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вишеградський інструмент для розвитку зелених підходів*

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Розділ № 3 \ Chapter № 3

Antimicrobial resistance: mechanisms and ways to combat

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1. Introduction

Antibiotics play a key role in treatment and controlling bacterial infections. Resistance to antibiotics that are widely used in clinical practice is the global unsolved problem of healthcare that leads to the increase in morbidity and mortality of infections and causes significant economic loss. Despite different approaches taken in recent decades to tackle this issue, the trends of global antimicrobial resistance (AMR) spread show no signs of slowing down [1-3]. The consequences of AMR rise will be increasing use of older less effective techniques in controlling infections such as debridement, disinfection, amputation. The process of treating infections will take longer, be more invasive, and will be less successful [4]. The rapid growth of AMR infection rate and the lack of new antimicrobial medications being introduced to combat this issue are the main reasons that AMR has emerged as one of the greatest global concerns in the 21st century and has received favorable conditions for its development during any cataclysms, especially terrible war in Ukraine [5,6].

The proposed section of the monograph contains analysis of the antimicrobial resistance mechanisms, ways to combat resistant bacteria with focus on the use of newly synthesized chemical compounds and photochemical methods as well as their combination.

2. Mechanisms of antimicrobial resistance in bacteria

There are different mechanisms and types of resistance using which bacteria overcome the effectiveness of the antibiotics [7]. Understanding of these mechanisms in turn facilitates development and improvement of both the rational use of current antibiotics and new ways to combat infections caused by resistant microorganisms.

Antimicrobial resistance (AMR) can be defined as ability of bacteria or other microorganisms to withstand the impact of antibiotics to which they used to be susceptible [8]. This in turn allows resistant microorganisms to survive, spread, and gradually substitute susceptible ones. Last years of great concern is emergence of multi-drug resistant (MDR), extensively drug resistant (XDR), and even pan-drug resistant (PDR) bacteria. MDR – resistance to at least one antibiotic from three or more antimicrobial categories. XDR – resistance to at least one antibiotic from all but two (or fewer) antimicrobial categories. PDR – resistance to all antimicrobial categories [9].

Antibiotics, disinfectants, food preservatives or another antibacterial means mainly act on the bacterial cell wall (β -lactams and glycopeptides), cell membrane (polymixins), protein synthesis (tetracyclines, macrolides, aminoglycosides, lincosamides, etc.), DNA replication (fluoroquinolones), and metabolic pathways (sulfonamides) [7, 9, 10]. Despite these different mechanisms of antimicrobial action, the misuse and overuse of antibiotics as well as natural mechanisms of resistance development have led to the global spread of resistance.

Generally AMR can be divided on natural or innate and acquired. Former is associated with the absence of a receptor for the antibiotic, low affinity, cell wall impermeability, or enzyme production. Acquired resistance in turn

can be subdivided on primary and secondary. Primary is the result of spontaneous mutations and appear without contact with a drug. Secondary resistance mechanisms are more complex and develop after interaction of antibacterial mean and microorganism [12]. Besides, primary resistance is associated with chromosomal genes, while secondary – with extrachromosomal genetic elements – plasmids. Rapid spread of resistant microorganisms in particular is possible due to the horizontal gene transfer mechanisms which are conjugation, transduction, and transformation [8].

Mechanisms of drug resistance fall into several categories: inactivation or alteration a drug, modification of drug binding sites (targets), active drug efflux, changes in cell permeability (limiting uptake of a drug) [8-11]. Specified types also can be unified as biochemical resistance. Biofilm formation is another important aspect that facilitates the survival of bacteria and can be considered as the mode of AMR.

In this chapter will be described the above mentioned mechanisms of AMR with separately emphasized biofilm formation.

2.1. Biochemical resistance mechanisms

2.1.1. Destruction or alteration of drug

Inactivation of antibiotic is conducted by enzymes that are produced by bacterial cell [11]. There are two ways of antibiotic inactivation: destruction and chemical modification of the drug [8]. Process of inactivation is based on hydrolysis of antibiotics by microbial β -lactamases. These enzymes destroy β -lactamic ring of such antibiotics as penicillins, cephalosporins, monobactams and carbapenems, thus preventing their binding to penicillin binding proteins [8, 133]. About 300 different β -lactamases are known at present. They can be classified according to their structure (Ambler's classification) and functional peculiarities (Bush–Jacoby–Medeiros' classification) [11, 133]. Chemical modification of drugs is based on the transfer of phosphoryl, acetyl, and adenyl groups to particular sites of antimicrobial means. This process is facilitated by the enzymes acyltransferase, phosphotransferases, and thioltransferases. By the chemical modification can be inactivated aminoglycosides, chloramphenicol,

streptogramins, and fluoroquinolones [8, 9].

2.1.2. Modification of drug binding sites

Modification of target sites allows resistant bacteria to avoid recognition by antimicrobial agents [11]. The most common example of this type of resistance is production by methicillin resistant *Staphylococcus aureus* (MRSA) strains modified penicillin-binding protein (PBP2a) that prevents β -lactam antibiotics from binding to the target site [12]. In the presence of PBP2a, β -lactam drugs are not able to bind effectively to their usual PBP targets. PBP2a is encoded by *mecA* gene which is a part of the staphylococcal chromosome cassette *SCCmec* genetic element [144].

Another example of drug binding sites modification is ribosomal methylase that modifies adenine at the target site of the antibiotics in the 23S rRNA subunit. This enzyme is encoded by *erm* genes (erythromycin ribosome methylase) and provides resistance to antibiotics that inhibit protein synthesis at the level of the 23S rRNA subunit – macrolides, lincosamides and streptogramin [8, 12].

Resistance to fluoroquinolones – drugs that interfere with DNA replication – takes place due to the mutation of topoisomerase II (gyrase) and topoisomerase IV. Mutations make impossible drug's ability to attach to these components [8, 12, 144, 155].

2.1.3. Drug efflux

Efflux pumps are membrane proteins that transport nutrients inside the cell and export toxic compounds including antibiotics from the cell maintaining their low intracellular concentration [9, 133]. There are five primary families of efflux pumps, which are classified according to their structure and energy supply. Pumps can be specific to single classes of antibiotics or extrude variety of different groups of antibiotics. Latter are known as multidrug efflux pumps [8, 9]. All classes of antibiotics except polymyxins are susceptible to the efflux system. Major classes of antibiotics that can be effluxed by bacterial efflux systems are macrolides, β -lactams, fluoroquinolones, etc. [9, 133]. Efflux pumps are major determinants of the multidrug resistance phenotypes in *Pseudomonas aeruginosa* [155]. Thus

this mechanism provides resistance to almost all classes of antibiotics with different mechanisms of action.

2.1.4. Limiting uptake of a drug

Decreased permeability of the bacterial cytoplasmic membrane prevents antibiotics from reaching intracellular targets [9]. Due to the presence of outer membrane, Gram-negative microorganisms are naturally less permeable to some antibiotics comparing to Gram-positive ones. This is the reason of Gram-negative bacteria resistance to vancomycin and glycopeptide [8]. The natural resistance of Enterococci to low concentrations of aminoglycosides is based on the low permeability of bacterial cell membranes for molecules of the antibiotic. This precludes the use of these drugs in monotherapy of enterococcal infections. Reducing the number of porin channels in the outer membrane of Gram-negative bacteria limits the ability of β -lactam molecules to enter the cell space [12]. Modifications in the permeability of the outer membrane significantly decrease the ability of hydrophilic molecules including tetracyclines, and certain fluoroquinolones penetrate inside microbial cell [8]. Decreased antibiotic penetration is the reason of *Mycobacterium tuberculosis* natural resistance to a variety of antibiotics [9]. Recent studies suggest that reductions in porin expression lead to resistance to carbapenems in *Pseudomonas* and *Acinetobacter*. Thus, the functional loss of OprD porin results in imipenem resistance in otherwise beta-lactam-susceptible strains of *P. aeruginosa* [8, 15].

Table 1 summarizes the mechanisms of antibiotic action and mechanisms of AMR development to them [8, 9, 12].

Table 1

Mechanisms of the main antibiotic groups' action and AMR development to them

Antibiotic group	Targets	Mechanism of action	AMR mechanisms
β -lactams	Penicillin binding	Inhibition	Enzyme

Carbapenems Cephalosporins Monobactams Penicillins Glycopeptides	protein (PBP), peptidoglycan subunits	of cell wall synthesis	inactivation by β -lactamases; efflux pumps; production of altered PBP2a, reducing the number of porin channels
Aminoglycosides Tetracyclines Macrolides Lincosamides Streptogramins Chloramphenicol Oxazolidinones	30 S and 50 S ribosome subunits	Inhibition of protein synthesis	Decrease of intracellular concentration by efflux; enzymatic inactivation; drug binding sites modification

Continuation of Table 1

Antibiotic group	Targets	Mechanism of action	AMR mechanisms
Fluoroquinolones	DNA	Inhibition of nucleic acid synthesis	Modification of drug binding sites – topoisomerase II (gyrase) and topoisomerase IV
Polymyxins	Lipopolysaccharides of Gram-negative bacteria	Cell membrane disruption	Modification of lipid A of LPS

Sulfonamides	Enzymes taking part in synthesis of tetrahydrofolic acid	Anti- metabolites	Presence of dihydropteroate synthase with reduced affinity for sulphonamides
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2.2. Biofilm formation as the mode of antimicrobial resistance exertion

According to the Costerton's definition, biofilms are matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces [166]. Biofilms can be formed on numerous substrates like indwelling medical devices, living tissues, aquatic systems, etc. Term 'biofilm' is used to distinguish aggregated microorganisms from the free living or planktonic [177, 188].

Biofilm has increased antibiotic resistance comparing to the planktonic form, and involved in many persistent disease – generalized periodontitis, chronic prostatitis, endocarditis, otitis media, etc. Inside biofilm, several mechanisms provide the multi-factorial resistance to antibiotics [188, 199]. The high resistance of biofilms is determined by the extracellular matrix which facilitates the adhesion of bacterial cells to each other and the surface. This decreases diffusion of antimicrobials inside biofilm as well as protects against host defensive mechanisms [188]. Matrix mainly consists of extracellular polymeric substances – polysaccharides, proteins, lipids, and extracellular DNA from the microbes that form glue-like substance for the attachment and colonization of substrate and for the three dimensional architecture of biofilms [11, 20]. Besides biofilms can be made of several different species of microorganisms, which increases the rate of horizontal gene transmission as cells may exchange resistance plasmids within biofilms [188].

There are two main theories that explain mechanisms of biofilms resistance to antibiotics: complicated penetration of antimicrobials through

extracellular matrix and decreased rate of the cell growth [188]. Another mechanism of antimicrobial tolerance is the depletion of the antimicrobial agent in the fluid bathing the biofilm. Antimicrobial penetration into a biofilm depends on biofilm thickness. Latter also correlates with the age of biofilm. Age or phase of microbial growth in turn impacts the susceptibility of bacteria to chemical and physical factors. The most susceptible are microorganisms at the beginning of the exponential phase. In the stationary phase microorganisms grow slowly, are less metabolically active, and thus are much less susceptible to environmental factors [21].

3. Strategies to combat antimicrobial resistance

Among numerous ways and methods to combat infections caused by resistant microorganisms, can be highlighted three main groups: designing of new antibiotics or improvement of known antibacterial means; discovering of new chemical compounds that on common or new targets in microbial cell; some alternative ways such as the use of bacteriophages, monoclonal antibodies, photochemical methods, etc. [22]. Undoubtedly, to overcome AMR complex and systemic multidisciplinary collaboration is needed. This approach requires appropriate measures at international, national, community, hospital, individual, or patient levels [2, 233-25].

3.1. Discovery of new antibiotic types.

As almost all microbial pathogens rapidly acquire resistance to currently active antibiotics, medicine urgently requires new antibiotics – either new classes with clinically validated modes of action, or new classes with different modes of action. After the first antibiotics discovering the main question that has been asked was “What is the ideal antibiotic?” Latter can be defined as an antibacterial agent that selectively inhibits a wide range of Gram-positive and Gram-negative bacteria without affecting beneficial gut microflora [266, 277].

Over the last few decades decline in the discovery of new and effective antibiotics can be stated. Pharmaceutical companies are facing several

challenges, such as short durations of treatment, high cost of clinical trials, a brief window before the products become generics, and rapid rate of antibiotic resistance acquisition [288].

Modern Antibiotic Discovery Platforms have yielded discoveries that failed in translation to the clinic. This dimmed the overly optimistic expectations created by developing of novel technologies throughout the genomics era. During last years the total antibiotic pipeline appears to be timidly increasing, although the number of drug candidates close to approval remains alarmingly low [299].

Chemical modifications of the antibiotic lead structures improve antibiotics that continue to be active and provide the current reservoir of clinical antibiotics. At the same time, this does not change the mode of resistance. Besides, additional improvements on existing chemical scaffolds are challenging [277]. It should be noted that over the last 30 years, none new drugs were produced using traditional screening environmental isolates or compound library methods [30].

Examples of successful discovering of novel antibiotic derivatives are tridecaptin A₅, tridecaptin D [31] and kibdelomycin [277]. Formers are produced by bacteria *Paenibacillus* sp. and are active against Gram-positive and Gram-negative bacteria including ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) pathogens by binding to lipid II on the surface of the inner membrane [31]. Kibdelomycin is produced by the soil bacterium *Kibdelosporangium* sp. Chemical-genetic profiling technique was a key to the discovery of kibdelomycin. Its mechanism of action is based on DNA inhibition by acting on type II bacterial topoisomerase [277].

Another successful direction is the discovery and development of novel inhibitors of β -lactamases – clavulanic acid and tazobactam that inhibit serine β -lactamases and are used in combination with amoxicillin and piperacillin, respectively [30].

Until recently, the main route for antibiotic discovery was to make new

antimicrobials that act on common microbial targets. In recent years several new antimicrobial means that act on principally new targets were discovered. An example is diaminopimelate aminotransferase pathway for lysine biosynthesis inhibitors. This pathway is characteristic for *Chlamydia*, *Leptospira*, and *Treponema* and thus drugs that affect this process can be considered as narrow-spectrum antibiotics. Another group of drugs with novel mechanism of action are quorum-sensing inhibitors. As about 80% of all microbial infections are associated with biofilms, disrupting quorum-sensing can prevent the formation of biofilms and clear chronic infections [32].

3.2. Novel antimicrobial compounds

There is a large amount of novel antimicrobial compounds both natural and synthesized in the laboratory. Their discovery and introduction into the clinical practice are undoubtedly of great relevance as drug-resistant infections have presented a serious challenge to antimicrobial therapies. In this chapter, some main groups of these means will be discussed with emphasis on antimicrobial peptides, newly synthesized chemicals, and essential oils.

3.2.1. Antimicrobial peptides.

Antimicrobial peptides (AMP) are natural and synthetic oligopeptides with a varying number (from five to over a hundred) of amino acids that have a broad spectrum of microbial targets including viruses, bacteria, fungi, and parasites [333, 34]. Natural AMPs are of microbial (gramicidin, tyrocidine), plant (purothionin), animal (defensin, bombinin, lactoferrin) origin. Besides human leucocytes contain own AMPs in lysosomes [333].

AMPs are considered as the first line of defense against pathogens in all multicellular organisms. Their main advantages are broad spectrum of activity, higher efficacy comparing to traditional antibiotics, and reduced possibility of bacterial drug resistance. AMPs can be used for the treatment of infections caused by drug-resistant microbes [355].

As natural AMPs are not stable with a short half-life period, it is necessary to synthesize the long-acting peptide to apply them in clinic [355]. To design

new AMPs is also important to understand their mechanism of action. The targets for AMPs in the bacterial cell are the cell wall (glycopeptides, lantibiotics), cell membrane (cationic peptides, bacteriocins, aureins), and nucleic acids (bofurins, defensins). Anti-biofilm activity possesses cathelicidins, pleurocidins, and cecropins. Cathelicidins and defensins have an immunomodulatory effect [366]. Despite the numerous advantages of AMPs, certain side effects limit their clinical application: toxicity, drug resistance, hemolytic activity, and immunogenicity [355].

3.2.2. Newly synthesized chemical compounds

Another perspective way to combat infections caused by resistant microorganisms is the use of newly synthesized chemicals, especially derivatives of small heterocycles [3, 37-42]. Also for this purpose thiazole-based heterocycles [43-45], nitro molecules [46], antioxidants [47], silver-containing compounds [48], etc., are used.

Antimicrobial activity of heterocyclic compounds varies and depends on the type of the heterocycle and the position of substituents [43]. These chemical means show high efficiency against both Gram-positive (*S. aureus*, including MRSA, *Bacillus spp.*) and Gram-negative (*E.coli*, *Proteus vulgaris*, etc.) and fungi (*C. albicans*, *A. niger*). Besides, promising is examination of anti-tumor and hepatoprotective activities of heterocycles [43-45].

At present such thiazole-containing drugs as Abafungin, Alagebrium, Acotiamide, Amiphenazole, Brecanavir, Cefepime, Carumonam, and Cefmatilen are already commercially available [44].

The strategy of obtaining halide, chalcogenide, and chalcogen halide condensed azoles turned out to be quite promising for the synthesis of new perspective antimicrobial agents. (Fig. 1) [49-51]

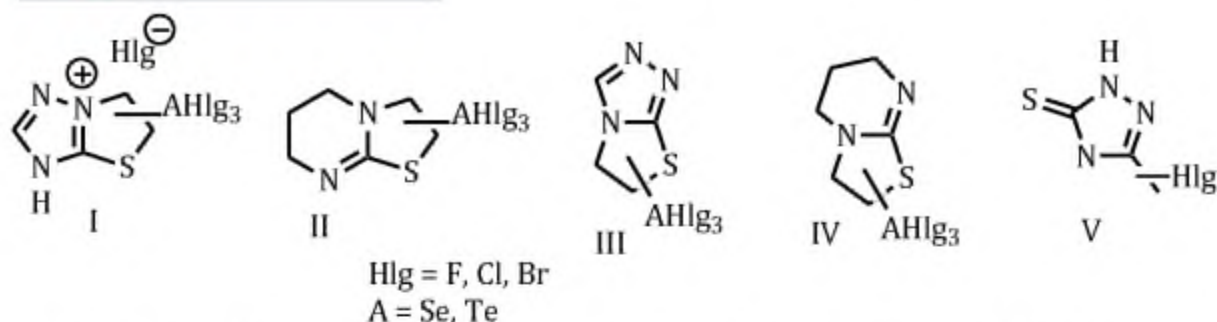


Fig. 1. General structures of halide and chalcogen halide condensed thiazoles

Authors shows that compounds of structure **V** exhibit substantial binding affinities towards their target enzymes, outperforming vancomycin and meropenem in several instances (Fig.2). This suggests that these compounds may possess superior binding capabilities, which could translate into enhanced therapeutic effectiveness [52].

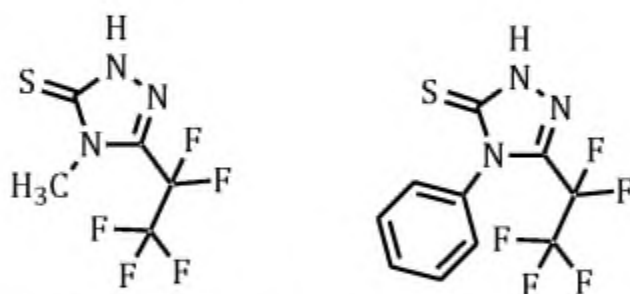


Fig. 2. Fluorine-substituted compounds of structure **V**

It should be noted that structurally similar triazole-3-thiones (Fig. 3), which did not contain fluorine atoms, exhibit only moderate fungicidal activity. [53].

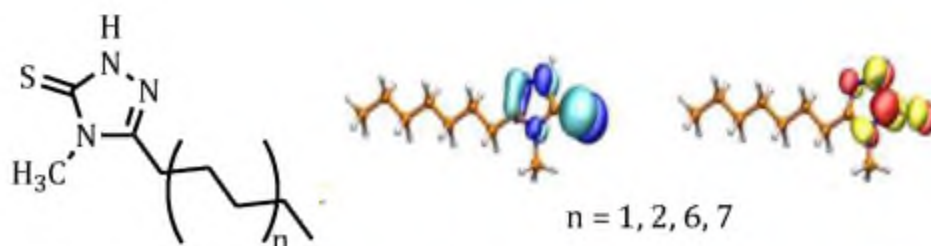


Fig. 3. Alkyl-substituted compounds of structure **V**

The authors observed similar trends for chalcogen halide condensed thiazolotriazoles of structures I and III (Fig. 4).

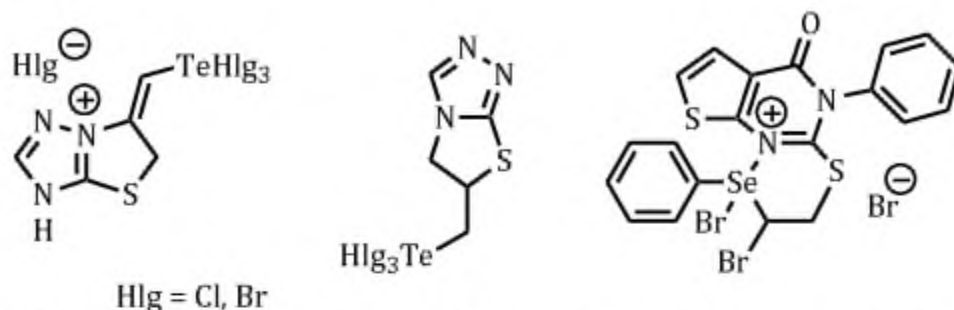


Fig. 4. Molecules of chalcogen halide condensed compounds that exhibit antimicrobial properties

In the case of introducing a tellurium halide fragment into the molecule in structures I, III, and IV (Fig. 4), high bactericidal and fungicidal activity was observed, while in the case of proton- or halogen-induced cyclization, the indicated biological activity was moderate, and in some cases absent [54-56].

It is also worth noting that the introduction of selenium-(tellurium) halide fragments into an organic molecule, on the one hand, dramatically increases the bactericidal and fungicidal effect of the latter [54-56], and on the other hand, the question of their toxicity arises. Therefore the question of their real application is relevant! On the one hand, recent studies of the mechanism of toxic action of tellurium-organic compounds have not given an unambiguous answer [57]. On the other hand, the calculation of the toxicity of such compounds shows a significant reduction in comparison with the corresponding inorganic precursors [58].

Abafungin is a member of a novel group of antifungal drugs – arylguanidines. Showing pronounced activity regarding actively growing and resting fungi, abafungin is considered as a promising antifungal agent [59]. Brecanavir particularly acts on human immunodeficiency virus (HIV) inhibiting viral protease, which is an important stage of viral replication [60]. Cefepime belongs to the fourth generation of cephalosporin. It is being stable to hydrolysis by different β -lactamases and thus can be used for the

treatment of infections resistant to earlier Cephalosporins [61].

Nitro compounds (NO_2 group) possess antimicrobial, antiparasitic, antineoplastic, and antihypertensive activities. Currently used antimicrobial compounds that contain some degree of nitration are metronidasol, chloramphenicol, and nitrofurantoin [46]. Pronounced antifungal activity of nitro-compounds is associated with their action on cell wall components – chitin and β -glucan, which increases the release of intracellular material [62].

Antioxidants are another compound that has pronounced activity against a wide range of microorganisms by themselves or in combination with antibiotics, enhancing their action [47]. Some antioxidants, particularly phenolic ones, can be used in food products such as in meat and its products, poultry and its products, milk and its products, seafood, rice, applesauce and food ingredients. The mechanism of antimicrobial action of phenolic antioxidants is affection of the cell membrane and nucleic acids synthesis [63].

Silver containing compounds constitute a promising approach in novel antimicrobial systems development. Silver has been in use for the treatment of burns, chronic wounds, and bacterial infections for many centuries [48]. Ag as antimicrobial agent can be used as ionic silver, chemically produced nanosilver, or so called biogenic silver which is produced by some species of bacteria [64-66]. Ionized silver inhibits bacterial cell by changing microbial cell wall structure [48]. Besides, it has recently been suggested that silver nanoparticles possess antiviral activity by binding with the external membrane of lipid-encased viruses. In this way was demonstrated activity on Human Immunodeficiency Virus [67]. Experimental data [65, 66] show that ionic and biogenic silver have equal antimicrobial activity on Gram-positive and Gram-negative bacteria which is much higher, comparing to chemically produced nanosilver. At the same time silver nanoparticles show much lower ecotoxicity on eukaryotic saprophytic protozoan representatives what obviously should be taken into account when using silver compounds.

3.3. Alternative ways

Among alternative ways to combat AMR can be highlighted the use of bacteriophages and photochemical methods [25].

3.3.1 Use of bacteriophages

Bacteriophages or simply phages are viruses that infect bacteria and, in the case of lytic phages, disrupt bacterial cells causing their lysis [68]. Phages as therapeutic agents were used 2 years before the first clinical use of an antibiotic drug, but due to widespread application of antibiotics, bacteriophages were displaced by them [68, 69]. High abundance and diversity of phages in the nature determines their use in decontamination, infection control, detection, diagnosis. Particularly specific bacteriophages can be applied for the establishing the source of infection in case of intrahospital, or other outbreaks. This method is known as phage typing [69].

There are several advantages of bacteriophage therapy over antibiotics. Phages are more specific to the pathogens, so they do not affect normal microflora. Also, phages replicate at the site of infection and do not spread through the body, which minimizes side effects. Lastly, bacteriophages are environmentally friendly and unlike antibiotics do not require high costs for their developing [70].

At the same time there are some disadvantages of the bacteriophages use. The major one is the need to determine the etiological agent before phage therapy. This problem can partially be solved by the use of phage cocktails that consist of several bacteriophages active against a variety of the most common bacterial pathogens. The ability to transfer genetic material between bacteria through phages or transduction is also worrying, as this process can be responsible for the acquisition of pathogenicity determinants and virulence factors by microorganisms [71]. Another major problem can be development of phage-resistant bacteria. Latter is associated with spontaneous mutations, adaptive mechanisms via the CRISPR-Cas system and DNA restriction-modification enzymes [72].

Despite some disadvantages and concerns, phage therapy is considered a

potential complement or even alternative to antibiotics [70-73]. Standardization of the quality of phage preparation, sensitivity testing, dosages, and access to the infection site should solve the main issues and promote wider use of bacteriophages in clinical practice [73].

3.3.2. Photochemical methods.

Photodynamic therapy (PDT) is a modern and non-invasive method, used in the treatment of both non-oncological and oncological diseases various types and locations [74]. The principle of PDT is based on a photochemical reaction, which is induced by light activation of a photosensitizer (PS) causing cell death [75-77]. Antimicrobial photodynamic therapy (APDT) is the area of photochemical methods that develops the most dynamically nowadays [76, 77]. APDT consists of using photosensitizers with the subsequent application of low-intensity radiation of appropriate wavelength, which triggers a photodynamic response resulting in the generation of reactive oxygen species [76].

The main advantages of APDT are its effective action on both Gram-positive and Gram-negative microorganisms, as well as fungi, protozoa and viruses, low invasiveness and lack of induction of resistant strains [78].

Although PDT in particular APDT is already widely used in many branches of medicine, some aspects are still not completely clear and require subsequent more detailed study. Particularly questions about the direct impact of polarization and coherence on biological objects remain open.

In some our works [79-81] we studied the complex impact of photosensitizers and different sources of low-power light – LED, laser, polarized radiation on the growth rate of some opportunistic bacteria. Figure 5 shows the irradiation of investigated microorganisms by specified types of low-power radiation.

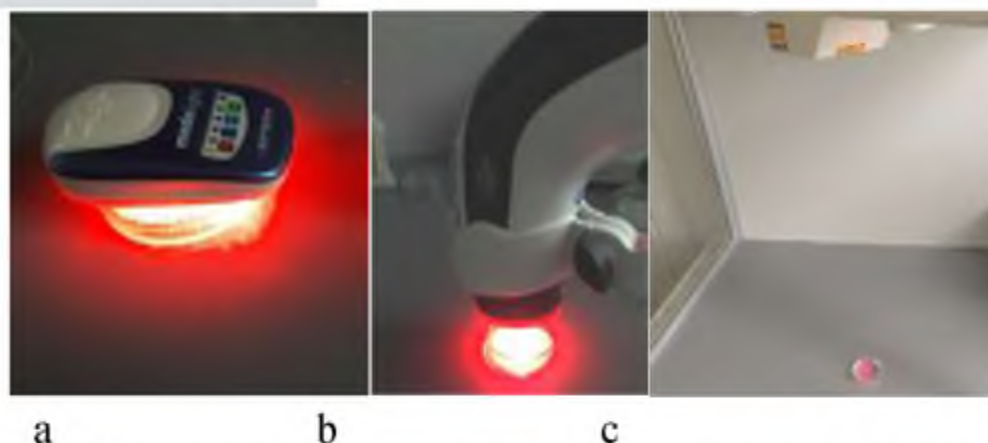


Fig.5. The use of different sources of low-intense radiation in combination with photosensitizers. a – LED radiation; b – PILER light c – laser radiation.

In these studies to examine the complex impact of photosensitizer and low-energy light, microorganisms were divided into 4 groups: the 1st – control group was subcultured on a solid nutrient medium in Petri dishes. Microorganisms of the 2nd group were irradiated with low-power radiation. To the inoculum of microorganisms of the 3rd group, photosensitizer was added in a ratio of 1:10, kept in the dark for 20 minutes, and subcultured on Petri dishes with nutrient agar. Finally, photosensitizer was added to the inoculum of the 4th group and irradiation was conducted after a dark phase. Growth intensity was determined by counting the number of colonies of microorganisms on Petri dishes after daily cultivation in a thermostat.

Obtained data showed that simple irradiation of microbial inoculum (2nd group) with low duration showed no significant effect on the growth rate of microorganisms. Adding of photosensitizers (3rd group) caused some decrease in colonies number, comparing to the control group. The most pronounced antimicrobial effect was described for the 4th group microorganisms. The biggest germicidal action was noticed in case of combined action of methylene blue and red spectrum light [79-81].

Described results correspond with similar studies by a number of authors [77, 82-85]. Comparing obtained results with different sources of low-power light, we can note their similarity [79-81]. Above mentioned allows

assuming that the most important light parameters that possess biological impact are wavelength and power density. At the same time polarization and coherence probably do not play a decisive role in interaction with biological objects.

3.3.3. Other alternative ways.

In this subparagraph, we discuss other alternative ways of combating AMR, such as ozone therapy, essential oils, and phototherapy.

Ozone has been used in medicine and dentistry since the middle of the XX century. It has a high oxidation potential, approximately 1.5 times that of chloride when used as an antimicrobial agent against bacteria, viruses, fungi, and protozoa [86]. At the same time O_3 is able to promote antioxidant enzymes [87]. Activity of ozone gas against microorganisms is related to its chemical properties. As being unstable molecule, it rapidly decays to molecular oxygen (O_2) and releases atomic oxygen. The oxygen atom reacts with the surface components of the microorganisms, and the latter are inactivated by osmotic lysis [88]. Thus, due to wide spectrum of action, ozone therapy is successfully used in many occupations of medicine, dentistry and veterinary [86-89]. Some contraindications that might limit its use are pregnancy, anemia, myasthenia, hyperthyroidism etc. [86].

Essential oils (EO) possess diverse biological activities including antimicrobial effect against a wide range of microorganisms [90]. In vitro studies [91] showed higher susceptibility to EOs of gram-positive bacteria comparing to gram-negative. Antimicrobial activity of EOs can be enhanced by the encapsulation into nanocapsules [90, 92]. Encapsulation increases antimicrobial properties of EOs mostly by facilitation of interaction with the microorganisms and controlling their sustained release [90]. Perspective occupation in which EOs can be applied is the food industry. By impeding the proliferation of food-borne pathogens EOs can be an alternative to synthetic food preservatives [93].

Sunlight treatment or heliotherapy as a therapeutic factor is known the ancient times and has been used for the treatment of a variety of diseases for many centuries [94]. The Discovery of the electric generator or the electric

lightbulb and later laser and LED radiation contributed transformation of heliotherapy into phototherapy [95].

Phototherapy is widely used in the treatment and diagnosis of diseases and various fields of medicine [96]. In particular, for the treatment of nervous system complications; skin and mucous membrane diseases, oncogenic diseases [97], dentistry [98], tissue repair processes [99] pain relief, inflammation process resolution [100]. Such a broad spectrum of phototherapy usage is determined by the almost complete absence of side effects on the human body. The beneficial effects of low-power radiation are based on its ability to increase cellular viability, proliferation rate, DNA integrity, and damaged DNA reparation [101].

In vitro studies [102, 103] show the impact of low-power radiation on some biological properties of microorganisms. Results of own studies [104-107] show the dose-dependent effect of different types of low-power radiation on the growth rate and antibiotic susceptibility of opportunistic bacteria. Thus, low-intensity radiation is considered as promising complement to traditional antibiotic therapy.

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References

1. Dadgostar, P. Antimicrobial Resistance: Implications and Costs. *Infection and Drug Resistance* 2019, 12, pp 3903–3910. <https://doi.org/10.2147/IDR.S234610>
2. Cella, E.; Giovanetti, M.; Benedetti, F.; Scarpa, F.; Johnston, C.; Borsetti, A.; Ceccarelli, G.; Azarian, T.; Zella, D.; Ciccozzi, M. Joining Forces against Antibiotic Resistance: The One Health Solution. *Pathogens* 2023, 12, 1074. <https://doi.org/10.3390/pathogens12091074>

3. Gattu, R., Ramesh, S.S., Ramesh, S. Role of small molecules and nanoparticles in effective inhibition of microbial biofilms: A ray of hope in combating microbial resistance. *Microbial Pathogenesis* 2024, 188, 106543. <https://doi.org/10.1016/j.micpath.2024.106543>
4. Michael, C. A., Dominey-Howes, D., & Labbate, M. The antimicrobial resistance crisis: causes, consequences, and management. *Frontiers in public health*. 2014, 2, 145. <https://doi.org/10.3389/fpubh.2014.00145>
5. Tang, K. W. K., Millar, B. C., & Moore, J. E. Antimicrobial resistance (AMR). *British Journal of Biomedical Science*. 2023, 80, 11387. <https://doi.org/10.3389/bjbs.2023.11387>
6. Loban', G.; Faustova, M.; Dobrovolska, O.; Tkachenko, P. War in Ukraine: incursion of antimicrobial resistance. *Irish J Med Sci*. 2023, 192, 2905–2907. <https://doi.org/10.1007/s11845-023-03401-x>
7. Abushaheen, M. A., Fatani, A. J., Alosaimi, M., Mansy, W., George, M., Acharya, S., ... & Jhugroo, P. Antimicrobial resistance, mechanisms and its clinical significance. *Disease-a-Month*. 2020, 66(6), 100971. <https://doi.org/10.1016/j.disamonth.2020.100971>
8. Uddin, T. M., Chakraborty, A. J., Khusro, A., Zidan, B. R. M., Mitra, S., Emran, T. B., ... & Koirala, N. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *Journal of infection and public health*. 2021, 14(12), 1750-1766. <https://doi.org/10.1016/j.jiph.2021.10.020>
9. Pulingam, T., Parumasivam, T., Gazzali, A. M., Sulaiman, A. M., Chee, J. Y., Lakshmanan, M., ... & Sudesh, K. Antimicrobial resistance: Prevalence, economic burden, mechanisms of resistance and strategies to overcome. *European Journal of Pharmaceutical Sciences*. 2022, 170, 106103. <https://doi.org/10.1016/j.ejps.2021.106103>
10. Reygaert, W. C. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS microbiology*. 2018, 4(3), 482–501. doi: 10.3934/microbiol.2018.3.482

11. Santajit, S., & Indrawattana, N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed research international*. 2016, 2016(1), 2475067. <https://doi.org/10.1155/2016/2475067>
12. Urban-Chmiel, R.; Marek, A.; Stępień-Pyśniak, D.; Wieczorek, K.; Dec, M.; Nowaczek, A.; Osek, J. Antibiotic Resistance in Bacteria – A Review. *Antibiotics*. 2022, 11, 1079. <https://doi.org/10.3390/antibiotics11081079>
13. Kapoor, Garima; Saigal, Saurabh; Elongavan, Ashok. Action and resistance mechanisms of antibiotics: A guide for clinicians. *Journal of Anaesthesiology Clinical Pharmacology*. 2017, 33(3), 300-305. 10.4103/joacp.JOACP_349_15
14. Watkins, R. R., Holubar, M., & David, M. Z. Antimicrobial resistance in methicillin-resistant *Staphylococcus aureus* to newer antimicrobial agents. *Antimicrobial agents and chemotherapy*. 2019, 63(12), 10-1128. <https://doi.org/10.1128/aac.01216-19>
15. Ruppé, É., Woerther, P.L. & Barbier, F. Mechanisms of antimicrobial resistance in Gram-negative bacilli. *Ann. Intensive Care*. 2015, 5, 21 (2015). <https://doi.org/10.1186/s13613-015-0061-0>
16. Costerton, J. W., Lewandowski, Z., Caldwell, D. E., Korber, D. R., & Lappin-Scott, H. M. Microbial biofilms. *Annual Review of Microbiology*, 2013, 49, 711-745. <https://doi.org/10.1146/annurev.mi.49.100195.003431>
17. Høiby, N. A short history of microbial biofilms and biofilm infections. *Apmis*. 2017, 125(4), 272-275. <https://doi.org/10.1111/apm.12686>
18. Donlan, R. M. Biofilms: microbial life on surfaces. *Emerging infectious diseases*. 2002, 8(9), 881. 10.3201/eid0809.020063
19. Singh S, Singh SK, Chowdhury I, Singh R. Understanding the Mechanism of Bacterial Biofilms Resistance to Antimicrobial Agents. *Open Microbiol J*. 2017, 11, 53-62. 10.2174/1874285801711010053.
20. Ghannoum, M., Parsek, M., Whiteley, M., & Mukherjee, P. K. *Microbial biofilms*. 2nd edition John Wiley & Sons, 2020

21. Stewart P. S. Antimicrobial Tolerance in Biofilms. *Microbiol Spectr.* 2015, 3, 10.1128. <https://doi.org/10.1128/microbiolspec.mb-0010-2014>
22. Ehud Banin, Diarmaid Hughes, Oscar P. Kuipers, Editorial: Bacterial pathogens, antibiotics and antibiotic resistance, *FEMS Microbiology Reviews.* 2017, 41(3), 450-452. <https://doi.org/10.1093/femsre/fux016>
23. Uchil, R. R., Kohli, G. S., KateKhaye, V. M., & Swami, O. C. Strategies to combat antimicrobial resistance. *Journal of clinical and diagnostic research: JCDR.* 2014, 8(7), ME01. 10.7860/JCDR/2014/8925.4529
24. Schrader, S. M., Vaubourgeix, J., & Nathan, C Biology of antimicrobial resistance and approaches to combat it. *Sci. Transl. Med.* 2020, 12, eaaz6992. 10.1126/scitranslmed.aaz69
25. Murugaiyan, J.; Kumar, P.A.; Rao, G.S.; Iskandar, K.; Hawser, S.; Hays, J.P.; Mohsen, Y.; Adukkadukkam, S.; Awuah, W.A.; Jose, R.A.M.; et al. Progress in Alternative Strategies to Combat Antimicrobial Resistance: Focus on Antibiotics. *Antibiotics.* 2022, 11, 200. <https://doi.org/10.3390/antibiotics11020200>
26. Singh, S. B., Young, K., & Silver, L. L. What is an “ideal” antibiotic? Discovery challenges and path forward. *Biochemical pharmacology.* 2017, 133, 63-73. <https://doi.org/10.1016/j.bcp.2017.01.003>
27. Singh, S. B. Discovery and development of kibdelomycin, a new class of broad-spectrum antibiotics targeting the clinically proven bacterial type II topoisomerase. *Bioorganic & Medicinal Chemistry.* 2016, 24(24), 6291-6297. <https://doi.org/10.1016/j.bmc.2016.04.043>
28. Martens, E., Demain, A. L. An overview of the industrial aspects of antibiotic discovery. *Microbial resources.* 2017, 7, 149-168. <https://doi.org/10.1016/B978-0-12-804765-1.00007-2>
29. Ribeiro da Cunha B, Fonseca LP, Calado CRC. Antibiotic Discovery: Where Have We Come from, Where Do We

- Go? Antibiotics. 2019, 8(2), 45.
<https://doi.org/10.3390/antibiotics8020045>
30. Lewis, K. The science of antibiotic discovery. Cell, 2020, 181(1), 29-45. 10.1016/j.cell.2020.02.056
31. Machushynets, N. V., Al Ayed, K., Terlouw, B. R., Du, C., Buijs, N. P., Willemse, J., ... & van Wezel, G. P. Discovery and Derivatization of Tridecaptin Antibiotics with Altered Host Specificity and Enhanced Bioactivity. ACS Chemical Biology. 2024, 19(5), 1106-1115. <https://doi.org/10.1021/acschembio.4c00034>
32. Mantravadi, P.K.; Kalesh, K.A.; Dobson, R.C.J.; Hudson, A.O.; Parthasarathy, A. The Quest for Novel Antimicrobial Compounds: Emerging Trends in Research, Development, and Technologies. Antibiotics. 2019, 8(1), 8. <https://doi.org/10.3390/antibiotics8010008>
33. Bahar, A.A.; Ren, D. Antimicrobial Peptides. Pharmaceuticals. 2013, 6, 1543-1575. <https://doi.org/10.3390/ph6121543>
34. Zhang, L. J., Gallo, R. L. Antimicrobial peptides. Current biology. 2016, 26(1), R14-R19. 10.1016/j.cub.2015.11.017
35. Lei, J., Sun, L., Huang, S., Zhu, C., Li, P., He, J., ... & He, Q. The antimicrobial peptides and their potential clinical applications. American journal of translational research. 2019, 11(7), 3919-3931. PMCID: PMC6684887 PMID: 31396309
36. Browne, K., Chakraborty, S., Chen, R., Willcox, M. D, Black, D. S., Walsh, W. R., Kumar, N. A New Era of Antibiotics: The Clinical Potential of Antimicrobial Peptides. International Journal of Molecular Sciences. 2020, 21(19), 7047. <https://doi.org/10.3390/ijms21197047>
37. Marinescu, M. Benzimidazole-Triazole Hybrids as Antimicrobial and Antiviral Agents: A Systematic Review. Antibiotics 2023, 12 (7), 1220. <https://doi.org/10.3390/antibiotics12071220>

38. Ambade, S.S.; Gupta, V.K.; Bhole, R.P.; Khedekar, P.B.; Chikhale, R.V. A Review on Five and Six-Membered Heterocyclic Compounds Targeting the Penicillin-Binding Protein 2 (PBP2A) of Methicillin-Resistant *Staphylococcus aureus* (MRSA). *Molecules* 2023, 28 (20), 7008. <https://doi.org/10.3390/molecules28207008>
39. Hryhoriv, H.; Kovalenko, S.M.; Georgiyants, M.; Sidorenko, L.; Georgiyants, V. A Comprehensive Review on Chemical Synthesis and Chemotherapeutic Potential of 3-Heteroaryl Fluoroquinolone Hybrids. *Antibiotics* 2023, 12(3), 625. <https://doi.org/10.3390/antibiotics12030625>
40. Rusu, A.; Moga, I.-M.; Uncu, L.; Hancu, G. The Role of Five-Membered Heterocycles in the Molecular Structure of Antibacterial Drugs Used in Therapy. *Pharmaceutics* 2023, 15(11), 2554. <https://doi.org/10.3390/pharmaceutics15112554>
41. Tian, G.; Song, Q.; Liu, Z.; Guo, J.; Cao, S.; Long, S. Recent advances in 1,2,3- and 1,2,4-triazole hybrids as antimicrobials and their SAR: A critical review. *European Journal of Medicinal Chemistry* 2023, 259, 115603. <https://doi.org/10.1016/j.ejmech.2023.115603>
42. Ungureanu, D.; Tiperciuc, B.; Nastasă, C.; Ionuț, I.; Marc, G.; Oniga, I.; Oniga, O. An Overview of the Structure–Activity Relationship in Novel Antimicrobial Thiazoles Clubbed with Various Heterocycles (2017–2023). *Pharmaceutics* 2024, 16(1), 89. <https://doi.org/10.3390/pharmaceutics16010089>
43. Sadek, B.; Al-Tabakha, M.M.; Faelelbom, K.M.S. Antimicrobial Prospect of Newly Synthesized 1,3-Thiazole Derivatives. *Molecules* 2011, 16, 9386–9396. <https://doi.org/10.3390/molecules16119386>
44. Abu-Melha, S.; Edrees, M.M.; Salem, H.H.; Kheder, N.A.; Gomha, S.M.; Abdelaziz, M.R. Synthesis and Biological Evaluation of Some Novel Thiazole-Based Heterocycles as Potential Anticancer

- and Antimicrobial Agents. *Molecules*. 2019, 24, 539. <https://doi.org/10.3390/molecules24030539>
45. Korol, N., Slivka, M., Fizer, M. et al. Halo-heterocyclization of butenyl(prenyl)thioethers of 4,5-diphenyl-1,2,4-triazol-3-thiole into triazolo[5,1-b] [1,3]thiazinium systems: experimental and theoretical evolution. *Monatsh Chem.* 2020, 151, 191-198. <https://doi.org/10.1007/s00706-019-02545-w>
 46. Noriega, S., Cardoso-Ortiz, J., López-Luna, A., Cuevas-Flores, M.D.R., Flores De La Torre, J.A. The Diverse Biological Activity of Recently Synthesized Nitro Compounds. *Pharmaceuticals*. 2022, 15, 717. <https://doi.org/10.3390/ph15060717>
 47. Marković, B.A., Marinković, A., Stanković, J.A., Mijatović, S., Cvijetić, I., Simić, M., Arandjelović, I. Synthesis and Antimicrobial Activity of Newly Synthesized Nicotinamides. *Pharmaceutics*. 2024, 16, 1084. <https://doi.org/10.3390/pharmaceutics16081084>
 48. Rai, M., Yadav, A., & Gade, A. Silver nanoparticles as a new generation of antimicrobials. *Biotechnology advances*. 2009, 27(1), 76-83. <https://doi.org/10.1016/j.biotechadv.2008.09.002>
 49. Slivka, M.V., Korol, N.I., Fizer, M.M. Fused bicyclic 1,2,4-triazoles with one extra sulfur atom: Synthesis, properties, and biological activity. *Journal of Heterocyclic Chemistry*, 2020, 57(9), pp. 3236–3254. <https://doi.org/10.1002/jhet.4044>
 50. Slivka, M.V., Korol, N.I. Condensed pyridopyrimidines and pyridopyrazines containing a bridgehead nitrogen atom: Synthesis, chemical properties and biological activity. *Current Organic Chemistry*, 2021, 25(12), pp. 1429–1440. <https://www.eurekaselect.com/article/115778>
 51. Korol, N., Molnar-Babilya, D., Slivka, M., Onysko, M. A brief review on heterocyclic compounds with promising antifungal activity against *Candida* species. *Organic Communications*, 2022, 15(4), pp.

- 304–323. <https://www.acgpubs.org/doc/20221229214120A1-141-OC-2210-2609.pdf>
52. Korol, N., Holovko-Kamoshenkova, O., Mariychuk, R., Slivka, M. Insights into bacterial interactions: Comparing fluorine-containing 1,2,4-triazoles to antibiotics using molecular docking and molecular dynamics approaches. *Heliyon*, 2024, 10(17), e37538. <https://doi.org/10.1016/j.heliyon.2024.e37538>
53. Maksym Fizer, Oksana Fizer, Hanna Hryhorka, Mikhaïlo Slivka, Michal Šoral, Viera Dujnič, Mária Kopáčová, Valerii Pantyo, Ruslan Mariychuk. New 5-alkyl-1,2,4-triazole-3-thione surfactants with anti-fungal and silver nanoparticles stabilization activity. *Journal of Molecular Liquids*, 2024,
54. Mikhaïlo Slivka, Maksym Fizer, Ruslan Mariychuk, Marek Ostafin, Olexander Moyzesh, Galyna Koval, Oksana Holovko-Kamoshenkova, Ivan Rusyn and Vasil Lendel. Synthesis and Antimicrobial Activity of Functional Derivatives of thiazolo[2,3-c][1,2,4]triazoles. *Letters in Drug Design and Discovery*, 2022, 19(9), pp. 791–799. <https://www.eurekaselect.com/article/120070>
55. Mikhaïlo Slivka, Nataliya Korol, Valerij Pantyo, Vjacheslav Baumer and Vasil Lendel. Regio- and stereoselective synthesis of [1,3]thiazolo[3,2-b][1,2,4]triazol-7-ium salts via electrophilic heterocyclization of 3-S-propargylthio-4H-1,2,4-triazoles and their antimicrobial activity. *Heterocyclic Communications*, 2017, 23(2), pp. 109–113. <https://doi.org/10.1515/hc-2016-0233>
56. Sharga, Boris M.; Krivovjaz, Andrij O.; Slivka, Mikhaïlo V.; Lambruch, Larisa M.; Cheypesh, Antonina V.; Lendel, Vasil G.; Nikolaychuk, Vitaly I.; Markovich, Vladimir P. Synthesis and antimicrobial activity of phenylselenenyl tribromide and its fused thienopyrimidine derivatives. *Farmacia*, 2016, 64(4), pp. 512–520. <https://www.scopus.com/record/display.uri?eid=2-s2.0-84983294384&origin=resultslist>

57. Vávrová, S.; Struhárňanská, E.; Turňa, J.; Stuchlík, S. Tellurium: A Rare Element with Influence on Prokaryotic and Eukaryotic Biological Systems. *Int. J. Mol. Sci.* 2021, 22, 5924. <https://doi.org/10.3390/ijms22115924>
58. M.M. Fizer; M.V. Slivka; R.T. Mariychuk; O.I. Fizer; N.I. Korol; A.O. Kryvoviaz; V.G. Lendel. Theoretical estimation of toxicity of new condensed heterocyclic cationic surfactants. ICTEP 2019 - International Council of Environmental Engineering Education - "Technologies of Environmental Protection" - Proceedings, 2019, pp. 87–90, 8968972. <https://ieeexplore.ieee.org/document/8968972>
59. Borelli, C., Schaller, M., Niewerth, M., Nocker, K., Baasner, B., Berg, D., ... & Korting, H. C. Modes of action of the new arylguanidine abafungin beyond interference with ergosterol biosynthesis and in vitro activity against medically important fungi *Chemotherapy*. 2008, 54(4), 245-259. <https://doi.org/10.1159/000142334>
60. Lalezari, J. P., Ward, D. J., Tomkins, S. A., & Garges, H. P. Preliminary safety and efficacy data of brecanavir, a novel HIV-1 protease inhibitor: 24 week data from study HPR10006, *Journal of Antimicrobial Chemotherapy*. 2007, 60(1), 170–174. <https://doi.org/10.1093/jac/dkm122>
61. Barradell, L.B., Bryson, H.M. Cefepime. *Drugs*. 1994, 47, 471-505. <https://doi.org/10.2165/00003495-199447030-00007>
62. Andrade, J.T., Alves, S.L.G., Lima, W.G. et al. Pharmacologic potential of new nitro-compounds as antimicrobial agents against nosocomial pathogens: design, synthesis, and in vitro effectiveness. *Folia Microbiol.* 2020, 65, 393-405. <https://doi.org/10.1007/s12223-019-00747-7>
63. Raccach, M. The antimicrobial activity of phenolic antioxidants in foods: A review. *Journal of Food Safety*, 1984, 6(3), 141-170. <https://doi.org/10.1111/j.1745-4565.1984.tb00479.x>

64. Le Ouay, B., & Stellacci, F. Antibacterial activity of silver nanoparticles: A surface science insight. *Nano today*. 2015, 10(3), 339-354. <https://doi.org/10.1016/j.nantod.2015.04.002>
65. Sintubin, L., De Gusseme, B., Van der Meer, P. et al. The antibacterial activity of biogenic silver and its mode of action. *Appl Microbiol Biotechnol*. 2011, 91, 153-162 (2011). <https://doi.org/10.1007/s00253-011-3225-3>
66. Kvítek, L., Panacek, A., Prucek, R., Soukupova, J., Vanickova, M., Kolar, M., & Zboril, R. Antibacterial activity and toxicity of silver–nanosilver versus ionic silver. In *Journal of Physics: Conference Series*. 2011, 304(1), 012029. 10.1088/1742-6596/304/1/012029
67. Lara, H.H., Garza-Treviño, E.N., Ixtapan-Turrent, L. et al. Silver nanoparticles are broad-spectrum bactericidal and virucidal compounds. *J Nanobiotechnol*. 2011, 9, 30. <https://doi.org/10.1186/1477-3155-9-30>
68. Sulakvelidze, A., Alavidze, Z., & Morris Jr, J. G. Bacteriophage therapy. *Antimicrobial agents and chemotherapy*, 2001, 45(3), 649-659. <https://doi.org/10.1128/aac.45.3.649-659.2001>
69. Nikolich, M.P.; Filippov, A.A. Bacteriophage Therapy: Developments and Directions. *Antibiotics*. 2020, 9, 135. <https://doi.org/10.3390/antibiotics9030135>
70. Golkar, Z., Bagasra, O., & Pace, D. G. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. *The Journal of Infection in Developing Countries*. 2014, 8(02), 129-136. <https://doi.org/10.3855/jidc.3573>
71. Wittebole, X., De Roock, S., & Opal, S. M. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. *Virulence*, 2013 5(1), 226–235. <https://doi.org/10.4161/viru.25991>

72. Oechslin, F. Resistance Development to Bacteriophages Occurring during Bacteriophage Therapy. *Viruses* 2018, 10, 351. <https://doi.org/10.3390/v10070351>
73. Walter, N., Mirzaei, M., Deng, L., Willy, C., Alt, V., & Rupp, M. The potential of bacteriophage therapy as an alternative treatment approach for antibiotic-resistant infections. *Medical Principles and Practice*, 2024, 33(1), 1-9. <https://doi.org/10.1159/000534717>
74. Kwiatkowski S., Knap B., Przystupski D., Saczko, J., Kędzierska E., Knap-Czop, K, & Kulbacka, J. Photodynamic therapy - mechanisms, photosensitizers and combinations. *Biomedicine & Pharmacotherapy*, 2018, 106, 1098-1107.
75. Kübler, A. C. Photodynamic therapy. *Medical Laser Application*, 2005, 20(1), 37-45. <https://doi.org/10.1016/j.mla.2005.02.001>
76. Piksa, M., Lian, C., Samuel, I. C., Pawlik, K. J., Samuel, I. D., & Matczyszyn, K. The role of the light source in antimicrobial photodynamic therapy. *Chemical Society Reviews*, 2023, 52(5), 1697-1722. [10.1039/D0CS01051K](https://doi.org/10.1039/D0CS01051K)
77. Mahmoudi, H., Bahador, A., Pourhajibagher, M., & Alikhani, M. Y. Antimicrobial photodynamic therapy: an effective alternative approach to control bacterial infections. *Journal of lasers in medical sciences*, 2018, 9(3), 154-160. [10.15171/jlms.2018.29](https://doi.org/10.15171/jlms.2018.29)
78. Polat E, Kang K. Natural Photosensitizers in Antimicrobial Photodynamic Therapy. *Biomedicines*. 2021, 9(6), 584. <https://doi.org/10.3390/biomedicines9060584>
79. Pantyo V.V., Koval G.M., Danko E.M., Pantyo V.I. Complex impact of polarized and non-polarized low intense light and methylene blue on growth rate of some opportunistic microorganisms. *Regulatory Mechanisms in Biosystems*, 2020, 11(4), 520-523. <https://doi.org/10.15421/022079>
80. Pantyo V. V., Danko E. M., Fizer M. M., Koval G. M., Pantyo V.I. Impact of polarized low-intense radiation and photosensitizers on

- growth of *Staphylococcus aureus*. Bulletin of problems biology and medicine, 2022, 2(165), 12-16. 10.29254/2077-4214-2022-2-2-165-12-16
81. Pantyo V. V., Danko E. M., Kostenko Y.Y., Pantyo V.I., Koval G. M. Antimicrobial activity of methylene blue and LED radiation in vitro and in vivo. 2024, 2, 66-70. <https://doi.org/10.32782/2786-7684/2024-2-11>
 82. Soria-Lozano P, Gilaberte Y, Paz-Cristobal MP, Pérez-Artiaga L, Lampaya-Pérez V, Aporta J, et al. In vitro effect photodynamic therapy with different photosensitizers on cariogenic microorganisms. BMC microbiology 2015, 15(1), 1-8. <https://doi.org/10.1186/s12866-015-0524-3>
 83. Fu, X. J., Fang, Y., & Yao, M.. Antimicrobial photodynamic therapy for methicillin-resistant *Staphylococcus aureus* infection. BioMed research international, 2013, 2013(1), 159157. <https://doi.org/10.1155/2013/159157>
 84. Gonçalves, A. S., Leitão, M. M., Fernandes, J. R., Saavedra, M. J., Pereira, C., Simões, M., & Borges, A. Photodynamic activation of phytochemical-antibiotic combinations for combatting *Staphylococcus aureus* from acute wound infections. Journal of Photochemistry and Photobiology B: Biology, 2024, 258, 112978. <https://doi.org/10.1016/j.jphotobiol.2024.112978>
 85. Rajesh S, Koshi E, Philip K, Mohan A. Antimicrobial photodynamic therapy: An overview..Journal of Indian Society of Periodontology. 2011, 15(4), P. 323. <https://doi.org/10.4103/0972-124X.92563>
 86. Nogales, C. G., Ferrari, P. H., Kantorovich, E. O., & Lage-Marques, J. L.. Ozone therapy in medicine and dentistry. J Contemp Dent Pract, 2008, 9(4), 75-84. PMID: 18473030
 87. Sciorsci, R. L., Lillo, E., Occhiogrosso, L., & Rizzo, A. Ozone therapy in veterinary medicine: A review. Research in Veterinary

- Science, 2020, 130, 240-246.
<https://doi.org/10.1016/j.rvsc.2020.03.026>
88. Song, M., Zeng, Q., Xiang, Y., Gao, L., Huang, J., Huang, J., ... & Lu, J. The antibacterial effect of topical ozone on the treatment of MRSA skin infection. *Molecular medicine reports*, 2018, 17(2), 2449-2455. <https://doi.org/10.3892/mmr.2017.8148>
 89. Silva, E. J. N. L., Prado, M. C., Soares, D. N., Hecksher, F., Martins, J. N. R., & Fidalgo, T. K. S. The effect of ozone therapy in root canal disinfection: a systematic review. *International endodontic journal*, 2020, 53(3), 317-332. <https://doi.org/10.1111/iej.13229>
 90. Chouhan, S.; Sharma, K.; Guleria, S. Antimicrobial Activity of Some Essential Oils – Present Status and Future Perspectives. *Medicines* 2017, 4, 58. <https://doi.org/10.3390/medicines4030058>
 91. Murbach Teles Andrade, B. F., Nunes Barbosa, L., da Silva Probst, I., & Fernandes Júnior, A. Antimicrobial activity of essential oils. *Journal of Essential Oil Research*, 2014, 26(1), 34-40. <https://doi.org/10.1080/10412905.2013.860409>
 92. Donsi, F., Annunziata, M., Sessa, M., & Ferrari, G. Nanoencapsulation of essential oils to enhance their antimicrobial activity in foods. *LWT-Food Science and Technology*, 2011, 44(9), 1908-1914. <https://doi.org/10.1016/j.lwt.2011.03.003>
 93. Angane, M.; Swift, S.; Huang, K.; Butts, C.A.; Quek, S.Y. Essential Oils and Their Major Components: An Updated Review on Antimicrobial Activities, Mechanism of Action and Their Potential Application in the Food Industry. *Foods* 2022, 11, 464. <https://doi.org/10.3390/foods11030464>
 94. Barros, N. D. M., Sbroglio, L. L., Buffara, M. D. O., Baka, J. L. C. E. S., Pessoa, A. D. S., & Azulay-Abulafia, L. Phototherapy. *Anais brasileiros de dermatologia*, 2021, 96(4), 397-407. <https://doi.org/10.1016/j.abd.2021.03.001>

95. Grzybowski, A., Sak, J., & Pawlikowski, J. A brief report on the history of phototherapy. *Clinics in Dermatology*, 2016, 34(5), 532-537. <https://doi.org/10.1016/j.clindermatol.2016.05.002>
96. Khalkhal, E., Razzaghi, M., Rostami-Nejad, M., Rezaei-Tavirani, M., Beigvand, H. H., & Tavirani, M. R. Evaluation of laser effects on the human body after laser therapy. *Journal of Lasers in Medical Sciences*, 2020, 11(1), 91-97. [10.15171/jlms.2020.15](https://doi.org/10.15171/jlms.2020.15)
97. Mansouri, V., Arjmand, B., Tavirani, M. R., Razzaghi, M., Rostami-Nejad, M., & Hamdih, M. Evaluation of efficacy of low-level laser therapy. *Journal of Lasers in Medical Sciences*, 2020, 11(4), 369-380. <https://doi.org/10.34172/jlms.2020.60>
98. Rajan, J. S., & Muhammad, U. N. Evolution and advancement of lasers in dentistry-A literature review. *International Journal of Oral Health Sciences*, 2021, 11(1), 6-14. https://doi.org/10.4103/ijohs.ijohs_2_21
99. Loreti, E. H., Pascoal, V. L. W., Nogueira, B. V., Silva, I. V., & Pedrosa, D. F. Use of laser therapy in the healing process: a literature review. *Photomedicine and Laser Surgery*, 2015, 33(2), 104-116. <https://doi.org/10.1089/pho.2014.3772>
100. de Souza da Fonseca, A., da Silva Sergio, L. P., Mencalha, A. L., & de Paoli, F. Low-power lasers on bacteria: stimulation, inhibition, or effectless?. *Lasers in Medical Science*, 2021, 36, 1791-1805. <https://doi.org/10.1007/s10103-021-03258-5>
101. Musstaf, R. A., Jenkins, D. F., & Jha, A. N. Assessing the impact of low level laser therapy (LLLT) on biological systems: a review. *International Journal of Radiation Biology*, 2019, 95(2), 120-143. <https://doi.org/10.1080/09553002.2019.1524944>
102. Wei, G., Yang, G., Wang, Y., Jiang, H., Fu, Y., Yue, G., & Ju, R. Phototherapy-based combination strategies for bacterial infection treatment. *Theranostics*, 2020, 10(26), 12241-12262. [10.7150/thno.52729](https://doi.org/10.7150/thno.52729)

103. Yoshimura, M., Namura, S., Akamatsu, H., & Horio, T. Antimicrobial effects of phototherapy and photochemotherapy in vivo and in vitro. *British Journal of Dermatology*, 1996, 135(4), 528-532. <https://doi.org/10.1016/j.nantod.2024.102327>
104. Pantyo, V. V., Koval, G. M., Pantyo, V. I., Danko, E. M., & Gulyar, S. A. Influence of led radiation on the *Staphylococcus aureus* sensitivity to antibiotics. *Photobiology and Photomedicine*, 2019, 26, 56-62. <https://doi.org/10.26565/2076-0612-2019-26-07>
105. Pantyo, V. V., Pantyo, V. I. & Danko, E. M. ANTIMICROBIAL ACTION OF LED RADIATION ON CAUSATIVE AGENTS OF OPPORTUNISTIC INFECTIONS. *Odesa National University Herald. Biology*, 2018, 23(1(42)), 69-77. [https://doi.org/10.18524/2077-1746.2018.1\(42\).118457](https://doi.org/10.18524/2077-1746.2018.1(42).118457)
106. Pantyo, V. V., Pantyo, V. I., & Danko, E. M. The impact of piler-radiation on the growth rate of opportunistic microorganisms. *Reports of Vinnytsia National Medical University*, 2018, 22(2), 272-275. [https://doi.org/10.31393/reports-vnmedical-2018-22\(2\)-07](https://doi.org/10.31393/reports-vnmedical-2018-22(2)-07)
107. Pantyo, V. V., Haleha, O. V., Kut, D. Z., Kut, M. M., Onysko, M. Y., Danko, E. M., Koval, G. M., Pantyo, V. I., Haza, K. V., & Bulyna, T. B. The effect of low-intensity laser radiation on the sensitivity of *Staphylococcus aureus* to some halogen-containing azaheterocycles. *Regulatory Mechanisms in Biosystems*, 2014, 15(2), 230-234. <https://doi.org/10.15421/022434>