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THE BIOCIDE ACTION OF METABOLITES OF *STREPTOMYCES GLOBISPORUS* 3-1 AND *STREPTOMYCES CYANOGENUS* S136 STRAINS

Research of the biocide action of streptomycete-antagonist metabolites on the causative agent of bacterial canker of tomato and on the host-plant fertility is the actual question. ***Aim.*** *To determine the action of metabolites of Streptomyces globisporus 3-1 and Streptomyces cyanogenus S136 on the phytopathogen Clavibacter michiganensis 10_2 in vitro and on seed germination, growth and yield of tomatoes in vivo.* ***Methods****. Microbiological methods in laboratory conditions and descriptive-comparative analysis of growth and development of tomatoes in hothouse conditions were used.* ***Results****. S. globisporus 3-1 and S. cyanogenus S136 metabolites inhibited the growth of the phytopathogen C. michiganensis 10_2 with the formation of clean zones 45 and 35 mm in vitro, respectively. Pre-sowing treatment with metabolites of S. globisporus 3-1 and S. cyanogenus S136 of tomatoes Lana seeds reduced germination by 27% for both and led to defects in leaf shape and plant sterility, respectively. Treatment by metabolites of both Streptomyces strains of phytopathogen infected seeds did not improve germination, growth, and yield compared to grown plants from infected seeds, though it were visually not defective, sterile and with signs of bacterial canker of tomato.* ***Conclusion****. It was found that metabolites of S. globisporus 3-1 and S. cyanogenus S136 had a biocide action on the phytopathogen C. michiganensis 10_2 in vitro and on Lana tomatoes in hothouse conditions.*

Key words: Biocide, Clavibacter michiganensis subsp. michiganensis, bacterial canker of tomato, Streptomyces

The term "Biocides" combines toxic substances used in agriculture, industry, veterinary and human medicine against organisms that cause damage to the respective sphere [4].

Phytopathogenic bacterium *Clavibacter michiganensis subsp. michiganensis* (Cmm) is the causative agent disease of tomato canker, manifested by spots and ulcers on leaves, fruits, stems and peduncles, affects the vascular system due to the expression of chromosome genes (pathogenicity island *chp*/*tom*A) and plasmids pCM1 (*cel*A), pCM2 (*pat*-1) [2, 16, 17].

Today, the literature offers ecological means of combating infectious diseases in the agricultural sector, which contain metabolites of soil microorganisms, including streptomycetes [1, 3]. According to the literature, more than a third (37–45%) of soil isolates of cultured streptomycetes have an antagonistic activity

to Cmm [13, 18], although their effectiveness does not go beyond laboratory conditions. One of the reasons for the small number of drugs against phytopathogens against the background of the mass of the claimed antagonists is the toxicity (biocide) of their metabolites against the host plant. Determination of the active substance after unproductive field studies is usually not performed, and results of works are not published, to break such a closed circle is logical to study the biocide action of known antagonists.

Streptomyces globisporus 3-1 and *Streptomyces cyanogenus* S136 strains, which synthesize landomycins E and A, respectively, were active against Cmm. Landomycins (L) E and A belong to the group of angucycline antibiotics that induce apoptosis of cancer cells (human and animal) due to increase levels of reactive oxygen species (ROS), do not intercalate into DNA and have medical potential of antitumor activity [6, 15]. Little attention has been paid to the study of the effects of such metabolites on phytopathogen-host systems, due to the recommendation not to use medical antibiotics in agriculture [9]. On the other hand, isolates have been isolated from natural niches (*S. globisporus* 3-1 soils of Armenia, *S. cyanogenus* S136 mountains of India [8, 14]), where they affect plant systems, which requires studying the biocide action of their metabolites in different natural models, in particular the phytopathogen-host.

The aim of the study was to determine the action of metabolites of *S. globisporus* 3-1 and *S. cyanogenus* S136 on the phytopathogen *C. michiganensis* 10_2 *in vitro* and on the seed germination, growth and yield of tomatoes *in vivo*.

Materials and methods

The following were used: strain *S. globisporus* 3-1 – landomycin E producer [7, 8] from the Laboratory of Genetics of Microorganisms collection of the Zabolotny Institute of Microbiology and Virology (IMV) of the NASU; strain *S. cyanogenus* S136 – landomycin A producer, kindly provided by D.A. Hopwood of the University of East Anglia; phytopathogen *C. michiganensis* 10_2 – tester [2] from the collection of the Department of Phytopathogenic Bacteria of the IMV NASU. Experiments in the hothouse were carried out using seeds of Lana tomatoes, fruit weight 80–110 g, manufacturer "Yaskravyy".

Streptomycetes growth mediums consist of (g/l): soy flour 20, NaCl 5, glucose 20, pH 7.2 for strain *S. globisporus* 3-1 [7]; oat flour 20 [10], glycerin 10, pH 6.8 for strain *S. cyanogenus* S136; cultures were grown on appropriate agar mediums (15g/l agar) for 3 and 5 days, respectively, 28 °C. Liquid mediums for growing producers contained similar components without agar. Suspensions for cultivation in the liquid medium were obtained by washed off a 7-day culture from surfaces of slants with sterile water V=5 ml. Cultivation of *S. globisporus* 3-1 and *S. cyanogenus* S136 strains in liquid mediums was performed for 2 and 4 days, respectively, shaking at 240 rpm in dark condition at 28 °C. Microbiological agar with phytopathogen cells *C. michiganensis* 10_2 (MA) was prepared on King's B medium [12]. The suspension for MA was prepared from 7-day culture, washed from a slant surface and was filtered through a sterile cotton filter. The final titer MA was 10^6–10^7 CFUs.

The antagonistic activity of metabolites of *S. globisporus* 3-1 and *S. cyanogenus* S136 strains against the phytopathogen was investigated by diffusion of substances into agar MA. Blocks of streptomycetes d=10 mm were cut from agar medium, placed on MA, cultured at t 28 °C and analysed during 3–14 days. Extraction of metabolites was performed from agar medium V=40 ml with chloroform-acetone (2:1), 2–3 hours. The extract was evaporated, dissolved in 2.0 ml of 96% ethanol (alcohol extract) and 100 µl of an aqueous solution of alcohol extract (1:1) was carried into holes MA d=10 mm. Separation of extracts of the metabolites complexes was done by thin-layer chromatography (TLC) [7], followed by determination of the active ingredient by diffusion into agar MA.

Tomato seeds were treated with substances V=10 ml for all variants according to the scheme shown in table 1. The seeds were sown in non-sterile soil of the hothouse and were lightly watered every day.

Table 1

Conditions and time of treatment of Lana tomatoes seeds

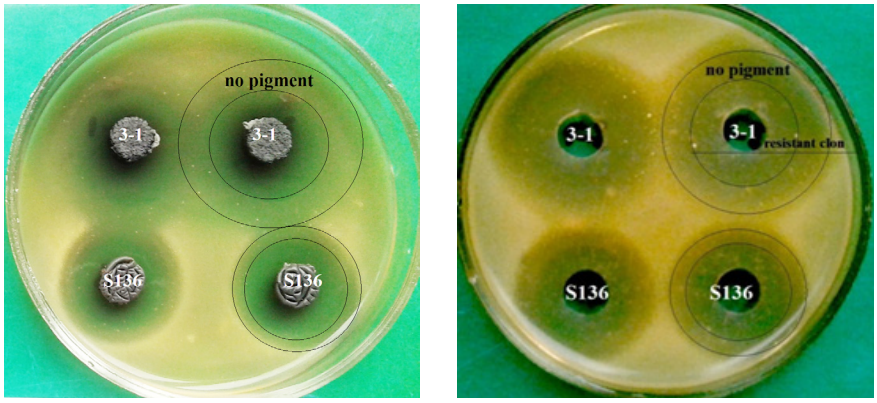
Code	Seed processing conditions (15 pcs.), Time of treatment
Control	Tap water, 1 hour
B	Suspension of *C. michiganensis* 10_2, titer 108–109 CFUs, 1 h
M3-1	Culture fluid with **M**etabolites of strain *S. globisporus***3-1**, 2 hours
MS136	Culture fluid with **M**etabolites of strain *S. cyanogenus***S136**, 2 hours
B+M3-1	**B**acterial suspension, 1 h Culture fluid with **M**etabolites *S. globisporus* 3-1, 2 h
B+MS136	**B**acterial suspension, 1 h Culture fluid with **M**etabolites *S. cyanogenus* S136, 2 hours

The content of landomycins in the metabolites complex of the studied strains was calculated mathematically. Landomycin E (LE) accumulates in the medium in the amount of 200 mg/l [7], landomycin A (LA) – 80 mg/l [10]. The 50 µl of extracts introduced into the well theoretically contained up to 0.2 mg LE and 0.08 mg LA, the concentration during seed treatment was up to 0.2 mg/ml LE and 0.08 mg/ml LA.

Results and discussion

Metabolites of *S. globisporus* 3-1 and *S. cyanogenus* S136 strains have demonstrated an antagonistic activity against the phytopathogen. Clean zones (inhibition of phytopathogen growth) with diameters of 45 and 35 mm formed around agar blocks (Fig. 1.A) and holes with extracts (Fig. 1B) of *S. globisporus* 3-1 and *S. cyanogenus* S136 strains, respectively. However, after 7 days, the clean zones around the blocks of the studied strains and holes with streptomycetes metabolites decreased with the formation of no pigment zones of phytopathogen with zone widths in 10±3 mm and 5±1 mm, respectively. It should be noted that the biocide action of extracts of metabolites *S. globisporus* 3-1

and *S. cyanogenus* S136 against the phytopathogen were equivalents. Clean zones on the phytopathogen lawns around holes into which the same volumes of extracts were applied, almost did not differ in size (Fig. 1B). However, the concentration in the LE extract (0.2 mg) was 2.5 times higher than the concentration of LA (0.08 mg). It can be assumed that the phytopathogen *C. michiganensis* 10_2 is more sensitive to *S. cyanogenus* S136 metabolite than to *S. globisporus* 3-1 ones *in vitro*.



A **B**

Fig. 1. Actions of metabolites *S. globisporus* 3-1 (photo 3-1) and *S. cyanogenus* S136 (photo S136) strains (A) and their extracts (B) against *C. michiganensis* 10_2 (lawn), 10 days

The effect of *Streptomyces* metabolites on the formation of no pigmented zones of phytopathogen after 7 days of cultivation was proved by the holes method. According to the literature, *C. michiganensis* 10_2 cells accumulate lipids, the synthesis of which is visually manifested by pigmentation on certain media [2]. Probably, lipids oxidation could protect phytopathogen cells on the periphery of the zones against the action of metabolites of the studied strains, which was manifested by the absence of culture pigmentation.

Separated by TLC metabolites LE and LA showed antagonism to phytopathogen without formation of no pigment zones after 7 days. An unequivocal mind response of the effect of purified metabolites of the studied strains on the growth of phytopathogen without pigmentation was not obtained. According to the literature, the strain *C. michiganensis* 10_2 does not synthesize enzymes of oxidative protection [2], which would protect the culture from ROS, provoked by LE and LA. Whereas lipid synthesis probably depended on the complex action of metabolites of *S. globisporus* 3-1 and *S. cyanogenus* S136 strains.

The next step was to compare the biocide activity of metabolites *S. globisporus* 3-1 and *S. cyanogenus* S136 on the germination, growth and yield of Lana tomatoes whose seeds were infected with phytopathogen and uninfected in the hothouse (Table 2). Seeds germination in all treated variants was lower than control: B, B+M3-1 and B+MS136 had almost twice lower level of germination; M3-1 and MS136 had 73% seeds germination for both (Table 2). Shoots length of the juvenile period of the tomato were different in variants: M3-1 and MS136

were at the level of control; B and B+M3-1 were twice lower than control; B+MS136 had severe growth retardation. In last variant the additive effect of phytopathogen and producer metabolites on tomato seeds and plants was observed. In all, the effect of *S. globisporus* 3-1 metabolite on the processes of the juvenile period of tomato development was less than that of *S. cyanogenus* S136 ones.

Table 2

The analysis of treatment seed germination Lana tomatoes their growth and yield in hothouse conditions

Code*	Germination, pcs (%)	Shoot length**, cm	Fruits number from the bush, pcs	Fruit weight, g
Control	15 (100)	8–9	10–13	30–110
B	8 (53)	4–5	10–13	20–50
M3-1	11 (73)	8–10	6–8	20–50
MS136	11 (73)	7–8	Flowers without ovary, no fruit	
B+M3-1	9 (60)	5–5.5	6–8	20–50
B+MS136	8 (53)	2–3	5–6	20–50

Note: *code of variants see in table 1; ** shoot length was measured after one month of growth.

During the flowering and fruiting period, differences were observed for MS136 tomatoes, the plants of which did not form ovaries for fruit formation without visual defect of flowers. The appearance of plants from seeds M3-1 was been with lowered and twisted leaves throughout the growing season (Fig. 2), in other cases similar leaves was not observed.

Fig. 2. Defective leaves of plants from seeds treated with metabolites *S. globisporus* 3-1

Fruit ripening for all plants was timely and even, without acceleration and delay. Yield of variant B tomatoes did not differ quantitatively from controls, but their fruits were smaller and the plants had visual signs of bacterial cancer of tomatoes: spotting on the surface of the fruit, dense streaks inside the fruit, drying of shoots during fruiting. The yield of tomatoes of variants M3-1, B+M3-1 and B+MS136 was less fruits than of control and variant B, although the weight of fruits did not differ from variant B ones. Visually, plants from seeds infected and treated with metabolites of seeds (B+M3-1 and B+MS136) had no signs of bacterial canker of tomatoes in the hothouse.

As a result of research in the hothouse, the biocide action of metabolites of researched strains on Lana tomatoes *in vivo* was revealed. Metabolites of *S. globisporus* 3-1 and *S. cyanogenus* S136 strains with 0.2 mg/ml LE and 0.08 mg/ml LA were toxic to Lana tomatoes, which led to the defect of leaves and plants sterility, respectively. Plants from infected and treatment of metabolites seeds visually showed no signs of bacterial canker of tomatoes, shoots developed normally, sterility was absent. However, their germination, growth and yield were lower than those of infected seeds.

Our results show the negative action on the host plant of the use ofstreptomycetes metabolites, which are active against the phytopathogen *C. michiganensis* 10_2 in the laboratory. *Streptomyces* are promising as antagonists to phytopathogens, but sometimes only *in vitro* because researchers in the initial analysis do not know of their active substances and continue to work with the most active of them, which may not meet expectations. For example, we studied the soil streptomycete-isolate active against *C. michiganensis* 10_2 *in vitro*, but treatment by its metabolites of tomato seeds led to plant sterility. The studies were not continued due to economic inexpediency.

Cells of the phytopathogen penetrate to seed, develops in the intercellular space of the shoot, clogging vessels and preventing the access of nutrients to plant organs, which contributes to delayed shoot growth or seed lysis. Dry seeds in a humid environment absorb the liquid with substances that pass through the seed coat (testa) and through the micropyle (pore). In our case, these are metabolites *S. globisporus* 3-1 and *S. cyanogenus* S136, in particular LE and LA. According to the literature, the antitumor effect of landomycin E is provided by increasing hydrogen peroxide, which reduces transmembrane mitochondrial potential and ATP synthesis in tumor [6], the action of landomycin A after 1 h increases 5 times the level of ROS, which after 6 h led to the fragmentation of the nucleus [15]. That is, the action of both landomycins results in the degradation of nuclear material due to the formation of ROS. The latter are also products of seed synthesis during germination, as they are involved in testicular destruction, cellular respiration, protection against pathogenic microorganisms and are controlled by seed enzymes oxidoreductases [11]. However, it was shown that the action of the complex of metabolites *S. globisporus* 3-1 with a LE 0.2 mg/ml provided a defective condition of the plant, which is characteristic of the violation of abiotic factors (water, P, K and Mg) [5]. Treatment of seeds by metabolites of *S. cyanogenus* S136 strain with LA in the amount of 0.08 mg/ml led to the sterility of Lana tomatoes. The effect of metabolites of *S. globisporus* 3-1 and *S. cyano-*

genus S136 strains with concentrations of 0.2 mg/ml LE and 0.08 mg/ml LA on infected Lana tomato seeds had a contradictory effect: on the one hand, the plants showed no signs of tomato bacterial canker, on the other hand, the metabolites had a negative effect on the growth and yield of Lana tomatoes, but without defective shoots and sterility of flowers.

Conclusions

The antagonism of *S. globisporus* 3-1 and *S. cyanogenus* S136 metabolites against the phytopathogen *C. michiganensis* 10_2 in laboratory conditions was established. The biocide action of metabolites of the studied strains on Lana tomatoes developed from phytopathogen-infected and uninfected seeds in hothouse conditions was revealed. Metabolites of *S. cianogenus* S136 (with LA 0.08 mg/ml) had a more pronounced inhibitory effect on the seed germination and yield of Lana tomatoes than metabolites of *S. globisporus* 3-1 (with LE 0.2 mg/ml).

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БІОЦИДНА ДІЯ МЕТАБОЛІТІВ ШТАМІВ *STREPTOMYCES GLOBISPORUS* 3-1 ТА *STREPTOMYCES CYANOGENUS* S136

Реферат

Актуальним є дослідження біоцидної дії метаболітів стрептоміцетів-антагоністів до збудника бактеріального раку помідорів та на плодовитість рослини-хазяїна. ***Мета.*** *Визначити дію метаболітів штамів Streptomyces globisporus 3-1 та Streptomyces cyanogenus S136 проти фітопатогенну Clavibacter michiganensis* 10_2 *in vitro та на схожість насіння, ріст та урожайність помідорів in vivo.* ***Методи****. Застосовували мікробіологічні методи в лабораторних умовах та описово-порівняльний аналіз росту та розвитку помідорів в умовах теплиці.* ***Результати****. Метаболіти S. globisporus 3-1 та S. cyanogenus S136 пригнічувати ріст фітопатогену C. michiganensis* 10_2 *з зонами 45 та 35мм in vitro, відповідно. Передпосівна обробка метаболітами продуцентів S. globisporus 3-1 та S. cyanogenus S136 насіння помідорів сорту Ляна знижувала схожість на 27% для обох, призводила до дефектів форм листя та стерильності рослин, відповідно. Обробка інфікованого насіння метаболітами обох штамів стрептоміцетів не покращували схожість, ріст та урожайність в порівнянні з розвитком рослин з інфікованого насіння, хоча вони візуально не мали дефектності та стерильності та ознак бактеріального раку помідорів в умовах теплиці.* ***Висновок****. Встановлено, що метаболіти штамів S. globisporus 3-1 та S. cyanogenus S136 мають біоцидну дію до фітопатогену C. michiganensis* 10_2 *invitro та на помідори сорту Ляна в умовах теплиці.*

Ключові слова: Біоцидна дія, Clavibacter michiganensis subsp. michiganensis, бактеріальний рак помідорів, Streptomyces

СПИСОК ВИКОРИСТАНОЇ ЛІТЕРАТУРИ

1. *Белявская Л.А., Ефименко Т.А., Ефременкова О.В., Козырицкая В.Е., Иутинская Г.А.* Идентификация и антагонистические свойства почвенного стрептомицета *Streptomyces sp*. 100 // Мікробіол. журн. – 2016. – Т. 78, № 2. – С. 61–73.
2. *Гвоздяк Р.І, Мороз С. М., Яковлева Л. М.,. Черненко Є. П.* Етіологія масового захворювання томатів у господарствах України // Мікробіол. журн. – 2009. – Т. 71, № 5. – С. 33–40.
3. *Громико О.* Антагоністичні властивості актиноміцетів, виділених із ризосфери чистотілу великого *Chelidonium majus* L // Вісник Львівського ун-ту, Серія біологічна. – 2014. – Т. 64. – С. 279–286.
4. Електроний ресурс – Режим доступу: https://itd.rada.gov.ua/billInfo/Bills/pubFile/442335
5. Електронний ресурс – Режим доступу: https://valest.com.ua/skruchujutsja-listja-na-pomidorah/
6. *Кориневська А.В.* Механізми цитотоксичної дії ландоміцину Е на пухлинні клітини *in vitro*: Дис. канд. біол. наук. Л., 2009. – 126 с.
7. *Лаврінчук В.Я., Котенко К.А., Голембіовська С.Л., Мацелюх Б.П.* Одержання і характеристика мутантів *Streptomyces globisporus* 1912 з підвищеним біосинтезом ландоміцину Е // Мікробіол. журн. – 2011. – Т. 73, № 6. – С. 31–35.
8. *Поліщук Л.В., Ганусевич І.І., Мацелюх Б.П.* Вивчення протипухлинної дії антибіотиків, що продукуються *Streptomyces globisporus* 1912, на моделі карциноми Ґерена щурів // Мікробіол. журн. – 1996. – Т. 58, № 2. – С. 55–58.
9. *Романчук Л.В., Кравець Н.Я., Клімнічук С.І.* Антибіотикорезистентність умовно-патогенних мікроорганізмів: актуальність, умови виникнення, шляхи подолання // *Інфекційні хвороби*. 2019. – Т. 4. – С. 63–71.
10. *Тодосійчук Т.С., Федоренко В.О., Молочко М.В., Громико О.М.* Розроблення умов глибинного біосинтезу антибіотика ландоміцину А // Вісник КПІ. – 2017. – № 3. – С. 82–88.
11. Electronic resource – Available from: *https://www.intechopen.com/chapters/57019*. Free radicals and antioxidant system in seed biolodgy. 2017.
12. Electronic resource – Available from: *https*://*wiki.bugwood.org*/*Kings_medium_B*4.Laboratory Guide for the Identification of Plant Pathogenic Bacteria.1980.
13. *Golembiovska S.L., Bambura O.I., et al.* Antagonism of *Streptomyces* species 26UF7and 35NG3 to *Clavibacter michiganensis* subsp. *michiganensis* 10_2 // Mikrobiol.Z. – 2020. – Т. 82, № 2. – С. 60–66 (in Ukrainian).
14. *Henke l.T., Rohr J., Beale J.M., Schwenen L.* Landomycins, newangucycline antibiotics from *Streptomyces sp.* I. Structuralstudies on landomycins A-D // J Antibiot. – 1990. – V. 43. – P. 492–503
15. *Lehka L.V., Panchuk R.R., Berger W., Rohr Ju., Stoika R.S.* The role of reactive oxygen species in tumor cells apoptosis induced by landomycin A // Ukr. Biochem.J – 2015. – V. 87, № 5. – P. 72–82.

16. *Nandi* M.*, Macdonald* J.*, et al. Clavibacter michiganensis* ssp. *michiganensis*: bacterial canker of tomato, molecular interactions and disease management // Mol Plant Pathol. – 2018. – V. 19, № 8. – P. 2036–2050.
17. *Thapa S.P., Pattathil S., et al.* Genomic analysis of *Clavibacter michiganensis* reveals insight into virulence strategies and genetic diversity of a Gram-positive bacterial pathogen // Mol.Plant–Microbe Interact. – 2017. – V. 30. – P. 786–802 .
18. *Zhang W., Yang W., Meng Q., Li Y., Liu D.* Screening and identification of antagonistic *Streptomyces spp.* against *Clavibacter michiganensis subsp. michiganensis* from tomato rhizoshere // Frontiers of Agriculture in China. – 2010. – V. 4, № 2. – P. 159–164.

REFERENCES

1. *Biliavska LA, Efimenko TA, et al.* Identification and antagonistic properties of the soil streptomycete *Streptomyces sp*. 100. Microbiol. Z. 2016; 78(2):61-73 (in Russian) doi: https://doi.org/10.15407/microbiolj78.02.061
2. *Gvozdyak RI, Moroz SM, Yakovleva LM, Chernenko EP.*Etiology of mass disease of tomatoes at the farms of Ukraine. Mīkrobiol. Z. 2009; 71(5):33-40 (in Ukrainian) *http://nbuv.gov.ua/UJRN/MicroBiol_2009_71_5_7*
3. *Gromyko O.* Antagonistic properties of actinomycetes isolated from the rhizosphere of celandine large *Chelidonium majus*. Bulletin of Lviv University. Biological series. 2014; 64:279–286 (in Ukrainian) Available from:file:///D:/Downloads/8222-16122-1-PB%20(1). pdf
4. Electronic resource – Available from: https://itd.rada.gov.ua/billInfo/Bills/pubFile/442335
5. Electronic resource – Available from:https://valest.com.ua/skruchujutsja-listja-na-pomidorah/
6. Korynevska AV. Mechanisms of cytotoxic action of landomycin E on tumor cells in vitro. Dissertation for the degree of Biological Sciences Candidate. L. 2009; 126p (in Ukrainian)
7. *Lavrinchuk VYA, Kotenko KA et al.* Obtaining and characterization of mutants of *Streptomyces globisporus* 1912 with increased biosynthesis of landomycin E. Microb.Z. 2011.73 (6):31-35 (in Ukrainian) doi: 10.20535/1810-0546.2017.3.96444
8. *Polishchuk LV, Hanusevych II, Matseliukh BP.* The antitumor action of antibiotics produced by *Streptomycesglobisporus* 1912 studied in a model of Guerin's carcinoma in rats. Mikrobiol.Z. 1996; 58(2):55-8 (in Ukrainian)
9. *Romanyuk LB, Kravets N.Ya. et al.* Antibiotic resistance of opportunistic pathogens: relevance, conditions of occurrence, ways to overcome. 2019; (in Ukrainian) doi: 10.11603/1681-2727.2019.4.10965
10. *Todosiychuk TS, Fedorenko VO, Molochko MV, Gromyko OM.* Development of conditions for deep biosynthesis of the antibiotic landomycin A. KPI. 2017; (3):82-88 (in Ukrainian)
11. Electronic resource – Available from: *https://www.intechopen.com/chapters/570193*.

12. Electronic resource – Available from: *https://wiki.bugwood.org/Kings_medium_B*
13. *Golembiovska SL, Bambura OI, et al.* Antagonism of *Streptomyces* species 26UF7and 35NG3 to *Clavibacter michiganensis* subsp. *michiganensis*$10_{2.}$ Mikrobiol.Z. 2020; 82(2): 60-66 doi: https://doi.org/10.15407/microbiolj82.02.060 (in Ukrainian).
14. *Henkel T, Rohr J, Beale JM, Schwenen L.* Landomycins, new angucycline antibiotics from *Streptomyces sp.* I. Structural studies on landomycins A-D. J Antibiot 1990. 43:492–503. doi: 10.7164/antibiotics.43.492.
15. *Lehka LV, Panchuk RR, Berger W, Rohr Ju., Stoika RS.* The role of reactive oxygen species in tumor cells apoptosis induced by landomycin A. Ukr. Biochem. J., 2015; 87(5):72-82. doi:https://doi.org/10.15407/ubj87.05.072.
16. *Nandi* M*, Macdonald* J*, et al. Clavibacter michiganensis* ssp. *michiganensis*: bacterial canker of tomato, molecular interactions and disease management. Mol Plant Pathol. 2018; 19(8):2036-2050. doi: 10.1111/mpp.12678.
17. *Thapa SP, Pattathil S, et al.* Genomic analysis of *Clavibacter michiganensis* reveals insight into virulence strategies and genetic diversity of a Gram-positive bacterial pathogen. Mol. Plant–Microbe Interact. 2017; 30:786–802. doi: 10.1094/MPMI-06-17-0146-R.
18. *Zhang W, Yang W, Meng Q, Li Y, Liu D.* Screening and identification of antagonistic *Streptomyces spp.* against *Clavibacter michiganensis subsp. michiganensis* from tomato rhizoshere. Frontiers of Agriculture in China. 2010; 4(2):159–164. doi: https://doi.org/10.1007/s11703-010-0095-x.

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