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ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ НЕКРАХМАЛЬНЫХ ПОЛИСАХАРИДОВ РАСТИТЕЛЬНОГО ПРОИСХОЖДЕНИЯ В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Ингибирование белка-транспортера гликопротеина-Р (ABCB1-белок, Pgp) представляется перспективной задачей для повышения эффективности фармакотерапии ряда патологий: опухолевых заболеваний, эпилепсии, нарушения мозгового кровообращения. Pgp представляет собой крупный трансмембранный белок, осуществляющий эффлюкс широкого спектра эндо- и ксенобиотиков из клетки, он играет важную роль в фармакокинетике многих лекарственных веществ. На данный момент ни один синтетический ингибитор транспортера не применяется в клинической практике вследствие неизбирательности действия, токсичности и высокой стоимости. Лекарственные растительные средства оказывают разносторонние фармакологические эффекты, обладают большой широтой терапевтического действия, редко вызывают нежелательные лекарственные реакции, экономически доступны. В настоящем обзоре представлены результаты экспериментов, анализирующих принадлежность олиго- и полисахаридов к субстратам и ингибиторам Pgp, что является предпосылкой к проведению соответствующих исследований для других полисахаридов растительного происхождения. Описаны возможности применения некрахмальных растительных полисахаридов в комплексной терапии опухолей, так как наряду с потенциальным ингибированием транспортера, они оказывают противоопухолевое действие, а также могут способствовать коррекции побочных эффектов цитостатиков. Представлены перспективы использования некрахмальных полисахаридов растительного происхождения для повышения эффективности нейропротекторной терапии, поскольку они не только могут увеличить проникновение нейропротекторов через гематоэнцефалический барьер, ингибируя Pgp, но и обладают собственной нейропротекторной активностью, а также рядом фармакологических эффектов, которые могут дать положительный результат в комплексном лечении патологий головного мозга. Таким образом, исследование некрахмальных растительных полисахаридов, их выделение и создание лекарственных средств на их основе является перспективным направлением современной медицины.

Ключевые слова: *гликопротеин-Р, ABCB1-белок, ингибиторы, полисахариды растительного происхождения, противоопухолевые средства, нейропротекторы.*

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POSSIBILITIES OF USE OF PLANT DERIVED NON-STARCH POLYSACCHARIDES IN CLINICAL PRACTICE

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Inhibition of P-glycoprotein transporter protein (ABCB1-protein, Pgp) is a promising method to increase the effectiveness of pharmacotherapy in different pathologies: neoplastic diseases, epilepsy, cerebral circulation disorders. Pgp is a large transmembrane protein that provides efflux of a wide range of endo- and xenobiotics from cells, and plays a significant role in pharmacokinetics of many medical drugs. Nowadays not a single synthetic inhibitor of the transporter is used in clinical practice due to non-selectivity of action, toxicity and high cost. Medicinal herbal remedies possess different pharmacological and therapeutic effects, rarely cause side effects and are economically accessible. This review presents the results of experiments in which affiliation of the oligo- and polysaccharides to substrates and inhibitors of Pgp was analyzed, and which precondition further studies of other plant derived polysaccharides. Possibilities of using plant derived non-starch polysaccharides in complex therapy of tumors are described, since along with potential inhibition of the transporter, they possess an antitumor effect and can also assist in correction of side effects of cytostatics. The prospects of using plant derived non-starch polysaccharides for improvement of the effectiveness of neuroprotective therapy are presented, because they not only can increase the penetration of neuroprotective drugs across the blood-brain barrier through Pgp inhibition, but also possess their own neuroprotective activity, as well as a number of pharmacological effects that can give a positive result in the complex treatment of brain pathologies. Thus investigations of plant non-starch polysaccharides, their isolation and development of medical drugs on their basis is a promising direction of modern medicine.

Keywords: *P-glycoprotein, ABCB1-protein, inhibitors, plant derived polysaccharides, antineoplastic agents, neuroprotective drugs.*

Актуальной проблемой современной An important problem of modern medicine is resistance of diseases to pharmacotherapy. One of causes of ineffectiveness of medical drugs is considered to be enhanced activity of glycoprotein-P transporter protein (ABCB1-protein, Pgp), which removes medical substances that are its substrates, out of target cells, or reduces their concentration in blood and tissues [1].

Pgp is a large transmembrane protein with a wide substrate specificity that provides efflux of numerous endo- and xenobiotics including medical drugs, out of cell [1]. It was first found in tumor tissue where its intense functioning causes reduction in the permeability of cell membranes to antitumor drugs leading to the phenomenon of multidrug resistance [2]. In further studies Pgp was found in many organs and tissues of humans and animals (gastrointestinal tract, liver, kidneys, tissues barriers), thus it is believed to play a key role in pharmacokinetics of medial drugs.

Being localized in enterocytes, the transporter decreases absorption of substrates in the intestine; in histohematic barriers (hematoencephalic, hematoovarian, hematotesticular and hematoplacental) it prevents entry of substrates to the sequestered organs; besides, it mediates release of substrates from hepatocytes and renal epithelium into the lumen of bile ducts and of renal tubules [1,3].

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Of special attention is the function of the transporter in hematoencephalic barrier, since increase in its activity in the barrier may reduce the effectiveness of antiepileptic and neuroprotective therapy [1,3]. Taking the above into account, inhibition of Pgp transporter protein is a prospective way to increase effectiveness of pharmacotherapy of some pathologies.

At present three generations of Pgp inhibitors has been developed. Their brief characteristics are given in Table 1.

Table 1

Characteristics of Pgp Inhibitors [4-6]

Generation	Examples	Properties	Disadvantages
1	Verapamil, yohimbine, quinidine, cyclosporin, reserpine, tamoxifen, toremifene, triflyoroperazine	Non-selective, low affinity to Pgp	They are substrates of Pgp, of other transporters and enzymatic systems of metabolism; possess pharmacological activity; to achieve transporter inhibition high doses are required
2	Dexniguldipine, dexverapamil, dofequidar fumarate [MS-209], valspodar [PSC 833]	Possess higher specificity as compared to the first generation inhibitors	They are substrates of Pgp and of other transporters and enzymatic systems
3	Biricodar [VX-710], cyclopropyldibenzosuberanezosuquidar [LY335979], elacridar [GF120918/GG918], laniquidar [R101933], mitotane [NSC-38721], tariquidar [XR9576], ONT-093, HM30181	High specificity; selective and effective inhibition of Pgp	Absent

The optimal synthetic transporter inhibitors are those of the third generation, possessing low toxicity and selectivity of action. However, their application may lead to enhancement of side effects of the prescribed medical drugs. Thus, use of tariquidar is associated with increase in the concentration of cytostatic and antiepileptic drugs not only in the target cells, but also in blood plasma with the result of development of unwanted drug-related reactions [7]. It is worth noting that Pgp inhibitors of the third generation are costly. Thus, at the moment synthetic inhibitors of transporter protein are not used in clinical practice.

An important direction in the development of modern pharmacology is search and investigation of new medical drugs of plant origin [8]. Plant derived medical drugs possess certain advantages: they are capable of various pharmacological effects, possess a wide range of therapeutic actions, seldom induce side effects including allergic reactions, and are affordable [9].

Polysaccharides of plant origin possess these advantages, they are actively used in medicine in the form of galenical preparations containing a complex of active substances. Thus, roots of sweatweed *(Althaea officinalis L.)* are used as an expectorating drug in the form of a syrup; thallus of luminaria (*Laminaria japonica Aresch)* are used as a laxative; mucus of flax seeds *(Linum usitatissimum L.)* is used as a softening and coating agent, etc. [10].

Recently, research works have been conducted concerning pharmacological activity of non-starch polysaccharides (non-hydrolysable with amylase) of higher plants and algae, and development of medical drugs on their basis containing individual substances.

Application of non-starch plant polysaccharides as Pgp inhibitors is possible due to their chemical structure, since molecules of polysaccharides often contain functional groups characteristic of blockers of the transporter protein. [11]. Such chemical structure is inherent to the so called inlay polysaccharides and water-soluble pectins (structural

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heteropolysaccharides) which contain amino sugars, polypeptide chains and uronic acids that can form ester groups. Besides, structure of polysaccharides permits to introduce additional functional groups into their molecules by chemical synthesis. It should be noted that polysaccharides contain high-electronegative atoms of oxygen which make electron pairs for formation of intramolecular hydrogen bonds and bonds with Pgp molecule.

In some works affiliation of poly- and oligosaccharides to substrates of the transporter is shown. One of mechanisms of changing the functional activity of Pgp consists in the interaction of a substance with parts of its molecule (substrate-binding and other sites) with probable alteration of its spatial structure, therefore substrates of the transporter are considered its potential inhibitors [12].

It was found that processing of culture of cells overexpressing Pgp with modified cyclodextrin (heptakis (2,6-di-O-methyl)-beta-cyclodextrin) increases permeability of membranes to the transporter substrates in both directions, that is, it decreases activity of the transporter, probably due to derangement of microenvironment in the membrane [13].

In *in vitro* experiment on the culture of tumor cells it was found that heparin which is a negatively charged high-sulfated polysaccharide, increases penetration of chemopreparations – Pgp substrates – into cells through suppression of the functional activity of the transporter. This phenomenon may be associated with the ability of heparin to interact with the extracellular proteins (growth factors, matrix components) and to modulate their activity by its charge [14]. In a study on the culture of human breast tumor cells MDA-MB231, intracellular penetration of the transporter substrate – calcein-AM – was analyzed, and it was shown that unfractionated heparin inhibits functioning of Pgp [15].

It is found that some resin glycosides (glycolipids, or lipo-oligosaccharides) obtained from seeds of *Ipomoea alba* increase susceptibility of the culture of chemoresistant cells of human breast carcinoma to vinblastine [16].

It was identified in *in vitro* experiment that oligomers of hyaluronic acid promote penetration of doxorubicin into tumor cells of peripheral nerve sheaths and also increase cytotoxicity of the drug *in vivo* [17].

It was shown that incubation of the culture of Pgp-expressing tumor cells within 4 hours with solid lipid nanoparticles (stearic acid and surfactant: lecithin and poloxamer) with paclitaxel subject to modification by ultrasound with use of 2-hydroxypropyl-β-cyclodextrin system resulted in accumulation of the chemical drug inside the cell to a higher extent than in incubation with classic transporter inhibitor – verapamil [18].

Dextran-based nanoparticles were found to be promising for delivery of doxorubicin to multidrug-resistant tumor cells [19].

The results of the mentioned experiments suggest further study of use of other available plant polysaccharides as Pgp inhibitors.

Of special attention is a propable use of non-starch plant polysaccharides for complex treatment of tumors, since besides potential inhibiton of transporter and increase in penetration of chemical drugs into tumor cells, some polysaccharides can produce antitumor effect of their own. Thus, it was found that plant polysaccharides reduce growth and metastasizing of blastomas due to induction of apoptosis in tissues [20]. It was also shown that butyric acid synthesized in the intestine in fermentation of polysaccharides, promotes differentiation and apoptosis of cells of colon carcinoma and suppresses their proliferation, possessing antineoplastic effect [21].

In experiments on mice with Lewis carcinoma increase in the activity of chemotherapy was found in combined use of cyclophosphan and polysaccharide complex of sweet calamus rhizome and its fractions. The most expressed antitumor and antimetastatic activity was characteristic of the acidic fraction of the complex [22].

It was shown that the mechanism of antitumor effect of pectin polysaccharides containing D-galacturonic acid is based on their ability to interact with specific receptors on

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the membrane of macrophages which results in formation of cytokines and tumor necrosis factor [20]. Polysaccharides containing galacturonan enhance expression of MHC complex on the surface of tumor cells thus activating immune cells that participate in antitumor protection [23].

It was found that introduction of polysaccharides of sweet calamus rhizome in case of cyclophosphan-induced immune depression, stimulates specific T-type immune response increasing the activity of cells of lymph nodes toward tumor cells [24].

Plant derived polysaccharides may correct side effects of cytostatics. It was shown in experiments on mice with Lewis carcinoma that water-soluble polysaccharides of foalfoot (*Tussilago farfara L.*) and sweet calamus rhizome reduce hepatotoxicity of paclitaxel [25]. Plant polysaccharides can effectively reduce gastrotoxicity of antitumor drugs: antiulcer effect was found in fucoidans, chitosan, colloid bismuth-pectin complex, low-esterified pectins [26-28]. Pectin polysaccharides may also be considered as prebiotics for correction of intestinal dysbiosis associated with intake of cytostatics [29].

Of interest is a possibility of using plant derived polysaccharides to improve the effectiveness of neuroprotective therapy, since they can not only increase penetration of neuroprotectors across the hematoencephalic barrier by potential inhibition of Pgp, but possess neuroprotective activity of their own, as well as some pharmacological effects, that may add to the positive result of complex treatment of pathologies of the brain.

Nitric oxide (NO) in high concentration is known to cause damage and death of neurons [30]. Sulfated polysaccharides produce a neuroprotective effect through inhibition of NO-synthase [31]. Fucoidan isolated from *Laminaria japonica* alga in the concentration 125 μg/ml decreases release of nitric oxide in microglial cells by inhibition of phosphorylation of mitogen-activated protein kinase and of intracellular signal-regulated kinase [32]. In the dose 62.5 μg/ml the polysaccharide decreases expression of CD11b receptors on the surface of granulocytes, natural killers and macrophages. Fucoidan produces a protective effect for proliferation of astrocytes through regulation of inducible NO synthase [33].

Inhibitory effect of fucoidan isolated from kelp *Fucus vesiculosis* on synthesis of nitric oxide was shown in cultures of BV2 glial cells and C6 glioma cells induced by proinflammatory cytokines (tumor necrosis factor α, γ-interferon and interleukin 1β) [34].

Oxidative stress is an important pathogenetic factor of many neurologic diseases. In *in vitro* and *in vivo* experiments the antioxidant effect of fucoidan isolated from kelp *Laminaria japonica* was demonstrated [35]. This effect of polysaccharide results from block of production of oxygen radicals and from increase in the levels of glutathione peroxidase, superoxide dismutase and malondialdehyde [35]. Antioxidant activity is also found in polysaccharides of some higher plants – mountain ash, St. John's wort, and carregeenans [36].

Hypolipidemic, anticoagulation and antiischemic effects of non-starch polysaccharides may assist in complex therapy of acute disorder in brain circulation.

Hypolipidemic effect of polysaccharides (chitosan, fucoidans and others) consist in prevention of absorption of cholesterol in the intestine, increase in relative concentration of hydrophobic bile acids which more powerfully than hydrophilic ones inhibit activity of cholesterol-7α-hydroxylase, and in suppression of synthesis of cholesterol in the liver under influence of short-chain fatty acids (propionic, acetic and butyric acid) produced in fermentation of polysaccharides [37]. Besides, chitosan can form ionic complexes with fats including cholesterol, and inhibit their absorption and recirculation from the intestine into the liver [37].

Anticoagulation effect is found in pectins. They change the characteristic of fibrin meshwork so that it becomes more permeable, loses strength and readily lyses [38].

Fucoidans can activate formation of vessels and produce an antiischemic effect. Binding with fibroblast growth factors, they

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protect them against proteolysis and promote angiogenesis [39]. Besides, high-molecular fucoidans induce liberation of glucosaminoglycan-bound stromal factor-1 which mobilizes progenitors of stem cells of the bone marrow participating in angiogenesis [40].

Thus, it seems reasonable to evaluate affiliation of non-starch polysaccharides of some plants (alecost, foalfoot, calamus root, kelp) possessing gastroprotective, hepatoprotective, antioxidant, membranoprotective [26-41], and also antitumor and neuroprotective [34] effects, to glycoprotein-P inhibitors. Isolation, modification and development of medical drugs on the basis of plant derived polysaccharides is a promising direction of modern pharmacology. A study of specific activity of non-starch plant derived polysaccharides including their ability to inhibit glycoprotein-P transporter protein, permits to clarify peculiarities of their pharmacokinetics and pharmacodynamics and to optimize pharmacotherapy of some diseases.

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