High-molecular compounds of humic nature - promising biologically active compounds

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High-molecular-weight compounds of humic nature - promising bioactive compounds

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SUMMARY

Natural biominerals and geopolymers, such as natural products of humification (peat, sapropel, mummy, leonardite), have recently become attractive as food additives and starting materials for the development of medicines based on them. High-molecular compounds of a humic nature are generally understood to mean humic substances of various caustobiolites. The polyfunctionality and zwitterionic character are unique properties of humic substances, since they characterize them as the most active chelating agents among natural organic substances. The unique chemical properties of humic substances make it possible to use them in various sectors of the national economy, including medicine. In nature, there are no compounds with an identical set of the same important chemical and biological properties and biospheric functions, therefore, humic substances are promising biologically active substances for the search and development of new generation drugs. Due to the planetary distribution and constant replenishment of raw materials of humic substances, as well as a wide range of their pharmacological effects, today there are great opportunities for the practical use of humic substances in medicine.

Keywords:humic substances, biological activity, pharmacological properties.

RESUME

Natural biominerals and geopolymers, such as natural humification materials (peat, sapropel, mummy, leonardite), have recently become attractive as health supplement and primary materials for the development of medicines based on them. By highmolecular compounds of humic nature in general terms humic substances of various combustible minerals are understood. Multifunctionality and zwitterionic character are a unique property of humic substances, since they are described as the most active chelating agents among natural organic substances. The unique chemical properties of humic substances make it possible to apply them in various branches of the national economy, including medicine. In nature, there are no compounds with an identical set of the similar important chemical and biological properties and biospheric functions, therefore, humic substances are promising biologically active substances for the search and development of next generation drugs. Thanks to planetary distribution and constant replenishment of primary

resourses of humic substances, as well as a wide range of their pharmacological effects, today there are great opportunities for the practical use of humic substances in medicine.

Keywords: humic substances, biological activity, pharmacological properties.

High-molecular compounds of a humic nature - humic substances. Humic substances (HS) are dark-colored organiccompounds, polyfunctional polyampholytes, formed in the process of oxidative destruction of plant residues under the action of microbiota and / or air oxygen [1]. Humic substances are a necessary component of all metabolic processes in nature and the most thermodynamically stable form of conservation of organic substances in the biosphere [1]. Biosynthesis of HS is a unique continuous biospheric dynamic process, which involves from 0.6 to 2.5 × 10^9 tons of carbon per year [2]. At the same time, this process involves the entire vegetation cover from uninhabited arctic deserts and arid steppes to the fauna of the deepest oceanic trenches and small artificial reservoirs [1, 2]. This process is called humification. Its result is the formation of a unique class of organic substances - HS, which ensure the existence of modern life forms and coding in their composition the conditions of the period of their formation. Humification regulates the balance between mineralization and conservation of organic residues.

Humic substances are cosmopolitan, they are part of various caustobioliths (peat, marine and lacustrine sediments, coal, shale, soil, etc.) and are their basic components. In terms of the structure and content of elements, HS are stochastic and do not have a specific chemical structure, while they represent a unique stabilized form of organic matter, uncontrollable by the conditions of the biological code and consistent only with the laws of thermodynamics [1]. Humic substances can be considered as biopolymer macromolecules, or as colloidal micelles, supramolecules, consisting of relatively small molecules. This ambiguity in the structure of HS is due to their different chemical behavior depending on the environmental conditions. In this case, the GWs themselves have emergent properties. Humic substances are characterized by the presence of a large number of different functional groups and stable radicals in their molecules, which ensures their ability to form a variety of intra and intermolecular bonds that determine their redox properties, chelating and protolytic properties, participation in ligand exchange and heterogeneous processes. All these properties are the main ones in the manifestation of biological activity and determine the unique chemical and pharmacological properties of HS.

BIOLOGICAL ACTIVITY OF HUMIC SUBSTANCESThe highest content of HS was noted for such natural formations as peat, sapropel and mummy, which have been used for more than 3000 years in folk medicine and veterinary medicine [3, 4] as biogenic stimulants, adaptogens and stress protectors, anti-inflammatory and antitumor agents,

antioxidants and antihypoxants, hepatoprotectors, immunomodulators and cardioprotectors, enterosorbents and detoxicants, antimicrobial, antiviral, wound healing agents. There is a lot of information in the literature on the high and multidisciplinary pharmacological activity of HS, but, based on the specificity of their action, all the biological effects of HS can be combined into several broad groups.

Antioxidant (AO) action

Antioxidant activity (AOA) of HS is an important biological property that determines such pharmacological effects as hepatoprotective, cytoprotective, cardioprotective, neuroprotective, antitumor, etc. Humic substances can act as proton donors [5] due to the presence of phenolic hydroxyls and quinoid fragments in their structure, free radical traps [5] due to high paramagnetism.

Thus, experiments on rats with DOUMG intoxication showed [6] the protective effect of HS (Gumival) on the body with an excess of reactive oxygen species (ROS), judging by the state of the POLAOS system in acute aseptic inflammation. Tolpa Peat Preparation (TPP), a Polish preparation based on HS peat, suppresses lipid peroxidation (LPO) in mitochondria from the human placenta [7]: reduces the severity of lipid peroxidation and lowers the level of malondialdehyde (MDA), not inferior in efficiency to vitamin E. Confirmation of the AO mechanism The action of HS in suppressing the growth of malignant tumors is described in [8], where in 80–90% of cases, complete cure of the thyroid tumor was noted (within 2 years). It is also noted in [8] that

Hepatoprotective action

The hepatoprotective effect of HS, which has been repeatedly proven in various pathological models, is also due to their AO and antitoxic properties and characterizes them as inducers of microsomal enzymes capable of affecting the metabolism and biosynthesis of polyamines and participating in the formation of the ribosome structure and protein biosynthesis in hepatocytes [3]. Models of intoxication with barbiturates revealed the ability of HS to reduce the duration of medinal and hexenal narcotic sleep, which characterizes them as inducers of enzymes of the microsomal monooxygenase system of hepatocytes of the cytochrome P family.450 subfamily CYPIIA, which metabolize barbiturates [9]. On the toxic CCl model40 hepatitis found [10] that under the action of HS, the activity of hepatic transaminases decreases while maintaining the activity of ceruloplasmin and preventing hypoproteinemia. When administered intragastrically, HSs prevent the damaging effect of CCl_4 on functional, metabolic and morphological parameters of rat liver,

reducing the intensity of lipid peroxidation and destruction of hepatocyte membranes, the severity of the cytolytic syndrome, improving the excretory function of the liver and preventing the development of fibrotic changes in the liver of rats [11]. In experiments to study the effect of long-term use of TPP on liver regeneration in rats (at a daily dose of 20 mg / kg), 2/3 of the liver was resected [12]. An increase in the mass of the regenerating liver was observed as a result of an increase in the activity of ornithine decarboxylase, the level of spermidine, RNA and DNA in hepatocytes [12]. According to the results of histological studies in the study of the protective effect of HS on the liver on the model of intoxication with polychlorinated biphenyls, it was found that they have the ability to restore the body's oxidation-reduction status to the physiological norm due to their high AOA [13].

The neuroprotective effect of HS is also associated with their AO properties [15], which has been proven in a model of focal cerebral ischemia of the rat brain after intraperitoneal injection. The authors of [15] believe that HS can be used as a prophylactic agent in patients with a high risk of ischemic brain damage.

In the case of damage to renal reperfusion in rats, the therapeutic effects of HS are also associated with the prevention of oxidative stress [16]. In [17], with iron-induced hepatotoxicity and cardiotoxicity, high AO and antiradical effects were also noted, which are associated with the hemato and cardioprotective effects of HS. High AOA GW was noted with respect to their influence on superoxide anion radical ($O_2^{-}\bullet$) and hydroxyl radical ($HO\bullet$) [18]. In this case, the reactivity of HS with respect to ROS is explained by the presence of phenolic and quinoid fragments in their structure [5]. Humic substances have a protective effect during ischemia and reperfusion of the myocardium [19] and block the formation of oxygen radicals during tissue damage due to their AOA [19]. In [20], with subcutaneous administration of TPP as an inducer of TNFα on the model of ischemic and spontaneous angiogenesis in experimental rat myocardial infarction, proangiogenic and cardioprotective action of HS was established, preventing the development of ischemic cardiomyopathy. This drug is also used as an angio and cardioprotector in geriatric patients and patients with coronary artery disease (IHD) [21], TTP increases the viability of human mononuclear leukocytes and induces neovascularization during transplantation in patients with coronary artery disease. The effect of HS on angiogenesis plays a key role in other physiological processes, including embryogenesis, reproductive function, and wound healing [22].

In some studies [19, 23], an improvement in hematological parameters with the use of HS is noted. With prolonged use, they are able to enhance the accumulation of iron in endothelial cells and induce an increase in intracellular chelated iron, preventing the generation of ROS and LPO [19].

Humic substances reduce the prothrombin time of human plasma, the mechanism of anticoagulant action is associated with inhibition of the prothrombinase complex (active factors II, X, and VII) [24]. Humic substances inhibit proteolytic enzymes, normalize blood counts (lower glucose levels, increase the level of immunoglobulins, erythrocytes, hemoglobin and hematocrit, lower total cholesterol and lipids, increase HDL levels) [23], stimulate some functions of human neutrophils [25]. Humic substances are able to block the processes of uncoupling of oxidative phosphorylation in the mitochondria of the liver and brain of rats (in experimentsin vitro) [26], to normalize the activity of succinate and NAD-dependent energy production processes. On the models of normobaric hypercapnic hypoxia and histotoxic (sodium nitroprusside) hypoxia, a pronounced antihypoxic effect of HA was proved [27]. The mechanisms of the hypoglycemic and antidiabetic activity of HS were established [28] on the models of glucose tolerance test, alloxan and streptozocin diabetes mellitus. The authors of [28] suggest that the mechanism for the implementation of the antidiabetic effect in alloxan diabetes is a high AOA of HS, and in streptozocin diabetes - the ability of HS to regulate the processes of oxidative phosphorylation associated with the effect of NAD-dependent processes on the activity of NAD. The true mechanism of antidiabetic action of HBs is their agonism in relation to PPARγ receptors [28];

Immunotropic action

Humic substances affect cellular and humoral immunity [14, 29–33], increase the phagocytic activity of leukocytes and serum lysozyme [6, 10, 34], can inhibit the growth of breast cancer cells (in the presence of glucan) [31], inhibit metastatic growth of Lewis lung cancer cells (without the presence of glucan) [14] are able to positively influence the compliment system [35]. Humic substances stimulate the secretion of IL2 of splenocytes in mice (in vitro) and the production of ovalbumin-specificantibodies, reduce apoptosis of spleen cells at early stages [14], increase the number and functionality of macrophages, neutrophils, and Tkiller cells [25, 29–31].

Thus, the TPP preparation based on HS has an interferonogenic effect and is an inducer of tumor necrosis factor: it stimulates the production of α and γ interferons, TNF α by human peripheral blood leukocytes [36], enhances the production of β interferon and TNF α by peritoneal macrophages of mice, which is also used in sports medicine as oral immunomodulator [36]. Similar cytokine-stimulating effects of HS were also noted by other authors [37]: in the presence of exogenous LPS, HS stimulate the release of TNF α, which indicates that HS are not capable of causing inflammation under normal conditions. Intravenous administration (5 mg / kg) of TPP to rabbits increases the percentage of phagocytosing

cells and enhances the phagocytic activity of neutrophils, while against the background of LPS-induced fever, there is complete inhibition (50 mg / kg) of endotoxic shock [38]. The same drug TPP [22] is used as an immunomodulator to restore the immune system after antibacterial (ampicillin, amikacin, doxycycline, rifampicin) therapy. TPP is able to restore abnormally high angiogenic activity of human leukocytes and spontaneous production of IL1 monocytes in patients with rheumatoid arthritis [20, 21]. This drug also accelerates the healing of gastric ulcers induced in rats [39].

Humic substances are capable of inhibiting phagocyte degranulation, activating cytokines and SOD, their migration and adhesion to sites of allergic reactions and damaged tissues [33]. Humic substances have the ability to inhibit the expression of one (CR1) and three (CR3) complement receptors in LPS [40], suppress LPS-induced expression on the surface of adhesion cells of proteins, induce human umbilical vein endothelial cells (HUVECs) by inhibiting the activation of the nuclear factor NFkB [41] ... As surface active compounds, HS play an important role in the process of inflammation due to cell adhesion to the walls of blood vessels in the immediate vicinity of inflammatory reactions, for example, in autoimmune diseases [35]. The mechanism of action of HS can be mediated by both the classical and alternative methods of complement activation, as well as degranulation of phagocytes and the production of inflammatory cytokines (IL1, IL6, IL10, and TNF α) [33, 35, 37]. Oral administration of HS (60 mg / kg) in rats showed the ability to inhibit delayed-type hypersensitivity reactions immunized with sheep erythrocytes, carrageenan-induced edema and graft rejection reactions [42], contact hypersensitivity reactions in rats sensitized with dinitrofluorobenzene [43] (in comparison with indometha and prednisolone for inflammatory edema of the auricle of rats).

Anti-inflammatory and pro-inflammatory properties of HS have been shown in the work. [37] in a rat paw edema model. The anti-inflammatory mechanism is associated with the inhibitory effect of 5-lipoxygenase, the pro-inflammatory - with the release of neutrophilic granulocytes. The bimodal effect of HS at low concentrations (10–80 μg / ml) is characterized as the release of TNF-α from differentiated LPS-stimulated U 937 cells [37]. Oral administration of HS in patients with allergic rhinitis showed a decrease in edema and cone reaction [44], and in patients with osteoarthritis of the knee [45], the physical condition of patients improved, the level of C reactive protein (CRP) in the blood decreased.

The anti-inflammatory effect of HS from silt sulphide mud was shown in [46] on a model of experimental adjuvant polyarthritis. There was a decrease in the activity of autoimmune reactions (a decrease in ESR, leukocytosis, myeloperoxidase, fibronectin, IL1β, TNF α), normalization of the properties of the monocytic macrophage system, leveling of the imbalance of immunoregulatory subpopulations of T lymphocytes.

In various models of pain and inflammation, analgesic and

the anti-inflammatory activity of HS (Lignohumate) [47], comparable to diclofenac sodium, as a result of inhibition of the enzyme 5-lipoxygenase, a decrease in the release of pro-inflammatory cytokines, and a decrease in the permeability of the endothelium of histohematogenous barriers due to their manifestation of macrocolloid properties. At the same time, HS are less toxic (2.8 times) and do not exhibit ulcerogenic effects; therefore, they are recommended for symptomatic therapy of post-traumatic pain syndromes accompanied by inflammation and edema.

In experiments on the use of the HS preparation (Ligfol) [48] to reduce the toxicity of the anthelmintic agent, a prolonged action of HS after intramuscular administration was noted, which ensures the long-term presence of their molecules in muscle tissue and their gradual entry into the bloodstream. As a result, HS relieve toxicosis resulting from metabolic disorders (in terms of gradual normalization of the leukocyte index of intoxication due to a decrease in neutrophils, basophils and eosinophils and an increase in the percentage of lymphocytes and monocytes in the leukoformula, as well as a low level of free histamine, leading to a decrease in the level of eosinophils), the level of immunoglobulins G, A and M likewise increases [32].

The literature [14] describes the pleiotropic effects of HS associated with their ability to influence the secretion of IL2 and antibodies, wound healing (in the model in vitro using cells HaCaT), lung cancer growth (in a Lewis carcinoma model) and protection from LPS-induced hepatotoxicity, depending on their chemical structure. At the same time, the authors of [14] argue that the role of the carbohydrate component of the HS macromolecule plays a key role in their manifestation of immunotropic activity, similar to the effect of glucan.

Detoxifying action

Due to the complexing properties, HS are able to form chelates, which is why their significant antitoxic effects are manifested in relation to many unwanted metal toxicants and xenobiotics. Humic substances are capable of inactivating heavy metals, salts and complex compounds of lead, cadmium, copper, zinc, aluminum, manganese, iron, etc. [4, 49-51], bacteria and viruses [25, 52], invasions [48], aflatoxins (B1) [53], mutagens [4, 54], pesticides and ammonia [4], mono and polyaromatic compounds [4, 53, 54], radiation exposure [55].

It was found [49] that the simultaneous use of HS and lead acetate reduces the intake of Pb in the liver in chickens by an average of 30%, kidneys - by 44%, muscles - by 58%, and bone tissue - by 51% (in comparison with the group of untreated animals). A single injection of HS for 5–10 minutes. after irradiation with a dose of 193.5 mCi / kg leads to the survival of animals after 60 days in 43.3% of cases, and after irradiation with a dose of 232.2 mCi / kg, a tendency to an increase in the life span of irradiated rats was observed [55]. Humic substances reduce toxic effects in the liver and kidneys of brown trout caused by cadmium poisoning in contaminated

waters [50], as well as manganese (^{54}Mn (II)) [51]. The ability of HS to form chelate complexes with cadmium is also described in [4], where the authors recommend using them to remove heavy metals from living organisms.

In addition to chelating properties in the manifestation of the detoxification effect of HS, mechanisms are realized with the formation of ionic bonds, Vander Waals interactions, ligand exchange, hydrophilic hydrophobic interactions, and redox processes [3]. It is believed [3] that when administered orally, HS are capable of forming a barrier layer on the surface of the gastrointestinal mucosa, retaining water and preventing its loss through the intestine, providing protection of the mucous membrane from various aggressive factors. Due to these properties of HS, several pharmacological effects are realized at once.

- detoxifying, enterosorbing, gastroprotective and antidiarrheal

[3]. With the prophylactic administration of GV to rats with experimental ulcerative gastric ulcer and duodenal ulcer, a significant decrease in gastric damage caused by ethanol and an acceleration of the healing process were noted [39]. In combination with iron, HS is used in veterinary medicine for the treatment of small intestinal iron deficiency syndrome [56], because HBs increase the absorption of iron. Humic substances are used as a means to stop bleeding in the treatment of peptic ulcer and duodenal ulcer [57], treatment of metabolic disorders in the digestive system [58], while there are no side effects and complete elimination of the drug from the body. The antiulcirogenic effect of HS [3, 59] is realized due to their macrocolloidal properties and the ability to reduce the permeability of histohematogenous barriers, to create a protective barrier layer on the gastric mucosa. Humic substances in this respect are of interest [3, 59], due to the fact that usually substances with anti-inflammatory properties, on the contrary, exhibit ulcirogenic action, in contrast to HS, which have both anti-inflammatory and antiulcirogenic action, ie. HS are able to independently reduce the severity of NSAID gastropathy and stress ulcerogenesis [59].

It was found [54] that HS inhibit the mutagenicity of benzo [α] pyrene, 2 aminoanthracene, 2nitrofluorene, and 1nitropyrene in the test with S. typhimurium. At this desmutagenic effect was caused by the adsorption of mutagens on HS molecules [4]. There is information [10, 27] that peat HS reduces the death of animals caused by the introduction of various toxic substances (strychnine, phenylhydrazine, sodium nitroprusside, carbon tetrachloride) in lethal doses. When studying the detoxification properties of HS (Lignohumate) [9] on the model of acute poisoning with the neuroleptic clozapine, a decrease in mortality, an improvement in the clinical state of animals, and a decrease in the phenomenon of cytolysis of hepatocytes were found. In the case of intoxication with oxidized oleic acid and mesoxalylurea, an antiradical mechanism of the detoxification activity of HS, due to their reducing properties, has been established [9].

Antibacterial and antiviral action

The use of HS along with prebiotics and probiotics as an alternative to antibacterial therapy was noted [57]. There is data on

antibacterial activity of HS [34, 60], antimutagenic and antiviral action in combination with anti-inflammatory and immunotropic action [52]. The antibacterial activity of HS has been shown against various pathological microbes: Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Neisseria gonorrhea, Klebsiella pneumoniae and against yeasts such as Candida albicans [60]. The most probable mechanism of antibacterial action of HS [3] is a violation of the metabolism of proteins and carbohydrates by the catalytic mechanism, as well as the ability to form interionic bonds with high-molecular substrates of microorganisms.

Humic substances are selective inhibitors of herpes simplex virus HSV (types 1 and 2), human respiratory and cytomegalovirus (HCMV, RSV), influenza virus types A and B [61]. Humic substances are capable of acting as powerful anti-prion agents in the treatment of neurodegenerative disorders and exhibiting a synergistic cytotoxic effect on β-amyloid protein in the SKNMC model of human nerve cells [62]. Humic substances inhibit the effect on HIV1 infection of MT2 cells with IC50 (at a dose of 12.5 μg / ml) [63], an irreversible decrease in the infectivity of HIV cells was established, which is inhibited by interference with the binding of CD4 and V3-mediated loops at the stage of virus introduction. The susceptibility to the virus of target cells treated with peat HS before infection was not impaired (in experiments in vitro during 12 week period) [63]. The drug Oxygumate increases the proliferative response of phytohemagglutin-stimulated human lymphocytes (at a concentration of 20 μg / ml and higher) in healthy people and even higher in HIV-infected patients (at a dose of 4 g per day for two weeks) due to increased production of IL2, as well as the expression of the IL2 receptor in conditions of reduced production of IL10 [64]. Water-soluble HS from brown coal have high antiviral activity against viruses: influenza A (pandemic, avian influenza A), herpes simplex II, human immunodeficiency type I, and did not show activity against the Newcastle disease virus (vaccine strain) [65].

Thus, the combination antioxidant, immunotropic, detoxification, antibacterial and antiviral effects of HA determines their ability to act as stress correctors and adaptogens that increase the nonspecific resistance of animals and humans [3, 6, 10, 66].

Adaptogenic action

Humic substances are the last generation of the most modern adaptogens of stress correctors [6], the protective effect (prevention of adrenal hypertrophy, antiulcerogenic) of which has a conserving regulatory energy-plastic nature, and the potentiating activity (primarily the mobilization of the cellular link of immunity) contributes to an increase in the body's defenses. The mechanism of the implementation of the immunoantioxidant hypothesis of the adaptogenic action of HS is as follows [6]: at the site of HS injection, they induce an active rush of blood and the release of phagocytes from the vessels into the intercellular fluid (where the HS polymer molecules are concentrated). Then the process starts

follow the type of chain reaction, i.e. low molecular weight oligophenolic derivatives are gradually absorbed into the bloodstream, enter the liver and other tissues, where they act as natural phenolic antioxidants and detoxifiers that are constantly ingested with plant foods. Polyphenolic derivatives that do not enter the body through the gastrointestinal tract are actively phagocytosed at the site of application. Here the process bifurcates again: some of the phagocytes that have absorbed phenolic polymers return to the blood and, in the presence of a pathological focus, accumulate in it, and the other part is carried throughout the body. In phagocytes, HS are absorbed by lysosomes and undergo lysis. The contents of lysosomes are extruded into the cytoplasm, then into the bloodstream and, ultimately, enters the pathological focus, organs and tissues in the form of mono and oligomers. This process is renewed and continues continuously as long as at least one HS molecule remains in the body. At the same time, they can exhibit antiradical, AO and prooxidant activity. At the same time, low-level prooxidant activity initiates the body's AO defense system and stimulates phagocytic activity. The process is closed by the other side of the immuno-antioxidant mechanisms of adaptogenic stress-correcting action [6].

The drug Tomed (1% aqueous solution of HS from peat) under conditions of experimental placental insufficiency in rats stimulates the development of adaptive processes in the placenta and placental bed, preventing the death of embryos and intrauterine growth retardation [67]. The activation of metabolism in the placenta was established based on the results of an increase in the amount of DNA, RNA and glycogen in the trophoblast and amniotic epithelium; in the labyrinth and the basal part of the placenta, the specific volume of glycogen cells increased [67]. Similar results related to the activation of DNA and RNA synthesis have been described in experiments on rat liver regeneration [68]. The mechanism of this action of HS [68] is associated with the fact that, as a result of endocytosis, cells absorb HS, subject them to enzymatic hydrolysis, and as a result, amino acids, monosaccharides, and nucleotides are formed, which are included in metabolism. When studying the morphological characteristics of various organs of rats under the influence of peat HS, incl. and pregnant female rats, it was noted [68] that under the influence of HS in their thymus, hypertrophy of the cortex is observed with an increase in the cortical cerebral index, and an increase in the specific proportion of the vascular component, the number of differentiated lymphocytes in the cortex and medulla, in the spleen increases the volume of the white pulp, the number of differentiated lymphocytes, macrophages and plasma cells, there is an increase in the blood supply to the red pulp [68]. In the fetal thymus, an acceleration of lymphocyte differentiation is noted, in the spleen - an increase in the number of erythro and granulocytopoiesis precursor cells, blasts, the mitotic activity of lymphoid cells increases, and vascular differentiation accelerates [68].

Regenerative action

Humic substances are used in the treatment of various skin diseases and to accelerate the healing of the wound surface [34, 57, 69–71]. The regenerative and wound-healing effect of HS is due to various effects, the most probable mechanism [34] is their ability to form hydrogen and covalent bonds with biopolymers such as collagen. Peat humic preparations are effective in the treatment of rheumatoid arthritis, eczema [72, 73], osteoarthritis (with progressive destruction of cartilage) [72, 73]. A stimulating response to the contractile activity of smooth muscles by the mechanism of dopaminergic (through the involvement of D2 opioid receptors, inducing itching) and α2 adrenergic stimulation was established [74]. Therefore, HS preparations as neurogenically mediated mediators of hyperemia and inflammation are of great interest in the treatment of rosacea [75] due to the implementation of the mechanism of inhibition of serotonin reuptake and stimulation of α-adrenergic receptors. When HS is applied to the skin of rats, the processes of proliferation and activation of water, protein, and fat metabolism are enhanced; the number of fibroblasts, cellular composition, and histamine increases in the skin [66], which leads to an acceleration of the healing process. Humic substances increase the tensile strength of the heel tendon of rats [70], increase the mechanical and chemical resistance of collagen fibers, and accelerate their maturation. The biostimulating effect of HS [71] was shown in rats with laparotomy, in which the number of adhesions formed significantly decreased.

The protective effect of HS against UV damage to cells is of considerable interest [69, 76]; their protective effect in UV-induced cytotoxicity is comparable to that of solcoseryl and beloderm. Humic substances effectively inhibit the processes of passive cutaneous anaphylaxis sensitized with egg albumin [69, 76]. The wound-healing effect of HS, regeneration of the monolayer, and rapid wound healing in the model with scratches were revealed [14]. The mechanism of wound healing action is associated with paracrine stimulation of cytokines, rather than autocrine stimulation of proliferation [14], judging by the absence of an increase in the proliferation of HaCaT cells. Clinical results show that HS are able to stimulate osteoclastic resorption of grafted bones and hydroxyapatite, which is used for bone repair [77].

SAFETY OF APPLICATION OF HUMIC SUBSTANCES

Numerous scientific studies have shown that HS are not dangerous, not teratogenic, not mutagenic, do not cause allergic reactions, do not possess sensitizing and irritating properties [4, 6, 43, 49, 78–81], are characterized by very low toxicity, have high LD_{50} values [43, 82], belong to III (with intraperitoneal administration) and IV (with intragastric administration) hazard classes. In a preclinical study of chronic toxicity in rats treated with brown coal HS at a dose of 500 mg / kg and 1 g / kg for a month, no toxic effects were revealed, incl. and in relation to puppies (when administered to pregnant female rats) [43], there are no side effects [49] and complete elimination of the drug from the body. In work [6]

it is said about the harmlessness and non-toxicity of HS based on the results of studies of acute and chronic toxicity, cumulation, mutagenicity, embryotropic activity, teratogenic action, embryotoxicity, irritating and resorptive action of HS preparations. When studying the effect of peat HS (at a dose of 10 mg / kg body weight) on pregnant female rats [68], it was noted that they do not have an embryotoxic effect and do not cause the formation of external and internal malformations in the fetus. Moreover, observation of the dynamics of the first generation rat pups receiving HS at the ante and postnatal stages up to the period of maturity revealed the outstripping physical development in comparison with the control group from the 1st month of postnatal development, and the second generation - from the 15th day of the postnatal period [68].

In works devoted to studies of the TPP preparation, no embryotoxic or teratogenic effects were revealed (in experiments with hamsters and rats, at a daily dose of 5 to 50 mg / kg) [81], as well as mutagenic and genotoxic properties [80]. caused and did not increase allergic sensitization (in an experiment with mice and guinea pigs) [78, 79].

When using HS at known lethal doses (480 mg / kg) in rats, it was noted [82] that the death of animals occurred from acute heart failure resulting from ischemic myocardial dystrophy. A decrease in the electrical stability of the heart was observed as a result of a decrease in the ventricular fibrillation threshold (1.8 times) and a shortening (2.8 times) of the QRS complex in comparison with intact animals.

CONCLUSION

Thus, the polyfunctionality and zwitterionic character of HS are their unique properties characterizing them as powerful chelating agents among other natural organic substances. The unique chemical properties of HS are responsible for their multidisciplinary pharmacological activity, which does not at all indicate the nonspecificity of their action, but is the result of cascade reactions caused by the effect on the main systems in which AOA is the trigger, detoxification activity (including antibacterial and antiviral) and immunomodulating action, including adaptive and regenerative activity as a manifestation of the totality of all types of activity together. In nature, there are no compounds with a similar set of important chemical and biological properties,

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