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Editor of series: Ljiljana Rašković, e-mail: ral@junis.ni.ac.yu
Address: Univerzitetski trg 2, 18000 Niš,YU, Tel. +381 18 547-095, Fax: +381 18 547-950
http:// ni.ac.yu/Facta

THE IMPORTANCE AND ADVANTAGES OF THE BIOTECHNOLOGICAL METHODS FOR THE PRODUCTION OF ANTIBIOTICS AND FOR THE DISCOVERY OF NEW STRUCTURES

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Andrija Šmelcerović[1], Siniša Djordjević[2]

[1]Chemical Industry 'Nevena', Djordja Stamenkovića b.b., 16000 Leskovac, Yugoslavia
[2]Faculty of Technology, Bulevar Oslobodjenja 124, 16000 Leskovac, Yugoslavia

Abstract. *Today, antibiotics belong to the most profusely used medications both in human and veterinary medicine. For the production of the antibiotics, as well as for the discovery of new structures, biotechnological procedures compete with synthetic ones. The choice of the optimum procedure is complex and due attention must be given to the ecological aspect.*

Key words: *biotechnology, antibiotics, production, new structures*

1. ANTIBIOTICS

Waksman defined antibiotics as the low molecular product of metabolism of microorganisms, with moll mass of < 2000 Dalton, which, in small quantities (< 200 μg/ml), inhibit the growth of other microorganisms, without affecting the producers themselves [1].

The original definition of the antibiotics had for various reasons to be modified, which questioned the limits of other active substances and synthetics.

Some peptide-antibiotics were isolated from the microorganisms whose moll masses were in greater part above the given maximum values. The exclusive action against microorganisms, as given in the original definition, was relativized by use of fermentatively produced antibiotics in the cancer chemotherapy, as well as by use in animal cultures and in plant protection. Besides, total synthetics were found without structural reference to microbiology, that can be compared with the classic antibiotics with respect to their effect on microorganisms [2] although these were never described as antibiotics.

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2. THE IMPORTANCE OF ANTIBIOTICS FOR THE PHARMACEUTICAL INDUSTRY

Today, antibiotics belong to the most profusely used medications both in human and veterinary medicine. The development of the antibiotics therapy after the World War II played an active part in the control and eradication of epidemic diseases and the general increase of life expectancy in the industrial countries. The new applications of antibiotics in non-therapeutic fields (animal cultures, plant protection) were also opened as well as the production of the pharmacologically active substances (i.e. immunosuppressors or cholesterol level lowering therapeutics, antihypertensives, etc.). The antibiotics also have an important part as a 'biochemical tool' in the molecular biology and cell function research.

Until now, nearly 10000 antibiotics and similar bioactive natural substances are known that are obtained from microorganisms, plants and animals. In addition, there are more than 100000 partially or totally synthetic derivatives, produced on a large scale by representatives of some smaller antibiotics groups (β - lactame, macrolide, aminoglycoside, tetracycline, chloramphenicol and anthracycline). From this great potential of active substances only about 100 products have found application [3].

In the yearly growth rate of the pharmaceutics market the antibiotics have a 5 to 8% share. In 1980 the share of antibiotics in the overall medicines market in the USA was 13%, this being the greatest value share in the technologically produced pharmaceutical products. The market value of the overall antibiotics production is higher than for any other medicine. In 1986 approximately US$ 11 milliard worth of antibiotics were produced for humane therapy (antiinfectives, cancerostatics (cytostatics)), where cephalosporin and penicillin had the major deliveries share of more than 60% [4]. In 1981 about 17000 tons od penicillin, 5000 tons of tetracycline, 12000 tons of cephalosporin and 800 tons of erythromycin were produced, plus fungistatics, cancerostatics, and similar tonnage of ergotrop active antibiotics and biopesticides [5]. With the increased use of chinolon carbon acids the market shares for the individual antiinfectives were substantially changed.

The few preparations on the market present sharp competition for one another which is indicated by marketing similar or identical products under different trade names. For shortness sake, only the scientific names are given here without the synonyms used. In 1986 the top of the list of the pharmaceutical preparations was held by β-lactam antibiotics such as amoxicillin (9th place), cefoxitin (11th place), cephalexin (14th place) and cytostatics such as doxorubicin (adriamycin, 29th place) [6, 7]. About 40% of the cytostatics market with general turnover fast growing tendency, belongs to the natural substances produced by microbiological method, such as anthracycline and bleomycin.

The number of newly introduced products remained constant in the last years, and even declining, because the high development cost (> US$ 100 million), long periods of time necessary for the marketing research (8 to 15 years), stricter license regulations and the competition of the preparations already existing on the market impede the introduction of new preparations [7]. Only 30% of the costs is spent on the new active substances investigations, compared to 55% for the determination of effects and digestibility. Finally, with 1:15000 to 1:50000 chances of getting a new active substance ready for the market, the risks of modern pharmaceutical research are obvious, the natural substances having a slightly more favourable position than the complete synthetics. However, as was always the case, a great scientific potential is used for the research and development of active substances, and the classical pharmaceutical strategy is complemented with new methods,

e.g. development of genetically produced substances. Today, the production of antibiotics is a large-scale production run on a breed capacity scale of up to 300 m^3, partly with more than 40 g/lit (e.g. with penicillin). The biotechnological production of cheaper basic structures, such as 6α-aminopenicillan or 7α-amino cephalosporan acids, fulfill the necessary prerequisites for the desired drug-design and molecular modelling [8].

The production development dynamics of antibiotics ranges from the interdisciplinary scientific development from the genetics of product producers to the research of basic active substances interaction with the live cells.

3. COMPARISON OF BIOTECHNOLOGICAL AND SYNTHETIC METHODS FOR THE PRODUCTION OF ANTIBIOTICS AND THE DEVELOPMENT OF NEW STRUCTURES

The biotechnological and synthetic methods compete with one another for the production of the known antibiotics, and for the development of new structures. In the meantime, the possibilities of chemical synthesis have become so perfect that today it is possible to synthesize complicating antibiotics such as polyether, anthracycline and tetracycline, by total syntheses, at least for the purpose of structure determination. In some cases (chloramphenicol, fosfomycin) the chemical synthesis prevails over the biotechnological production. In other cases (mitoxanthron, aztreonom), the natural substances structure served as model for total synthesis [9].

With respect to the invention of new antibiotics biotechnology has a slight advantage. Classical synthesis chemistry, complemented with combinatory synthesis, certainly has good prospects. However, the nature's fantasy in creating new structures is greater than that of synthesists. With the known bioactive structures of microbiological origin, at Zähner's rough estimate, only 10% of the total potential of microorganisms are included into the biosynthesis of active substances [10]. Therefore, one must expect ever increasing number of new biotechnologically obtained antibiotics to be developed in the future.

Naturally, when choosing the optimum method for the production of antibiotics, due attention must be paid to the ecological aspect, i.e. to comprehensive application of modern trends in organic chemical technology, the 'ecotechnology'. With respect to that, the synthesis methods are on top of the list as possible environment pollutants. Many raw materials used in these methods are toxic, flammable and explosive, and present a serious risk factor, so that the production procedure must be carried out under most up to date methods and security measured. Besides, the toxic effluents must be treated so that man and the environment remain completely safe. However, in biotechnological methods, some of the effluents can often be recycled, so that they do not present additional danger for the environment.

In our country, the production of antibiotics is in great discord with the consumption of this group of medication. Therefore, the development of antibiotics production methods must be one of the priorities in the strategy of the pharmaceutical production. The choice of optimum method is complex and, beside the pharmacological, medical, technical and technological aspects, also includes the ecological aspect of the problem, as accentuated in this work.

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ZNAČAJ I PREDNOSTI BIOTEHNOLOŠKIH POSTUPAKA ZA PROIZVODNJU ANTIBIOTIKA I PRONALAŽENJE NOVIH STRUKTURA

Andrija Šmelcerović, Siniša Đorđević

Antibiotici spadaju danas u terapeutska sredstva koja se najčešće primenjuju u humanoj i veterinarskoj medicini. Za proizvodnju antibiotika, kao i za pronalaženje novih struktura, međusobno konkurišu biotehnološki i sintetički postupci. Izbor optimalnog postupka je kompleksne prirode, a značajna pažnja mora da se posveti ekološkom aspektu.

Ključne reči: *biotehnologija, antibiotici, proizvodnja, nove strukture*