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ACTUAL APPROACHES TO DEVELOPMENT OF NEW ANTIMICRIBIAL MEDICINES IN THE CONDITIONS OF EXTENSION OF ANTIBIOTIC RESISTANCE

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Мета. *Обґрунтування доцільності вивчення характеру взаємодії наночастинок металів з плазмідною ДНК бактерій на етапі фармацевтичної розробки антимікробних засобів на основі наночастинок металів як самостійних антимікробних агентів, а також композицій наночастинок металів з відомими антимікробними речовинами.*

Методи. *Використано методи інформаційного пошуку та аналізу даних літератури.*

Результати. *Плазмідна передача стійкості до лікарських засобів є найбільш важливим механізмом виникнення резистентності в бактеріальній популяції. Перспективним підходом до вирішення проблеми подолання резистентності мікроорганізмів є застосування в якості активних фармацевтичних інгредієнтів антимікробних засобів речовин, які будуть викликати деструкцію R–плазмід або забезпечувати їх незворотну елімінацію. Вивчення взаємодії речовин з плазмідною ДНК бактерій та дослідження їх впливу на передачу генів резистентності в бактеріальних популяціях доцільно застосовувати на першому етапі створення антимікробних лікарських засобів, на якому проводиться вибір потенційного активного фармацевтичного інгредієнта.*

Висновки. *Створення та впровадження у виробництво лікарських засобів на основі наночастинок срібла та золота є перспективним напрямком, оскільки наночастинки даних металів поряд з антимікробною дією будуть забезпечувати незворотну елімінацію плазмід з бактеріальних клітин та можуть стати вирішенням проблеми антибіотикорезистентності*

Ключові слова: *антимікробні засоби, наночастинки металів, інфекційні захворювання, резистентність мікроорганізмів, елімінація плазмід*

1. Introduction

The need to control the phenomenon of resistance of microorganisms to antimicrobial medicines in Ukraine and in the world is an extremely urgent problem. Today, the problem of antibiotic resistance goes beyond the purely medical and has an important socio-economic significance, and also becomes one of the priorities of the state policy of most countries.

2. Statement of the problem

According to official statistics, for reasons of antibiotic resistance and the impossibility of treatment of severe infections caused by resistant microorganisms, in the world every year die at least 7 million people. However, accurately calculate the number of victims of antibiotic resistance is not possible, in fact, they are much more [1].

Already at the global level, the topic of antibiotic resistance was discussed in the WHO reports in 2014, when, after gathering information from 114 countries worldwide, the spread of resistance to the "last line" of carbapenem and fluoroquinolones among the strains of *Klebsiella pneumoniae* and *Escherichia coli* was evident [2].

The issue of controling the resistance of microorganisms to antimicrobial agents was one of the four main topics of the health sector, which was put forward for consideration by the UN General Assembly. Moreover, at previous meetings only non-communicable diseases were discussed. Given the urgency of the problem, UN members in a joint statement undertook to develop national plans to counteract microbial resistance to antimicrobials based on the Global Plan of Action on Antimicrobial Resistance 2015, in particular to strengthen monitoring for infections resistant to antibiotics and control of the use of antibiotics in medicine, veterinary medicine and agriculture, as well as the growth of international cooperation and financing [3]. The Global Action Plan was also developed by the Food and Agriculture Organization of the United Nations for the period 2016–2020 (The FAO action plan for antimicrobial resistance 2016–2020). [4] In these plans, the idea of providing investment in the researches of antibiotic resistance is an important place.

As it is know, the World of Antibiotic Awareness Week takes place every year [5]. Such events contribute to informing the community and discuss ways to control antibiotic resistance. They are aimed at raising awareness of the problem and promoting the correct use of antibiotics.

3. Analysis of recent research and publications

In Ukraine, in 2016, on the initiative of the Verkhovna Rada Committee on Health Care, a round table discussion on "Antibiotic resistance and infection control" was held.

Taking into account the situation with the current antibiotic resistance are defined several solutions [6]:

– to intensify the development and introduction of new antimicrobial medicines;

– to develop new drugs of a completely different structure;

– to find methods for controlling the proliferation of microorganisms resistance to existing and used drugs.

4. Identification of aspects of the problem unsolved previously

In our opinion, at this stage, it is advisable to develop and implement in practice, in the first place, those

antimicrobials that will prevent the development of antibiotic resistance. The most promising advances are the development of the use of chemicals that provide effective elimination of antibiotic resistance determinants.

5. Objective statement of the article

The aim of the work is to substantiate the expediency of studying the nature of the interaction of metal nanoparticles with the plasmid DNA of bacteria at the stage of pharmaceutical development of antimicrobial medicines on the basis of nanoparticles of metals as independent antimicrobial agents, as well as their compositions with known antimicrobial substances.

6. Presentation of the main material of the research

Under the resistance of microorganisms (MO) is understood the ability of the MO to tolerate significantly higher concentrations of the drug than other MOs of this species, or develop at concentrations higher than those that can be achieved in macroorganism, when antibiotics are used in therapeutic doses [7–9].

Even Alexander Fleming, who discovered penicillin, warned that such a drug should be used rationally and should not allow bacteria to develop resistance to it [10].

For a long-time action of the antibiotic dies most of the bacteria in the population, but those microorganisms that have survived have genetic determinants of resistance to such antibiotics. Moreover, the carrier of antibiotic resistance genes is fixed for the selective action of the antibiotic and in subsequent generations of bacteria. Thus, antibiotic-resistant forms have the advantage and ability to pass the determinants of antibiotic resistance to other bacteria [8, 9].

In order to overcome the phenomenon of resistance of microorganisms to existing medicines, antimicrobial agents of new chemical groups are introduced and combined drugs are used [9, 11, 12]. However, the resistance of microorganisms grows many times faster than creating new antimicrobials. Against the background of a significant increase in acquired bacterial resistance in recent years, the activity of pharmaceutical companies has been significantly reduced in the development and research of new antibiotics [13–15]. Thus, since the beginning of the XXI century, no more than 5 new antibiotics have been created in the world, which is a very sad statistics, taking into account the pace of resistance of microorganisms.

Given the scale of the problem, WHO has developed a document entitled "WHO Global Strategy for the Containment of Antibiotic Resistance" [16]. It states that excessive and inappropriate use of antibiotics is considered one of the main causes of the spread of resistance to antimicrobial drugs.

In 2017, a new classification of antibiotics and recommendations on conditions for their use were published in WHO documents [5, 17]. According to this classification antibiotics are divided into three categories: I – antibiotics access group, II – group of watch and III – reserve (Table 1). Such categorization of antibiotics should contribute to their proper choice for the treatment of infections and to improve the results of therapy, to slow the development of bacteria resistant to drugs.

Table 1

Classification of antibiotics

Antibiotics access group	
Beta-lactam antibiotics	***Other antibacterials***
Amoxicillin	Amikacin
Amoxicillin + clavulanic acid	Azithromycin *
Ampicillin	Chloramphenicol
Benzathine benzylpenicillin	Ciprofloxacin *
Benzylpenicillin	Clarithromycin
Cefalexine	Clindamycin
Cephazoline	Doxycycline
Cefixime *	Gentamicin
Cefotaxime *	Metronidazole
Ceftriaxone *	Nitrofurantoin
Cloxacillin	Spectinomycin (adult only)
Phenoxymethylpenicillin	Sulfamethoxazole + trimethoprim
Piperacillin + Tazobactam *	Vancomycin (orally) *
Procaine benzylpenicillin	Vancomycin (parenteral) *
Meropenem *	
* group antibiotics included in the List of Essential Medicines and have specific limited indications for use	
Antibiotics watch group	
Antibiotics group	***Drugs***
Quinolones and fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
Cephalosporins of III generation (with or without beta-lactamase inhibitor)	Cefixim, ceftriaxone, cefotaxime, ceftazidime
Macrolides	Azithromycin, clarithromycin, erythromycin
Glycopeptides	Teicoplanin, vancomycin
Antipseudomonal penicillin with beta-lactamase inhibitor	Piperacillin + tazobactam
Carbapenems	Meropenem, imipenem + cilastatin
Penems	Faropenem
Antibiotics reserve group	
Antibiotics group	***Drugs***
Oxazolidinones For example: linezolid	Phosfomycin
Cephalosporins of IV generation For example: cefepime	Aztreonam
Cephalosporins of V generation For example: ceftaroline	Tigecycline
Polymyxins For example: polymyxin B, colistin	Daptomycin

WHO recommends that antibiotics can be provided at any time for the treatment of a wide range of infections. The WHO observes the antibiotics recommended for first and second-line drugs for the treatment of a limited number of infections. The reserve group includes antibiotics that should be considered as "last hope" drugs and used only in the worst cases where other possibilities

are exhausted, in particular for the treatment of life-threatening infections caused by bacteria with multiple drug resistance [5, 17].

The proposed classification of antibiotics and recommendations for their use are consistent with the WHO Global Strategy for Antibiotic resistance, which aims to control the resistance of MO to drugs through the optimal use of antibiotics [16].

Most often, resistant strains of MO arise when the genotype of the bacterial cell changes as a result of the horizontal transfer of antibiotic resistance genes. Acquired resistance is transmitted by heredity to the next generation of bacteria. The rate of development and the degree of severity of resistance associated with the species and even the strain of MO. The fastest and most often anti-bacterial drug resistance occurs in *Staphylococcus spp., Escherichia spp., Mycoplasma spp., Proteus spp. and Ps. aeruginosa* [9]. The rational choice of antibiotics to prevent the spread of antibiotic resistance involves, first of all, the account of the antibiotic resistance profile of the pathogen. In addition, the aim of a clinician in modern conditions should be not only safe and effective treatment of a particular patient, but also prevent the development of antibiotic resistance in a hospital through a series of measures that include a wide range of bacteriological and serological research methods [8]. To reduce the rate of development and spread of antibiotic resistance should clearly observe the dosage and duration of antibiotic therapy. Another aspect of controlling the spread of antibiotic resistance is the careful monitoring of resistance to all antimicrobials (antibiotics, antiseptic drugs, etc.), both in individual patients and in the microbial landscape of a specific treatment facility and institution [18].

The genetic basis of resistance is the presence in the bacteria of post-chromosomal factors of resistance to drugs - plasmids and transposones [8].

Plasmid transmission of drug resistance is the most important mechanism of resistance in the bacterial population. The circulation of plasmids from animals to animals, from animals to humans and from humans to animals promotes the rapid spread of drug resistance around the world [6]. Bacterial plasmids or so-called R-factors are associated with the transfer of markers of drug resistance in the process of conjugation of cells. Therefore, a promising approach to solve the problem of overcoming the resistance of microorganisms is the use as an active pharmaceutical ingredient of antimicrobial medicines that will cause the destruction of R-plasmids or to ensure their irreversible elimination.

Particular interest in this direction attract nanoparticles of metals, in particular silver, gold, and others, which exhibit an effective antimicrobial action and can become a solution to the problem of antibiotic resistance [19]. In recent years, the researches of physical, physicochemical, quantum-chemical properties of nanoparticles have been actively carried out, which will facilitate their more active introduction into practical human activity [20]. To date, many methods of obtaining nanoparticles have been developed and mastered in Ukraine: gas and plasmochemical synthesis, electron beam technology, sedimentation from colloidal solutions, thermal decomposition and recovery, and others [21].

In the Institute of Biocolloidal Chemistry named after F.D. Ovcharenko of the NAS of Ukraine studied the nature of the interaction of R-plasmids (on the example of recombinant plasmids pUC19 and pBR322) with nanoparticles of gold and silver, and it was proposed to use such nanoparticles as antibiotic resistance plasmid eliminators [22].

In order to overcome the antibiotic resistance of microorganisms - pathogens of infectious and inflammatory processes of the maxillofacial area, it is proposed to use a method that includes the detection of microorganisms that cause disease data, plasmid DNA, and the elimination of R-plasmids [23].

In our opinion, it is advisable to apply the proposed approaches to the first stage of the creation of antimicrobial drugs when choosing a potential active pharmaceutical ingredient and to study its interaction with the plasmid DNA of bacteria and the effect on the transfer of resistance genes in bacterial populations.

7. Conclusions and prospects for further research

Creation and introduction into the production of medicines based on nanoparticles of silver and gold is a promising direction, since nanoparticles of these metals, along with antimicrobial action, will provide irreversible elimination of plasmid from bacterial cells, changing the sensitivity of microorganisms to antibiotics towards a decrease in resistance.

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