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Antimicrobial activity of mono- and polynuclear platinum and palladium complexes

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Abstract:
Introduction. Infectious diseases remain a serious threat to humanity worldwide as bacterial pathogens grow more diverse. Bacteria, fungi, and parasites develop resistance to clinically approved antimicrobials, which reduces the efficacy of available drugs and treatment measures. As a result, there is an ever growing demand for new highly effective pharmaceuticals. This review describes mono- and polynuclear platinum and palladium complexes with antimicrobial properties. We compared several groups of antibacterial agents: antibiotics, antioxidant biologically active substances, antimicrobial nanoparticles, nanocomposite materials, biopolymers, micellar systems, and plant extracts.
Study objects and methods. The review covered relevant articles published in Web of Science, Scopus, and Russian Science Citation Index for the last decade. The list of descriptors included such terms as mononuclear and binuclear complexes of platinum, palladium, and antimicrobial activity.
Results and discussion. Chelates of platinum, palladium, silver, iridium, rhodium, ruthenium, cobalt, and nickel are popular therapeutic agents. Their antimicrobial activity against pathogenic microorganisms can be enhanced by increasing their bioavailability. Metal-based drugs facilitate the transport of organic ligands towards the bacterial cell. The nature of the ligand and its coordination change the thermodynamic stability, kinetic lability, and lipophilic properties of the complex, as well as the reactivity of the central atom. Polynuclear platinum and palladium complexes contain two or more bound metal (coordinate) centers. Covalent bonding with bacterial DNA enables them to form a type of DNA adducts, which is completely different from that of mononuclear complexes.
Conclusion. Metal-based drugs with functional monodentate ligands exhibit a greater antimicrobial effect compared to free ligands. Poly- and heteronuclear complexes can increase the number of active centers that block the action of bacterial cells. When combined with other antibacterial agents, they provide a synergistic effect, which makes them a promising subject of further research.

Keywords: Antimicrobial activity, antibacterial activity, antitumor activity, mononuclear complexes, polynuclear complexes, platinum (II), palladium (II), platinum (IV)

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INTRODUCTION

Infectious diseases represent a serious problem worldwide. The growing antimicrobial resistance of various pathogens reduces the efficacy of existing drugs and preventive treatment, thus fuelling the never-ending search for new drugs. Living organisms are in constant contact with a huge number of chemical compounds. Some of them are beneficial, e.g. proteins, lipids, carbohydrates, biologically active substances, mineral components, etc., while others are toxic. People in industrial regions are especially vulnerable to the negative impact of xenobiotics.

The antioxidative system of living organisms consists of the enzymes of oxidismutase, peroxidase, and catalase. It helps to destroy bacteria and substances absorbed by leukocyte cells. Antioxidants provide protection against the damage that results from the controlled production of reactive oxygen intermediates followed by lipid peroxidation, protein damage, and DNA rupture. Thus, antioxidants reduce the risk of chronic diseases, including cancer and heart diseases.

Enzymes and oxygen are responsible for regulated oxygenase and dioxigenase oxidation of biosubstrates in the organism. Biosubstrate comes in direct contact with oxygen only in the presence of enzymes. Therefore, oxidation processes can be controlled. In case of direct contact of the substrate with reactive oxygen intermediates, the redox process proceeds according

to the radical mechanism, and its rate depends on the concentration of free radicals in the cell.

Radiation exposure causes violation of the redox transformations of complexing ions in various biological complexes. Various radicals and other reactive oxygen intermediates form as a result of the activation and decomposition of water molecules.

Induced cytochrome enzyme system ensures the oxidative transformation of xenobiotics. It triggers the activation mechanism of the genes responsible for protein synthesis. Transcription of the corresponding part of the chromosome starts when the xenobiotic binds to the receptor protein in the cell. The resulting mRNA leaves the nucleus and becomes the template for the synthesis of the protein component of the monooxygenase. Drugs, polycyclic aromatic hydrocarbons, food components, e.g. flavonoids, xanthines, and indole derivatives, can exhibit monooxygenase-inducing properties. The intake of xenobiotics increases the number of monooxygenases, which leads to immunological exhaustion [1].

This review features mono- and polynuclear platinum and palladium complexes with antimicrobial properties. It contains a comparative analysis of various classes of antibacterial agents, e.g. antibiotics, antioxidant biologically active substances, antimicrobial nanoparticles, nanocomposite materials, biopolymers, micellar systems, and plant extracts.

STUDY OBJECTS AND METHODS

The review presents platinum and palladium complexes with antibacterial properties, various coordination structure, and different methods of ligand coordination. The list included mono- and polynuclear complexes with the central atom oxidation state of (+2) and (+4). The polynuclear complexes contained both mono- and polydentate bridging and terminal ligands. For comparison, we examined the main antibacterial agents – antibiotics, antioxidant biologically active substances, antimicrobial nanoparticles, and nanocomposite materials, as well as such biopolymers as polysaccharides, peptides, micellar systems, and plant extracts.

The review was based on highly relevant and recent publications retrieved from the Web of Science, Scopus, and Russian Science Citation Index bases. We limited the search to mononuclear and binuclear complexes of platinum and palladium and antimicrobial activity.

RESULTS AND DISCUSSION

Antibiotics. Antibiotics are natural substances of microbial, plant, and animal origin and products of their chemical modification that are capable of suppressing the growth of bacteria, lower fungi, protozoa, viruses, or cancer cells, when administered in low concentrations (10^{-3}–10^{-2} μg/mL). Science knows several thousands of natural antibiotics, and almost all of them are heterocyclic compounds. Synthetic and semi-synthetic antibiotics are more active and stable than natural ones.

Antibiotics can be divided into four main types according to the mechanism of action: 1) those that inhibit the synthesis of bacterial cell walls; 2) those that inhibit template (ribosomal) protein synthesis; 3) those that inhibit nucleic acid synthesis; 4) those that inhibit the functioning of the cytoplasmic membrane (Fig. 1). Antibiotics, antiseptics, bacteriophages, disinfectants, preservatives, and other antimicrobials are used in all industries. However, large doses of antibiotics and long treatment sessions may cause allergic or direct toxic reactions that affect kidneys, liver, gastrointestinal tract, central nervous and hematopoietic systems, etc.

The European system for surveillance and control of antimicrobial resistance has identified seven types of clinically significant bacteria that shape the antimicrobial resistance in Europe: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Enterococcus faecium*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

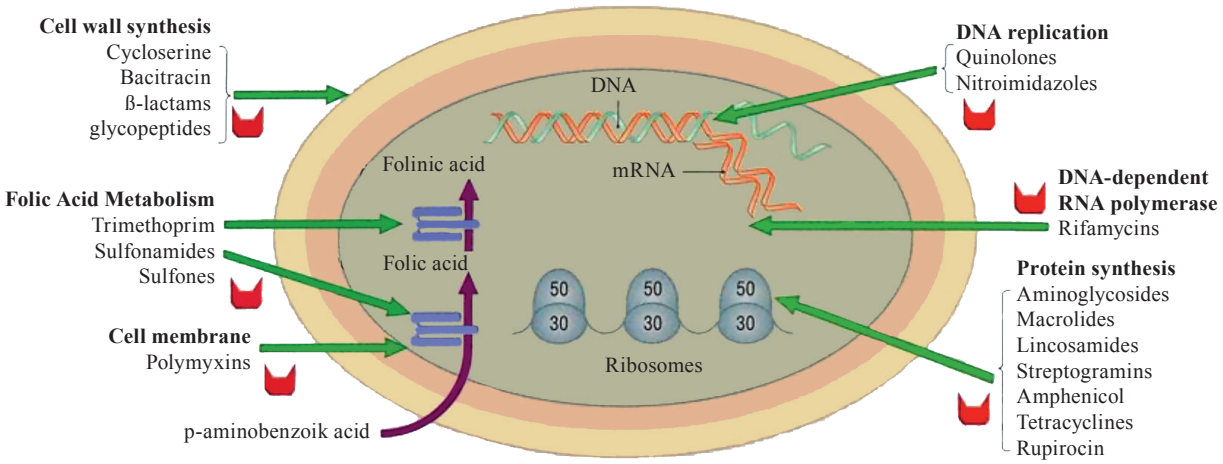

Figure 1 Antibiotics: mode of action

Strains of microorganisms isolated from various plant and animal raw materials demonstrate antibacterial properties, e.g. *Bacillus safensis*, *Bacillus endopheticus*, and *Bacillus subtilis* [2]. Bacteriocins of lactic acid bacteria strains of *Lactobacillus delbrueckii* B2455, *Lactobacillus paracasei* B2430, and *Lactobacillus plantarum* B884 are known to possess an antimicrobial potential [3].

As a rule, antimicrobial activity is determined by the optical density of culture fluid by using the method of serial dilutions, as well as the disk-diffusion method or diffusion E-test. The list of quantitative indicators that describe antibacterial activity includes: minimum inhibitory concentration (MIC); minimal inhibitory concentrations that inhibit 50% and 90% of bacteria (MIC_{50} and MIC_{90}, respectively); minimal bactericidal concentration that causes the complete death of bacterial cells (MBC).

Antioxidant biologically active substances. Scientists pay much attention to the antioxidant activity of organic and organometallic compounds against toxic active forms of oxygen and nitrogen. Antioxidants prevent oxidative reactions by stabilizing free radicals. However, the necessary amount of antioxidants can be obtained only with the regular use of biologically active additives. Plant-based bioflavonoids are popular food additives, e.g. rutin, quercetin, dihydroquercetin, eriodiktiol, resveratrol, etc. [4]. There are complex compounds that protect DNA from damage in the presence of hydrogen peroxide [5].

The growing prevalence of multiresistant bacterial pathogens has become a worldwide problem in the early XXI century. Infectious diseases remain a serious problem worldwide. When bacteria, fungi, and parasites become resistant to antimicrobials, it reduces the efficacy of drugs and preventive treatment. More and more microorganisms can withstand vaccines and antibiotics. For instance, methicillin-resistant *Staphylococcus aureus* is resistant to vancomycin [6]. The World Health Organization has already emphasized the need to develop new antimicrobial molecules because conventional antibiotics are growing helpless, especially in fighting the so-called ESKAPE pathogens with their gradually increasing antibiotic resistance: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* [7].

Fungal infections also cause high morbidity and mortality, especially in immunocompromised HIV and cancer patients. The growing cancer incidence is another global health concern as it remains one of the most common causes of death worldwide. The recent advances in cancer treatment, e.g. chemotherapeutic drugs, have significantly improved the prognosis and survival of cancer patients [7].

Antimicrobial nanoparticles and nanocomposite materials. Nanoparticles can target bacteria as an alternative to antibiotics. Nanotechnology can be especially useful in the treatment of bacterial infections. Nanoparticles cover antibacterial coatings of implantable devices to prevent infection and promote wound healing. They are used in treating diseases as antibiotic delivery systems. In bacteria detection systems, they facilitate microbial diagnostics. They also can control bacterial infections in antibacterial vaccines [8]. Metal nanoparticles have a pronounced wound healing effect.

Nanocomposite materials of silver, gold, platinum, and iron possess high antimicrobial activity when stabilized by arabinogalactan, which is a natural polysaccharide, as well as by other metal nanoclusters. A biologically active complex called Fullerene C60/Tween 80 affects the main pathogenesis of wound process [9]. There have been studies of the sorption activity of *Acetobacter xylinum* cellulose nano-gel films in various biological media in comparison with other sorbents.

Antibacterial bimetallic surfaces of implant biomaterials have also become focus of scientific attention [10]. The research featured platinum and silver nanoparticles that were 1.3–3.9 nm thick and 3–60 nm wide. To create an antimicrobial surface, they were subjected to magnetron sputtering on a titanium substrate, both separately and together. Sequential sputtering of silver and platinum nanoparticles increased the antimicrobial activity, if compared to co-sprayed silver and platinum samples or pure silver patches (Fig. 2).

Researchers have synthesized gold and platinum nanoparticles coated with a pyrimidine-based ligand [11]. The nanoparticles interacted with DNA due to hydrophobic forces and demoinstrated a good antioxidant activity. In addition, they possessed antimicrobial properties against *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas fluorescens*, *Shigella sonnei*, *Staphylococcus aureus*, *Aspergillus niger*, *Candida albicans*, *Candida tropicalis*, and *Rucoropus mucis indica*.

Antimicrobial nanoagents can be used in dentistry, medical devices, and food industry [12].

Antimicrobial nanoparticles and peptides can become new non-antibiotic antimicrobials that kill bacteria in biofilms. Biofilms can be produced by several species or one strain of bacteria. A biofilm is a template

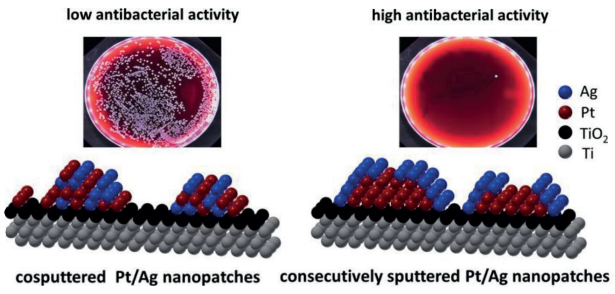

Figure 2 Antibacterial activity of silver and platinum particles [10]

coating of one or more strains of bacteria that adhere to biological or non-biological surfaces. Biofilms increase the resistance of microorganisms to antimicrobial agents by producing extracellular polymeric substances.

Many bacterial pathogens have developed antibiotic resistance, resulting in infections that cannot be treated with conventional antibiotics. New non-antibiotic antimicrobial agents, e.g. silver nanoparticles or new antimicrobial proteins, can bind and oxidize thiol groups, block DNA replication, alter the expression of bacterial genes and denaturing enzymes, induce reactive oxygen species, or damage bacterial membranes. Antimicrobial proteins, e.g. antimicrobial peptides, and natural enzymes, e.g. those derived from insects and bacteria, also demonstrate antibacterial properties [2, 3]. As a result, they can be used in biomedicine and food industry as antibacterial agents. The antimicrobial properties of peptides are not as strong as those of conventional antibiotics, but sufficient enough to kill pathogenic microorganisms. The mechanisms of their action remain unclear, but they are believed to target bacterial membranes and intracellular molecules.

Chronic infections lead to inflammation and deplete immune defense, thus contributing to the proliferation of cancer cells. Cisplatin (CDDP) has been approved by the Food and Drug Administration (FDA) as an antitumor drug, which is now widely used to treat various types of cancer. Cisplatin owes its antitumor properties to the fact that it affects DNA directly [13]. DNA alkylation suppresses the biosynthesis of nucleic acids and kills the cell. However, cisplatin has no targeted effect: it spreads in all biological fluids and body tissues, causing renal function impairment, anaphylactic reactions, leukopenia, thrombocytopenia, anemia, and neuropathy [14]. The antiproliferative effect that cicplatin produces on rapidly dividing cells explains its toxic impact on the functional state of organs and tissues.

As a result, scientists around the world have been trying to develop more effective antitumor platinum-based drugs with fewer complications. Currently, it is one of the most urgent tasks of bioorganic chemistry and biotechnology. The introduction into the internal sphere of a complex of powerful antiproliferative and functionally active ligands is another strategic direction in the search for methods of highly effective agents. Structural analogues of clinically tested platinum complexes have been subjects of numerous studies in the recent decades. Most of them feature monofunctional platinum (II) complexes that carry only one labile ligand, each complex binding to DNA only once [15].

The nature of the ligand and its coordination type affect the reactivity of the central atom. Coordination changes not only the thermodynamic stability and kinetic lability of the complex, but also its lipophilic properties. It either stabilizes or destabilizes the oxidative state of the central atom.

Biopolymers: polysaccharides and peptides. Micellar systems. Metals can produce complex biologically-active biopolymers with antimicrobial and antitumor properties.

Galactan-containing polysaccharides are known for their high biological activity and immunomodulatory effect. Arabinogalactans contain numerous galactose and arabinose residues, which allow them to interact with asialoglycoprotein receptors. This valuable property makes it possible to use these polysaccharides to deliver substances that are unable to pass through the outer membrane into the cell. For instance, Starkov *et al.* used arabinogalactan to deliver platinum into tumor cells [16]. Platinum has an antitumor effect as part of cisplatin, which is widely used in cancer treatment [14]. Starkov *et al.* also proved the antitumor effect of the equimolar platinum-arabinogalactan complex based on the interaction of cis-diamine(cyclobutane-1,1-dicarboxylate-O,O')platinum (II) with a polysaccharide [17].

Popova and Trifonov analyzed research results published over the past 15 years which featured the synthesis and biological properties of analogues and derivatives of amino acids with tetrazolyl fragments [18]. They concluded that tetrazolyl analogues and derivatives of amino acids and peptides have a great potential for medical chemistry. Tetrazoles are polyazitous heterocyclic systems which include four endocyclic nitrogen atoms. They are able to exhibit the properties of acids and bases, as well as form strong hydrogen bonds with proton donors and, less often, with proton acceptors. They are metabolically stable and can penetrate biological membranes. Another promising area is the synthesis of linear and cyclic peptides based on modified amino acids with a tetrazolyl fragment. Finally, some tetrazole-containing amino acids and peptides possess a high biological activity and can become a source of new drugs [18].

Porphyrins are tetrapyrrole compounds that form metal porphyrins when interacting with metal compounds, and metal porphyrins can easily enter into electrophilic substitution reactions. In addition, free and metal-bound porphyrins are easily reduced to produce mono- and dianionic compounds. Their nucleophilic properties allow them to interact with proton donors. Simulated solutions of porphyrin compounds help study photo-oxygenation.

Platinum-bound porphyrins can inhibit multiresistant bacteria, e.g. *Staphylococcus aureus* [19]. Tetra-platinum (II) porphyrin increased its hemolytic activity when exposed to light. Lopes *et al.* proved that platinized porphyrins had a good potential for wastewater treatment, biofilm control, and bioremediation since they can be used for microbial photodynamic inactivation [19].

Proline derivatives are known to possess antibacterial activity. Thioproline is an antioxidant, while phenylproline derivatives inhibit the *Staphylo-*

coccus aureus sortase SrtA isoform [20]. Gram-positive bacteria produce surface proteins that promote the attachment of the bacterial cell to the host and prevent phagocytosis. During catalysis, sortase enzyme sorts surface proteins on the bacterial cell wall. Surface proteins then bind covalently to the bacterial cell wall through the catalyzed *S. aureus* SrtA transpeptidase reaction. Deactivation of SrtA genes of Gram-positive microorganisms inhibits the fixation of surface proteins and reduces the virulence of the bacterium. Antibiotics are not the only *S. aureus* SrtA inhibitors: peptides, plant extracts, and low-molecular-weight organic compounds have the same properties [20].

Therefore, biopolymers and micellar systems with their ability to penetrate biological membranes can deliver metal complexes into cells.

Complex platinum and palladium compounds. Drugs based on organic ligand complexes exhibit a greater antimicrobial effect compared to organic pharmaceuticals. Complexation produces a synergistic effect between the organic ligand and the complexing agent. Chelates of platinum, iron, iridium, rhodium, ruthenium, palladium, cobalt, and nickel have a reputation of effective therapeutic agents.

Metal-containing active centers with a stable, inert, and non-toxic nature are quite rare in biological systems. They owe their activity to the bioavailability of the complexes. Metal complex-based drugs facilitate the transport of organic ligands towards the bacterial cell. Palladium complexes proved highly effective against resistant forms of microorganisms. For instance, tetracycline palladium (II) complex appeared sixteen times more effective against tetracycline-resistant bacterial strains of *E. Coli* HB101/pBR322 than traditional drugs [6].

There are a huge number of pharmacologically active heterocyclic compounds. Advanced medical chemistry has made it its main task to study the antimicrobial and antitumor properties of platinum and palladium complexes with heterocyclic ligands.

Benzothiazole derivatives are one of the most popular pharmacologically known heterocyclic compounds. Benzothiazole and its analogues demonstrate a wide range of biological properties, e.g. antitumor, antimicrobial, anticonvulsant, antiviral, antituberculous, antimalarial, anthelmintic, analgesic, anti-inflammatory, antidiabetic, fungicidal, etc. [21]. Thiazole nuclei that can be coordinated to metal atoms are often used as an ambidentate ligand in biologically active complexes.

Thiosemicarbazone and its derivatives can be used as synthetic antiviral agents. They are heterocyclic ligands and contain nitrogen, sulfur, and oxygen donor atoms. Platinum (II) and palladium (II) complexes with thiosemicarbazones exhibit anti-tuberculosis activity against *Mycobacterium tuberculosis* [22].

Suleman *et al.* described Schiff-base complexes that contained donor atoms of nitrogen, sulfur, and oxygen and possessed antimicrobial and antitumor activity. The antibacterial activity of these multi-dentate ligands and their complexes demonstrated great prospects pharmacy and agricultural chemistry. Coordination compounds of transition metals owe their unique configuration and chemical lability to their specific electronic and steric properties, which make them sensitive to the molecular environment [23].

The antimicrobial and antitumor properties of these complexes depended on the electron-donor and acceptor substituents in the aromatic ring. Bioligands modified by hydrophilic groups appeared to increase the solubility of compounds [24].

Platinum (II) complexes obtained from functionalized aroylaminocarbo-N-thioyl prolineates also demonstrated antibacterial and antifungal properties [25]. Sulfur and oxygen atoms allowed aroylaminocarbo-N-thioyl ligands to coordinate bidentally. Non-electrolyte complexes had a square-planar configuration.

Mawnai *et al.* synthesized complexes with N-coordinated pyridylpyrazolyl ligands that formed a six-membered metallocycle [26]. They conducted *in vitro* studies of the antibacterial activity of ligands and their complexes. The research featured both Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus* and *Bacillus thuriengiensis*) bacteria. The cationic nature of the complexes made them more effective against the Gram-negative bacteria.

Bakr *et al.* synthesized organometallic platinum and palladium complexes with heterocyclic derivatives of pyrazolone [5]. Pyrazolone derivatives had a five-membered ring with an additional keto group, which allowed them to form chelates. They studied the biological activity of azo-compounds to use them as antitumor, antioxidant, and antimicrobial agents. They also assessed their nuclease activity against DNA. They performed an MTT lab-test on four human cancer cell lines to study the antitumor activity of the compounds in question. The cell lines included hepatocellular carcinoma (HePG-2), colorectal cancer (HCT-116), human prostate carcinoma (PC-3), and breast carcinomas (CMC-7) [5].

As a rule, researchers employed standard methods to study the antimicrobial activity of the abovementioned compounds, e.g. the cut-plug method. Some experiments featured strains of pathogenic bacteria, e.g. *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilus*, *Salmonella typhi*, and *Proteus spp*, or such malicious fungi as *Candida albicans* and *Aspergillus niger* [5]. An *in vitro* anntioxidant analysis of pyrazolone derivatives and their metal complexes made it possible to compare the results of erythrocyte hemolysis. The palladium complexes demonstrated a greater antioxidant activity in comparison with platinum complexes. The free ligand had a more prominent increase in the antioxidant activity, compared to metal complexes. This result could

be explained by a greater ability to charge transfer of the condensed ring system. It increased the ability of the heterocycle to stabilize unpaired electrons of the azo-compound, thus binding free radicals.

Chitosan is an antimicrobial agent that can destroy bacteria, filamentous fungi, and yeast. Chitosan is a copolymer of 2-amino-2-deoxy-D-glucopyranose and 2-acetamido-2-deoxy-D-glucopyranose combined with β (1 → 4), which gives it high biocompatibility and biodegradability. Chitosan is widely used in food industry, agriculture, and medicine.

The antimicrobial activity of chitosan and its derivatives depend on pH, type of microorganisms, molecular weight of the biopolymer, and the degree of its deacetylation. If a chemical change occurs in the structure of the amino- and hydroxyl groups of the glucosamine chains of the biopolymer, it can affect not only the solubility and stability of chitosan, but also its antimicrobial activity. Berezin *et al.* described the synthesis of water-soluble conjugates of chitosan with tetrazoles. They bound tetrazoles by the chlorohydroxypropyl groups of N-(3-chloro-2-hydroxypropyl) chitosan, while the other part of the groups interacted with the amino groups of the polymer, which led to intra- or intermolecular crosslinking [27]. The antimicrobial properties increased as a result of the complexation of chitosan with various metals.

Barbosa *et al.* developed new platinum (II) and palladium (II) complexes with biopolymer amphiphilic Schiff-bases to increase the biological activity of chitosans. They performed the binding by fixing chitosans in templates of various molecular weights. The chitosans were modified with salicylic aldehyde and glycidol [24]. They introduced salicylaldehyde to obtain the complexing Schiff-base sites in the chitosan template. Glycidol made it possible to increase the water solubility of the resulting biopolymer complexes. The new complexes underwent spectral and thermal testing for antimicrobial and antitumor activity. When compared to the free ligand, the complexes demonstrated a higher antibacterial efficacy against gram-negative bacteria *Pseudomonas syringae* than against *Fusarium graminearum* fungi. They also demonstrated a high antitumor effect on MCF-7 breast cancer cells, with certain selectivity for non-tumor cells (Balb/c 3t3 clone A31) depending on the concentration and molar mass. In higher concentration, all complexes synthesized with different molecular weights of the polymer template decreased the viability of MCF-7 cancer cells [24].

Bobinihi *et al.* synthesized dithiocarbamide ligands based on primary amines, N-phenylaniline, 4-methylaniline, and 4-ethylaniline [28]. S,S-binding resulted in bidentate coordination, which led to the formation of squared complexes of platinum (II) [Pt (L) 2] and palladium (II) [Pd (L) 2]. They exhibited antimicrobial activity against gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*), gram-positive bacteria (*Bacillus cereus* and *Staphylococcus aureus*), and fungi (*Candida albicans* and *Aspergillus flavus*).

The mechanisms of the antitumor effect changed when naphthalenbenzimidisole was introduced as a ligand into the platinum-metal system. The antiproliferative activity, drug resistance, and toxicity increased. Liang *et al.* invented a synthesis method for naphthalene benzimidisole-platinum (II) complexes [29]. They studied their antiproliferative activity for eight cancer cell lines, namely Hela, HepG2, SKOV3, NCI–H460, BEL–7404, SMMC–7721, U251, and A549. Unlike cisplatin, the naphthalenbenzimidisole complexes did not show resistance to A549-CDDP. The mechanism of the antitumor effect appeared due to the covalent binding to DNA and an increase in the expression level of intracellular type I. An *in vitro* experiment showed that several complexes proved sensitive and selective to cell lines SMMC-7721 and U251 and possessed low toxicity to normal HL-7702 cells.

Antimicrobial activity depends on the alkyl chain length of N-substituted imidazolium salts, where long alkyl chain compound with 8–16 carbon atoms reached the lowest values of the minimum inhibitory concentration. While alkyl chains under six carbon atoms are usually inactive, the alkyl chain length affects the functioning of the bacterial membrane [30, 31]. When a long hydrocarbon chain integrates with a lipid bilayer of the cell membrane, cell contents may start leaking out [32]. The antimicrobial activity of imidazolium salts depends on such factors as hydrophobicity, adsorption, critical micelle concentration, and the transport rate in aqueous media.

Meng *et al.* synthesized a number of platinum (II) complexes with substituted 3-(2'-benzimidazolyl) coumarins (1-benzopyran-2-one) [33]. The complexes exhibited a high cytotoxic activity *in vitro* against cisplatin-resistant cancer cells, namely SK-OV-3/DDP with a low IC_{50}.

Choo *et al.* described a wide range of organometallic drugs with N-heterocyclic carbene (NHCs) ligands [34]. The new complexes were insoluble in most solvents except dimethyl sulfoxide. Complexes with several conjugated rings are highly hydrophobic and do not affect the activity of Gram-negative bacteria. Inhibition of the growth of Gram-positive bacterial strains occurs at low micromolar concentrations of the synthesized complexes. The different susceptibility of Gram-positive and Gram-negative bacteria results from their morphological differences, namely the permeability of the outer layer of bacteria. The difference in susceptibility can be explained by their morphological differences between Gram-positive and Gram-negative bacteria. Gram-positive bacteria have a lower permeability of the outer peptidoglycan layer, while the outer membrane of Gram-negative bacteria contains

structural lipopolysaccharide components. They make the cell wall impervious to lipophilic solutions. As a result, porins, membrane transport proteins, form a selective barrier for hydrophilic solutions [34]. The part of the channel protein that is responsible for transmembrane transport opens and closes depending on the hydrophilicity of the complex.

The synthesis of platinum (IV) antitumor drug precursors relies on the fact that the oxidation state of platinum (IV) leads to a greater stability than their platinum (II) analogues. The stability of platinum (IV) precursors results from their resistance to reduction, inertness to ligand exchange, and reactivity [35].

There have been successful attempts to synthesize antimicrobial platinum complexes with coumarin derivatives as heterocyclic biologically active ligands [36]. They inhibited the cyclooxygenase enzyme by coumarin complexes of platinum (IV) with cisplatin and oxaliplatin centers.

Oxygen atoms allow carboxylate ligands of RCO_2^- to possess electrodonor properties. Their coordination is monodentate, bidentate, and even tetradentate. The carboxylate platinum and palladium complexes are analogues of biologically active compounds. The acidoligand and synthesis conditions proved to affect the formation of the internal coordination sphere. The system of hydrogen bonds and/or $\pi - \pi$-stacking interactions between aromatic ligand segments also produced a certain effect on the processes of self-organization of complexes into supramolecular structures [37].

Carboxylate metal complexes often take the form of polynuclear compounds due to the oligomerization of oxo- and hydroxo-functional groups, thus developing M-O-M structural units. There are platinum (IV) carboxylate complexes with anticancer activity [35, 38].

Al-Khathami *et al.* synthesized several Schiff bases with various primary aromatic amines derived from pyridine-2-carboxaldehyde as ligands for platinum (II) complexes [39]. They studied their antimicrobial activity *in vitro* using the cut-plug method in nutrient media. Microorganisms were plated in wells filled with the test solution of ligands and complexes with subsequent incubation. Some complexes and ligands proved to have inhibitory effect on such pathogenic human bacteria as *Escherichia coli*, *Bacillus subtilus*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Staphlococcus aureus*, *Pseudomonas aeruginosa*, and *Candida fungus*. Studies of DNA binding showed that the electron-withdrawing groups facilitated the binding of platinum (II) complexes containing the Schiff base pyridyl ligands (Fig. 3). The complexes with an electron-withdrawing group demonstrated the highest antimicrobial effect. The complex with a nitro group proved effective against bacteria, but not against fungi. The acetyl group increased antimicrobial activity against almost all strains. Due to the hydroxyl group, free

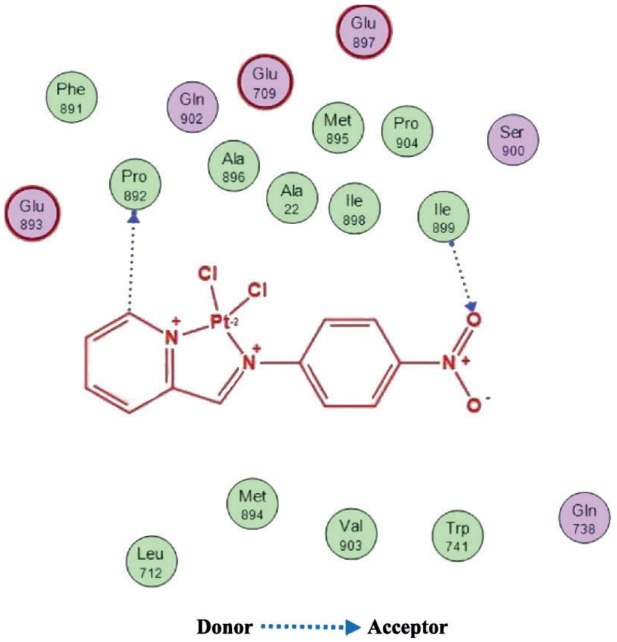

Figure 3 Methods of binding a mononuclear complex with a protein [39]

ligands possessed a higher antimicrobial activity against gram-negative bacteria, compared to their platinum (II) complexes.

Platinum complex compounds are not the only platinum group metals with pronounced antimicrobial and antitumor properties. Gold, silver, iridium, rhodium, and ruthenium complexes demonstrate similar activities. The cytotoxicity of gold complexes usually consists in the inhibition of thiol-containing enzymes. When gold binds with thiol groups, the reductases and proteases of cancer cells become potential targets for gold complexes (Fig. 4). Inhibition of the activity of these enzymes can disrupt the redox state of the cell and increase the production of reactive oxygen species (ROS), thus causing cellular oxidative stress and leading to its own apoptosis. This mechanism differs from that of platinum-based drugs [40].

Polynuclear platinum and palladium complexes. Binuclear and polynuclear platinum complexes have recently proved biologically active and antimicrobial. Bridging ligands contribute to the formation of cyclometallic complexes. Polynuclear compounds exhibit properties different from those of free ligands and monomeric complexes.

Johnstone *et al.* studied non-classical platinum (II) complexes with trans-geometry or a monofunctional

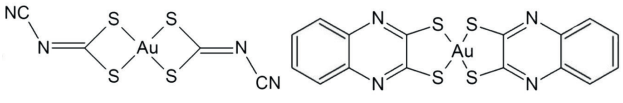

Figure 4 Binding of silver with thiol groups [40]

coordination center, as well as polynuclear platinum (II) compounds, platinum (IV) prodrugs, photoactivated platinum (IV) complexes, and other precursors [41].

Ligands and complexes differ in chemical nature, size, and geometric shape, which affect their DNA-binding properties. A detailed study of the method of binding polynuclear complexes of platinum with DNA produced a mixed result. The complexes were able to interact directly with DNA due to covalent binding, electrostatic forces, or intercalation [42]. Groove binding proved to be the cause of cell apoptosis [43].

Complexes owe their activity to the formation of new adducts with DNA. As a result, there are three important aspects to their binding: DNA pre-association, formation of DNA adducts, and induced conformational changes in DNA [44]. Multinuclear platinum complexes contain two or more bound platinum centers that can covalently bind to DNA and, therefore, are capable of forming a completely different kind of DNA adducts compared to cisplatin and its analogues. Multicore complexes represent a completely new paradigm of biologically active complexes, in particular, for platinum-based anticancer agents.

In our previous research, we proved that the bonds of bridged halide ligands had a greater lability, compared with the terminal ones [45]. This fact made it possible to introduce polynuclear platinum complex compounds into the biosystem. Their aquatization resulted in a break of bridging bonds with the formation of monomeric complexes.

P,N- and S,N-bidentate ligands have the properties of both soft and hard bases. As a result, they can direct organization of the metal coordination sphere (Fig. 5), as well as form bimetallic and polynuclear systems [43].

In our previous studies, we also described a method for the synthesis of binuclear complexes of divalent platinum. According to this method, amino acids (glycine, alanine, and valine) bound with two central atoms simultaneously via two donor atoms, i.e. bridges $[(NH_3)_2Pt(\mu\text{-}N,O\text{-}L)_2Pt(NH_3)_2](NO_3)_2$ [46]. The coordination of amino acids led to the formation of chelates, while the presence of a biogenic ligand in the internal coordination sphere reduced the overall toxicity of the platinum complex. The compounds showed cytotoxic activity[1].

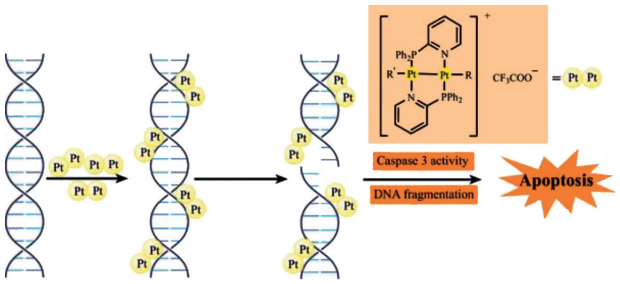

Figure 5 Binding of DNA with binuclear complex [43]

Popova and Trifonov synthesized antimicrobial binuclear platinum (II) complexes with tetrazole and 5-methyltetrazole with the composition of cis-$[\{Pt(NH_3)_2(L\text{-}H)Cl\}_2]Cl$ [18].

Lunagariya *et al.* studied the antibacterial activity of platinum (II) binuclear complexes based on pyrazolo [1,5-a] pyrimidine with neutral tetradentate ligands. The general formula was $[Pt_2LCl_4]$ [42]. The research featured five test organisms: two gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and three gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens*). It also included an *in vitro* study of anti-tuberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain.

Antibacterial actions include several phases of inhibition: cell wall synthesis, cell membrane functions, protein synthesis, nucleic acid synthesis, and folic acid synthesis. Chelation makes it possible to increase the values of the minimum inhibitory concentration of the complexes. This effect can be explained by the Tweedy's chelation theory: chelation allows the complex to penetrate the cell membrane. The complexes are toxic partially because the metal-ligand bond is strong. The toxicity differs from the type of substituent present in the synthesized compounds (Fig. 6) [42]. Active substituents in ligands have a high lipophilicity, which allows them to penetrate the complexes through the cell membrane. Complexes with a high-electronic substituent NO_2^- in its phenyl ring exhibit a greater antibacterial and anti-tuberculosis activity. Nitro groups act as chemical isosteres for oxygen atoms in the heterocyclic base of thymidine. However, they also participate in the "strong" O–H bond. As a result, the bond exhibits greater DNA-binding and antimicrobial activity than other complexes. The phenyl group is replaced with donor substituents, e.g. methoxy- or methyl group, and a hydrogen atom in the para position. Subsequently, the antibacterial activity against *P. Aeruginosa* and *E. coli* decreases, while acceptor chloro-, nitro-, and fluorosubstituents increase their efficacy against *S. Marcescens* and *B. Subtilis* [42].

Rubino *et al.* synthesized binuclear platinum (II) complexes with fluorinated heterocyclic ligands: 5-perfluoroalkyl-1,2,4-oxadiazolylpyridine and 3-perfluoroalkyl-1-methyl-1,2,4-triazolylpyridine [47]. Chlorine atoms served as bridges between the two platinum atoms. The complexes showed antimicrobial activity against *Escherichia coli*, *Kocuria rhizophila*, and two strains of *Staphylococcus aureus*. Azolate-bridged polynuclear platinum complexes formed DNA adducts as a result of additional electrostatic interaction.

[1] Salishcheva OV, Moldagulova NE, Proskynov IV. Investigation of the biological activity of organometallic complexes of platinum. XXI Mendeleev Congress on General and Applied Chemistry; 2019; St. Petersburg. St. Petersburg, 2019. p. 334.

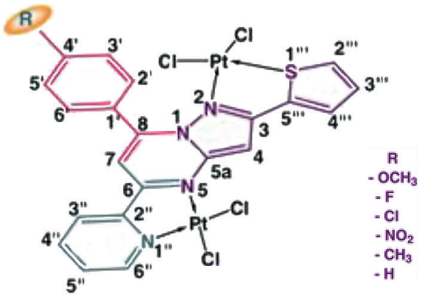

Figure 6 Coordination of tetradentate pyrazolo-pyrimidine in the binuclear platinum (II) complex [42]

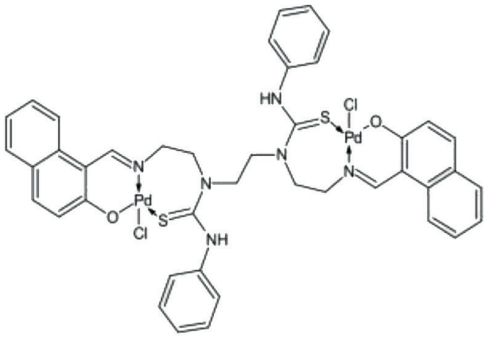

Figure 7 Tridentally coordinated bis-[1-(2-[(2-hydroxy-naphthalen-1-yl)methylidene]amino}ethyl)-1-ethyl-3-phenylthiourea] ligand in a binuclear palladium (II) complex [49]

Icsel *et al.* obtained mono- and binuclear palladium (II) and platinum (II) complexes with ligands L_1 = 5,5-diethylbarbiturate and pyridine derivatives L_2 = 2-phenylpyridine, 2,2'-bipyridine and 2,2'-dipyridylamine. The general formula was $[M(L_1\text{-}N)_2(L_2\text{-}N,N')]$ and $[M_2(\mu\text{-}L_1\text{-}N,O)_2(L_2\text{-}N,C)_2]$ [48]. The complexes appeared to have similar DNA binding mechanisms.

There have been much fewer medical studies concerning palladium (II) complexes for medicinal use. Palladium (II) and platinum (II) complexes have different chemical properties because palladium compounds have a greater lability of the ligand-complexing bonds. As a result, hydrolysis processes get accelerated, and the amount of dissociation products increases, e.g. aqua- or hydroxo-complexes, which are unable to fulfill their biological functions. To eliminate this factor, large heterocyclic and chelate ligands have to be introduced into the internal sphere.

Rubino *et al.* synthesized antibacterial palladium complexes with aromatic nitrogen, sulfur, and oxygen-containing ligands. They described the synthesis of binuclear platinum (II) and palladium (II) complexes with the 2,2'-dithiobis-benzothiazole (DTBTA) ligand $[Pd_2(\mu\text{-}Cl)_2(DTBTA)_2]Cl_2$. The research included an *in vitro* analysis of their antitumor activity against human breast cancer (MCF-7) and hepatocellular carcinoma (HepG2), as well as against *Escherichia coli* and *Kokuria rhizophila*. The complexes proved to have a greater antimicrobial effect against gram-positive bacteria than cisplatin. The low activity against gram-negative bacteria was explained by the fact that these bacteria have an additional outer membrane, which can interfere with the absorption of both compounds.

Terbouche *et al.* studied palladium (II) and ruthenium (III) binuclear complexes with phenylthiourea derivatives, namely their antibacterial properties, antioxidant activities, and stability (Fig. 7) [49]. They used the spectrophotometry method to assess the formation constants of the new Schiff-base alkali metal complexes and the systems formed by these chelates and cholesterol.

Chakraborty *et al.* described the synthesis and characteristics of binuclear palladium (II) complex [(3,5- dimethylpyrazole)$_2$Pd$_2$(μ-3,5-dimethylpyrazolate)$_2$(2,6-dipicolinate)] [50]. It was a dimer connected by two 3,5-dmpz units. One palladium atom contained two protonated 3,5-Hdmpz ligands and the other – one bidentate 2,6-dipicolinate, which made the complex asymmetric. The central nucleus of Pd_2N_4 consisted of six elements. It was a boat-like structure with palladium atoms located at the tops. The molecules assembled in an elongated zigzag one-dimensional network formed by 3,5-Hdmpz-carboxylate (2,6-dipic 2-) hydrogen bonds. The complex demonstrated antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*, and *Aspergillus niger*. The minimum inhibitory concentration was 100 μg/mL.

Another study featured pyrazolate binuclear Palladium (II) complex $[Pd_2(\mu\text{-dppz})_2(Hida)_2]\cdot CH_3OH\cdot 2H_2O$ (dppz = 3,5-diphenylpyrazolate) with monoprotonated iminodiacetate (Hida). It demonstrated antimicrobial activity against *Bacillus subtilis* [51]. The donor atoms of oxygen and nitrogen coordinated the pyrazolate ligand.

A binuclear pyrazolate square-planar palladium complex $Pd_2Cl_4L_2$ (L = 5-methyl-5-(3-pyridyl)-2,4-imidazolidenedione ligand) with *cis*- and *trans*-configurations also showed antimicrobial activity [52]. The *trans*-isomer appeared more stable in the liquid and gaseous phase than the *cis*-isomer. The pyridine-type nitrogen atoms provided for the square-planar geometry around the metal center. Each palladium atom was coordinated by one nitrogen atom and three chlorine atoms, one serving as terminal and two as bridging ligands (Fig. 8). The initial mononuclear complex and the binuclear palladium complex were tested for antibacterial activity against six types of microorganisms: *Staphylococcus aureus* (ATCC 6633), *Staphylococcus saprophyticus* (ATCC 15305), *Escherichia coli* (*Lio*), *Proteus vulgaris* (*Lio*), *Serratia marcescens* (PTCC 1330), and *Bacillus cereus* (ATCC 7064). Bacterial growth was studied by disk diffusion, while the minimum inhibitory concentration of the

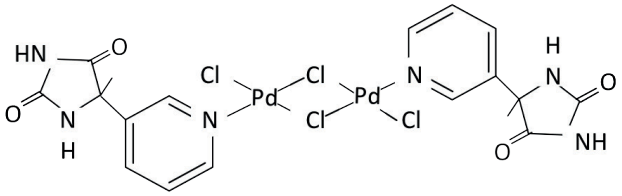

Figure 8 Binuclear pyrazolate square-planar palladium complex $Pd_2Cl_4L_{2of}$ (*trans*-configuration) with bridging chloride ligands [52]

chemicals was determined by *in vitro* dilution. The microorganisms were cultured in harvest broth and nutrient agar (Oxoid Ltd.). The agar culture medium included 0.5% of peptone, 0.3% of beef or yeast extract, 1.5% of agar, 0.5% of NaCl, and distilled water; pH = 6.8 at 25°C [52].

The compounds inhibited the metabolic growth of bacteria to varying degrees. The binuclear complex had a higher activity compared to the free ligand, while the ligand activity became more pronounced when coordinated with the metal. The increased activity of metal chelates could be explained by Tweedy's chelate theory: the polarities of the ligand and the complexing agent are restored by balancing the charges throughout the whole chelate ring. As a result, the lipophilic nature of the metal chelate increases and facilitates its penetration through the lipid layer of the bacterial membrane [53].

Plant extracts. Natural products or their extracts possess antimicrobial properties, e.g. grape skin or essential plant oils, e.g. of citrus fruits, wormwood, mint, and ginger [54–57]. When used in combination with nanoparticles, various functional essential oils produce a synergistic effect against multidrug resistant microbial pathogens (Fig. 9) [58].

CONCLUSION

Malicious microorganisms keep mutating. They grow ever more resilient to drugs, which triggers a never-ending search for new antimicrobial agents. Drugs based on organic ligand complexes exhibit an antimicrobial effect comparable to that of antibiotics. The complexation leads to a synergistic effect between the organic ligand and the complexing agent. Chelates of platinum, palladium, silver, iron, iridium, rhodium, ruthenium, cobalt, and nickel are therapeutic agents. Complexes with enhanced bioavailability have a better antimicrobial effect against pathogenic microorganisms. Metal-based drugs facilitate the transport of organic ligands towards the bacterial cell.

The reactivity of the central atom depends on the nature of the ligand and the coordination method. Coordination changes not only the thermodynamic stability and kinetic lability of the complex, but also the lipophilic properties that ensure the ability of the complex to penetrate the cell membrane. It stabilizes or destabilizes the oxidative state of the central atom. When complexes with functional multi-dentate ligands enter the internal sphere, it enhances the antimicrobial effect. The presence of a biogenic ligand in the coordination sphere reduces the general toxicity of platinum and palladium complexes. Drugs based on complexes with functional multi-dentate ligands exhibit a greater antimicrobial effect compared to free ligands. Inhibition of bacterial growth occurs at lower concentrations of metal complexes.

Active metal centers with a stable, inert, and non-toxic nature are of great value for biological systems. Polynuclear and heteronuclear complexes increase the number of active centers that block the action of bacterial cells and improve the formation of cross-links between different molecules. These valuable properties

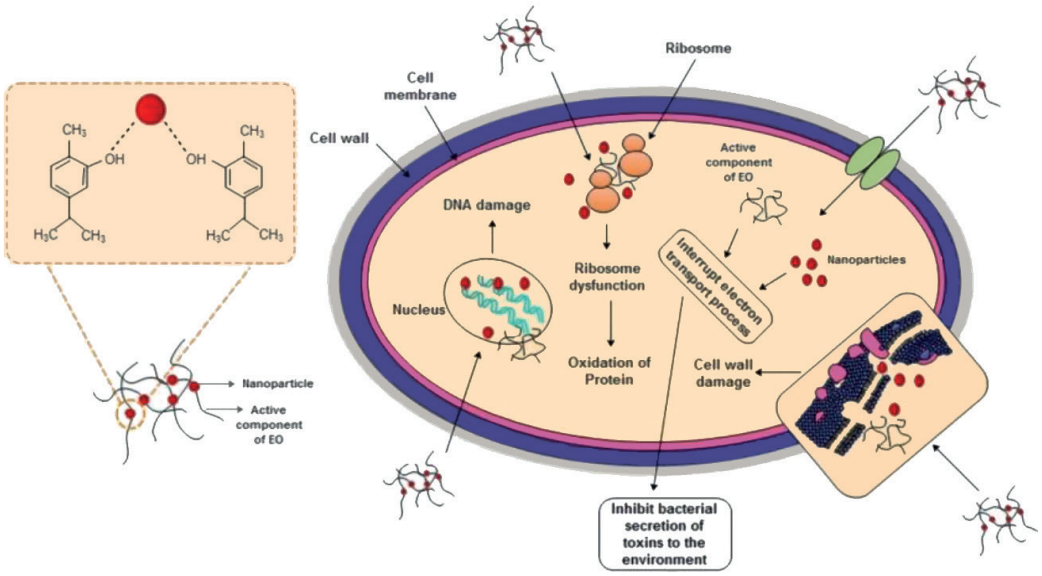

Figure 9 Antimicrobial effect of nanoparticles used with functional essential oils [58]

encourage researchers to synthesize new complexes with antibacterial and antitumor properties. Due to their ability for covalent binding to bacterial cell DNA, polynuclear platinum and palladium complexes contain two or more bound metal centers that can form a completely different kind of DNA adducts, as compared to mononuclear precursors.

The biological activity of structural analogues of clinically approved platinum complexes has been focus of scientific attention in the recent decades. A further synthesis of complex antimicrobial compounds used in combination with other agents may help to build up a rich bank of substances with a great antimicrobial potential. In the long term, further studies of their antimicrobial action and the way it changes under various factors will make it possible to promptly overcome local or global outbreaks of infectious diseases, such as the current pandemic.

CONTRIBUTION

Authors are equally related to the writing of the manuscript and are equally responsible for plagiarism.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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