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MORPHOLOGICAL CHARACTERISTICS AND CYTOTOXIC ACTIVITY OF THE BLACK SEA STRAIN *STREPTOMYCES* SP. LIM 10

Aim. *The aim of the work was to study the morphological characteristics and cytotoxic activity of the strain of actinobacteria Streptomyces sp. Lim 10 isolated from natural fouling of shell rock in the Odesa Bay of the Black Sea.* ***Materials and methods.*** *The object of the study was a strain of marine actinobacteria Streptomyces sp. Lim 10. The morphology and growth patterns were studied on the media of Gauze 2, Czapek, Eshbi, TSB and on the media of ISP (ISP-1–ISP-7). SG medium was used to accumulate secondary metabolites of actinobacteria. Extraction of exometabolites from the culture liquid was carried out with ethyl acetate followed by dissolution in dimethyl sulfoxide (DMSO). The cytotoxic activity of exometabolites of actinobacteria strain Streptomyces sp. Lim 10 was studied on the model of cultures cells human - rhabdomyosarcoma (RD,) and of the laryngeal adenocarcinoma (Hep-2). The cytotoxic effect of exometabolites of the actinobacteria strain Streptomyces sp. Lim 10 was determined after 24 hours of incubation by microscopy. The degree of destruction of the monolayer was assessed by the number of viable cells in terms of optical density, which was measured using a spectrophotometer at a wavelength of 630 nm. The exometabolites of actinobacteria strain Streptomyces sp. Lim 10 were identified using LC-ESIMS.* ***Results.*** *Study of the morphological properties of the Black Sea strain of actinobacteria Lim 10 showed that it is characterized by pleomorphism. A high cytotoxic activity of exometabolites of the marine strain of actinobacteria Streptomyces sp. Lim 10 was established. The level of cytotoxic effect of metabolites of the strain of actinobacteria Streptomyces sp. Lim 10 on Hep-2 cell culture depended on their concentration. RD cell culture was more sensitive to the cytotoxic effect of exometabolites of Streptomyces sp. Lim 10 – at all tested concentrations of exometabolites (from 2.5 to 500.0 μg/ml), the number of viable cells in the RD monolayer decreased to 51.3 ± 3.0 – 63.7 ± 5.4%, compared to the control. This can be at least partially explained by action of apoptosis-inducing agent staurosporine, which is produced by strain Streptomyces sp. Lim 10 along with itsstructural homologs.* ***Conclusion.*** *Strain Streptomyces sp. Lim 10 is a promising producer of antitumor compounds and can be recommended for further more in-depth studies.*

Key words: Streptomyces, Black Sea, morphological characteristics, exometabolites, cytotoxic activity.

Introduction. Actinobacteria are a widespread group of microorganisms in natural ecosystems that have been used as a source of material to search for useful secondary metabolites with antibiotic activity [2, 8].

Actinobacteria inhabit soils, and fresh and seawater bodies. Marine actinobacteria were first discovered in 1984. Since then, many representative species of marine actinobacteria have been found in aquatic systems around the world, and some species are very common in the world's oceans.

Today, marine actinobacteria are of active academic and commercial interest, as they live in a unique environment that facilitates the synthesis of new biologically active metabolites [3, 4, 12].

Actinobacteria are considered as one of the most important sources of biologically active compounds for the pharmaceutical industry, currently more than 5000 secondary metabolites with antibiotic activity have been identified.

According to some predictions, actinobacteria can produce up to 150000 different chemical antimicrobial agents [11, 13].

Secondary metabolites of actinobacteria differ in their various biological activities. Among actinobacteria, the genus *Streptomyces* deserves special attention, since this genus is the main source of bioactive molecules, bacteria of each strain are potentially able to produce up to 20 secondary metabolites with antimicrobial, antitumor, or anti-inflammatory activity [7, 9].

They are producers of biologically active substances that are actively used in the pharmaceutical industry, including antibiotics, exopolysaccharides, surfactants, antiviral, cytotoxic agents and enzyme inhibitors.

Marine strains of the genus *Streptomyces* are characterized as the most important producers of bioactive microbial metabolites with antitumor activity. For example, two rare steroidal alkaloids, anandin A and B, were identified in the marine actinobacteria *Streptomyces anandii* H41-59. Anandin A exhibited an inhibitory effect against the human mammary ductal adenocarcinoma cell line MCF-7, the human glioblastoma cell line SF-268, and the human lung epithelial carcinoma cell line NCI-H460 with IC50 values of 7.5, 7.9, 7.8 μg/mL, respectively [14].

Four new sesquiterpenoid naphthoquinones, marfuraquinocins A-D (1–4), and two new geranylated phenazines, phenaziterpenes A (5) and B (6), were isolated from the fermentation broth of *Streptomyces niveus* SCSIO 3406, which originated from a South China Sea sediment sample obtained from a depth of 3536 m. In a panel of cytotoxicity and antibacterial assays, 1 and 3 were found to inhibit a NCI-H460 cancer cell line with IC50 values of 3.7 and 4.4 μM, respectively.

Compounds 1, 3, and 4 exhibited antibacterial activities against S*taphylococcus aureus* ATCC 29213 with equivalent MIC values of 8.0 μg/mL; compounds 3 and 4 each showed antibacterial activity against methicillin-resistant (MRSE) *Staphylococcus epidermidis* shhs-E1 with MIC values of 8.0 μg/mL [15].

Thus, marine strains of bacteria of the genus *Streptomyces* are characterized as major producers of bioactive microbial metabolites with antitumor activity.

The aim of the work was to study the morphological characteristics and cytotoxic activity of the strain of actinobacteria *Streptomyces sp.* Lim 10 isolated from natural fouling of shell rock in the Odesa Bay of the Black Sea.

Materials and methods. The object of the study was a strain of marine bacteria *Streptomyces sp.* Lim 10, which is stored in the collection of microorganisms of the Department of Microbiology, Virology and Biotechnology of Odesa I. I. Mechnikov National University. Isolated from the fouling of natural shell rock collected at a depth of 0.2–1.0 m in the Odesa Bay of the Black Sea near the Hydrobiological Station of Odesa I. I. Mechnikov National University (Odesa, Ukraine, 46°27′01″N 30°46′14″E).

Nutrient media such as Gausse 2, Chapek, and Eshby were used to isolate actinobacteria [1]. The morphology and growth patterns were studied on the media of Gauze 2, Czapek, Eshbi, TSB, and on the media of ISP (ISP-1–ISP-7), according to the International Project of Streptomyces (ISP), during 14–21 days at 28 °C.

Synthesis of melanoid pigments was studied on ISP-6 and ISP-7 media by cultivating *Streptomyces* sp. Lim 10 for 14–21 days at 28 °C. Cell morphology was studied by microscopy of fixed preparations stained with a water solution of Pfeiffer's fuchsin (light microscope, x1500).

To obtain exometabolites, the studied strain of actinobacteria were grown in 500 ml flasks with glass balls on SG medium (Soy Glucose Broth: glucose – 20.0; yeast extract – 5.0; soy peptone – 10.0; calcium carbonate – 2.0 g/L) at 28 °C by culturing on a rotary shaker for 7 days at 180 rpm.

The cell mass of actinobacteria was separated by centrifugation at 10,000 g for 10 minutes. Exometabolites were extracted from the culture liquid with ethyl acetate in an equal ratio on a horizontal shaker with gentle agitation for 2 hours at room temperature [11].

The extract was taken using a 250 ml separatory funnel and ethyl acetate was evaporated at 40 °C in a stream of gaseous nitrogen. The mass of the dried extract was determined on an analytical balance and dissolved in an appropriate volume of dimethyl sulfoxide (DMSO). Working solutions of exometabolites were prepared with the applied nutrient medium for cell cultures.

The cytotoxic activity of exometabolites a strain of marine bacteria *Streptomyces sp.* Lim 10 was studied on the model of a monolayer of cultures of malignant cells of human – human rhabdomyosarcoma (RD) and of the human laryngeal adenocarcinoma (Hep-2), maintained in the museum collection of the Department of Microbiology, Virology and Biotechnology of the Odesa I. I. Mechnikov National University.

Cultures of Hep-2 and RD cells were seeded in 96-well plates with 100 µl of DMEM medium (BioWest, France) with the addition of antibiotics penicillin and streptomycin at a concentration of 100 U/ml, fetal bovine serum (FBS Premium) (BioWest, France) in the amount 10%. The seed concentration of cells is $4x10^4$ cells/ml. Cell cultures were incubated at 36 °C in a CCL-050T-8 CO_2 incubator for 24 hours [5].

Then exometabolites of strain *Streptomyces sp.* Lim 10 were added to each well at a concentration of: 2.5; 25.0; 50.0; 100.0; 250.0; 500.0 µg/ml of dried native extract. Controls were intact cell cultures in DMEM medium and cell cultures in DMEM medium with the addition of DMSO in the following concentrations of 0.5; 0.25; 0.1; 0.05; 0.025; 0.0025%.

After 24 h the cells were fixed by adding 100 µl of 70% ethanol to the wells. Incubated for 15 min at a temperature of 20 °C. Then the ethanol was removed from the plates and added 100 µl of methylene blue dye. Incubated for 15 min at room temperature. Then the plates were washed three times with tap water to remove the dye, incubated for 2 h at 37 °C.

The dye was eluted from the cells of the monolayer by adding 100 µl of 0.1 mol/L HCl to each plate well, and incubated for 5 min at room temperature [5].

The cytotoxic effect of exometabolites of the strain of marine actinobacteria Lim 10 was determined after 24 hours of incubation. Morphological changes of cells were determined by microscopy of the cell monolayer. The degree of destruction of the monolayer was assessed by the number of viable cells in terms of optical density (OD), which was measured using a spectrophotometer for microplates at a wavelength of 630 nm.

The composition of exometabolites of the marine strain Lim 10 was determined on a ThermoFischer Dionex UltiMate™ 3000 BioRS UPLC system connected to a Bruker Daltonics maXis II mass spectrometer (4G hr-ToF) A Waters BEH C18 column (100 mm x 2.1 mm, 1.7 µm) was used) at a temperature of 45 °C and a flow rate of 0,5 ml/min.

The following solvents were used: A – formic acid at a concentration of 0.1%; B – 100:20 acetonitrile + formic acid at 0.1%.

Detection took place in the range of 150–2000 m/z and 200–600 nm.

The exometabolites of strain *Streptomyces sp.* Lim 10 were identified using the electronic version of the Dictionary of Natural Products [6].

Mathematical processing of the results was carried out using Microsoft Office Excel-2016. The significance of differences between the mean values was determined by Student's t-test at a significance level of 95% ($p<0.05$).

Results. When actinobacteria strain *Streptomyces sp.* Lim 10 were inoculated on the dense medium of Gauze 2, Eshby, individual large colonies grew after 5 days.

On Gauze 2 medium, after 5 days of cultivation, the bacteria of this strain formed colonies with developed white aerial mycelium. It was well removable with a loop from the surface of the colony (Fig. 1).

Fig. 1. Morphology of *Streptomyces sp.* Lim 10 strain colonies on Gauze 2 nutrient medium. Exposure for 5 days

Similar colonies of bacteria of the strain were formed on Eshby's medium; on this medium, the aerial mycelium was cream-colored.

Strain *Streptomyces sp.* Lim 10 on agarized nutrient media (Gauze 2, Eshby, Chapek) produced a dark brown water-soluble pigment that diffused into the medium.

During the cultivation of actinobacteria strain *Streptomyces sp.* Lim 10 on TSB liquid nutrient medium, the most active production of water-soluble dark brown pigment was observed (Fig. 2).

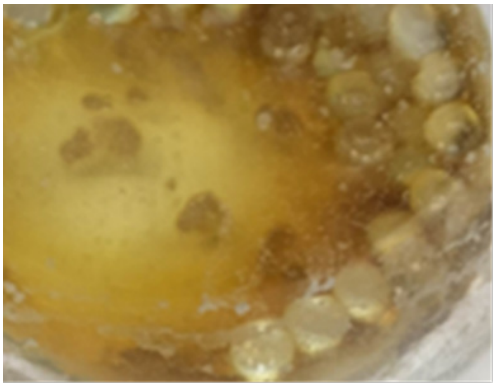
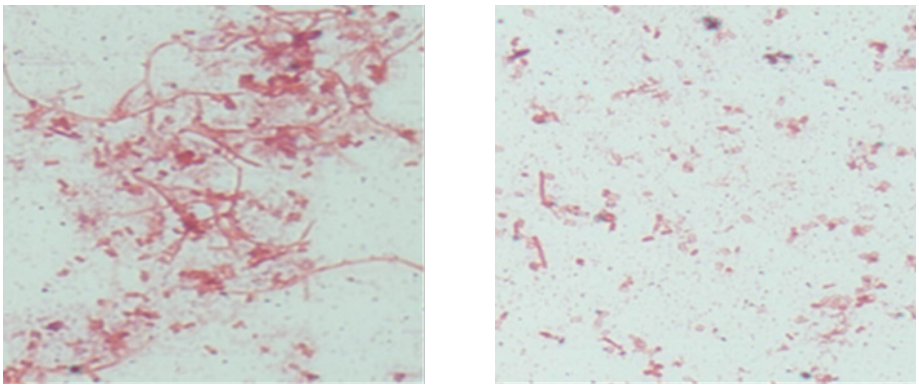


Fig. 2. Accumulation of water-soluble dark brown pigment during cultivation of strain *Streptomyces sp.* Lim 10 on liquid TSB nutrient medium. Exposure 10 days

At the same time, the bacteria of the strain did not synthesize melanoid pigments, the ability to synthesize which was determined on media ISP-6 and ISP-7.

The bacteria of the strain grew well on all ISP media, which differ in the composition of nutrients and trace elements.

Various forms of actinobacteria *Streptomyces* sp. were observed in the preparations. Lim 10: from filiform to cocci (Fig. 3).



A **B**

Fig. 3. Cell morphology of actinobacteria strain *Streptomyces sp.* Lim 10. A – filamentous cells; B – rods and cocci. Bright-field microscopy, Pfeiffer magenta stain (x1500)

Cells were mostly represented by short rods of small size, which were arranged singly, in pairs in chains, V-shaped, chaotic. Long filamentous cells were also detected, and some cells had a fragmented coccoid shape.

The marine strain of actinobacteria *Streptomyces sp.* Lim 10 is characterized by pleomorphism and intraspecific variability that are characteristic of actinobacteria. Based on the study of biological properties, the marine strain Lim 10 was confirmed to belong to the genus *Streptomyces.*

On the model of cultures of human malignant cells – connective tissue - human rhabdomyosarcoma RD and glandular epithelium cells – adenocarcinoma of the human larynx Hep-2, a high cytotoxic activity of exometabolites of the marine strain of *Streptomyces sp.* Lim 10 in a concentration from 250.0 to 500.0 μg/ml (Fig. 4).

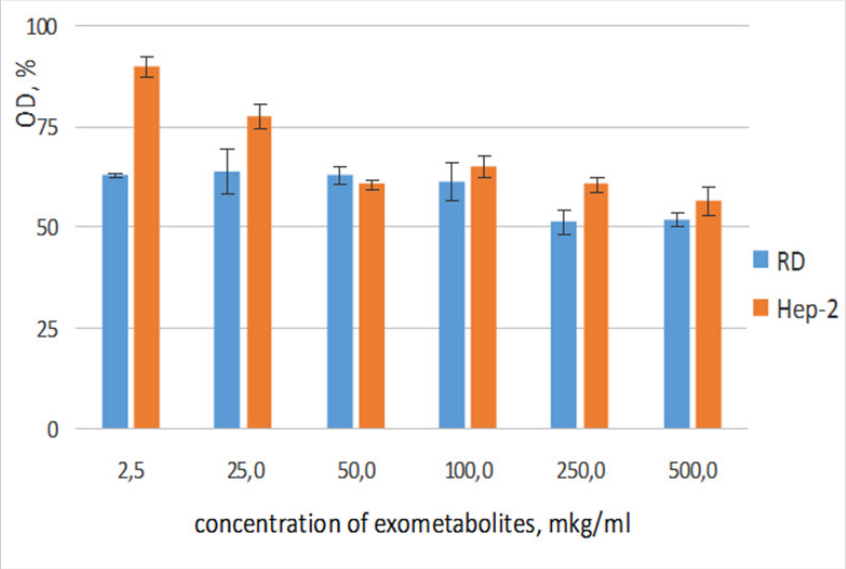


Fig. 4. Cytotoxic effect of exometabolites of actinobacteria *Streptomyces* sp. Lim 10 on the viability of cells in a monolayer of Hep-2 and RD cultures according to the OD indicator, %* (exposure for 24 hours)

Note: *in percentage of viable cells to control with DMSO

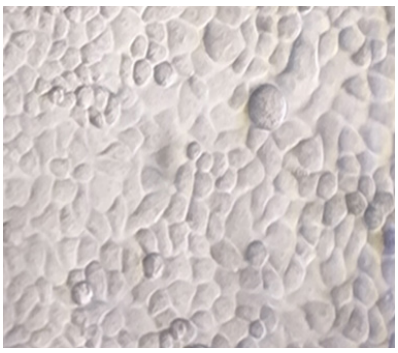
After 24 hours of exposure, morphological changes were detected in tumor cultures of human Hep-2 and RD cells - rounding of cells, vacuolization of the cytoplasm, shrinkage and pyknosis of the nucleus, and destruction of the monolayer (Fig. 5).

The level of cytotoxic effect on Hep-2 cell cultures depended on the concentration of exometabolites of *Streptomyces* sp. Lim 10. There was a high level of cytotoxicity at concentrations of exometabolites from 50.0 to 500.0 μg/ml – the number of viable cells in the Hep-2 monolayer decreased to 56.5 ± 3.3 – 60.5 ± 1.9%, compared to the control DMSO. A weak cytotoxic effect in the culture of Hep-2 cells was registered for the concentration of exometabolites of *Streptomyces* sp. Lim 10. In concentration range from 2.5 to 25.0 μg/ml – the number of viable

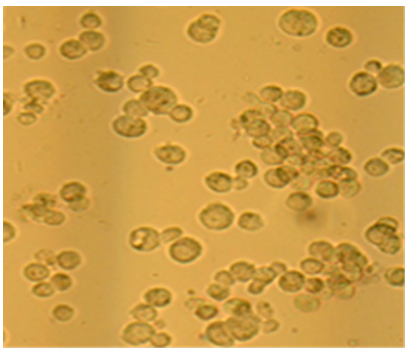
cells in the monolayer decreased to 89.7 ± 2.4 – 77.4 ± 3.0%, compared to the DMSO control.

RD cell culture was more sensitive to the cytotoxic effect of exometabolites of *Streptomyces* sp. Lim 10 – at all tested concentrations of exometabolites (from 2.5 to 500.0 µg/ml), the number of viable cells in the RD culture monolayer decreased to 51.3 ± 3.0 – 63.7 ± 5.4%, compared to the control DMSO.

In the metabolome of strain Streptomyces sp. Lim10, the only anticancer compound revealed was N- formylstaurosporine, and in the second - in addition to staurosporine itself, its derivatives: staurosporinone, 4'-demethylamino-4',5'-dihydroxystaurosporine, TAN 1030A 4'-De(hydroxyimino) 4'-oxo (or its 3'-epimer), and N13-glycosylated staurosporine derivative with an unidentified hydrocarbon radical (possibly α-L-rhamnopyranose) (Fig. 6).



Hep-2 cell culture, control (with the DMSO at a concentration of 0.1%)



The influence of exametabolites of *Streptomyces* sp. Lim 10 at a concentration of 500.0 µg/ml on Hep-2 cell culture

Fig. 5. Morphological changes of cells and destruction of a monolayer of transplantable culture of Hep-2 human laryngeal adenocarcinoma cells under the influence of exometabolites of *Streptomyces* sp. Lim 10 in concentration 500.0 µg/ml. Exposure 24 hours. (10x10, Zeiss AxioScope A1, Zeiss Axiocam 503; Zen 2.0)

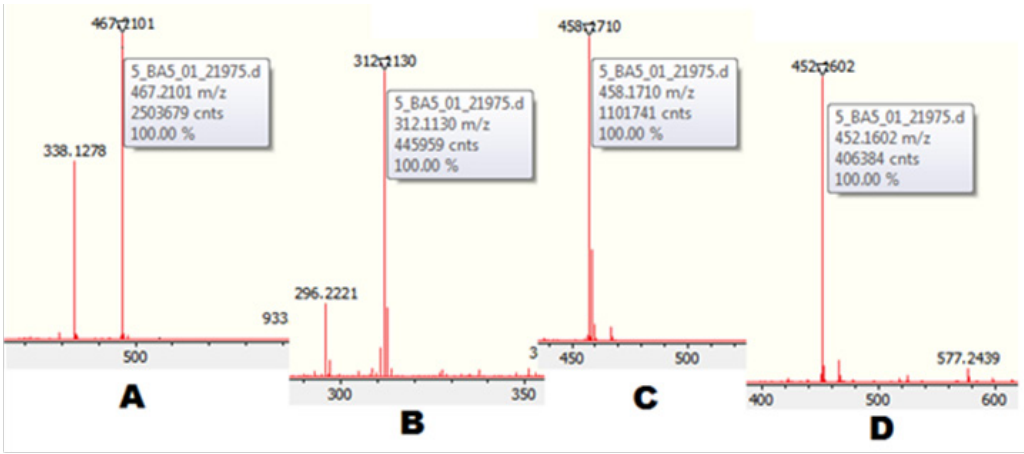


Fig. 6. Chosen ESI-MS mass-spectra for staurosporine and its homologs in positive ionization mode: A – staurosporine (retention time – 6.6 min), B – staurosporinone (retention time – 8.11 min), C – staurosporine N13- α-L-rhamnopyranosyl (retention time 8.01 min); D – TAN 1030A 4'- de(hydroxyimino)

These complex indolocarbazoles are powerful inhibitors of protein kinases and because of that, they have antitumor activity, stimulating malignant cells to apoptosis [10].

Most of the detected by LC-HRESIMS compounds (97 in positive mode and 134 in negative, respectively) were unidentified.

Thus, the results of our research indicate that the strain Streptomyces sp. Lim 10 is a promising producer of antitumor compounds and can be recommended for further more in-depth studies.

The Black Sea strain of actinobacteria *Streptomyces sp.* Lim 10, isolated from the fouling of shell rock, was characterized by high morphological variability, forming different colony morphotypes during growth.

Based on the study of biological properties of the Black Sea of actinobacteria strain Lim 10 can be attributed to the genus *Streptomyces*.

Cytotoxic activity of exometabolites of the marine strain *Streptomyces* sp Lim 10 was established on the RD (rhabdomyosarcoma) and Hep-2 (laryngeal adenocarcinoma) culture models in concentrations from 250.0 to 500.0 μg/ml. Dose-dependent cytotoxic effect of the exometabolite was found in Hep-2 culture. RD culture was more sensitive to exometabolites of *Streptomyces* sp. Lim 10 – at concentrations of exometabolites from 2.5 to 500.0 μg/ml, the number of viable cells in the monolayer decreased by 1.5–2 times compared to the control.

The strain *Streptomyces* sp. Lim 10 is a promising producer of antitumor compounds and can be recommended for more in-depth further studies *in vivo.*

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МОРФОЛОГІЧНА ХАРАКТЕРИСТИКА ТА ЦИТОТОКСИЧНА АКТИВНІСТЬ ЧОРНОМОРСЬКОГО ШТАМУ *STREPTOMYCES* SP. LIM 10

Мета. *Метою роботи було вивчити морфологічні характеристики та цитотоксичну активність штаму актинобактерій Streptomyces sp. Lim 10 виділеного з природного обростання черепашнику в Одеській затоці Чорного моря.* ***Матеріали та методи.*** *Об'єктом дослідження був штам морських актинобактерій Streptomyces sp. Lim 10. Морфологію та особливості росту вивчали на середовищах Гаузе 2, Чапека, Ешбі, TSB та на середовищах ІСП (ІСП-1–ІСП-7). Для накопичення вторинних метаболітів актинобактерій використовували середовище SG. Екстрагування екзометаболітів з культуральної рідини проводили етилацетатом з подальшим розчиненням у диметилсульфоксиді (ДМСО). Цитотоксичну активність екзометаболітів актинобактерій штаму Streptomyces sp. Lim 10 вивчали на моделі культур клітин людини – рабдоміосаркоми (RD) та аденокарциноми гортані (Hep-2). Цитотоксичну дію екзометаболітів актинобактерій штаму Streptomyces*

sp. Lim 10 визначали після 24 годин інкубації методом мікроскопії. Ступінь руйнування моношару оцінювали за кількістю життєздатних клітин за оптичною щільністю, яку вимірювали за допомогою спектрофотометра при довжині хвилі 630 нм. Екзометаболіти актинобактерій штаму Streptomyces sp. Lim 10 ідентифіковано за LC-ESIMS. ***Результати.*** *Вивчення морфологічних властивостей чорноморського штаму актинобактерій Streptomyces sp. Lim 10 показало, що для нього характерний плеоморфізм. Встановлено високу цитотоксичну активність екзометаболітів морського штаму актинобактерій Streptomyces sp. Lim 10. Рівень цитотоксичної дії метаболітів штаму актинобактерій Streptomyces sp. Lim 10 на культуру клітин Нер-2 залежав від їх концентрації. Культура клітин RD була чутливішою до цитотоксичної дії екзометаболітів штаму Streptomyces sp. Lim 10 – за всіх досліджених концентрацій екзометаболітів (від 2,5 до 500,0 мкг/мл) кількість життєздатних клітин у моношарі RD зменшувалася до 51,3 ± 3,0 – 63,7 ± 5,4%, порівняно з контролем. Це принаймні частково можна пояснити дією апоптоз-індукувального агенту стауроспорину, який продукується штамом Streptomyces sp. Lim 10 разом їз структурними гомологами.* ***Висновок.*** *Штам Streptomyces sp. Lim 10 є перспективним продуцентом протипухлинних сполук і може бути рекомендований для подальших більш поглиблених досліджень.*

Ключові слова: Streptomyces, Чорне море, морфологічні характеристики, екзометаболіти, цитотоксична активність.

СПИСОК ВИКОРИСТАНОЇ ЛІТЕРАТУРИ

1. *Білявська Л.О.* Актинобактерії роду *Streptomyces* і їхні метаболіти у біорегуляції рослин: дис. док. біол. наук : 03.00.07. Київ. – 2018. – 485 с.
2. *Галкін Б.М., Філіпова Т.О., Іваниця В.О., Гудзенко Т.В.* Біоактивні вторинні метаболіти морських мікроорганізмів: монографія. – Одеса: ОНУ, 2022. – 220 с.
3. *Потапенко К.С.* Вторинні метаболіти морських актинобактерій з антибіотичною активністю // Мікробіологія і біотехнологія. – 2021. – № 3. – С. 28–43.
4. *Abdel-Mageed W.M.* Dermacosins, a new family of phenazines from deep-sea dermacocci isolated from the sediment of the Mariana Trench // Org. Biomol. Chem. – 2021. – № 8. – P. 2352–2362.
5. *Abdelfattah M.S., Elmallah M.I.Y, Hawas U.W., El-Kassema L.T.A., Eid M.* Isolation and characterization of marine-derived actinomycetes with cytotoxic activity from the Red Sea coast // Asian Pacific Journal of Tropical Biomedicine. – 2016. – V. 6 (8). – P. 651–657.
6. *Buckingham J.* Dictionary of natural products, supplement 4 // CRC press. – 1997. – V. 11.
7. *Lewin G.R.* Evolution and Ecology of *Actinobacteria* and their bioenergy applications // Microbiological Research. – 2016. – V. 70 (1). – P. 235–254.
8. *Malve H.* Exploring the ocean for new drug developments: Marine pharmacology // Journal of pharmacy bioallied sciences. – 2016. – V. 8. – P. 83–91.
9. *Manivasagan P.* Pharmaceutically active secondary metabolites of marine actinobacteria // Microbiological Research. – 2014. – V. 169 (4). – P. 262–278.

10. *Ōmura S., Asami Y., Crump A.* Staurosporine: New lease of life for parent compound of today's novel and highly successful anti-cancer drugs // The Journal of Antibiotics. – 2018. – V. 71 (8). – P. 688–701.
11. *Paulus C., Rebets Y., Tokovenko B., Nadmid S., Terekhova L.P., Myronovskyi M., Zotchev S.B., Ruckert C., Braig S., Zahler S., Ralinovski J., Luzhetskyy A.* New natural products identified by combined genomics-metabolomics profiling of marine *Streptomyces* sp. MP131-18 // Scientific Reports. – 2017. – № 7. – P. 423–82.
12. *Purves K.* Using molecular networking for microbial secondary metabolite bioprospecting // Metabolites. – 2016. – V. 6 (1). – P. 133–121.
13. *Ramesh S.* Marine Rare *Actinomycetes*: A Promising Source of Structurally Diverse and Unique Novel Natural Products // Mar. Drugs. – 2019. – V. 17. – 249 p.
14. *Wang Y.P.* Metabolite sensing and signaling in cell metabolism // Signal Transduction and Targeted Therapy. – 2018. – V. 3. – P. 30–41.
15. *Yang-Mei Z., Anandins A.* Two Rare Steroidal Alkaloids from a Marine *Streptomyces anandii* H41-59 // Marine drugs. – 2017. – V. 15 (11). – P. 355–369.
16. *Song Y., Huang H., Chen Y., Ding J., Zhang Y., Sun A., Zhang W., Ju J.* Cytotoxic and antibacterial marfuraquinocins from the deep South China Sea-derived *Streptomyces niveus* SCSIO 3406 // J Nat Prod.–2013. – V. 76 (12). – P. 2263–2268.

REFERENCES

1. Belyavskaya LA. Actinobacteria of the genus Streptomyces and their metabolites in plant bioregulation: dis. … doc. biol. sciences: 03.00.07. Kyiv. 2018: 485 (in Ukrainian).
2. Galkin BM, Filippova TO, Ivanytsia VO, Gudzenko TV. Bioactive secondary metabolites from marine microorganisms: monograph. Odesa. ONU. 2022: 220 (in Ukrainian).
3. Potapenko KS, Korotaeva NV, Ivanitsa VO. Secondary metabolites of marine actinobacteria with antibiotic activity. Microbiology and biotechnology. 2021; 3: 28–43 (in Ukrainian).
4. Abdel-Mageed WM. Dermacosins, a new family of phenazines from deep-sea dermacocci isolated from the sediment of the Mariana Trench. Org. Biomol. Chem. 2021; 8: 2352–2362.
5. Abdelfattah MS, Elmallah MIY, Hawas UW, El-Kassema LTA, Eid M. Isolation and characterization of marine-derived actinomycetes with cytotoxic activity from the Red Sea coast. Asian Pacific Journal of Tropical Biomedicine. 2016; 6 (8): 651–657.
6. Buckingham J. Dictionary of natural products, supplement 4. CRC press. 1997; 11.
7. Lewin GR. Evolution and Ecology of *Actinobacteria* and their bioenergy applications. Microbiological Research. 2016; 70 (1): 235–254.
8. Malve H. Exploring the ocean for new drug developments: Marine pharmacology. Journal of pharmacy bioallied sciences. 2016; 8: 83–91.

9. Manivasagan P. Pharmaceutically active secondary metabolites of marine actinobacteria. Microbiological Research. 2014; 169 (4): 262–278.
10. Ōmura S, Asami Y, Crump A. Staurosporine: New lease of life for parent compound of today's novel and highly successful anti-cancer drugs. The Journal of Antibiotics. 2018; 71 (8): 688–701.
11. Paulus C, Rebets Y, Tokovenko B, Nadmid S, Terekhova LP, Myronovskyi M, Zotchev SB, Ruckert C, Braig S, Zahler S, Ralinovski J, Luzhetskyy A. New natural products identified by combined genomics-metabolomics profiling of marine *Streptomyces* sp. MP131-18. Scientific Reports. 2017; 7: 423–82.
12. Purves K. Using molecular networking formicrobial secondary metabolite bioprospecting. Metabolites. 2016; 6 (1): 133–121.
13. Ramesh S. Marine Rare *Actinomycetes*: A Promising Source of Structurally Diverse and Unique Novel Natural Products. Mar. Drugs. 2019; 17: 249.
14. Wang YP. Metabolite sensing and signaling in cell metabolism. Signal Transduction and Targeted Therapy. 2018; 3: 30–41.
15. Yang-Mei Z, Anandins A. Two Rare Steroidal Alkaloids from a Marine *Streptomyces anandii* H41-59. Marine drugs. 2017; 15 (11): 355–369.
16. Song Y, Huang H, Chen Y, Ding J, Zhang Y, Sun A, Zhang W, Ju J. Cytotoxic and antibacterial marfuraquinocins from the deep South China Sea-derived *Streptomyces niveus* SCSIO 3406. J Nat Prod. 2013; 76 (12): 2263–2268.

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