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VARIABILITY OF CAROTENOID-SYNTHETIC STRAINS *STREPTOMYCES GLOBISPORUS* 1912 AFTER DEEP CULTIVATION AND STORAGE

Aim. *To determine the variability of the trait of carotenoids biosynthesis in two mutant strains Streptomyces globisporus 1912 after deep cultivation and storage.* ***Relevance.*** *Study of the spontaneous variability of strains-producers of carotenoids after deep cultivation and long-term storage is necessary for understanding the mechanisms of intrapopulation inheritance and the possibility of their control.* ***Methods.*** *Visually the analysis of phenotype of streptomyces colonies, statistical analysis was performed with Windows Software Excel 2007.* ***Results.*** *The appearance of non-productive/non-active variants (yellow, creamy and colorless) in populations of strains S. globisporus 4Lcp-Hp7 and S. globisporus 7Crt after cultivation in corn-soy liquid medium was 10^{-3} and 10^{-2}, at 1–2 orders of magnitude higher than their standard cleavage with frequent transplantation of subcultures. The variability during storage had high indexes, which were dependent on storage temperature. Non-productive variants of strains S. globisporus 4Lcp-Hp7 and S. globisporus 7Crt at storage temperature of 4 °C were about 50% and 10% of the population, respectively. There were near 10% non-active colonies in the population of strain S. globisporus 4Lcp-Hp7, and 20–30% ones in the case strain S. globisporus 7Crt at storage temperatures of 21 °C and 28 °C. After one-year storage near 52% and 66% colonies of the populations of lyophilized cultures S. globisporus 4Lcp-Hp7 and S. globisporus 7Crt supported the high level of synthesis of corresponding carotenoids.* ***Conclusions.*** *It has been shown, that the trait of carotenoids biosynthesis in the mutant strains S. globisporus 4Lcp-Hp7 and S. globisporus 7Crt was showing variability with the high frequency after deep cultivation (10^{-3} and 10^{-2} non-active colonies) and during long storage on slants and in lyophilized state (10–50%).*

Key words: Streptomyces, carotenoid biosynthesis, variability, storage.

The variability of microorganisms is a result of changes in a cell under the influence of endo- and exogenous factors. This term is used to detect the changes of a trait in populations. The variability is determined by the high frequency of variants, which differ from the typical ones with respect to the total number of tested units, in particular, sown bacteria *in vitro*. The reasons of variability in the population can be the substrate deficiency, the deactivation of synthesis enzymes, a cryptic form of a gene or its defects.

Our work is devoted to the variability of the trait of carotenoids biosynthesis in two mutants of strain *Streptomyces globisporus* 1912. Founded in 1998 the collection of carotenoid-synthetic mutants today includes about two dozen of mutant strains. The sequences of the *crt*-genes of one of the collection strain were presented in the NCBI database (Accession number KM349312) [10]. Mutant strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt are the leaders of the collection by biotechnological characteristics. They are characterized by high productivity and stability of carotenoid biosynthesis in compared with other strains of the collection. The standard cleavage with the formation of non-active variants at constant work with fresh 7–10 day-old cultures *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt on corn-soy agar has been 10^{-5} and 10^{-3}, respectively, that we have researched earlier [6, 9, 13]. Also, the addition of bacteria biomass of researched strains into the diet of oviparous hens has contributed to their productivity and improvement of physiological parameters [4].

Unfortunately, the researched strains can maintain stable values of spontaneous variability only with frequent transplantation of the subcultures. Deep cultivation, long-term storage, and lyophilization have contributed to the accumulation of a large number of non-active colonies in populations of strains. The variability indicators were different and differed from the standard ones. Therefore, in order to understand the mechanisms of intrapopulation inheritance of the carotenoid biosynthesis trait during long-term storage and the possibility of its control in deep cultivation, the actual tasks were to study the indices of spontaneous variability in strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt in the named processes.

The aim of study was to determine the variability of the trait of carotenoids biosynthesis of strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt in the processes of deep cultivation and storage. The objectives of the study were to determine: 1) spontaneous variability frequency of strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt after cultivation in a corn-soy liquid medium; 2) variability indexes of researched strains after 3 and 6 months storage on corn-soy slants; 3) variability indexes of carotenoids strains-producers after a year of storage in the freeze-dried state.

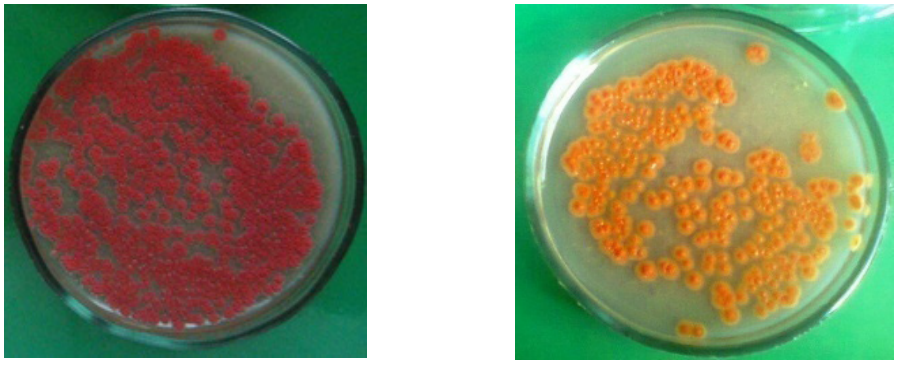
Materials and Methods

Carotenoid-producing strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt were used in the work (Fig. 1). Strain *S. globisporus* 4Lcp-Hp7 accumulates carotenoid lycopene, 50+2.5 mg/l [9, 13]. Strain *S. globisporus* 7Crt synthesizes a mixture of carotenoids of lycopene and beta-carotene, 35+2.0 mg/l [6, 13].

Mediums and growth conditions. Bacteria cultures of researched strains were grown on a corn-soy medium, (g/l): corn flour 20.0; soybean flour 10.0; NaCl 5.0; pH 7.0. Faybich's medium for the lyophilization of the samples contained 10% sucrose and 2% gelatin. The solutions of sucrose and gelatin were separately sterilized and then were mixed in appropriate proportions. Agar-agar content for solid mediums has been 15,0 g/l. The level of pH was been correcting by hydrochloric acid and sodium hydroxide. Sterilization was at t 120 °C, for 30 min.

The analysis of the variability of researched strains. Carotenoids lycopene and beta-carotene are pigments, the presence of their synthesis is visible by a naked

eye. Their accumulation appears in the coloration of mycelium. The synthesis of lycopene by strain *S. globisporus* 4Lcp-Hp7 is morphologically manifested the staining of mycelium by pink color (Fig. 1A). The accumulation of mixture of lycopene and beta-carotene stains colonies of strain *S. globisporus* 7Crt by orange color (Fig. 1B). Amount of carotenoids accumulation is proportional to the saturation of colony color. Cream and yellow colonies of researched strains accumulate corresponding carotenoids in smaller quantities than productive variants, whereas colorless ones have not synthesized carotenoids [13]. Given the biotechnological perspective of the strains, colonies with color intensity lower than of productive ones were considered non-productive/non-active analogically of colorless.



A **B**

Fig. 1. Five-day colonies of *S. globisporus* 4Lcp-Hp7 (A) and *S. globisporus* 7Crt (B) on corn-soy agar with standard cleavage

Washed mycelium off the surface of slants and suspensions after cultivation in a liquid medium were used for research. Suspensions with mycelium of strains were being homogenized, were being filtered and were being sown in dilutions on the surface of the corn-soy agar in Petri dishes. Cultures were incubated at t 28 °C for 4–7 days, under dark conditions (thermostat). Activity of carotenoids biosynthesis was analyzed visually according to the intensity of colony staining. Calculation of the number of colonies was done by the traditional way of enumerating CFUs. The variability frequency of carotenoids biosynthesis of researched strains was made on the basis of calculation of unproductive variants among the total number of tested colonies. Statistical analysis was performed with Windows Software Excel 2007.

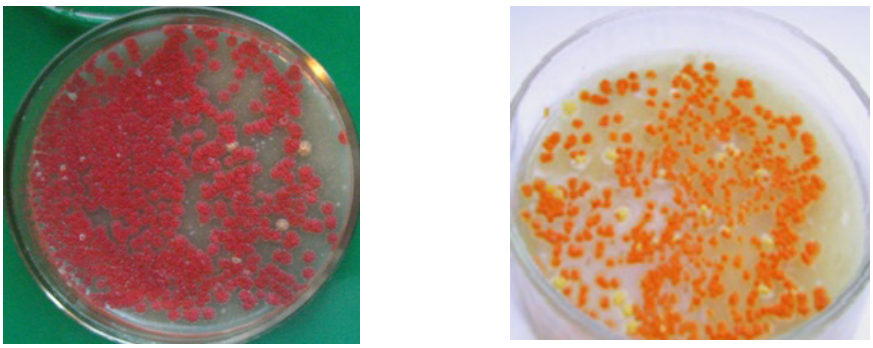
The storage. Carotenoid-synthetic mutants every three or six months were transferred to fresh slants with corn-soy agar (tubes 20x150). Cultures of cells were washed off from the surface of agar-medium by sterile distilled water and were transferred by sterile pipettes to slants with fresh nutrient agar-medium and were incubated under thermostat conditions at t 28 °C, for 7 days. Half of the duplicated subcultures were filled up with sterile mineral oil. Studied storage temperatures were 4 °C in the refrigerator, 21 °C at room temperature and 28 °C under thermostat conditions. The periods of storage were 3 and 6 months. The percentage of active variants in bacteria populations of researched strains during storage for 3 and 6

months was calculated based on the data of last 4 and 6 years, respectively.

Methods of lyophilization described in the literature were used for freeze-dried researched strains [5]. Biomasses of cultures were mixed with protective medium and obtained suspensions were carried into ampoules (V 10 ml) of 1 ml (10^9–10^{10} CFUs) in each one. The samples were lyophilized at 40 °C, were dried, were sealed and were stored away from direct light at 21 °C. After one year of storage sterile distilled water was added to the material in ampoules to the level of V 1ml. The obtained suspension was poured by pipette into the liquid medium with the volume of 9 ml and was cultured at 240 rpm, 28 °C for 2 hours for adaptation. After that, the cultures were sown in dilution on the surface of the nutrient agar in Petri dishes and grown. The material from each ampoule of identical cultures (3pcs) was counted separately.

Results and Discussion

The variability of researched strains after cultivation in liquid medium. Selected cultures of producers *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt with early and intensive carotenoids synthesis has been used for deep cultivation. The variability of carotenoids producers before deep cultivation in the liquid medium was standard. The yield of carotenoids from strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt after cultivation in the liquid medium was 41+2,0 mg/l and 29+1,5 mg/l, respectively. The productivity of strains was decreasing by almost 20%. Non-active variants in bacteria populations of strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt were accumulating with the frequency of 10^{-3} and 10^{-2}, respectively (Fig. 2). The variability of the trait of carotenoids biosynthesis of researched strains under cultivation in the liquid medium was on 1–2 orders of magnitude higher of standard cleavage that was the reason of decrease of yield of carotenoids.



A **B**

Fig. 2. Five-day colonies *S. globisporus* 4Lcp-Hp7 (A) and *S. globisporus* 7Crt (B) after cultivation in liquid medium

Reduction of oxygen access under liquid cultivation conditions is probably one of the reasons of cleavage of the researched phenotypic trait in strain populations. In particular, the growth of strains has been accompanied by rapid

absorption of oxygen under liquid cultivation conditions. In particular, the amount of dissolved oxygen after 17 hours of cultivation has been 7+1% at the initial 70%. The frequency of mixing has been 200 rpm and volume of supplied air has been 3.5V/Vs. In literature the cases of increasing of cleavage in the process of liquid cultivation conditions due to lack of oxygen have been describing. The need of oxygen is described for the processes of accumulation of carotenoids in fermentation conditions for fungi [1, 16].

The variability of the trait of carotenoid biosynthesis of strains after storage on nutrient slants. All carotenoid-synthetic mutants at first years after obtaining were storing in the refrigerator at t 4 °C, which as it turned out later contributed to the accumulation of non-active variants. It was suggested that the storage temperature can influence their variability. It was decided to research cleavage of producer cultures after 3 and 6 months of storage at t 4 °C, 21°C and 28 °C with the protective coating (mineral oil) of air mycelium of strains on slants and without it. The results are shown in Figure 3.

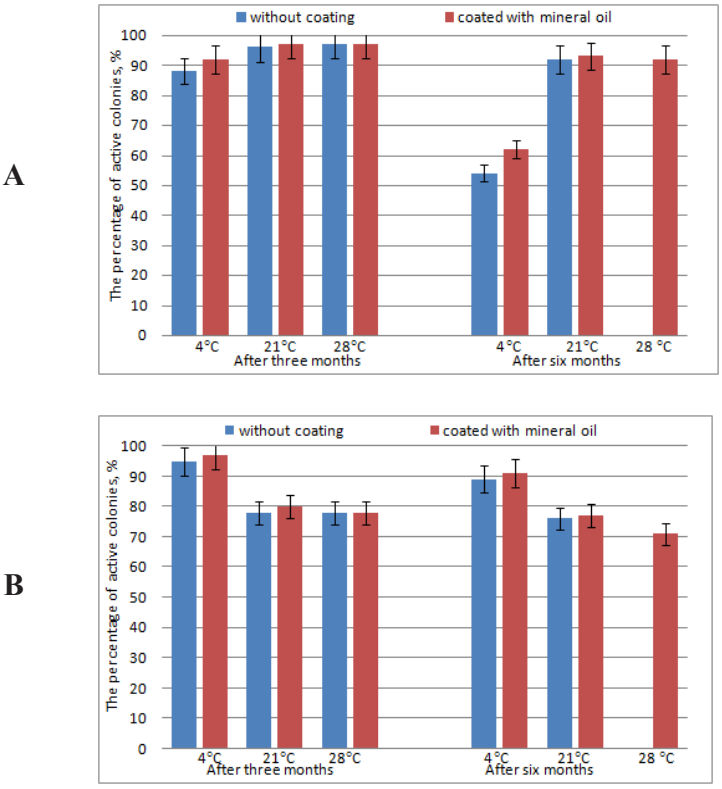


Fig. 3. The percentage of active colonies of strains *S. globisporus* 4Lcp-Hp7 (A) and *S. globisporus* 7Crt (B) during storage

As a result of the studies, it was noted the absence of a fundamental difference in results of storage «without» and «with a protective coating», except for slants at t 28 ºC. The cultures were drying up completely on the slant surface at t 28 ºC after 6 months of storage without the use of mineral oil. Also, the variability of carotenoids

producers *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt differed depending on storage temperatures. The most negative index at t 4ºC during 6 months of storage was for strain *S. globisporus* 4Lcp-Hp7. The percentage of productive/active colonies from strain *S. globisporus* 4Lcp-Hp7 at t 4 ºC was 90+7% and 58+6% for 3 and 6 months of storage, respectively. The cleavage of the strain *S. globisporus* 7Crt at t 4 °C was a lower, 96+4% 89+3% after 3 and 6 months storage, respectively.

The variability of the trait of carotenoids biosynthesis of strain *S. globisporus* 4Lcp-Hp7 at t 21 °C and 28 °C was slightly lower than at 4 °C. Active colonies in populations of strains were 90%, whereas the number of same colonies at high temperatures from *S. globisporus* 7Crt has varied in a range of 70–80%. That is, a room temperature of 21 °C is permissible for storage of the strain *S. globisporus* 4Lcp-Hp7. In the literature it is noted the data of storage of carotenoids producers at high temperatures, for example for *Blakeslea trispora* [2].

After storage, carotenoid-synthetic mutants have been transferring to slants with optimal medium for producers several times with weekly intervals [9, 13]. Frequent transferring of subcultures contributes to the stabilization of carotenoid biosynthesis. One of the reasons for the accumulation of non-productive variants at the long-time storage can be the exhaustion of medium components necessary for the formation of carotenoids. Therefore, the variability of carotenoids producers during storage for 6 months was higher than in the course of 3 ones.

The variability of lyophilized cultures S. globisporus 4Lcp-Hp7 *and S. globisporus* 7Crt. The ampoules of lyophilized samples were left to stand for 1 hour with distilled water as in standard methods [5]. It this case, cultures by microcolonies was germinating for 7–10 days on agar- medium in Petri dishes, whereas by a rule, their growth can be observed on the second day of growing. Therefore, lyophilized cultures were cultured in liquid medium for 2 hours to adaptation. The survival of lyophilized cultures for 1-year storage has not decreased, although cleavage of researched strains was huge. The percentage of colonies with biosynthesis of corresponding carotenoids from strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt were 52+2% and 66+2%, respectively. It is known that lyophilization processes have an effect on the viability and enzymatic properties of microorganisms [5]. High indexes of variability of lyophilized cultures of carotenoids producers can be the result of inhibition of carotenoids biosynthetic enzymes in the processes of lyophilization.

The variability of non-active variants of researched strains. The study of the variability of inactive variants has been carried out in order to exclude modification. Arbitrary variants from bacteria populations of researched strains were selected for the analysis. The appearance of colored colonies from colorless ones was not observed among thousands checked for both strains. Productive colonies were not accumulating in bacteria populations low-active colonies (cream and yellow) among thousands checked at pH 6-7 but were watched at pH 8. The frequency of appearance of pink and orange colonies from low-active variants of researched strains was 10^{-2} for both ones (Fig. 4). Also, the colonies with lycopene biosynthesis (pink) were accumulating in the bacteria population of low-active variants of strain *S. globisporus* 7Crt with the frequency of 10^{-1}. The pH level of the medium has stimulated their formation. It is known the lycopene is a precursor of beta-carotene.

The beta-carotene biosynthetic enzyme (lycopene cyclase) at pH8 is inhibited and does not create beta-carotene from lycopene, which contributes to the accumulation of last one. The biotechnological method as the change of the pH level is using to accumulate lycopene in fungi [3].

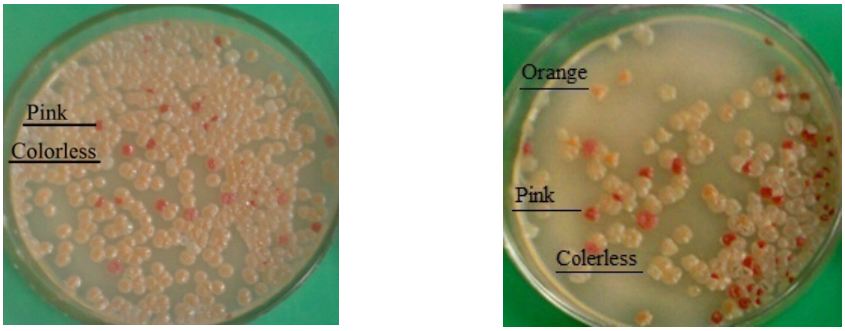


Fig. 4 The cleavage of low-activity colonies of strains *S. globisporus* 4Lcp-Hp7 (A) and *S. globisporus* 7Crt (B), pH 8.0

Today, *crt*-genes for some *Streptomyces* have been registered in the bioinformational databases GenBank, KEGG, and the others. The expression of *crt*-genes in *S. setonii* and *S. griseus* IFO13350 is controlled by the *crt*S gene, the product of which is a stress-sensitive sigma-like factor. Expression of *crt*-genes in *S. coelicolor* A3 (2) is controlled by a photosensitive cluster of *lit*-genes. The products of genes *crt*S and *lit*S initiate the transcription of *crt*-operon in these *Streptomyces* [7, 8, 14].

According to the literature, amount of carotenoids accumulation for the most *Streptomyces* are very low and are measured in μg/L. The exception is the strain *S. rimosus,* which synthesizes lycopene 230 mg/L [15]. The yield of carotenoids from mutant strains *S. globisporus* is lower than from *S. rimosus.* Their productivity depend on the stability of inheritance of carotenoids biosynthesis. The stability of a feature of the carotenoids biosynthesis, in turn, depends on the components of medium, temperature, pH and storage conditions. On the other hand, the cause of strains variability with carotenoids biosynthesis is considered to be the localization of a cluster of *crt*-genes in the regions of terminal inverted repeats (TIR) of chromosome, which leads to increased mutagenicity and elimination of gene [10, 12, 14]. Also, the formation of *Streptomyces* colonies after homogenization is the result of random breaks of mycelium, which increases the likelihood of creating a colony with different genetic material. This, in turn, affects the composition of the synthesized metabolites in separated colonies. Also, according to the latest data of regulation of interactions in microorganisms [11, 17], the accumulation of non-active colonies may even be necessary to support the variants with carotenoids biosynthesis.

It has been shown, that the trait of carotenoids biosynthesis in the mutant strains *S. globisporus* 4Lcp-Hp7 and *S. globisporus* 7Crt was showing variability

with high frequency after deep cultivation (10^{-3} and 10^{-2} non-active colonies) and during long storage on slants and in lyophilized state (10–50%).

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ИЗМЕНЧИВОСТЬ КАРОТИНСИНТЕЗИРУЮЩИХ ШТАММОВ *STREPTOMYCES GLOBISPORUS* 1912 ПОСЛЕ ГЛУБИННОГО КУЛЬТИВИРОВАНИЯ И ХРАНЕНИЯ

Реферат

Цель. *Определить изменчивость признака биосинтеза каротиноидов у двух мутантных штаммов Streptomyces globisporus 1912 в условиях глубинного выращивания и после хранения.* ***Актуальность.*** *Изучение спонтанной изменчивости штаммов-продуцентов каротиноидов после глубинного культивирования и длительного хранения необходимо для понимания механизмов внутрипопуляционного наследования и возможности их контроля.* ***Методы.*** *Визуальный анализ фенотипа колоний стрептомицетов, статистический анализ проводили с помощью Windows Software Excel 2007.* ***Результаты.*** *Появление непродуктивных/неактивных вариантов в популяциях штаммов S. globisporus 4Lcp-Hp7 и S. globisporus 7Crt после выращивания в жидкой кукурузно-соевой среде составляло 10^{-3} и 10^{-2}, что на 1–2 порядка выше их стандартного расщепления при частых пересевах субкультур. Изменчивость изучаемого признака в результате хранения зависела от температуры. Непродуктивные варианты у штаммов S. globisporus 4Lcp-Hp7 и S. globisporus 7Crt при температуре хранения 4°C составляли около 50% и 10% популяции, соответственно. При температурах хранения 21 °C и 28 °C у популяции штамма S. globisporus 4Lcp-Hp7 таковых накапливалось до 10%, тогда как у штамма S. globisporus 7Crt – 20–30%. После года хранения около 52% и 66% колоний популяции лиофилизированных культур S. globisporus 4Lcp-Hp7 и S. globisporus 7Crt поддерживали высокий уровень синтеза соответствующих каротиноидов.* ***Выводы.*** *Установлено, что признак биосинтеза каротиноидов у мутантных штаммов S. globisporus 4Lcp-Hp7 и S. globisporus 7Crt проявляет изменчивость с высокой частотой как после глубинного культивирования (10^{-3} и 10^{-2} неактивных колоний), так и после длительного хранения на косяках и в лиофилизированном состоянии (10–50%).*

Ключевые слова: Streptomyces, биосинтез каротиноидов, изменчивость, хранение.

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МІНЛИВІСТЬ КАРОТИНСИНТЕЗУВАЛЬНИХ ШТАМІВ *STREPTOMYCES GLOBISPORUS* 1912 ПІСЛЯ ГЛИБИННОГО ВИРОЩУВАННЯ ТА ЗБЕРІГАННЯ

Реферат

Мета. *Визначити мінливість ознаки біосинтезу каротиноїдів у двох мутантних штамів Streptomyces globisporus 1912 в умовах глибинного вирощування та після зберігання.* ***Актуальність.*** *Вивчення спонтанної мінливості штамів-продуцентів каротиноїдів після глибинного культивування та довготривалого зберігання необхідно для розуміння внутрішньопопуляційних механізмів успадкування та можливості їхнього контролю.* ***Методи.*** *Візуальний аналіз фенотипу колоній стрептоміцетів, статистичний аналіз проводили з використанням Windows Software Excel 2007.* ***Результати.*** *Поява непродуктивних/неактивних варіантів у популяціях штамів S. globisporus 4Lcp-Hp7 і S. globisporus 7Crt після вирощування в рідкому кукурудзяно-соєвому середовищі становила 10^{-3} та 10^{-2}, що на 1–2 порядки вище за їх стандартне розщеплення при частому перевиванні субкультур. Мінливість досліджуваної ознаки в результаті зберігання залежала від температури. Непродуктивні варіанти штамів S. globisporus 4Lcp-Hp7 і S. globisporus 7Crt при температурі зберігання 4 °С становили біля 50% і 10% популяцій, відповідно. За температурах зберігання 21°С та 28 °С в популяції штаму S. globisporus 4Lcp-Hp7 таких накопичувалося до 10%, в той час як у штаму S. globisporus 7Crt – 20–30%. Після року зберігання біля 52% та 66% колоній популяції ліофілізованих культур S. globisporus 4Lcp-Hp7 та S. globisporus 7Crt підтримували високий рівень синтезу відповідних каротиноїдів.* ***Висновки.*** *Встановлено, що ознака біосинтезу каротиноїдів у мутантних штамів S. globisporus 4Lcp-Hp7 та S. globisporus 7Crt проявляє мінливість з високою частотою як після глибинного культивування (10^{-3} та 10^{-2} неактивних колоній), так і після довготривалого зберігання на скошених агаризованих поверхнях та у ліофілізованому стані (10–50%).*

Ключевые слова: Streptomyces, биосинтез каротиноидов, изменчивость, хранение.

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