JOURNAL OF CRITICAL REVIEWS

ISSN- 2394-5125 VOL 7, ISSUE 08, 2020

Application of Bacteria of the Genus Rhodococcus in Biotechnology

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Received: 11.03.2020 Revised: 12.04.2020 Accepted: 28.05.2020

ABSTRACT: In this review, the data on the use of bacteria of the genus *Rhodococcus* in the biocatalytic synthesis of amides and other compounds by biotransformation of the corresponding precursors have been presented. An adaptation ability of these bacteria to various extreme environmental conditions, the synthesis of different enzymes and the participation in the biodegradation of organic pollutants makes them promising for use in microbial biotechnology. The areas reflecting the importance of this microorganism and the need for its further study and application in science and industry were presented.

KEY WORDS*:* Rhodococcus, nitrile hydratase, strain, biomass, biocatalizator, bioconversion, biodestruction, biotransformation, organic pollutants.

I. INTRODUCTION

Recently, researchers' interest in the biotechnological potential of using alkanotrophicrhodococci has significantly increased. Active and stable strains of Rhodococcus have found wide practical application in the preparation of amides and their derivatives, the preparation of various pharmaceutical substances, bioremediation of the environment from xenobiotics, purification of hydrocarbon pollution of the biosphere, purification of wastewater and soil from oil pollution, biodegradation of persistent organic pollutants and pharmaceutical pollutants [1, 2].

Rhodococcus has a high level of adaptation to extreme conditions of existence [1, 2]. They are characterized by unique biological properties such as pleomorphism, ability to coaggregate, and a complex morphogenetic cycle of development, which determine their presence of various methods of cell cooperation [3], which facilitate the contact of cells with each other, their retention in colonies, and adsorption of hydrophobic substrates on the surface of droplets and soil particles, as well as the formation on the surface of carriers of biofilms used in biotechnological processes. Due to the fragmentation of the rhodococcal cell mycelium into short rod-shaped forms, the ratio of the cell surface to the total cell volume increases, which, in turn, increases the ability of the rhodococci to absorb a hard-to-digest hydrophobic substrate [4].

II. THE USE OF RHODOCOCCUS IN BIOCATALYSIS

Today, alkanotrophic rhodococci are one of the most developed groups of eubacteria. At the end of the twentieth century, strains of this group of microorganisms were first used as a biocatalyst for large-scale synthesis of acrylamide by Nitto Chemical Ltd. (Japan) with a capacity of 30,000 t/y. After this, their use as biocatalysts in chemical or fine organic synthesis was widely developed.

Using this group of microorganisms, biotechnologies for the production of propylene oxide and active forms of epoxides, the conversion of hydrocarbons and phenols, acrylamide and acrylic acid, which are the basis for synthetic polymers, are being developed. The bacterial strain Rhodococcuserythropolis E84 was obtained, which showed nitrile hydratase activity of 240-265 U/mg [4]. Known bacterial strain R. rhodochrous NCIMB 41164 - capable of producing 140 U/mg nitrile hydratase [5]. A bacterial strain R. ruber 8/4/1, an active producer of nitrile hydratase, which effectively transforms acrylonitrile into acrylamide, was isolated at the Institute of Microbiology of the Academy of Sciences of the Republic of Uzbekistan [6]. Biotechnological methods for producing acrylamide have been developed [7, 8].

The biocatalytic method for the preparation of (S) 1-heptenyl 3-acetate was studied using morphological R- and S-dissociants of the culture *Rhodococcus sp. USPTU 21*. It was shown that in the presence of S-dissociant, which

ISSN- 2394-5125 VOL 7, ISSUE 08, 2020

forms mucous colonies during growth on an agar medium due to the formation of an extracellular polymer, the enzymatic reaction proceeds more quickly and with a higher yield of (S) 1-heptenyl 3-acetate than in the presence of R-dissociant cells. At the same time, in the presence of R-dissociant cells, which form wrinkled colonies and are unable to synthesize an extracellular polymer, acylation proceeds more selectively and allows one to obtain more enantiomerically pure (S) 1-heptenyl 3-acetate [9].

As known, pyridine substituted amides and carboxylic acids are vitamins - the precursors of pharmaceuticals. Nicotinamide (vitamin B3, niacin) is used in medicine as a vasodilator for the treatment of diabetes, heart disease and the gastrointestinal tract. Currently, strains of bacteria Rhodococcushave been actively used in the production of such chemical substances for pharmaceuticals. Using cell biomass of *R. ruber gt1* and *Rhodococcus sp. A0* possessing nitrile hydratase activity, the conditions for obtaining nicotinamide by hydration of 3-cyanopyridine were optimized. The biomass of strain *R. ruber gt1* (39 mg) transformed 3-cyanopyridine into nicotinamide with a concentration of 3.9% in the strain *Rhodococcus sp. A0* (39.8 mg) - 4.2% [10].

MaximovaYu.G. et al. studied the dynamics of the biotransformation of 2- and 4-cyanopyridine by immobilized cells of the strain R. ruber gt1 with nitrile hydratase activity and P. fluorescens C2 containing nitrilase. It was determined that the nitrile hydratase and nitrilase activity of 2-cyanopyridine in immobilized cells is 1.5–4 times lower than 4-cyanopyridine and 1.6–2 times lower than the activity of free cells in 2-cyanopyridine. The immobilization of rhodococcal cells on raw coal and pseudomonad cells on kaolin made it possible to obtain a heterogeneous biocatalyst for efficient biotransformation of cyanopyridines into the corresponding amides and carboxylic acids [11].

Pyridoxamine (vitamin B6) is also a promising target for the prevention and treatment of diabetic diseases. Yamamura E.T. et al. carried out bioconversion of pyridoxine to pyridoxal using recombinant R. eritropolis expressing the pyridoxine 4-oxidase gene obtained from *Mesorhizobium loti.* Further, in the bioconversion of pyridoxal to pyridoxamine using recombinant *R. eritropolis* expressing the pyridoxamine-pyruvate aminotransferase gene obtained from *M. loti*, the bioconversion rate was approximately 80% under the same conditions as in the preparation of pyridoxal [12].

Most steroid drugs currently used in medicine and veterinary are structural modifications of natural compounds that have higher biological activity and fewer side effects [13]. Using a culture of *R. erythropolis*VKPM Ac-1740 from 11 steroids of the androstane series (AD) and pregnane with a substrate content of 0.5-10.0 g/l in the reaction medium, the corresponding 9α-hydroxy derivatives were obtained. The content of 9α-hydroxy-AD formed in 6 cycles of 22-24 hours each was 98% [14].

Optically active organic sulfoxides are widely distributed in nature, and are widely used in chemical and pharmaceutical practice [15]. However, only a few publications are known concerning the use of native Rhodococcus cells in the oxidation of prochiral sulfides to the corresponding (R) sulfoxides with an optical purity of more than 90% [16]. A comparative study of the sulfide-oxidizing activity of free and immobilized cells of R. rhodochrous IEGM 66. The biocatalyst form immobilized in a gel carrier provided the complete conversion of thioanisole to (S) -thioanisole sulfoxide with an optical purity of 82.1% using high (1.0–1.5 g/l) sulfide concentrations substrate [17].

Leneva N.A. et al. showed adaptation to phenanthrene of R. opacus 412 and R. rhodnii 135 cells. In the process of adaptation, the cells acquired the ability to use this hydrocarbon as the sole source of carbon and energy. Whereas non-adapted cells of these cultures carried out only partial biotransformation [18].

Zhu et al. demonstrated the feasibility of using quinoline in Rhodococcus sp. QL2 in the concentration range from 60 to 360 mg/l as the sole source of nitrogen, carbon and energy, as well as in conditions of cometabolism [19]. Chloroquine is a drug compound from the group of 4-aminoquinoline derivatives. Used in medical practice, the drug is a racemic mixture of the optical isomers (enantiomers) of chloroquine. However, the dextrorotatory enantiomer, to a greater extent than levorotatory, binds to plasma proteins, is less toxic, and is more rapidly excreted from the body. Therefore, the separation of racemic mixtures of chloroquine by the biochemical method and the determination of enantiomers is of practical importance for the creation of preparations containing only the isomer with the desired therapeutic effect.

Vladimirova E.V. et al. used 4 strains of R. erythropolis: 25, 15, 17 and 7T, which are capable of biotransformation of a number of quinoline derivatives. Minimum inhibitory concentrations were determined for various strains of R. erythropolis. It was found that the minimum inhibitory concentration of chloroquine was 6.25-25 g/l. The possibility of biotransformation of a chloroquine solution in phosphate buffer (1 g/l) by enzyme systems of grown biomass was also investigated. As a result of the work done, the authors selected cultures that effectively transform chloroquine [20].

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III. SURFACTANT BIOSYNTHESIS

Today, active research is underway on the practical use of biosurfactants - surface-active substances of biological origin (bio-surfactants). There is a lot of information in the literature that surfactants of microbial origin have certain advantages, they exhibit antimicrobial activity in relation to a wide range of microorganisms, are non-toxic, do not cause allergies, and are able to prevent the formation of biofilms on the surfaces of various materials. Rhodococci have a hydrophobic cell wall and are able to synthesize bio-surfactants, ensuring the interaction of these bacteria with inaccessible hydrophobic substrates - petroleum hydrocarbons [21]. Ivshina et al. showed that biosurfactants synthesized by Rhodococcus exhibit metal chelating properties and promote the accumulation of heavy metals in the cell wall, preventing their entry into the cell [22]. The ability to synthesize surfactants is also shown with growth on hydrophobic and hydrophilic substrates by R. erythropolis IMB Ac-5017 culture. Surfactant preparations of R. erythropolis IMB Ac-5017 culture reduced the number of adherent cells of Candida albicans D-6, B. subtilis BT-2, E. coli IEM-1, Proteus vulgaris BT-13 and Staphylococcus aureus BMS-1 on the material of urethral catheters. It was shown that surfactant preparations of the strain R. erythropolis IMB Ac-5017 can be used as anti-adhesive agents in medicine [23].

The authors showed the ability of R. erythropolis H-5 to form surfactants that are bound and unbound with cells when they grow on different carbon sources. It was found that the highest surfactant yield in R. erythropolis H-5 was detected when the culture was grown on a medium with 2% kerosene at a neutral pH value. The surfactant yield and emulsification index of various hydrocarbons depended on the form of the nitrogen source used by the bacteria and increased when KNO3 was replaced by NaNO3. The yield of biomass and surfactant in R. erythropoliss H-5 also depended on the cultivation temperature and reached a maximum at 30°C [24].

Pirog T.P. et al. shows the intensification of surfactant synthesis during cultivation of R. erythropolis EK-1 on hexadecane. In the cells of the strain producing producer of surfactant R. erythropolis EC-1 grown on n-hexadecane, the activity of key enzymes of the metabolism of n-alkanes was determined. A 1.5-1.7-fold increase in the concentration of surfactants when 0.2% of fumarate (a precursor of gluconeogenesis) and 0.1% of citrate (a lipid synthesis regulator) was added to the medium with n-hexadecane was due to the intensification of the synthesis of trehalosemecolates, as indicated by a 3-5-fold increase in phosphoenolpyruvate synthetase and trehalose phosphate synthetase, respectively [25].

IV. BIODEGRADATION OF ORGANIC POLLUTANTS

The main sources of environmental pollution are substances synthesized by humans and released into the environment as a result of their widespread use, as well as production waste. Particularly persistent pollutants are polychlorinated biphenyls (PCBs), (poly) chlorophenols, explosives, synthetic amines and medical substances. Bacteria of the genus Rhodococcus exhibit degrading activity to a wide range of aromatic compounds of natural and anthropogenic origin. Among them, PCB destructor strains have been described [26]. Strains of R. jostii and R. globerulus P6, which decomposed PCBs both separately and as part of mixtures [27]. Strain R. jostii RHA1 under conditions of cometabolism utilized PCBs. A feature of this strain is the presence of a large number of oxygenases. The study of its complete genome showed that it contains 9145 genes encoding proteins, including 203 oxygenases, 30 of which are involved in the decomposition of aromatic compounds [28, 29]. Destructive strains R. ruber P25, Rhodococcus sp. B7a and Rhodococcus sp. G12a decomposedto 78-95% PCB mixturecontainingtrihexachlorinatedbiphenyls. They carried out the destruction of all tri-, tetra-, penta-, hexa-chlorobiphenyls present in the mixture without accumulation of toxic chlorinated metabolites. The studied bacteria were able to decompose the most resistant to oxidation of PCBs: 2.5, 2 ‘, 5’-CB, 3,4,3’, 4’-CB and 2,4,5,2 ‘, 4’, 5’- CB. These bacteria were recommended for use in biotechnologies for cleaning the environment from highly toxic pollutants [30, 31]. The authors of [30, 31] also studied the possibility of destruction of high concentrations of a commercial mixture of PCB Delor 103 strain R. wratislaviensis KT112-7 and the degree of destruction amounted to 95.1%. The specific destruction rate was directly correlated with the Delor 103 concentration and varied from 0.11 (mg/ml) / day to 0.29 (mg/ml) / day. High PCB concentrations and the presence of medium- and highly substituted congeners did not adversely affect the degrading activity of the strain [32].

Shumkova E.S. et al. demonstrated the ability of the strain R. oparus IG to cleave phenol at a concentration of up to 0.75 g/l. With the immobilization of this strain, the ability of cells to grow at high concentrations of phenol also increased. Complete utilization of the substrate in the amount of 1.0 and 1.5 g/l occurred within 24 and 48 hours, respectively [33].

Polycyclic aromatic hydrocarbons (PAHs) are some of the toxic pollutants. The low solubility of compounds of this class in water gives them increased resistance to decomposition and is the cause of accumulation in various ecosystems. The most promising way to detoxify PAHs is considered to be their decomposition by microorganisms. The bioconversion of 2576otulin (0.5 g/l) to betulone by R. rhodochrous strain IEGM 66 was

ISSN- 2394-5125 VOL 7, ISSUE 08, 2020

75%. Under conditions of using higher (3.0 g/l) concentrations of 2577otulin, non-growing cells catalyzed the formation of up to 60% of betulone within 24 hours. The ability of rhodococci to efficiently transform 2577otulin at high concentrations makes it possible to use this group of microorganisms for targeted oxidative bioconversion of 2577otulin [34].

Dioxigenases induced during the decomposition of benzoate in actinobacteria R. wratislaviensis G10, a destructor (halogen) of aromatic compounds, were studied [35]. Two dioxygenases that split the aromatic ring, protocatechoate-3,4-dioxygenase and pyrocatechin-1,2-dioxygenase, are isolated and characterized. Pyrocatechin inhibited the activity of protocatechoate 3,4-dioxigenase. No inhibitory effect of protocatechoate on the activity of pyrocatechin-1,2-dioxygenase was found. Using the methods of MALDI-TOF and gene amplification, a high identity of the protein profiles of the cells of R. wratislaviensis G10 and R. opacus 1CP, highly active destructors of aromatic pollutants grown on benzoate or rich medium, was shown. The revealed high similarity of genes (99%) for the degradation of aromatic compounds in R. opacus 1CP and R. wratislaviensis G10 isolated from soil samples separated by distance (1400 km) and the time of isolation of microorganisms (20 years) indicates a common origin of biodegradation genes and their wide distribution among Rhodococci [35].

The ability of the strain R. opacus 1CP to use 3-hydroxybenzoate (3-GBA) in concentrations up to 600 mg / l and gentisate in concentrations up to 700 mg / l as the only sources of carbon and energy in a liquid mineral medium is shown in the works of Subbotin N.M. [36]. The authors identified a key intermediate of the transformation of 3-hydroxybenzoate strain – 2,5-dihydroxybenzoate (gentisate). In cell-free extracts of a strain grown on 3-hydroxybenzoate and gentisate, the activities of 3-hydroxybenzoate 6-hydroxylase, 1,2-dioxygenase gentisate and maleylpyruvate isomerase were found. When the strain was grown on 3-hydroxy benzoic acid (3-GBA), a slight catechol-1,2-dioxygenase activity was observed. Based on the data obtained, a metabolic pathway of 3-GBA by R. opacus 1CP strain is proposed. [36].

Actinobacteria of the genus Rhodococcus are also active biodestructors of pharmaceutical pollutants. Environmental pollution by pharmaceutical industry wastes is due to the inefficiency of their disposal methods [37, 38]. A large number of pharmaceutical pollutants detected in the environment are nitrogen-containing heterocyclic compounds. Mukhutdinova A.N. studies have been conducted on the influence of cultivation conditions of R. Rhodochrous IEGM-647 on the biodegradation of drotaverine hydrochloride, a pharmaceutical ecotoxicant [38]. The influence of abiotic (temperature, acidity, aeration) and biotic (biomass amount) environmental factors determining the optimal conditions for the growth of R. rhodochrous IEGM-647 in the presence of drotaverine hydrochloride, as well as glucose as an additional source of carbon and energy, was studied. It was established that effective biodegradation of drotaverine is possible at 28°C and pH 6.8 under the conditions of using the hydrodynamic regime with alternating intensive and moderate mixing (160, 60, 160 rpm) [39].

The possibility of biological destruction of unsuitable for medical use medicinal substances containing phenolic hydroxyl in their structure was studied by Ivshina IB and others using actinobacteria of the genus Rhodococcus [40].

6 species and 64 strains of actinobacteriawere studied. It was established that rhodococci have the ability to transform paracetamol, while individual strains of R. rafter showed a high level of conversion of the investigated substrate. An effective method has been developed for the identification and quantification of paracetamol and its transformation products (p-aminophenol, pyrocatechol, hydroquinone) directly in the culture fluid. The optimal conditions for the complete bioconversion of paracetamol in the form of a finished dosage form (tablets) were selected. The obtained experimental data are recommended for biotechnological developments in the utilization of medicines – falsified, defective and expired [40].

V. WASTEWATER TREATMENT

Every year, millions of tons of liquid and solid wastes of the oil and oil refining industry are generated in the world. Among the whole range of methods for eliminating the consequences of hydrocarbon pollution, biological methods are recognized in the world as the most environmentally friendly and economically viable. Particularly promising is the bioremediation method, based on the use of microorganisms that can utilize hydrocarbons in the process of their life. The effectiveness of biological treatment of wastewater contaminated with petroleum products depends on the stable functional activity of the microorganisms used. Among hydrocarbon-oxidizing microorganisms, a promising group used to clean oil-contaminated media are actinobacteria of the genus Rhodococcus [41].

Oil oxidizing strains of Pseudomonas sp. TY10, Bacillus sp. TU22 and Rhodococcus sp. showed the ability to grow on hydrocarbon substrates. Bacteria proved to be ineffective diesel fuel destructors, however, each of them

ISSN- 2394-5125 VOL 7, ISSUE 08, 2020

in a short time showed high destructive activity against engine oil and crude oil. It was shown that the addition of surfactants had a stimulating effect on the growth of oil-oxidizing bacteria and had a positive effect on the destruction of oil in soil samples. The degree of purification of the soil sample of Rhodococcus sp. in the presence of detergents increased significantly [42].

Khudokormov A.A. et al. show differences in growth parameters between S- and R-forms of oil-oxidizing actinobacteria. For S-forms of actinobacteria, the maximum specific growth rate, a wide spectrum of hydrocarbon degradation, and a high degree of destruction of pollutants were established. In our experiments, using oil and fuel oil of the S-form of actinobacteria as a substrate, they quickly adapted to environmental conditions [43].

Promising methods for treating oil-contaminated wastewater are also developments using the association of immobilized bacterial cells. This is due to the fact that individual strains of microorganisms can degrade a limited number of substrates; therefore, the use of several strains having different enzyme systems will lead to more complete degradation of a complex mixture of hydrocarbons. In addition, the unequal solubility of petroleum hydrocarbons in water requires the use of hydrocarbon-oxidizing microorganisms with varying degrees of hydrophobicity of the cell wall, which contributes to the differentiated intake and assimilation of hydrocarbons in cells. The efficiency of oil biodegradation by bacterial associations is 67–69% higher than when using monocultures. Adapted strains of R. ruber and R. opacus to petroleum hydrocarbons were immobilized on modified sawdust in a column bioreactor. Under the bioreactor conditions, the resistance of the bacterial population to hydrocarbons and antibiotics increased [44]. At the same time, the degradation potential of the bacterial consortium is the result of establishing synergistic relationships between its components, and not a simple summation of their oxidative abilities. Rambeloarisoa et al. found that the removal of one of the bacterial components from the consortium leads to a significant decrease in the efficiency of oil degradation [45]. Apparently, the metabolites formed during the oxidation of petroleum products are a substrate for the development of other groups of microorganisms that effectively remove the remaining pollutants. However, Zhukov D.V. and others believe that as a result of cometabolism of oil products in the system, the accumulation of intermediate persistent and toxic oxidized compounds can occur, which can inhibit the development of the microbial population [46].

From soil and water samples from Russia, Kazakhstan and Antarctica, 86 strains of oil destructive bacteria were isolated, of which 13 were thermo-tolerant [47]. These bacteria utilized the oil at 45-50°C and had an optimum (35-37°C) and growth range (20-53°C) different from the mesophilic bacteria. Thermo-tolerant strains have been identified as representatives of the genera Rhodococcus and Gordonia. It was shown that their ability to degrade petroleum products at 24 and 45°C did not differ significantly. Strains of Rhodococcus sp. Par7 and Gordonia sp. 1D utilized 14 and 20% oil for 14 days at 45°C. All isolated thermo-tolerant bacteria grew in a medium containing 3% NaCl, and the strains G. amicalis 1B and Gordonia sp. 1D - up to 10% NaCl. The bacteria G. amicalis and R. erythropolis were able to utilize oil and individual hydrocarbons at elevated (up to 50°C) temperatures [47].

VI. CONCLUSION

The above data show that active strains of bacteria of the genus Rhodacoccus have unique properties for use in the reactions of biocatalysis, bio-purification, bioremediation, biodegradation and biotransformation. Naturally adapted or mutant strains of Rhodococcus withstand highly toxic environments, while catalyzing the synthesis of industrially important compounds such as acrylamide, nicotinamide or other pharmaceutical substances. To reuse and increase the operational stability of biocatalysts based on cells or rhodococcal enzymes, their immobilized forms on various carriers are obtained. They are very unpretentious for cultivation under the conditions of the fermenter and their enzymes have an excessively high reaction rate. In this regard, interest is steadily growing in this group of microorganisms and their enzyme system, as an object of industrial use in various industries and the development of promising biotechnologies.

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