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Молекулярные механизмы противомикробной защитной стратегии бактериальной клетки

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АННОТАЦИЯ

Актуальность. Решение проблемы антибиотикорезистентности (АБР) и продолжающегося распространения штаммов с множественной лекарственной устойчивостью является стратегической задачей практического здравоохранения. Важным инструментом совершенствования антимикробной фармакотерапии наряду с активным поиском новых эффективных лекарственных соединений может служить детальное изучение первопричины возникновения и влияния внеклеточной среды на молекулярные механизмы устойчивости бактерий к химиопрепаратам.

Цель. Проанализировать литературу, посвященную молекулярным механизмам противомикробной защитной стратегии бактериальной клетки от воздействия лекарственных средств и перспективным стратегиям борьбы с антибиотикоустойчивыми возбудителями.

Материалы и методы. Выполнен поиск и анализ научной литературы за последние 5 лет в базах PubMed, eLibrary, Europe PMC, WoS, CyberLeninka и др. Поисковые запросы включали следующие сочетания слов: для русскоязычных публикаций — проблема АБР, экологические факторы антибиотикочувствительности, механизмы резистентности, гены резистентности, мобильные генетические элементы; для англоязычных публикаций — *antibiotic resistance evolution*, *antibiotic resistance genes*, *antibiotic resistance in biofilms*, *transmission of antibiotic resistance*. Проанализировано 100 источников литературы, опубликованных за период 2018–2022 гг., из них в обзор вошло 44.

Анализ отечественных и зарубежных источников показал, что значительная роль в развитии АБР микроорганизмов отведена ферментативной бета-лактамазной активности, специфическим защитным белкам микроорганизмов, а также способности патогенных штаммов к формированию биопленок. Кроме того, по результатам исследований основным источником генов резистентности предстает окружающая среда, где происходит перенос генов АБР между представителями разных таксонов бактерий. Перспективными направлениями в борьбе с антибиотикоустойчивыми возбудителями являются математическое моделирование, синтетическая биология, фаговая терапия.

Заключение. В современных исследованиях тенденция АБР среди микроорганизмов представляется серьезной эволюционной и экологической проблемой. Бесконтрольное и необоснованное использование на сегодняшний день антибактериальных препаратов в медицине, ветеринарии и сельском хозяйстве спровоцировало активизацию известных к настоящему моменту механизмов защитной стратегии бактериальной клетки, вызвав усиление адаптивной способности бактериальных патогенов и распространение штаммов с множественной лекарственной устойчивостью. Также в обзоре приводятся данные о разнообразных стратегиях, направленных на решение проблемы АБР.

Ключевые слова: *антибактериальные агенты; лекарственная устойчивость; бета-лактамазы; фаговая терапия; биопленки; антибиотикорезистентные штаммы; эффлюксные помпы; молекула-мишень MfpA; мобильные генетические элементы; рибосомные белки*

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Molecular Mechanisms of Antimicrobial Defense Strategy of Bacterial Cell

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ABSTRACT

INTRODUCTION: Solution to the problem of antibiotic resistance (ABR) and the continuing spread of multidrug resistant strains is a strategic task of practical healthcare. An important tool for improving antimicrobial pharmacotherapy, along with active search for new effective drug compounds, can be a detailed investigation of the prime cause of the emergence and effect of the extracellular environment on the molecular mechanisms of bacterial resistance to chemotherapeutic drugs.

AIM: Analysis of the literature devoted to the molecular mechanisms of antimicrobial defense strategy of the bacterial cell against the effect of medical drugs, and to promising strategies of combating antibiotic-resistant agents.

MATERIALS AND METHODS: A search and analysis of the scientific literature was conducted in PubMed, eLibrary, Europe PMC, WoS, CyberLeninka and other databases for the last 5 years. The search queries included the following word combinations: for Russian-language publications the problem of ABR, environmental factors of antibiotic sensitivity, resistance mechanisms, resistance genes, mobile genetic elements; for English-language publications: *antibiotic resistance evolution*, *antibiotic resistance genes*, *antibiotic resistance in biofilms*, *transmission of antibiotic resistance*. A total of 100 literature sources published from 2018 to 2022 have been analyzed, of which 44 were included in the review.

An analysis of domestic and foreign sources showed that a significant role in the development of ABR in microorganisms is assigned to enzymatic beta-lactamase activity, specific protective proteins of microorganisms, as well as the ability of pathogenic strains to form biofilms. Besides, according to the results of studies, the main source of resistance genes is the environment, where the transfer of ABR genes between representatives of different bacterial taxa occurs. Promising areas in the fight against antibiotic-resistant pathogens are mathematical modeling, synthetic biology, phage therapy.

CONCLUSION: In modern studies, the tendency of microorganisms to ABR presents a serious evolutionary and ecological problem. The uncontrolled and unjustified current use of antibacterial drugs in medicine, veterinary medicine and agriculture provoked the activation of the mechanisms of bacterial cell defense known by the moment, and caused enhancement of the adaptive capacity of bacterial pathogens and spread of multidrug resistant strains. The review also provides data on various strategies aimed at solving the ABR problem.

Keywords: *antibacterial agents; drug resistance; beta-lactamases; phage therapy; biofilms; antibiotic–resistant strains; efflux pumps; MfpA target molecule; mobile genetic elements; ribosomal proteins*

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ECO•VECTOR

LIST OF ABBREVIATIONS

ABR — antibiotic resistance
CRISPR-Cas — clustered regularly interspaced short palindromic repeats, CRISPR-associated proteins
DNA — deoxyribonucleic acid
sRNA — small untranslated ribonucleic acid

INTRODUCTION

The leading place among the most promising classes of pharmaceutical preparations and the most important achievements in medicine rightfully belongs to antibiotics that marked the beginning of the 'golden era' since the discovery of penicillin by A. Flemming in 1928 [1, 2]. The uncontrolled and unjustified current use of antibacterial drugs in medicine, veterinary medicine and agriculture provoked the activation of the protective mechanisms of bacterial strains, and, as a consequence, an increase in the diversity of antibiotic-resistant pathogens, that entailed a high level of morbidity and mortality [1, 3, 4].

Pathogens with extremely high resistance and virulent properties include agents of infectious diseases of humans and animals: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, bacteria of the *Enterobacteriaceae* family, etc. [5, 6].

According to published data from the World Health Organization for 2019, mortality from infections caused by antibiotic-resistant strains amounted to 700 thousand people. According to forecasts for 2050, this figure will increase to 20 million, with economic losses of more than 2.9 trillion dollars [1].

Solving the problem of antibiotic resistance (ABR) and continuing dissemination of multidrug-resistant strains is a strategic task of practical healthcare. To improve antimicrobial pharmacotherapy, along with an active search for new effective drug compounds, it is necessary to study in detail the root cause of the emergence and impact of the extracellular environment on the molecular mechanisms of bacterial resistance to chemotherapeutic drugs [3, 7].

The **aim** of this study to analyze the literature devoted to the molecular mechanisms of defense strategy of the bacterial cell against the effect of medical drugs, and to promising strategies of combating antibiotic-resistant agents.

MATERIALS AND METHODS

A search for full-text articles in Russian and English published in the period 2018–2022 was conducted in PubMed, eLibrary, Europe PMC, WoS, CyberLeninka databases. Initially, the title and abstract were screened, and in case of insufficient information content, the full text of the article was studied. A total of 100 literature sources were analyzed, 44 of them were included in the review. The obtained data were structured by areas: the basic mechanisms of antibacterial resistance, environmental factors that influence the development and spread ABR, strategies for combating antibiotic-resistant pathogens. Priority publications included investigations of the genetic, evolutionary and ecologic aspects of the emergence of the bacterial defense mechanisms.

Main Mechanisms of Antibacterial Resistance

Some microorganisms initially possess the drug resistance (native resistance), in others it develops as a result of random mutations (acquired resistance) [8]. The current knowledge is that the ***antibacterial resistance mechanisms*** are based on:

1) *principle of activation of efflux pumps and removal of antibiotics from the microbial cell*, which conditions the emergence of polyresistant strains in many kinds of microorganisms [9]. Thus, for example, Bmr efflux pumps found in *B. subtilis*, block the effects of chloramphenicol, puromycin, ethidium bromide, rhodamine and tetraphenylphosphone. The best studied efflux pumps in *S. aureus* are QacA and QacB consisting of 514 amino acid residues with mass of 55 kDa and extruding monovalent and bivalent cationic drugs, diamidines and biguanidines [9];

2) *modification of the structure of medical drugs*. An example of the resistance strategy is the ability of pathogenic strains of *K. pneumoniae*, *E. coli*, *P. aeruginosa* to hydrolyze beta-lactam antibiotics by beta-lactamase enzymes of the microbial cell [9];

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3) *modification of an alternative target molecule for antibacterial agents*, most often associated with mutations of ribosomes and disruption of their functioning, for example, methylation of 23S rRNA in actinomycetes avilamycin producers, is mediated by three genes encoding methyltransferase [2, 7, 10].

Beta-lactam drugs. It is worth considering in more detail the beta-lactam drugs (penicillins, cephalosporins, carbapenems, monobactams, etc.) one of the most effective, low-toxic and proven classes of antibiotics. Annual expenses on this group of drugs amount to more than 15 billion dollars, which makes 65% of the entire pharmaceutical market [11, 12]. It was during the use of beta-lactams that the alarming phenomenon of antibiotic resistance was encountered, which is associated with the rapid evolution of microorganisms' own beta-lactamases [13]. About 2000 beta-lactamase enzymes of molecular class A have been identified, most of which were found in various bacteria of the genera and orders *Bacillus*, *Clostridium*, *Nocardia*, *Nocardiopsis*, *Staphylococcus*, *Enterococcus* and *Streptomyces*, *Bacteroidetes*, *Bacteroidales*, *Chitinophagales*, *Cytophagales*, *Flavobacteriales* and *Sphingobacteriales* and belong to certain functional types: TEM, CTX-M, KPC and CARBA [14].

Mycobacteria's own mechanisms of protection against drug effects also include enzymatic *beta-lactamase activity*. Class A beta-lactamases (BlaC и Bla Mab), produced by mycobacterial agents (*M. tuberculosis*, *M. abscessus*, *M. fortuitum*), possess extended range of action (beta-lactamases of extended range), degrade cephalosporins and are less sensitive to clavulanic acid [14]. The *M. tuberculosis* genome contains regions coding for beta-lactamase and also synthesizing MfpA protein target molecule, which protects mycobacteria against the effect of quinolones through binding of DNA gyrase with antibiotic leading to decrease in concentration of the latter [14].

The production of beta-lactamases by gram-negative urinary tract infectious agents *K. pneumoniae* and *E. coli* underlies resistance to penicillins, cephalosporins and monobactams, which significantly hinders the therapeutic effect [15]. Besides, enzymes facilitate the development of resistance to other classes of antimicrobial drugs fluoroquinolones, co-trimoxazole and aminoglycosides.

Specific protective proteins. An important role in the development of antibiotic resistance is assigned by researchers to the ability of bacterial cells to produce specific protective proteins, for example, ribosomal proteins Tet(S), Tet(T), Tet(Q), TetB(P), Tet(W), Tet(O), Tet(M) and OtrA in some gram-positive and gram-negative microorganisms [7, 16]. Currently, of the 13 known protein species that block binding of ribosomes to tetracycline antibiotics, Tet(O) and Tet(M) have been studied in most detail. Soluble cytoplasmic proteins were first found in bacteria of *Streptococcus* and *Campylobacter jejuni* families, while the genes encoding these proteins, have also been found in many other microorganisms [16].

Microbial biofilms. The ability to form biofilms is not only a way to maintain the viability of microorganisms in various biotopes, but also a successful mechanism of resistance to the effects of antibacterial agents. Biofilms are a consortium of related and unrelated specialized bacterial cells adhered to a surface or to each other, contacting with each other and embedded in the self-produced extracellular mucous matrix of polymer compounds. The phenomenon of biofilm formation, discovered at the end of the 20th century, is characteristic of many microbial species and is considered an important factor of pathogenicity [17–21].

It is known that the development of bacterial biofilms, as one of the options for antimicrobial protection, is characteristic of approximately 70.0% of infectious pathogens [17, 22]. The highest tendency to form biofilms was found in the following bacterial strains: *Staphylococcus spp.*, *Streptococcus spp.*, *P. aeruginosa*, *H. influenzae*, *M. catarrhalis*, *E. coli* [22].

Studies show that the resistance of polymicrobial biofilms to antibacterial agents is much higher than of unrelated biofilm communities [21, 23]. Interactions between microbial representatives of different physiological groups in a biofilm determine the overall resistance of the population to antimicrobial drugs [23].

The protective mechanisms of microbial biofilms are extremely complex and poorly understood, but it is known that the mucous matrix prevents the diffusion of antibiotics to bacterial cells, and a decrease in the supply of oxygen and nutrients changes metabolic activity, stimulating the emergence of persistent forms of microorganisms that are less sensitive to drugs [21]. The biofilm functions as a physical barrier in the form of numerous anionic and cationic protein molecules, glycoproteins and glycolipids that bind antimicrobial agents [21]. There is an opinion that limited access of antibiotics to the biofilm matrix 'turns on' *adaptive immunity* processes, promoting the phenotypic diversity of more tolerant microbial cells [23].

Another reason for the low efficiency of antibiotics in the structure of biofilms is the accumulation of enzymes that degrade antibacterial drugs. It has been shown that beta-lactamases that enhance the hydrolysis of imipenem and ceftazidime, accumulate in biofilms of *P. aeruginosa*. The activity of beta-lactamases of *K. pneumoniae* prevents ampicillin from reaching the deep layers of the biofilm matrix [21].

Another factor of biofilm resistance is extracellular DNA, which, being an anionic molecule,

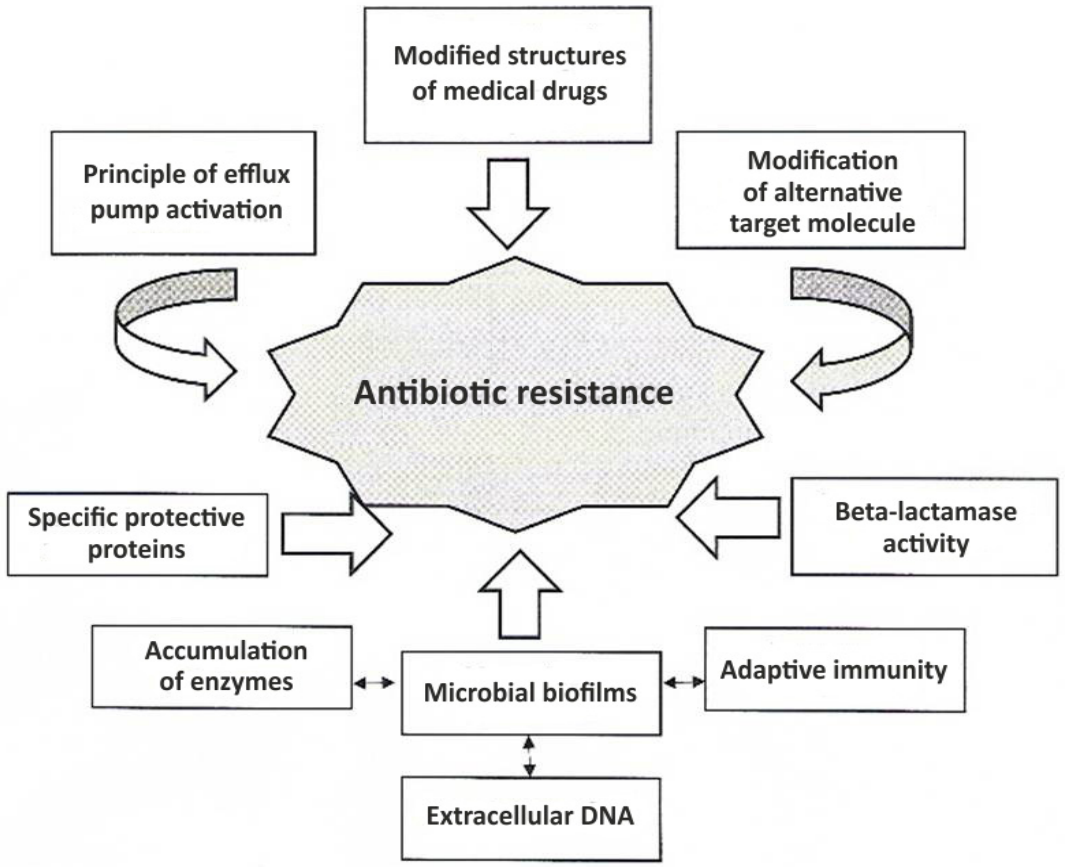

Fig. 1. Basic mechanisms of antibacterial resistance.

chelates cations, reducing the concentration of magnesium ions in the outer membrane, and activates the two-component regulatory systems PhoPQ and PmrAB in the genera *Pseudomonas* and *Salmonella*, responsible for resistance to antimicrobial drugs [18, 21]. The main mechanisms of antibacterial resistance are shown in Figure 1.

Environmental Factors Influencing Development and Spread of ABR

The results of numerous studies highlight a potentially important role of the environment as a source of the emergence and spread of multidrug-resistant pathogens through the emergence of adapted tolerant strains, which may affect the functioning of the natural bacterial populations involved in the biogeochemical processes [24, 25]. It has been proven that antibiotic resistance genes first appeared exactly in the environment, since many microorganisms themselves produce antibiotics, inhibiting the growth of competitive strains, and also performs a signaling function for cell-to-cell communication in microbial communities [26].

Evolutionary origin of ABR genes. The biomass of microorganisms on the globe, reaching several thousand billion cells, represents a colossal gene pool for mutations, horizontal transfer and genetic drift [26]. The resistance genes were found in microbial communities of ecosystems even not subjected to any anthropogenic intervention, for example, in remote caves and in the permafrost zone [3]. Data from phylogenetic studies indicate the emergence of class A β-lactamases in prokaryotes billions of years ago, which proves the ancient origin of ABR genes. Data are presented that resistance genes could initially participate in metabolic processes not associated with antibiotics [27].

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At the same time, the evolutionary and ecological processes leading to mobilization, replication and clinical manifestations of the bacterial response remain poorly understood [26]. Pathogens protecting themselves against the effects of antimicrobial agents, can simultaneously recruit several resistance strategies, which leads to the appearance of new adapted strains [5].

Physiological features of bacteria. At the same time, the emergence of new resistance factors is limited by certain energy expenditures of the bacterial organisms, since many other cell functions may appear under threat [26]. The emerging resistances genes develop in conditions of tough competition undergo tough selection and are transferred between different pathogens [9, 26]. Thus, new competitive genetic determinants are fixed in bacterial populations, increasing the drug resistance of microbial cells and the ability to survive on exposure to increasing concentrations of the antibiotic. Such processes of natural selection maintain the ecological 'pool' of ABR genes, and only indirectly affect their final formation, since they do not activate the mobilization of viability factors. Despite the continuous emergence of new, and the activation of existing protective strategies, only a few genetic determinants of resistance are fixed in bacterial populations. Of potential threat to health are pathogenic species with pronounced genetic polymorphism and plastic metabolism [9, 26].

Horizontal gene transfer, where resistance factors are transmitted from a specific cell outside the bacterial population, has a significant impact on the spread of both known and new resistance genes [9, 26].

Mobile genetic elements. Improvement of molecular genetic approaches revealed the priority role of the mobile genetic elements (plasmids, transposons, integrins) in the emergence of resistance to antibiotics, adaptation to new ecological niches and abiotic conditions, coding for new beneficial metabolic pathways and pathogenicity factors [27–31]. Besides, mobile genetic elements permit bacteria to assimilate new carbon sources and form resistant spores [32].

The most probable is the exchange between phylogenetically related saprophytic and pathogenic microorganisms populating the same biotope, with resistance genes, even for a short period [19, 20]. On the other hand, the transfer of antibiotic resistance genes has been proven between representatives of different taxa *C. perfringens*, *S. pneumoniae*, *E. faecalis* and *Bacteroides* [26]. Besides, the plasmid-coded qnrA gene found in various species of the *Enterobacteriaceae* family, was probably transferred from the marine and fresh-water *Shewanella* algae, which confirms the aquatic route of transmission of genes that cultivate drug resistance [27].

According to the authors, opportunistic microorganisms *B. cepacia*, *O. intermedium* and *S. maltophilia*, soil habitants, may be recipients of resistance genes for bacteria associated with human microflora, transfer them in the opposite direction and be causative agents of infections [26].

It is known that pathogens of nosocomial infections belonging to the genera *Acinetobacter*, *Burkholderia*, *Enterobacter*, *Klebsiella*, *Pseudomonas*, *Stenotrophomonas* or *Serratia*, are usually plant symbionts in nature [26].

Strategies to Combat Antibiotic-Resistant Pathogens

Defensins. A clear understanding of the formation of ABR mechanisms permits to develop promising strategies to combat resistant strains. Along with large-scale studies of the reactivity of pathogenic microbiota to the effects of medical drugs, principally new approaches to combating antibiotic-resistant pathogens are needed, including the search for the ways to trigger the synthesis of the immune system's own cationic peptides defensins, in combination with the introduction of the 'conventional' antibiotics. Defensins are cationic antimicrobial peptides with a molecular mass of 3.5 kDa–4.5 kDa, possessing antimicrobial activity against a large number of gram-positive and gram-negative bacteria, fungi and viruses. For example, defensins HNP 1–3 and RTD-1 have a bactericidal effect against methicillin-resistant *S. aureus* and *P. aeruginosa* [33].

Synthesis of new antibacterial drugs using mathematical modeling. In the modern world, there is a crying need for developing innovative antibacterial drugs. One of the promising directions in creating such drugs is the use of synthetic small untranslated RNA (sRNA) and guide CRISPR Cas associated RNA, which are aimed at inactivating the currently epidemically significant genetic determinants of ABR. This methodological direction allows for simultaneous programming of the inactivation of several targets, which increases the effectiveness of new antibacterial drugs. Besides, the results obtained in the study of sRNA and CRISPR Cas systems permit to consider them as new classes of antimicrobial drugs that open up opportunities not only for the treatment of infections caused by MDR pathogens, but also for the study of microbial consortia and the control of industrial fermentations [34]. An important approach to overcome the problem of ABR is a possible change the protocols of using targeted drugs, forecasting and managing the spread of resistance. The most convenient tool in this direction is mathematical modeling, which is necessary for a quantitative understanding of the

effect of multitarget therapy. For example, a mathematical model for predicting the development of bacterial resistance based on the relationship between the level of resistance and the volume of antibiotic consumption has been constructed and validated [35]. Besides, research is actively underway on the development of new multitarget drugs, using iterative modification, molecular docking methods and artificial neural networks [36]. In addition, increasing knowledge of the molecular mechanisms of innate immune responses is being actively used in the development of novel antimicrobial drugs [36].

Of great interest in the development of innovative antibacterial drugs is synthesis of novel pyrimidine compounds with potential antimicrobial and antimycobacterial activity. A number of publications have proven the bactericidal effect of pyrimidine derivatives on *S. aureus*, *K. pneumonia*, *E. coli*, *A. baumannii*, *P. aeruginosa* [37, 38], *M. tuberculosis* [38].

Phage therapy. There is a renewal of interest in phage therapy implying the use of moderate lysogenic phages associated with human microbial pathogens and containing double-stranded or single-stranded DNA in the genome, the majority of which are assigned to the orders *Caudovirales* and *Microviridae* [39]. The mechanism of action includes adsorption of bacteriophage on special receptors within the cell walls, in polysaccharide capsules, piles and flagella of bacteria. After adsorption, the virus-phage incorporates its genetic information into the microbial cell for further DNA replication. The replication process causes lysis of the pathogen, the synthesized bacteriophages leave the cell, and the cycle is repeated. To note, bacteriophages are specific, they destroy only certain pathogens, not harming other microorganisms [39].

Synthetic biology. The active development of a novel research area synthetic biology that uses genomic and metagenomic approaches to design and create biological systems with the preset properties and functions, is aimed at search for antibacterial agents of the natural origin [1, 40, 41]. For example, in the work of O. N. Sineva, antibiotic activity was demonstrated against gram-positive, gram-negative microorganisms, yeasts and rare species of actinomycetes [42].

Phytopharmaceutics. Phytopharmaceuticals based on plant extracts and essential oils, possessing antimicrobial, antiviral and cytotoxic properties, may be promising agents to combating the increasing resistance of bacteria [43]. There are known synergistic effects of rosemary (*Rosmarinus officnalis*) essential oil in combination with ciprofloxacin against gram-negative bacteria [44]. P. Knezevic, et al. [44] identified the antibacterial activity of the essential oils of *Eucalyptus camaldulensis* (0.5 μl/ml–2 μl/ml) in combination with ciprofloxacin, gentamycin and polymyxin B against *Acinetobacter baumannii* strain with multidrug resistance. Given one essential oil containing various functional groups of chemical compounds (alcohol, aldehyde, formaldehyde, carbonyl, etc.), it is likely that antibacterial activity is not conditioned by one specific component and mechanism. For example, essential oils have a destructive effect on bacterial cell membrane and inactivate viruses by destroying the lipid layer of vibrios [43]. Strategies for combating antibiotic-resistant pathogens are presented in Figure 2.

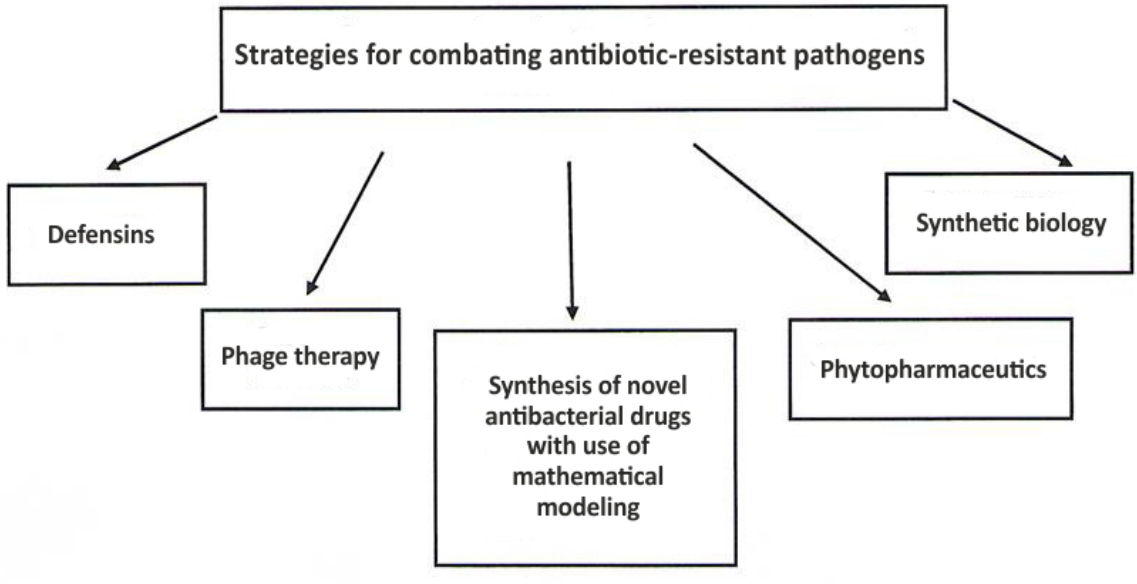

Fig. 2. Strategies for combating antibiotic-resistant pathogens.

CONCLUSION

Discovery of antibiotics permitted to combat many infectious diseases and played an important role in increasing the human life expectancy. The situation worsened by the emergence of a large number of resistant strains.

In modern studies, the antibiotic resistance tendency among microorganisms presents a serious evolutionary and ecological problem. The uncontrolled and unjustified current use of antibacterial drugs in medicine, veterinary medicine and agriculture provoked the activation of the mechanisms of bacterial cell defense known by the moment (activation of the efflux pumps, modification of the medical drug structure, modification of an alternative target molecule, microbial biofilms, etc.), and caused enhancement of the adaptive capacity of bacterial pathogens and dissemination of multidrug resistant strains.

An objective assessment of the effectiveness of measures aimed at reducing the threat to public health is possible with the development of strategies for detailed genetic and genomic analysis of resistant pathogens, improvement of measures to control the use of drugs and the spread of antibiotics in the environment. Besides, detailed studies of the molecular-genetic nature of resistance of microorganisms to antibiotics will minimize the possible risk of resistance to new antibacterial agents.

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