolled tissue damage, and therefore a countermeasure mechanism is needed. Thus, substances capable of inhibiting excessive activation of the TA and adjusting the balance of the TA (IFN-gamma and IL -2) and Th2 (IL -4 and IL -10) of mediated cytokines are of significant interest as immunomodulatory agents for restoring the immune homeostasis of the body in various pathologiesassociated with the deficiency of the Th2-dependent immune response (chronic infectious diseases caused by extracellular bacteria and parasites).

[7] The object of the present invention is to expand the arsenal of immunomodulating agents of natural origin, having low toxicity and the ability to selectively stimulate the production of Th2-type cytokines-IL -4 and IL -10 and to suppress the production of Th1-type cytokines-IFN-gamma and IL -2.

[8] This problem is solved by the use of water-soluble humic acids separated by a solution of sodium pyrophosphate from high-moor sphagnum peat, taken from a depth of 20-70 cm from the seedbed-urine complex of the Goiter Bog Bog Mass of the Ygo-Eastern Marsh Bog Between the Caviar and Bactepa, with a number average molecular weight of 8916.6 Da, a weight average molecular weight of 32652.1 Da, a polydispersity of 5.7 and a median 16453.9 Da, as an agent having an immunomodulatory effect.

[9] The above-mentioned water-soluble humic acids have a high selective ability to stimulate IL -4, IL -10 secretion and suppress the production of IFN-gamma and IL -2, to correct disorders of the immunity system in pathological conditions requiring activation of the Th2-dependent type of immune response,

ie chronic infectious diseases caused by extracellular bacteria and parasites.

[10] Fundamentally, the invention is used for the effective immunomodulation of water-soluble humic acids isolated from high-moor sphagnum-moth peat taken from a depth of 20-70 cm from the Gashadin-moattic complex of the Goiter Bog Bog Mass of the South-Eastern Process of the Russian Swamp Between the Caviar and Bactepalt has been found by experimental studies and the skilled person clearly does not result from the prior art, and the description of this property is not found by the authors in patent and scientific medical literature. Thus, the proposed technical solution meets the criteria of the invention, namely, the novelty of the invention, the inventive level of age-related and industrial applicability.

[11] A representative average peat sample, maximally reflecting the heterogeneity of the chemical composition of the entire batch of the analyzed material, was taken by the TBG -1 drill in the genetic center of the ridge of the Gashadin-Mohort complex of the Gbactskoye Bog Mass of the South-Eastern Process of the Russian Marsh in the Interriver of the Caviar and Bactepa of the Bakcharsky District of the Tomsk Region, from the middle of the horizon-uniform horizon from the depth of 20-70 cmDuring summer period [June-August], according to GOST 17644-83, Peat. Reservoir Sampling and Treatment Methods for Laboratory Tests. In the well from the specified depth, each sample [weighing not less than 600 g, the number of wells—at least 50] was taken only once, the average mass of the peat sample was more than 30 kg [Table 1].

[12] The resulting peat sample was dried at room temperature in air in a well-ventilated room, periodically stirring, to an air-dry state [humidity of 15-20%], ground in a rotary knife mill and sieved through a sieve with a hole diameter of 1-3 mm, treated with 0.1 mol/l solution of sodium pyrophosphate [Na 4P 20 7;] in a weight ratio of 1: 100 for 8 hours with constant stirring in reactor P -100 at a temperature of 25-27° C, the liquid phase was separated

[13]

Таблица 1 - Общая характеристика исследуемого образца гуминовых кислот

Вид торфа, глубина отбора	Шифр	Место отбора проб торфа
Верховой сфагново-мочажинный, 20-70 см	ГК-1	Мочажина грядово-мочажинного комплекса олиготрофного болота Бакчарского болотного массива юго-восточных отрогов Васюганского болота в междуречье Икса и Бакчар

[14] [humic acid extract] from the residue [peat residue] by filtration using a vacuum filtration system [nutsch filter], then to precipitate humic acids from the extract, the liquid phase was treated with 10% hydrogen chloride solution to pH 1-2, the released humic acids [HA] were separated by centrifugation, washed with cold water purified on Buchner funnel to pH 7 and dried at room temperature. The HA content of the peat was determined gravimetrically [Table 2].

[15]

Таблица 2 - Характеристика гуминовых кислот торфа ГК-1

Содержание ГК на органическую массу при экстракции, %	Степень разложения, %	Зольность, %
3,1	5-10	2,8

[16] All samples were a dark brown fine powder soluble in an aqueous medium. The study of the physicochemical parameters of the HA structure was carried out by the methods: infrared [IR] and ultraviolet [UV] spectroscopy. Registration of IR spectra of HA was carried out on the IR Fourier spectrometer PSM 1201 [LLC of Infunpek, g Sankt Peterburgh] by the method of pressing with KBr at a ratio of 1: 100, respectively, in the range of frequency values from 500 to 4000 cm -1.The absorption of 0.001% aqueous solutions of HA aqueous solutions was recorded on a Unison 2800 UV spectrophotometer [USA production] in a wavelength range of 190-700 nm in a quartz cuvette with a thickness of 1 cm [Table 3].

[17]

Таблица 3 - Оптические свойства гуминовых кислот исследуемых торфов

Исследуемое вещество	$E^{0.001\%ГК}_{465nm,1cm}$	$E^{0.001\%ГК}_{650nm,1cm}$	$Q_{E_{465}/E_{650}}$
ГК-1	0,1158±0,0044	0,0406±0,0009	2,8496±0,0455

[18] IR spectral analysis indicates that HA -1 peat is characterized by a predominance of aromatic structures over the alkyl.

[19] Humic acids obtained by the above-described method have been characterized by physical and chemical parameters: elemental composition and molecular weight.

[20] 1. The elemental composition of HA was determined by burning on C, H, N-analyzer with Carlo Erba Strumentazione model 1106, the oxygen content was determined by the difference [Table 4].

[21]

Таблица 4 – Элементный состав гуминовых кислот

Шифр ГК	Масса атома, атомн. % на беззольную навеску				Атомные отношения		
	C	H	N	O	H/C	N/C	O/C
ГК-1	41,71±0,18	40,14±0,24	1,88 ±0,01	16,27±0,13	1,15	0,04	0,55

[22] 2. The molecular weight [Table 5] was determined by gel permeation chromatography on Ultramate 3000 [Thermo Scientific, USA] using UltraHydroGel 250, 300 × 7.8 mm, mobile phase 0.1 M NaNO 3, 0.01% NaN 3 in water, flow rate 1 ml/min Detection spectrophotometric at 200 nm wavelength.The molecular weight was calculated from the calibration graph log M w = f [t R] based on PSS standards [polystyrene sulphodate] 891-976 000 Da [Polymer Standards Service GmBH, Germany].

[23]

Таблица 5 – Молекулярная масса гуминовых кислот

Шифр ГК	Среднечисленная молекулярная масса, Да	Среднемассовая молекулярная масса, Да	Полидис-персность	Медиана, Да
ГК-1	8916,6	32652,1	5,7	16453,9

[24] The immunomodulating properties of humic acids were studied in C57BL/6 linear mice and CDI outbred mice, outbred SD rats [18] were used as a source of mast cells. Animals (male/female) at the age of 8-10 weeks were obtained from the part of the experimental biological models HIOPM thereof U

[25] Goldberg. All procedures (content, administration of test substances, killing) were performed in accordance with GOST 33215-2014 with the Rule of Premises Equipment and the organization of procedures when working with laboratory animals.

[26] Mononuclear (MH) was isolated from the peripheral blood of healthy donors by layering heparinized blood (10 U/ml) on Histopaque -1077 cell separation fluid (Sigma-Aldrich, USA) with a density of 1.077 mg/ml, centrifuging for 15 minutes at 400 g, collecting cells having formed a ring on the density gradient. Next, Mn was resuspended in a complete culture medium (PKC) consisting of RPMI -1640 (Sigma, USA), 10% FBS (US Pat. No.), 20 mM HEPES (Sigma, USA), 0.05 mM 2-mercaptoethanol (Sigma, USA), 50 μg/ml gentamicin (Sigma, USA), 2 mM L-glutamine (Sigma, USA), the viability in the test with 0.1% trypan blue (cell suspensions with a viability of at least 95%) was evaluated.Mononuclear cells (2.5-3.0 × 10 6 cells/ml) were incubated in 96-well plates at 37°C in an atmosphere of 5% CO 2 and absolute humidity in the presence of HA -1 (10 μg/ml); 4 μg/ml concanavalin A (KOH A, Sigma, USA), or 5 μg/ml pokeweed mitogen (ML, Sigma, USA).After 24 hours from the start of cultivation, the supernatant was collected from the wells of supernatant and the concentration of cytokines was measured in it by a solid-phase immunoenzymatic method on an automatic ChemWell ® Combo analyzer using test systems according to the attached protocols: human cytokines IL -4, IL -10, IL -2 and IFN-gamma (AO Vector-Best, Russia].

[27] Th1-and Th2-immune response values in mice were evaluated at the end of intraperitoneal injection of HA -1 for 10 days at a dose of 1 mg/kg/day, the comparison preparation used was Lycopene (Peptek, Russia)-2 mg/kg day in 0.1 ml of saline (FR), the animals of the control group received a similar volume of PD

[28] For the study of the Th1-dependent type of immune response, the following was used: determination of antibody-forming cells (SVs) in the spleen and titer of specific hemagglutinins in the blood serum, a study of delayed-type hypersensitivity (HRT) after immunization of mice with sheep erythrocytes.

[29] The determination of the AFC in the spleen was performed by the Epy method [19]. The test substances (HA -1 and licopid) were administered to mice for 5 days before immunization and 5 days after. Animals on the 5th day after immunization with sheep erythrocytes at a dose of 1 × 10 8 cells ("Computers", Russia) in a volume of 0.2 ml of PBS were sacrificed, the spleen was removed, ground in a glass homogenizer, the cell suspension was filtered through 4-layered capron, washed three times with cold FR, resuspended in 4 ml of medium 199 (Sigma, USA)the number of viable cells was counted. To test tubes heated to 50-53° C, 0.9 ml of culture medium (0.7% agar ("Difco", USA) was introduced in medium 199 (Sigma, USA), 0.2 ml of 20% sheep erythrocytes suspension, 0.2 ml splenocyte suspension and 0.1 ml complement (FLIPS-Microgen, Russia). The mixture was filled with Goryaev chamber and conditions of 100%) humidity and 37°C were incubated for 2 h, then hemolysis zones were counted using a light microscope.

[30] Blood serum antibody titer was determined by hemagglutination reaction (PHA) [20]. Blood serum hemagglutinins were determined by the ability of antibodies contained in the blood serum of immunized animals to agglutinate antigen-erythrocytes.To do this, blood serum of mice obtained on day 5 after immunization was inactivated for 30 min at 56° C, triturated in a 96-well round bottom plate of 0.025 ml with a pitch of 1: 2, 0.025 ml of 1% suspension of sheep erythrocytes was added, incubated at 37° for 2 hours and the reaction was evaluated. The last dilution of the serum under study was taken as a titer, in which an antigen agglutination is still observed. The titer was expressed as log 2T.

[31] When carrying out the HRT reaction after 5 days from the beginning of GK -1 administration, animals were immunized with intraperitoneal injection of sheep erythrocytes (5 × 10 7) in 0.1 ml of FR On the 5th day after immunization with mice, a second (permitting) injection of sheep erythrocytes into the pad of the posterior paw is performed—a test paw (10 ... 8 sheep erythrocytes in 0.05 ml isotonic sodium chloride solution). 0.05 ml of FR (Control Lag) was introduced into the counter-lateral leg.After 24 hours, animals were slaughtered, both legs were cut along the bone lobe below the joint of the small and tibia and above the calcaneal joint, the local inflammatory reaction was evaluated by the difference in mass of the test and control paw.

[32] The development of the Th2-dependent immune response was simulated in outbred CDI mice by triple administration of 100 μg of ovalbumin (OVA) and 5 mg of aluminum hydroxide (both Sigma, USA) as an adjuvant in 0.1 ml of PBS every 3 weeks [21]. Administration of HA -1 in a volume of 0.1 ml against OVA immunization started 5 days prior to each OVA administration and for 5 days after the second immunization, a total of 15 injections. Mice of the control group were administered with 0.1 ml of FR

[33] The effect of course administration of HA -1 on antigen-dependent indirect degranulation of intact mast cells (CDTC) was examined by isolating mast cells from the abdominal cavity of outbred male rats SD [22]. To obtain mast cells, animal rats were euthanized by bleeding following CO 2-chamber, injected intraperitoneally with 5-8 ml of heated to 37°C solution of Tyrode without glucose, after easy massage of the abdominal wall for 1-1, 5 minutes were made with scissors cut along the midline and the exudate was collected into the siliconized tube. Preparations were prepared on degreased sample glasses stained with 0.3% alcoholic solution of neutral red and dried at room temperature. 0.03 ml of mast cell suspension, 0.03 ml of serum outbred CDI mice immunized with Ovalbumin (OVA) and treated with GK -1 course, and 0.03 ml of OVA solution (the dose of the drug were pre-selectedsuch that the rate of degranulation of mast cells when incubated with the test substance does not exceed 5%). The preparations were then covered with cover glasses, then incubated for 15 min in a thermostat at 37° c. the preparations were microscoped under magnification x 20.

[34] The evaluation of the results was carried out using a differential method of accounting, counted the index of degranulation of mast cells (UDTC) according to the formula:

[35]

$$\text{ПДТК} = \frac{1a + 2b + 3c + 3d}{100},$$

[36] where a, b, c, d are the number of degranulated cells, respectively, of the degree of degranulation (weakly expressed, moderate, sharp, and degree of completely degranulated cells].

[37] The experimental data was processed with the statistical program statistics of Statistics 8.0, verifying the normality of the distribution with the Shu-Wilk criterion, calculating for each sample the arithmetic mean [X], the arithmetic mean error [m], the arithmetic mean deviation [sigma]. Comparison of Sample Averages was performed by Dannet criterion to compare multiple experimental samples with one control.

[38] Example 1

[39] Course administration of HA -1 isolated from the upper sphagnum-moth peat taken from the depth of 20-70 cm of the Gashadin-Mohr peat complex of the Eggcharsky Bog's Bog Mass of the South-Eastern Process of the Russian Marsh in Between the Caviar and Bacila of the Bakcharsky District of the Tomsk Region, mice of the C57/BL6 line against the background of the development of the Th1-dependent immune response induced by the introduction of sheep erythrocytesresulted in the suppression of the marker reaction of the cellular TH1 immune response-HRT response (Table 6). The amount of edema in HA -1 was significantly reduced relative to the control and group of mice using licopid (2 and 1.8 times, respectively].

[40] The effect of humic acids on the humoral link of the Th1-dependent immune response was assessed by the number of SVs and PHA. It was found that the course administration of HA -1, isolated from the upper sphagnum-moth peat, taken from the depth of 20-70 cm of the Gashadin-Mohorin complex of peat of the Eggcharsky Bog Bog Mass of the South-Eastern Process of the Russian Marsh in Between the Caviar and Bacila of the Bakcharsky District of the Tomsk Regionresulted in a statistically significant decrease in the number of SVs as compared to the indicator in the control group of mice [3.7 times]

[41]

Таблица 6 – Влияние курсового введения гуминовых кислот (ГК-1) на реакции Th1 иммунного ответа – гиперчувствительность замедленного типа (ГЗТ), количество антителообразующих клеток (АОК) и титр синтезируемых ими гемагглютининов у мышей линии C57BL/6, иммунизированных эритроцитами барана, (X±m)

Исследуемое вещество	Концентрация, мкг/мл	ГЗТ, величина реакции, мг	Количество АОК, тыс./селезёнка	Титр гемаагглюти-нинов, log_2T
Контроль (физ. раствор)	-	23,60±1,74	13,59±1,44	21,13±1,67
Ликопид	2	20,90±2,37	29,62±2,15*	18,61±2,31
ГК-1	10	11,82±1,27*•	3,72±0,46*•	10,78±1,15*•

Примечание: *– различия показателя с контролем достоверны, p<0,05; • – различия показателя со ликопидом достоверны, n (количество животных) =10 (ГЗТ), n=7 (АОК и РГА).

[42] and with the value in the group of animals receiving licopid [8 times]. At the same time, the hemagglutinins titer was significantly reduced in mice treated with humic acids relative to the control parameters and the group of the comparison drug (Table 6].

[43] Example 2

[44] The effect of HA -1 isolated from the upper sphagnum-mohort peat taken from the depth of 20-70 cm of the Gashadin-moattic complex of the Gbactskoye Bog Bog Mass of the Ygo-Eastern Marsh Bog in Between the Caviar and Bactepa of the Bakcharsky District of the Tomsk Region, on the indicators of Th2-type of immune response during anaphylactic shock and indirect degranulation of mast cells of CDI mice immunized with Ovalbumin.Course administration of humic acids [HA -1] has been shown to reduce the manifestations of anaphylactic shock in mice, but only by 10%, as well as a licopid comparison drug [Table 7].

[45]

Таблица 7 – Влияние курсового введения гуминовых кислот (ГК-1) на летальность иммунизированных овальбумином мышей стока CDI в результате анафилактического шока, (X±m)

Исследуемое вещество и его концентрация,	Летальность, %

[46]

мг/кг		
Контроль (ФР)	–	100
Ликопид	2	90
ГК-1	1	90

[47] When studying the effect of the course administration of humic acids [HA -1] on indirect degranulation of mast cells of outbred SD rats by adding to them serum of CDI mice immunized with ovalbumin, it has been shown that the use of GC -1 tested significantly reduced degranulation compared to the control and comparison groups using licopid [Table 8].

[48]

Таблица 8 – Влияние курсового введения гуминовых кислот (ГК-1) на непрямую дегрануляцию тучных клеток (НДТК) аутбредных крыс SD (X±m)

Исследуемое вещество (сыворотка крови мышей)	НДТК в присутствии сыворотки крови + овальбумин
ФР	0,094± 0,009
Ликопид (2 мг/кг)	0,120± 0,021
ГК-1 (1 мг/кг)	0,038±0,012*•

Примечание: *– различия показателя с контролем достоверны, p<0,05; • – различия показателя по сравнению с ликопидом достоверны p<0,05, n=5.

[49] This indicates that the humic acids tested have membrane-stabilizing effects on mast cells, thereby reducing manifestations of allergic reactions.

[50] Example 3

[51] Incubation of peripheral blood mononuclear cells from healthy donors with humic acids (GC -1) reduced concanavalin A-stimulated production of main for polarization of Th1-type of immune response of cytokines-IL -2 (1.2 times) and IFN-gamma (1.4 times) relative to control values, and in case of IFN-gamma this decrease was statistically significant (Table 9).

[52]

Таблица 9 – Влияние гуминовых кислот (ГК-1) на продукцию ИЛ-2 и ИФН-γ мононуклеарами периферической крови здоровых доноров, стимулированных конканавалином А (X±m)

Исследуемое вещество	Концентрация, мкг/мл	ИЛ-2, пг/мл	ИФН-γ, пг/мл
Контроль (Кон А)	2	56,956± 3,274	1169,30±4,04
ГК-1	10	45,648 ± 2,514	864,75±86,92*

Примечание: *– различия показателя с контролем достоверны, p<0,05.

[53] Addition of humic acids to mitogen-activated mononuclear cells (in vitro inflammation model) revealed a significant increase in Th2-cytokine-IL -4 production (2 times) and IL -10 (1.5 times) relative to the corresponding values of the stimulated control group (Table 10).

[54]

Таблица 10 – Влияние гуминовых кислот (ГК-1) на продукцию ИЛ-4 и ИЛ-10 мононуклеарами периферической крови здоровых доноров, стимулированных митогеном лаконоса, (X±m)

Исследуемое вещество	Концентрация, мкг/мл	ИЛ-4, пг/мл	ИЛ-10, пг/мл
Контроль (митоген лаконоса)	2	9,56±1,43	5,67±0,45
ГК-1	10	19,21±0,28*	8,32±0,36*

Примечание: *– различия показателя с контролем достоверны, p<0,05.

[55] Thus, it has been experimentally established that humic acids isolated from the upper sphagnum-moth peat taken from the depth of 20-70 cm of the Gashadin-moattic complex of the Gbactskoye Bog Mass of the Ygo-Eastern Marsh Bog in Between the Caviar and Bactepa of the Bakcharsky District of the Tomsk Region, with a number average molecular weight of 8916.6 Da, a weight average molecular weight of 32652.1 Da, a polydispersity of 5.7 and a median 16453.9 Daln direct impact, the production of the main cytokines of the Th1 immune response type-IL -2 and IFN-gamma is reduced and the production of Th2-type cytokines-IL -4 and IL -10 by peripheral blood mononuclear cells of healthy donors is increased. Course Administration of Humic Acid Mice Isolated from High Sphagnum-Moth Peatfrom the depth of 20-70 cm of the Gashadin-Mohr complex of the Gbactskoye Bog Mass of the South-Eastern process of the Russian Marsh in the Interriver of the Bacila District of the Tomsk Region, reduces the indicators of Th1-type of immune response: a decrease in the number of antibody-forming cells in the spleen and the titer of antibodies in the blood serum in the hemagglutination reaction, as well as a reduction in the response of the hypersensitivity of the delayed type characterizing the cellular type of immune response.In this case, the course of humic acids (HA -1) in animals leads to reduction of anaphylactic shock and reduction of mast cell degranulation after immunization of mice with ovalbumin. This indicates that humic acids (HA -1) although stimulation of the production of Th2-type cytokines, but do not lead to an increase in allergic reactions.The data obtained indicate that humic acids extracted from high-moor sphagnum-moth peat taken from the depth of 20-70 cm of the Gashadin-Mohorin complex of the Goiter Bog Bog Mass of the South-Eastern Process of the Russian Marsh in Between the Caviar and Bacila of the Bakcharsky District of the Tomsk Region, have the ability to regulate the balance of pro-inflammatory (IL -2 and IFN-gamma) and anti-inflammatory (IL -4 and IL -10) cytokines and are of considerable interest as a basis for creating pharmacological regulators for restoring the immune homeostasis of the body in various pathologies associated with the deficiency of the Th2-dependent immune response (chronic infectious diseases caused by extracellular bacteria and parasites).

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