THE INFLUENCE OF CYANOBACTERIAL EXTRACT OF AMINO ACIDS AND OLIGOPEPTIDES ON BIO-PARAMETERS OF *Streptomyces canosus* CNMN-Ac-02 STRAIN

Maxim BYRSA*

*Institute of Microbiology and Biotechnology of Academy Science of Moldova, Chisinau, Republic of Moldova
Corresponding author: Maxim Byrsa, Institute of Microbiology and Biotechnology of Academy Science of Moldova, 1 Academiei Str., MD-2028, Chisinau, Republic of Moldova, phone: 00373725055, e-mail: mellon23@yandex.ru

Abstract. This study concerns the influence of a cianobacterial extract containing amino acids and oligopeptides on the growth, biomass and lipid accumulation, and quantitative and fractional lipid composition of *Streptomyces canosus* CNMN-Ac-02. The cyanobacterial extract was used as a supplement to growth liquid complex medium M-I. A significant increase of *S. canosus* CNMN-Ac-02 biomass yeld was registered for all concentrations in which the biological product was added. The best result was obtained using a concentration of 20.0 %/V of cyanobacterial extract, an increase by 81.38 % compared with control was recorded. Conversely, a larger amount of lipids (by 38.36 % compared with the control) was obtained using 0.1 %/V of cyanobacterial extract of amino acids and oligopeptides. Fraction of phospholipids in biomass of *S. canosus* CNMN-Ac-02 increased by 18.2 % - 25.39 % in comparison to the control, after cultivation on M-I medium with content of cyanobacterial extract of amino acids and oligopeptides, both in low concentrations (0.1-0.1 %/V). The cyanobacterial extract of amino acids and oligopeptides in concentration of 10.0-20.0 %/V, stimulate the accumulation of mono- and diglycerides by 8.91-16.2 % compared with the control. The fraction of sterols remained at the same level, but their esters increased by about 30 %.

Keywords: *Streptomyces*; cyanobacterial biological product; biomass; fractional lipid composition.

INTRODUCTION

Actinomycetes (Actinobacteria) are widely distributed in natural habitats and are used as producers of diverse biological active substances. The study of actinobacteria is necessary to develop the theoretical knowledge and to solve some problems in innovative technologies regarding innovative technologies used in biotechnology, medicine and agriculture [11, 46].

Actinobacteria of genus *Streptomyces* are interesting and studied because of their ability to produce more than half of biologically active substances necessary in different fields of human activity [13].

Streptomyces canosus CNMN-Ac-02 which is stored in the National Collection of Non-pathogenic Microorganisms (NCNM) of the Institute of Microbiology and Biotechnology (IMB) of the Academy of Sciences of Republic of Moldova particularly promising due to its capacity to produce complexes of metabolites as phytohormones (auxins and gibberellins), essential and immune active amino acids and lipids containing unsaturated fatty acids. Few information is available on *Streptomyces canosus* although one of the most distinguishing features of this strain is the ability to synthesize phosphatidylcholine and phosphatidylethanolamine [21, 34].

The quality and quantity of Streptomycetes biomass depends on the chemical nature of the growth substrate. The biomass is an important source of lipids which are of fundamental importance as energetic materials for the living organisms. Lipids of streptomycetes include mono-, di- and triglycerides of polyunsaturated fatty acids [5, 25]. Moreover, we must add that the antibiotics of lipidic nature have benefic action on animals and plants [2, 14, 44].

It is known that actinomycetes are frequently found in association with cyanobacteria to form a community. As a result of the growth and development of their biomasses, they produce biologically active substances of biotechnological interest [47]. Finally, the used substrate will influence the quality of obtained metabolites [8, 48].

The 80s and 90s of the twentieth century are characterized by a large number of studies on the use of algae biomass in animal husbandry, crop production, medicine, food and other industries. The authors of these studies have demonstrated that their use in feeding poultry, cattle and pigs, increase the metabolism and improve the immunity of young animals against diseases [26, 32, 43].

For example, in recent years spirulina is the topic of many studies regarding biotechnology, biomedicine and pharmacology. Multiplex cycle exploration of spirulina plays an important role to enhance the effectiveness of the production of biomass and bioactive compounds, development of new methods and procedures for extracting, purifying and conditioning of new biological products. Elaboration of technological schemes adapted for large-scale production constitutes the end point of this research. Several investigations have demonstrated the therapeutic effects of products obtained from spirulina biomass [38].

Spirulina biomass is a renewable and inexhaustible source of biologically active substances as: antioxidants [15, 18, 36, 43, 44], amino acids, lipids, polyunsaturated fatty acids, vitamins [4, 37], enzymes [38], carotenoids [27, 31], pigments [7, 24], phycobiliproteins, polysaccharides [38] and other important substances with further biological properties [22, 35].

Due to biotechnology, it is possible to obtain biological products from cyanobacterial origin that can be used in various industries. Of considerable importance in obtaining final product is the growth

media used, that contains macro and micronutrients useful for the synthesis of biologically active substances in the produced biomass [6, 19, 20]. Numerous researches have led to developement of technologies for obtining particular preparations i.e. dietary supplement SpirumCrom and antidiabetic $BioR^{Cr}$ product. These biological products containing chrome are caracterised by an enhanced capacity to stimulate insulin activity. They can be recommended in the prophylaxis and treatment of diabetes mellitus type II due to the high content of bioactive principles (phycobiliprotein, immune active amino acids, carbohydrates and lipids) [16]. In laboratory tests, farm animals were used to test the biological product BioR. Considerable results were achieved by BioR intramuscular administration in the rabbits, contributing to the amelioration of animal welfare [28].

Few information is available on the use of biological products or metabolites of microbial origin as nutritive compounds for growth medium, and the symbiosis or relationship between cyanobacteria and actinomycetes could represent a new investigation field [8].

Therefore, the aim of the present research was to study the influence of cyanobacterial extract containing amino acids and oligopeptides AAOP added to a complex nutritive medium M-I on the biomass growth, synthesis of lipids and modification of theirs fractional composition of strain *Streptomyces canosus* CNMN-Ac-02.

MATERIALS AND METHODS

Streptomyces canosus CNMN-Ac-02 was kept on Czapek agar media with glucose, Gause and oatmeal agar [11, 9, 23]. Inoculum was cultivated using an orbital shaker for 3 days at 27ºC in Erlenmeyer flasks (V=1,000 ml) with 200 ml of liquid mineral media Dulaney with glucose (pH=7.0) [44].

The inoculum suspension was added in a concentration of 8% to the liquid complex medium M-I (corn flour – 20 g/l; $CaCO_3$ – 1,5 g/l; baker's yeast – 5 g/l; pH=7.2), supplemented with biological product of cyanobacterial extract of AAOP in 0.1, 1.0, 5.0, 10.0, 20.0 and 30.0 %/V concentrations, obtained on the basis of *Arthrospira* (*Spirulina*) *platensis* CNMN-CB-02 [39]. Extract of AAOP were kindly provided by academician Rudic Valeriu (Laboratory of Phycobiotechnology).

The biomass of *S. canosus* CNMN-Ac-02 was grown using Erlenmeyer flasks of 1,000 ml with 200 ml of medium, for 5 days at 27°C on a stirrer. The biomass was separated from broth culture by centrifugation (5,000 rpm for 20 min). The absolutely dry biomass (ADB) was determined by classical dry weight [9].

The intracellular lipids were extracted from biomass by the modified Folch method [10].

Fractional composition of the lipids was determined by thin layer chromatography using „Sorbfil" plates (100x150 mm), in the solvent mixture hexane-diethyl: ether-glacial: acetic acid system (73:25:5). Quantity of each lipid fraction was determined using the method of densitometry [10, 12].

RESULTS

The biomass growth of the *S. canosus* CNMN-Ac-02 was influenced by the addition to culture medium M-I of AAOP in different tested concentrations. According to the data in table 1, the biomass yeld increased by 10.09-81.38% (in comparison with the untreated control) under the action of different concentrations (0.1-20.0 %/V) of cyanobacterial biological product. The highest maximum quantity was recorded using the concentration 20.0 %/V. Concentration at 30.0 %/V of the biological product increased less than previous, only by 46.66 %.

An increase of total lipids percent compared to the untreated control, was observed only at the two lower AAOP concentrations (0.1 and 1.0 %/V). In particular, the highest increase (by 38.36%) was observed at 0.1%/V AAOP concentration. In comparison to the control, the increase of concentration of the biological product led to a decreasing of total lipids content in biomass by 10.51% at 5.0 %/V AAOP and by 21.95% at 10.0 %/V AAOP (table 1).

Comparing our data with results of a previous experiment [12], it is necessary to mention that *S. canosus* CNMN-Ac-02 after long term storage by periodic transfer and lyophilization losses its biological activity. To increase biomass accumulation and lipids content, it is necessary to use moderate concentrations of AAOP in the growth M-I medium.

According to the data in figure 1, it is possible to trace the influence of the biological product AAOP added in M-I culture medium on fractional composition of lipids of *S. canosus* CNMN-Ac-02.

Table 1. Quantity of ADB and amount of total lipids produced during growth of *S. canosus* CNMN-Ac-02 on medium M-I with spirulina extract (AAOP)

Concentration	ADB (g/l)	ADB (% compared to control)	Total lipids (%)	% Total lipids compared to the control
Control	5.38±0.23	100	15.14±0.43	100
0.1 %/V AAOP	5.93±0.04	110.09	20.95±0.49	138.36
1.0 %/V AAOP	6.37±0.17	118.24	15.79±0.35	104.28
5.0 %/V AAOP	6.55±0.14	121.61	13.55±0.38	89.49
10.0 %/V AAOP	6.84±0.31	127.01	11.82±0.56	78.05
20.0 %/V AAOP	9.77±0.29	181.38	10.69±0.59	70.62
30.0 %/V AAOP	7.9±0.33	146.66	10.52±0.53	69.5

Note: p=0.05

The use of AAOP at low concentrations (0.1-1.0 %/V) stimulated increas of fraction of phospholipids by 18.2 % and 25.39 % in comparison with the untreated control. The remaining concentrations (5.0-30.0 %/V) also increased the phospholipidic fraction, varying from 1.85 % to 9.78 %, although less those recorded in the lower concentrations. It was observed slight decrease, in the range of 5.0 to 30 %/V AAOP, of phospholipidic fraction.

Analysis of the sterolic fractions showed no significant changes in the sterol content. At the two lower AAOP concentrations (1.0 and 1.0 %/V) final sterol content was 91.3 % and 97.0 % in comparison to the control. The highest increase (by 2.5%) compared to control was recorded at 10 %/V AAOP.

For the triglycerides fraction any increase was recorded in comparison to the untreated control for all tested AAOP concentrations. The triglyceride content in all samples resulted lower, from 6.1 to 26.8 % in comparison with control. In general, triglycerides amount decreased with increasing of the AAOP concentration in M-I growth substrate.

Considering the same growth conditions, the ratio of the different lipids in the fraction, such as mono- and diglycerides, sterol esters and waxes was also analysed (figure 2). According to data reported in figure 2, for the lower concentrations from 0.1 to 5.0 %/V AAOP, total amount of mono- and diglycerides, during *S. canosus* CNMN-Ac-02 growth, was not significantly different from that observed in the control. The increasing of the concentration of AAOP to 10.0-20.0 %/V stimulated the synthesis of this fraction by 8.91-16.2 % in comparison to control. The amount of this physiological fraction was not significantly different from the control at the higher AAOP concentration (30.0 %/V) (figure 2).

Sterol esters significantly increased when used 10.0, 20.0 and 30.0 %/V AAOP concentration, representing 30.5 %, 26.05 % and 28.7 %, respectively (Figure 2).

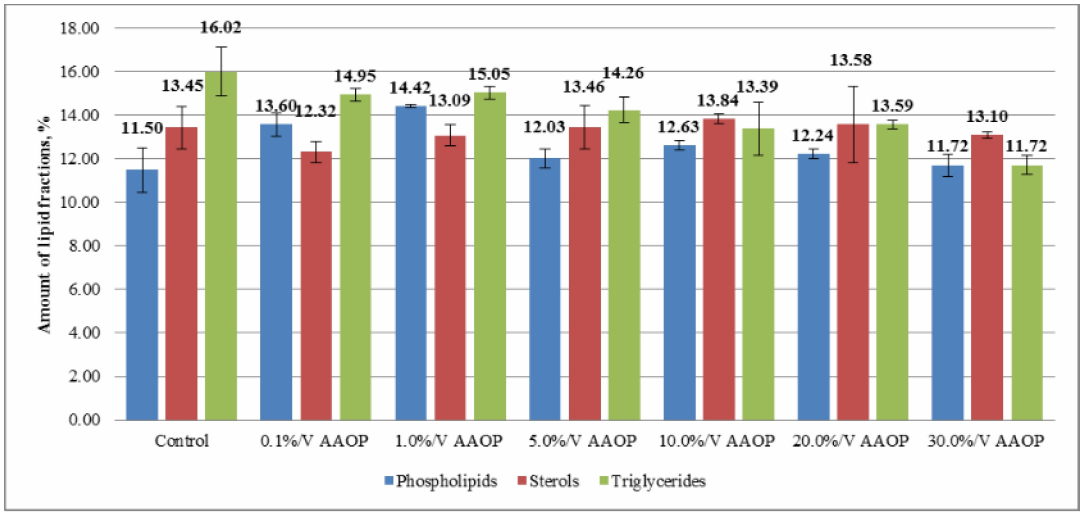

Figure 1. The amount of main lipid fractions of *S. canosus* CNMN-Ac-02 after growth on M-I medium with addition of spirulina extract (AAOP)

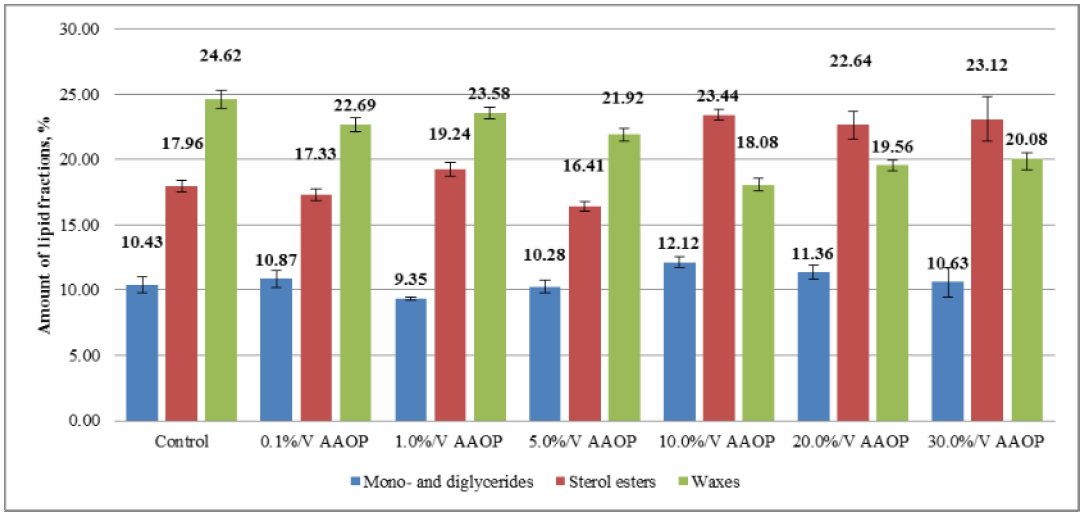

Figure 2. The amount of secondary lipid fractions of *S. canosus* CNMN-Ac-02 after cultivation on medium M-I with addition of spirulina extract (AAOP)

Regarding the fraction of waxes its amount was lower in all AAOP concentrations added to M-I medium in comparison to control. No significant differences, compared to control, were observed at 0.1, 1.0 and 5.0 %/V concentrations. On the contrary, a further increase in concentration to 10 and 30 %/V, significantly reduced the waxes fractions content. Only 77.4 % of waxes, compared to control, were observed at 30.0 %/V AAOP concentration.

Additionally to the foregoing, an unidentified lipid fraction was found and it was located on chromatographic plates between the spots of phospholipids and the total fraction of mono- and diglycerides. In all variants of experiment, its amount was higher than in the control, varying between by 24.25 and 53.48 % more in comparison with control.

DISCUSSION

The scientific approach to the development of balanced nutritive media, taking into account the needs of individual strains of microorganisms in individual components, is becoming more topical. By "balanced" nutrient medium is understood a such qualitative and quantitative composition that corresponds to the needs of culture, ensures the maximum amount of biomass with a minimum residual concentrations of elements [6, 12]. Cyanobacteria increasingly appear in the focus of researchers in various fields as food, pharmaceuticals, cosmetics, aquaculture and animal husbandry, because they possess an intense metabolism and a high growth rate [1, 45]. Usually, complex media that contain mineral salts and organic components (diverse sources of carbon) are used to increase the quantity of biomass and amount of biological active substances of different group of microorganisms, especially actinomycetes, [3, 30, 40]. The use of microbial metabolites by other microorganisms was observed only in natural conditions. Fungal and bacterial species form different consortia. Important role is attributed to secondary metabolites, which are also called biological products. Interspecific interaction between microorganisms represents a physiological trigger for activation of silent gene clusters leading to the formation of novel secondary metabolites by the involved species. An example in this perspective is the interaction between the filamentous fungi *Aspergillus nidulans* and *Aspergillus fumigatus* with *Streptomyces rapamycinicus*, which provides an excellent model system to enlighten molecular concepts behind regulatory mechanisms and will pave the way to a novel avenue of drug discovery through targeted activation of silent gene clusters through co-cultivations of microorganisms [33]. Similar experiments were provided by co-cultivation of marine-derived bacteria and fungi. Some examples occurred as the synthesis of necessary substances using metabolites of other strains: *Streptomyces tenjimariensis* co-cultivated with 12 unidentified bacteria synthesized the antibiotic istamycin; *Streptomyces rapamycinicus* co-cultivated with *Aspergillus fumigatus* during the growth produced Fumicyline B and *Streptomyces endus* synthesized Alchivemycin A after co-cultivation with *Tsukamurella pulmonis* [29].

Several researchers have used standardized products of microbial nature as component part of medium for cultivation of microorganisms. There is information about stimulation of growth of propionibacteria and synthesis of cyanocobalamin and porphyrins by utilization of biological extracts of cyanobacteria and microalgae. The best results of porphyrin production were obtained under the influence of biological products of *Nostoc linckia* (203.9-245.5 % more than control) and *Dunaliella salina* (113.3-123.7 %). However, synthesis stimulation of these biological compounds leads to the decrease of biomass production (74.5-96.5 % compared to control) [17].

In our recent studies were used cyanobacterial biological products as possible stimulators of growth and lipogenesis of streptomycetes. The addition of some of these biological products in nutrient medium has different effects on biomass growth and synthesis of lipids by *Streptomyces canosus* CNMN-Ac-02. It was also assessed a stimulating effect on biomass growth under the influence of biological product obtained from *Porfiridium cruentum*. In this experiment the concentration of 0.1-30.0 mg/l of algal product increased the amount of biomass by 4.78-17.5 %. The use of biological product obtained from *Nostoc linckia* in concentration of 1.0 mg/l, increased the yield of biomass (124.1 % compared to control). The changes in lipogenesis after the use of biological products obtained from *P. cruentum* and *N. linckia* both at 0.1-1.0 mg/l concentrations were 106.1-164.3 % and 111.8-119.2 %, respectively [12]. It is more efficient to use purified and an appropriate amount of metabolites which will be consumed by cultivated microorganisms than to use co-cultivation, where the quantity and quality of used metabolites produced by microorganisms in consortium could be spontaneous.

Our data regarding fractional content of lipids are in accordance with previously obtained data [12]. The use of AAOP obtained from *Arthrospira (Spirulina) platensis* CNMN-CB-02 leads to the stimulation of biomass production, of lipid content and not at last, of the synthesis of important lipid fraction of phospholipids.

Therefore, our previous and present results show new perspectives on optimization of cultivation processes giving possibility to obtain necessary quantity of actinomycetes biomass and increase the qualitative content of biological active substances.

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