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Use of lectins as vector molecules for delivery of drugs to cells and tissues. Report 2

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Aim. To determine cytotoxic effects towards a tumor cells culture of the heterocyclic derivative conjugated with lectins of different carbohydrate specificity. **Methods.** Conjugation of lectins (Pea seeds (PSA), peanuts (PNA) and erythroagglyutinin from bean seeds (PHA-E) with thiopyrano[2,3-d]thiazole Les-1895, biotesting these conjugates in the cell culture. **Results.** The conjugates of Les-1895 with specific lectins posses increased cytotoxic effects towards Jurkat cells — by 23 % for PSA-Les-1895, 34 % for PNA-Les-1895, and by 12 % for PHA-E-Les-1895. IC_{50} of Les-1895 conjugates was ≈ 10 μg/ml, whereas at using free Les-1895 — it was ≈ 30 μg/ml. The PNA and PHA-E conjugates with Les-1895 suppressed the viability of HCT 116 cells more considerably than the PSA conjugate. A cytotoxic action of PNA (IC_{50} = 4 μg/ml) and PHA-E (IC_{50} = 3 μg/ml) conjugates was more pronounced than the effect of free Les-1895 (IC_{50} = 10 μg/ml) or intact lectins. The conjugation of Les-1895 with human serum albumin (HSA) increased the water solubility, however, such conjugation decreased the cytotoxic effect towards Jurkat cells by 40 %. The pseudonormal cells line HEK 293 was less sensitive to the action of native lectins — PSA, PNA and PHA-E as well as to the action of conjugates of these lectins. **Conclusions.** Conjugation of Les-1895 with specific lectins enhanced a cytotoxic effect. The obtained results suggest a possibility of the addresed delivery of biologically active compounds to specific cells of tissues and organs of the human body.

Keywords: pea lectin, peanut lectin, FGA-R, conjugates, thiopyrano[2,3-*d*]thiazoles, antitumor activity.

Introduction

Various thiopyrano[2,3-*d*]thiazole derivatives with the anticancer, antiviral, anti-inflammatory, antimicrobial and antitrypanosomal activities were synthezized at the Department of the Pharmaceutical, Organic and Bioorganic Chemistry of Danylo Halytsky Lviv National Medical University [1]. A pharmaceutical potential of these derivatives can be significantly increased through the development of water soluble forms that also creates the conditions for their selective binding to the biological targets. In previous study [2], we have conjugated pea seeds lectin in the alkaline medium (pH 9.0) with the thiopyrano[2,3-*d*]thiazole derivative through the interaction of the aldehyde group of this compound with the amino groups of amino acids of the lectins. The biological activity of obtained conjugates towards the mouse leukemia cells of L1210 line was evaluated. It was shown that the obtained conjugates had a 2.5-fold increased antineoplastic effect (calculated as the amount of substance conjugated to the lectin) compared to the non-conjugated compound. It was assumed that such enhancement is caused by a selective interaction of lectin with certain types of cells in tissues. Thus, a targeted delivery of the substance to potential sites of its action is possible. The application of lectin conjugates with drugs might also have some disadvantages. The main one is a protein nature of the lectin carrier which can cause allergic reactions, especially after its direct administration into the bloodstream. At the same time, such conjugates could be useful at external application into the body cavities (oral or nasal) or as rectal suppositories. The advantage of lectins as drug carriers compared to the synthetic polymers is lectins biodegradability. There are numerous literature data describing commercially available lectins selectively binding to normal or pathological tissues. It has been established that peanut lectin (PNA) selectively binds the T-antigen present in 71 % of cancer cells and not detected by the monoclonal antibodies in healthy donors [3, 4]. Our investigation on binding capacity of the PNA-E receptors with colon cancer cells revealed that PNA-E interacted with the adenoma cells and with adenocarcinomas of high degree of differentiation. This lectin possesses a higher selectivity to the adenoma cells compared to the tumor cells with a low degree of differentiation. Thus, the lectin binding can be used as a selective histochemical marker of these pathologies [5], as well as for the targeted delivery of drugs to the specific colon cells. Therefore, the next step of our work was to investigate the action of such conjugates on the cells of other lines, in particular, the T-lymphoblastic leukemia Jurkat cells, HCT 116 line of human colorectal carcinoma cells, and HEK 293 pseudonormal cells of human embryonic kidney. In this study, thiopyrano[2,3-*d*]thiazole derivative (Les-1895) [6] was used as an adduct attached to the lectins.

Materials and Methods

In Fig. 1, one can see a schematic reaction of the thiopyrano[2,3-*d*]thiazole derivative (Les-1895) conjugation with lectins isolated from the pea seeds (PSA, *Pisum sativum* agglutinin), peanut seeds (PNA, peanut agglutinin), and erythroagglutinin of the common bean (PHA-E). In control, Les-1895 was conjugated to human serum albumin (HSA). These

conjugations were accomplished through the aldehyde group of Les-1895 interacting with the amino groups of amino acids of lectins under the alkaline conditions (pH 9.0).

Conjugation. 10 mg of lectin or HSA were dissolved in 1.0 ml of 1 % aqueous solution of sodium bicarbonate with addition of 0.025-0.2 ml of 1 % solution of Les-1895 in DMSO. The obtained solution was stirred and kept for 3 h at room temperature. After stirring the turbid solution was gradually highlighted, 5 mg of sodium borohydride were added to the solution and the obtained mixture was kept for 12 h. To separate the unreacted Les-1895 from its conjugate, the mixture was dialyzed against 50 ml of 20 % aqueous solution of DMSO, and then against 50 ml of phosphate buffered saline (PBS).

Investigation of the obtained conjugate. The obtained conjugate was characterized for its lectin activity measured as an ability to bind specific carbohydrates and glycoproteins of the plasma membrane. The content of protein and Les-1895 attached to the lectin was also calculated. The lectin's activity before and after conjugation was measured by determining the agglutination titer of 2 % rabbit erythrocyte suspension in PBS. The concentration of Les-1895 in the conjugate was determined by measuring the absorbance at 361 nm wavelength, where this compound has a characteristic maximum of absorption (Fig. 2). The content of total protein was measured using Lowry method with an absorbance at 740 nm.

Synthesis of Les-1895. Synthesis of 7-[4-(benzyloxy)phenyl]-2-oxo-3,5,6,7-tetrahydro-2*H*-thiopyrano[2,3-*d*][1,3]thiazole-6-carbaldehyde (Les-1895) was accomplished in the [4+2]-cyclocondensation reaction of 5-(4-benzyloxybenzylidene)-4-thioxothiazolidinone-2 as a heterodiene and acrolein as a dienophile under the refluxing for 1 h with a catalytic amount of the hydroquinone in a glacial acetic acid medium [**6**].

Cell culture. The human colorectal carcinoma HCT 116 cells, T-lymphoblastic leukemia Jurkat cells, and pseudonormal human embryonic kidney HEK 293 cells were obtained from Cell culture collection at R.E. Kavetsky Institute of Experimental Pathology, Oncology and

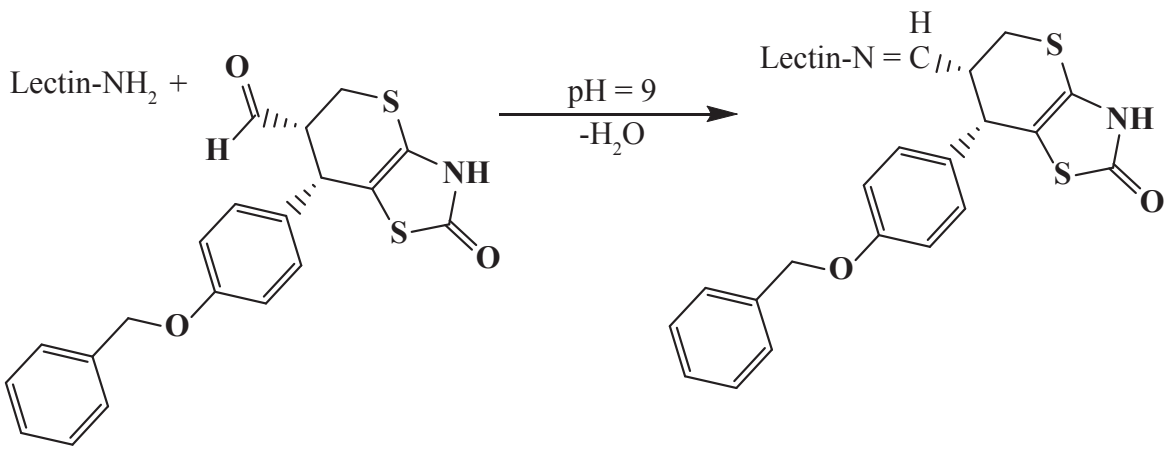

Fig. 1. Conjugation of Les-1895 with lectins.

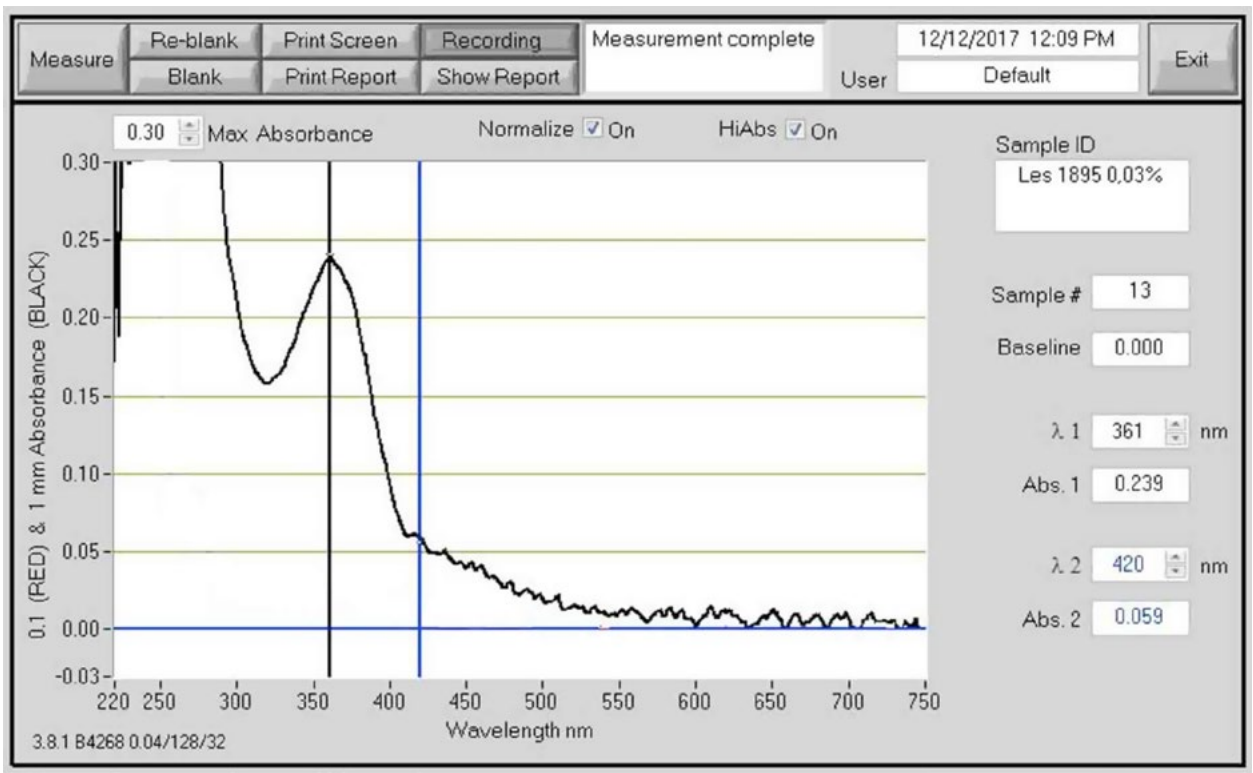

Fig. 2. Absorption spectrum of Les-1895 (0.03 % solution in DMSO).

Radiobiology, National Academy of Sciences of Ukraine (Kyiv). The HEK 293 cells were cultured in the Dulbecco's -modified Eagle's medium (DMEM, Sigma, USA) in the presence of 10 % of the decomposed blood serum of cattle embryos, using phenol red as an indicator of pH, and 50 μg/ml of gentamicin antibiotic (Sigma, USA). The cells of Jurkat and HCT 116 lines were cultured in the RPMI-1640 (Thermo scientific, USA) medium in the presence of 10 % decomposed blood serum of cattle embryos, phenol red, and 50 μg/ml of gentamicin (Sigma, USA). To evaluate cytotoxicity of the lectins (PSA, PNA, PHA-E), Les-1895, and the conjugates with these lectins, the appropriate samples were added in different concentrations to the medium in which the cells are cultured. After 24 h, the number of cells was counted in the hemocytometric chamber using the Trypan blue dye (DV-T10282, "Invitrogen", USA) that penetrates through the plasma membrane of the damaged (dead) cells. The cells colored in blue were considered as the necrotic ones. The number of cells in suspension was calculated according to the formula: c = 12500n, where: c — the number of cells in 1 ml of suspension, n — the average number of cells in 5 large squares of the hemocytometer chamber. The evaluation of cytotoxicity and antiproliferative activity of the tested compound was carried out after 72 h of incubation using the MTT assay. The cell viability was evaluated by measuring

a reduction of the MTT dye (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Sigma, USA) to water-insoluble formazan which has a purple color.

Statistical analysis. Each experiment was performed in triplicate and average values were recorded. The data were evaluated statistically using Student's t-test, and a value of $p \leq 0.05$ was considered to be statistically reliable.

Results and Discussion

Les-1895 is soluble only in organic solvents such as dimethylsulfoxide or dimethylformamide. Here we demonstrated that the conjugation of this compound with the lectin (see Materials and Methods section) led to creation of the water soluble product.

Comparing to the previously reported thiopyrano[2,3-*d*]thiazole derivative, Les-1351 [2], an increase of the amount of Les-1895 in the reaction mixture up to 1 mg per 10 mg of pea lectin (10 %) did not lead to the lectin inactivation. Noteworthy, Les-1895 present in the reaction mixture was not completely immobilized on lectin. According to our calculations, 10 mg of lectin bound 0.9 mg of Les-1895 (9 % of total weight of the conjugate). Similar results were obtained for PNA and PHA-E, where 10 mg of PNA bound maximum

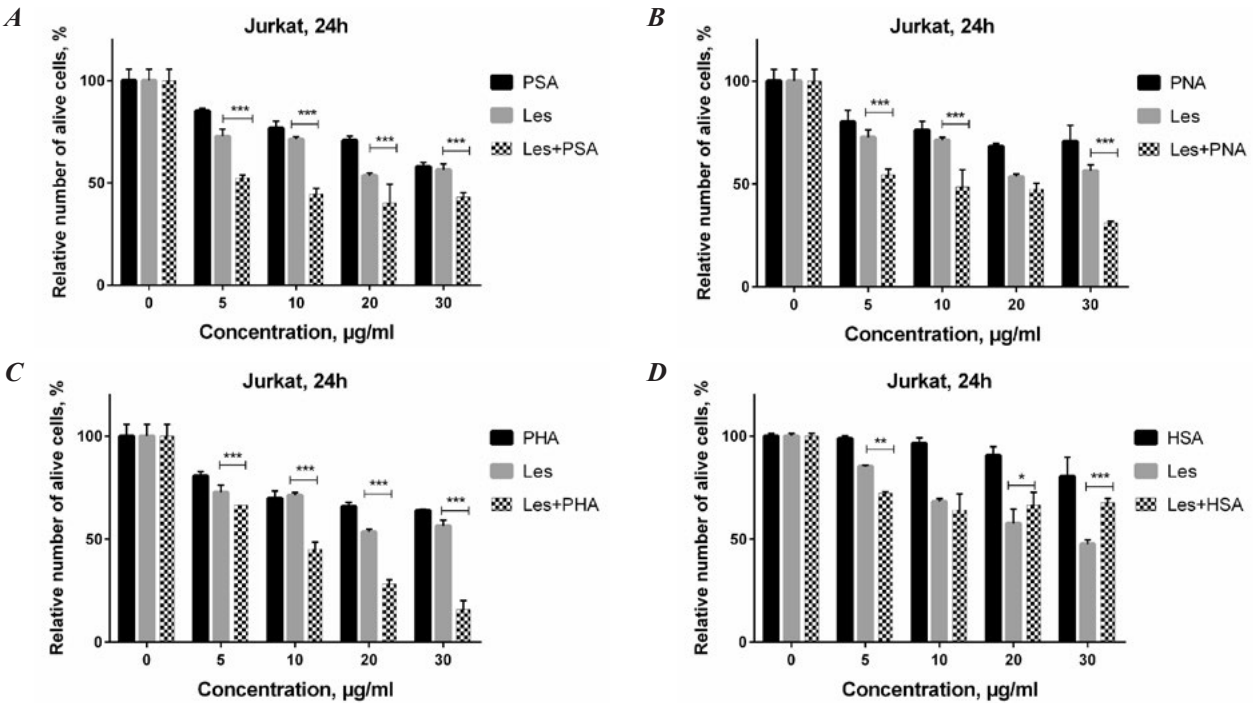

Fig. 3. The results of measuring the cytotoxic effect (Trypan blue exclusion test) of Les-1895, specific lectins, and their conjugates towards human T-lymphoblastic leukemia Jurkat cells. The cytotoxic activity of the conjugates (Les-1895 + PSA, PNA, PHA-E or HSA) was calculated taking into account the amount of the attached Les-1895.

* $p < 0.05$; ** $p<0.01$; *** $p<0.001$

0.5 mg of Les-1895 (5 % of total mass of the conjugate), and 10 mg of PHA-E bound 8 % of Les-1895 of total mass of the conjugate. At the same time, 10 mg of HSA could bind up to 1.6 mg Les-1895 (16 % of the total conjugate mass). The obtained conjugates of lectins with Les-1895 were soluble in water, phosphate buffered saline (PBS), and 1 % $NaHCO_3$ solution, whereas the initial Les-1895 compound was practically insoluble in these media.

Unlike the murine leukemia L1210 cells [2] that were insensitive to the pea lectin (PSA), the T-lymphoblastic leukemia Jurkat cells were subjected to a cytotoxic action of the PHA-E and PNA lectins. IC_{50} for PNA and PSA was 80 and 37 μg/ml, respectively, and for PHA-E — 20 μg/ml. IC_{50} for Les-1895 was 32 μg/ml. According to these data, PHA-E was more effective in targeting Jurkat cells than Les-1895. The conjugates of the lectins with this compound displayed a cytotoxic effect towards the T-lymphoblastic leukemia Jurkat cells — 23 % inhibition for PSA-Les-1895, 34 % — for PNA-Les-1895, and 12 % — for PHA-E-Les-1895. IC_{50} of the conjugates of lectins with Les-1895 was 10 μg/ml, whereas IC_{50} of free Les-1895 compound was 30 μg/ml. Though the conjugation of Les-1895 to HSA increased a water solubility of Les 1895, it at the same time reduced by 40 % a cytotoxic effect of the obtained conjugate towards the T-lymphoblastic leukemia Jurkat cells (Fig. 3).

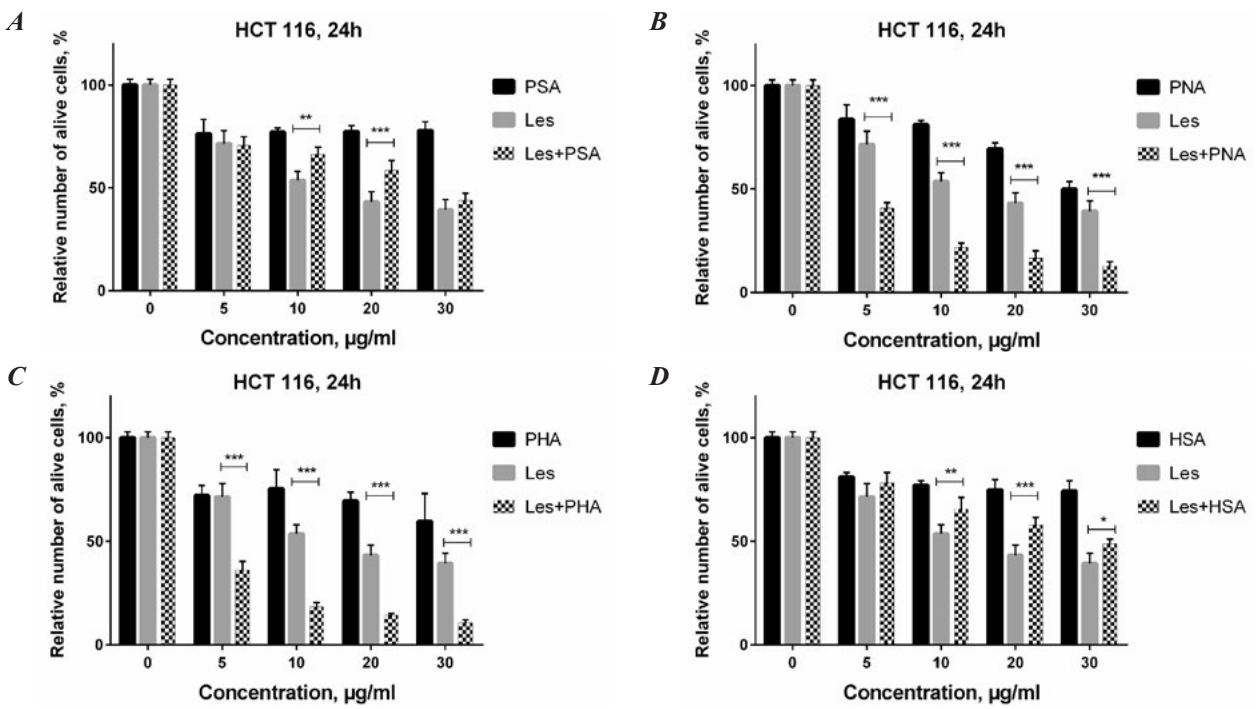

Fig. 4. The results of measuring cytotoxicity (Trypan blue exclusion test) of Les-1895, specific lectins, and their conjugates towards the human colorectal carcinoma cells of HCT 116 line.

* $p < 0.05$; ** $p<0.01$; *** $p<0.001$

Noteworthy, PNA and PHA-E significantly suppressed the viability of human colorectal carcinoma HCT116 cells comparing to the effects of intact HSA and pea lectin. The cytotoxic action of the Les-1895 conjugates with the PNA and PHA-E lectins was more potent than the action of free Les-1895 and non-conjugated lectins. IC_{50} of the PSA-Les-1895 conjugate was 28 μg/ml, PNA-Les-1895 — 4 μg/ml, and PHA-E-Les-1895 — 3 μg/ml. IC_{50} of Les-1895 was approximately 10 μg/ml, whereas the cytotoxic effect of the HSA-E-Les-1895 and the PSA-Les-1895 conjugates was weaker than that of free Les-1895 (Fig. 4).

Pseudonormal human embryonic kidney HEK 293 cells were insensitive to the action of PSA, PNA and PHA-E lectins, and at 30 mg/ml dose of these lectins there were ≈20 % of dead cells. The conjugation of Les-1895 with these lectins did not significantly enhance their cytotoxic effect as compared to the action of the Les-1895 free form (Fig. 5).

Taking into account the obtained results, one can suggest a positive correlation between the level of lectin binding with cells and a cytotoxic action of the Les-1895 conjugates with these lectins. This suggestion is in agreement with our preliminary results on the binding of specific lectins with histological specimens of the human adenocarcinoma colon cells compared to the cells of normal colon tissue [5].

Thus, the conjugation of Les-1895 with the pea and peanut lectins increased the antineoplastic activity of the resulting conjugates in the T-lymphoblastic leukemia Jurkat cells and human adenocarcinoma HCT 116 cells. At the same time, the pseudonormal HEK 293 line cells were insensitive to the action of tested lectins and their conjugates with Les-1895. The human adenocarcinoma HCT 116 cells were 2-fold more sensitive to the action of studied conjugates of lectins and tested compound. According to the literary data [7-9], an increased toxicity of conjugates towards tumor cells could be caused by a selective binding of specific lectins to the carbohydrate-containing receptors of the plasma membrane of cells. The HSA-Les-1895 conjugate was not toxic for the T-lymphoblastic leukemia Jurkat cells and only slightly toxic for the human adenocarcinoma HCT 116 cells, comparing to a high toxicity of the conjugates of Les-1895 with the lectins. A cytotoxic action of conjugates Les-1895 with lectins towards the pseudonormal cells HEK 293 line was manifested after 72 h only at high doses of the conjugates. Thus, the action of the conjugates was more pronounced for the adenocarcinoma HCT 116 cells than for the pseudonormal cells HEK 293 line (Fig. 6).

We had no the pseudonormal colon cells in our collection, thus, we used the human embryonic kidney cells that possess a similar structure of the glycoconjugates on their surface [10, 11]. Comparing to tumor cells, these cells have a significantly less amount of terminal sialic acids in the plasma membrane [12].

Lectins could interact specifically with the individual cell surface glycoconjugates creating an increased local concentration of bound substances. As noted in the Introduction section, using lectins as medicines has certain limitations. They can be used only externally at treatment of patients with diseases of skin, digestive tract, nasopharynx, lungs, or in the rinses and sprays, suppositoria and ointment bases. Lectin-containing medicines cannot be recommended for administration into the

bloodstream because of possible allergic reactions. However, their inclusion in the ointment or utilizing in suppositories may be helpful for the treatment of colorectal cancer.

Conclusions

1. Covalent attachment of the thiopyrano[2,3-*d*]thiazole derivatives to proteins (lectins) is accompanied by an increased solubility of

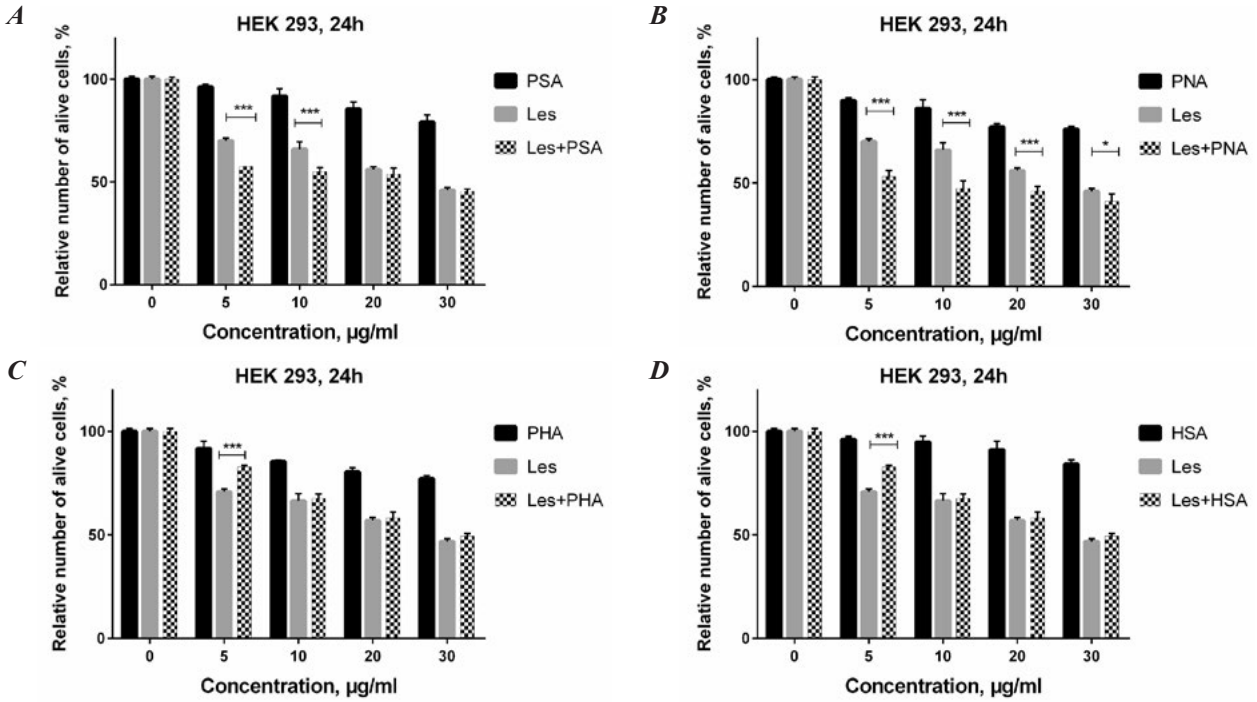

Fig. 5. The results of measuring cytotoxicity (Trypan blue exclusion test) of Les-1895, specific lectins, and their conjugates towards the pseudonormal human embryonic kidney HEK 293 cells.

* $p < 0.05$; ** $p<0.01$; *** $p<0.001$

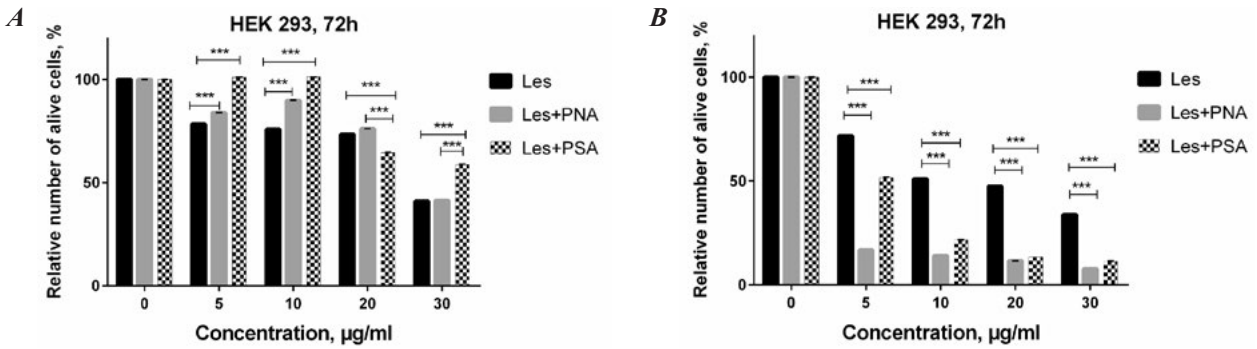

Fig. 6. The results of measuring viability (MTT assay) of Les-1895, specific lectins, and their conjugates towards the pseudonormal human embryonic kidney HEK 293 cells and the human colorectal carcinoma HCT 116 cells.

* $p < 0.05$; ** $p<0.01$; *** $p<0.001$

formed conjugates in water, however, such conjugation does not guarantee an enhacement of the biological activity of the attached ligands.

2. Native lectins exhibit more pronounced cytotoxic action on specific tumor cells, than on the pseudonormal cells, and a degree of such action depends on the carbohydrate specificity. Conjugation of lectins with a low molecular weight ligand posessing antitumor activity leads to an increase in the cytotoxicity of the resulting conjugates.

3. The cytotoxic effect of Les-1895 conjugates with lectin, which selectively binds to the HCT 116 human intestinal cancers, was dose-dependent. At the same time the effect of the developed conjugates of lectins towards the pseudonormal human embryonic kidney HEK 293 cells was more pronounced after 24 h, although it was manifested only at high doses of the conjugates.

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Використання лектинів як векторних молекул для доставки лікарських засобів до клітин і тканин. Повідомлення 2

В. О. Антонюк, Н. Р. Скорохід, А. В. Лозинський, Р. В. Антонюк, Р. Б. Лесик, Р. С. Стойка

Мета. Визначення на культурі клітин біологічної активності кон'югатів сполуки з протипухлинною активністю з лектинами різної вуглеводної специфічності, де

кон'югати використовували як векторні молекули для адресної доставки цих речовин. **Методи.** Кон'югування лектинів (насіння гороху (PSA), арахісу (PNA) та еритроаглютиніну з насіння квасолі звичайної (PHA-E) з похідним тіопірано[2,3-*d*]тіазолу Les-1895). Біотестування цих кон'югатів на культурі клітин різного походження **Результати.** Кон'югування сполуки Les-1895 з лектинами призводить до збільшення її цитотоксичних ефектів щодо клітин Jurkat на 23 % для PSA-Les-1895, на 34 % — для PNA-Les-1895 і на 12 % — для PHA-E-Les-1895. IC_{50} для кон'югатів Les-1895 було ≈ 10 мкг/мл, тоді як для нативного Les-1895 ≈ 30 мкг/мл. Кон'югати Les-1895 з PNA та PHA-E пригнічують життєздатність клітин лінії HCT 116 значно сильніше, ніж аналогічний кон'югат з PSA. Цитотоксична дія кон'югатів з PNA (IC_{50} = 4 мкг/мл) і PHA-E(IC_{50} = 3 мкг/мл) на ці клітини була сильнішою, ніж дія вільного Les-1895 (IC_{50} = 10 мкг/мл) та інтактних лектинів. Приєднання Les-1895 до альбуміну сироватки крові людини (HSA) підвищує розчинність Les-1895 у воді, однак, на відміну від кон'югатів Les-1895 з лектинами, знижує на 40 % цитотоксичний ефект утвореного кон'югату, зокрема, для клітин лінії Jurkat. Псевдонормальні клітини лінії HEK 293 виявилися мало чутливими до дії нативних лектинів PSA, PNA і PHA-E та до кон'юґатів цих лектинів. **Висновки.** Кон'югування сполуки Les-1895 із специфічними лектинами посилює цитотоксичний ефект. Одержані результати є важливими для моделювання адресної доставки біологічно активних речовин в специфічні клітини тканин організму.

Ключові слова: лектин насіння гороху, лектин арахісу, ФГА-Р, кон'югати, тіопірано[2,3-*d*]тіазоли, протипухлинна активність

Использование лектинов как векторной молекулы для доставки лекарственных средств в клетки и ткани. Сообщение 2

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Цель. Определение на культуре клеток биологической активности конъюгатов соединения с противоопухолевой активностью с лектинами различной углеводной специфичности, где конъюгаты использовали в качестве векторных молекул для адресной доставки этих веществ. **Методы.** Конъюгирование лектинов (семян гороха (PSA), арахиса (PNA) и эритроагглютинина из семян фасоли обыкновенной (PHA-E) из производным тиопирано[2,3-*d*]тиазола Les-1895). Биотестирование этих конъюгатов на культуре клеток различного происхождения. **Результаты.** Конъюгирование соединения Les-1895 с лектинами приводит к увеличению цитотоксических эффектов конъюгата для клеток Jurkat на 23 % для PSA-Les-1895, на 34 % — для PNA-Les-1895 и на 12 % — для PHA-E-Les -1895. IC_{50} для конъюгатов Les-1895 было ≈ 10 мкг/мл, тогда как для нативного Les-1895 ≈ 30 мкг/мл. Конъюгаты Les-1895 с PNA и PHA-E подавляют жизнеспособность клеток линии HCT 116 значительно сильнее, чем аналогичный конъюгат с PSA. Цитотоксическое действие конъюгатов с PNA (IC_{50} = 4 мкг/мл) и PHA-E (IC_{50} = 3 мкг/мл) на эти клетки было сильнее, чем действие свободного Les-1895 (IC_{50} = 10 мкг/мл) и интактных лектинов. Присоединение Les-1895 к альбумину сыворотки крови человека (HSA) повышает растворимость Les-1895 в воде, однако, в отличие от конъюгатов Les-1895 с лектинами, цитотоксический эффект образованного конъюгата снижается на 40 %, в частности, для клеток линии Jurkat. Псевдонормальные клетки линии HEK 293 оказались мало чувствительными к действию нативных лектинов PSA, PNA и PHA-E и к действию конъюгатов этих лектинов. **Выводы.** Конъюгирование Les-1895 со специфическими лектинами усиливает цитотоксический эффект. Полученные результаты показывают возможность адресной доставки биологически активных веществ в специфические клетки, ткани и органы тела человека.

Ключевые слова: лектин семян гороха, лектин арахиса, ФГА-Р, коньюґаты, тиопирано[2,3-*d*]тиазолы, противоопухолевая активность

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