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Review article

A COMPLEX BUT BENEFICIAL RELATIONSHIP BETWEEN PLATINUM COMPOUNDS AND ORGANIC DRUGS – A MINI-REVIEW ON THE ANTIMICROBIAL PERSPECTIVE

Nedelina Kostadinova[1], Valentina Belcheva[2], Pavlina Teneva[1], Dobrilina Yarkova[3], Krum Kafedjiiski[2]
1)Department of Health Care, Medical College, Trakia University - Stara Zagora, Bulgaria.
2)Department of Pharmaceutical Sciences, Medical College, Trakia University - Stara Zagora, Bulgaria.
3)Faculty of Medicine, Trakia University - Stara Zagora, Bulgaria.

ABSTRACT

Nowadays, a high number of diseases are connected to bacterial or viral infections. The treatment of the patients is getting more and more difficult, the reason being the smart strategies that microbes facilitate to escape the antibiotics' influence.

Purpose: This review presents a literature investigation conducted in 2025 regarding platinum as a source for developing metalloantibiotics and antibacterial agents.

Material/Methods: A study on scientific publications was done in different databases, using the necessary search terms in the scientific literature.

Results and discussion: We focus on the various mechanisms that could be used with the participation of platinum complexes and nanoparticles in order to affect the development of bacterial biofilms and the spread of infections. We discuss the beneficial combinations of platinum compounds with other drugs or metals that reveal a synergistic effect in the fight against microbial growth.

The **conclusion** is that the use of platinum complexes and antimicrobial drugs is getting a deeper perspective for developing new combination treatments as well as new metallodrugs that are potent and could have more effective application against antimicrobial resistance and for the treatment of various infections.

Keywords: platinum complexes, metallodrugs, antimicrobial activity, antimicrobial resistance

INTRODUCTION

In modern times, the problem of antibiotic resistance in bacteria has acquired global proportions. In their evolution, bacterial species have developed diverse and clever strategies to overcome the effects of antibiotics, and this nowadays creates enormous difficulty in treating many infections, which also leads to numerous victims. A lot of metals like copper, silver, zinc, iron, etc., have shown the ability to fight or inhibit the growth of bacteria [1]. Platinum compounds have also been investigated as a potential approach to fight against antibiotic resistance. Furthermore, there is some serious evidence in this regard, which makes it a valuable potential partner for traditional antibiotics. This combination aims to synergize the effect of the two compounds, thus achieving a stronger antimicrobial effect and overcoming the resistance mechanisms of bacterial species [2]. The aim of this mini-review was to summarize the effects and the possible combinations of platinum (in the form of metallic nanoparticles or coordination complexes) used for the design and development of perspective and more effective metallodrugs against microbes and the problem with antimicrobial resistance.

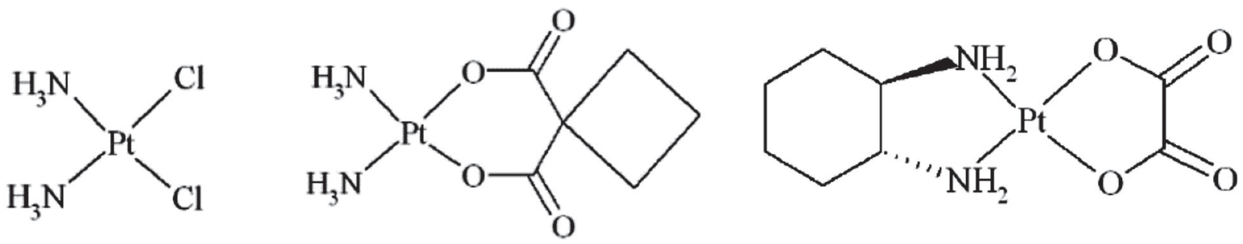
MATERIALS AND METHODS

For the purpose of this review, a study on scientific publications was done in the databases PubMed and Google Scholar. The terms used to search the literature were: "platinum complexes", "metallodrugs", "antimicrobial activity", "antimicrobial resistance". The literature search was conducted in 2025. To ensure comprehensiveness, the selection process was carried out based on different types of literature - full-text original research articles and reviews.

RESULTS AND DISCUSSION

The nature of a metal complex is a well-defined arrangement of ligands (organic and/or inorganic) around one or more metal centers. These complexes can be manipulated similarly to the compounds that are used in conventional drug development. Herein comes the possible role of these complexes as a novel type of antimicrobials called metalloantibiotics - the new agents in action [3, 4, 5, 6].

Fig. 1. Platinum complexes used as anticancer drugs.



Cisplatin carboplatin oxaliplatin

Mechanism of action of platinum compounds

Following a series of scientific investigation, it has now become obvious that metal complexes have the potential to become the next generation of antimicrobials. Therefore, it is crucial to understand how they are able to manifest their antibacterial effects.

• DNA attack. One of the most effective ways for a compound to fight bacterial species is by attacking the DNA replication and transcription processes, leading to cell death. Platinum compounds, especially those used in chemotherapy, have already proven to form covalent bonds with bacterial DNA, which leads to severe damage, thus demonstrating the perspective antimicrobial effect. This was discovered for Cisplatin (cis-diamminedichlorido-platinum II), once known to inhibit the growth of *Escherichia coli,* and further on was rediscovered for the antineoplastic and cytotoxic influence on cancer cells [7] (fig. 1). Another interesting study was conducted by Hummell and Kirienko [8] aiming to repurpose bioactive compounds for treating multidrug-resistant pathogens. They discovered that the used platinum complexes (carboplatin, which is a drug used in the chemotherapy of various cancers, and oxaliplatin – a medication usually used to manage colorectal cancer) displayed increased antimicrobial activity against *P. aeruginosa*.

• Combination with antibiotics. When combined with antibiotics that have other mechanisms of action (for instance, inhibition of cell wall synthesis or protein synthesis), a stronger impact is achieved on the bacterial cell. This synergy makes the platinum-antibiotic combination more effective than the use of either compound alone. For example, Lacerda et al. [9] tested platinum complexes as antibacterial agents against three strains of *Campylobacter jejuni*. The investigation demonstrates that the effect of platinum complex I on bacterial viability is achieved by the ligand's destructive cellular mechanisms coupled with the metal's attack on cellular processes. The effect is mainly directed towards destabilizing the bacterial outer membrane through interaction with electronegative chemical groups - this leads to increased permeability and disruption of internal processes, allowing greater effect and antibiotic activity [10].

• Most antimicrobial metal compounds are being triggered by bacteria-internal stimuli, however, some classes of them can also be switched on by external triggers such as light in photodynamic therapy [11]. Maldonado-Carmona et. al. [12] also describe the trends in photosensitizers' structure and delivery systems in photodynamic disinfection of Gram-negative bacteria.

• Formation of reactive oxygen species. There are some studies where model pathogens, *Escherichia coli* and *Aeromonas hydrophila*, were subjected to treatment with platinum nanoparticles (PtNPs). Colony count assay established that the PtNPs have a dose-dependent inhibition on bacterial proliferation and completely rescued the model animal from infection. According to the authors, the mechanism of antibacterial action is due to the impact on membrane integrity and the generation of reactive oxygen species, which are well known for their oxidative stress effects and mass structural destruction of the living cells [13].

• A combination of platinum nanoparticles with other metals. Interestingly, in the investigation of Ranpariya B, et al. [2], the tested AgPtNPs exhibited higher antibiofilm activity in comparison to individual AgNPs or PtNPs. Various reports showed that Ag nanocomposites (64 ìg/mL) and cationic amphiphile could penetrate into the biofilms and destroy them. All the more, AgNPs were reported to penetrate and disperse into biofilm matrixes and then deliver Ag+ flux to the bacterial wall to eliminate the biofilms [14]. The results of Ranpariya B, et. al. [2] showed that Gram-positive bacteria were more resistant to the complex NPs of Ag and Pt compared to Gram-negative bacteria. The difference in antimicrobial and antibiofilm activity between Gram-positive and Gram-negative species is often explained by the difference in the cell wall structures [15]. According to the authors, the strong antimicrobial and antibiofilm action in the results is due to the synergy between phytogenic hybrid nanoparticles composed of elemental silver and platinum, and could be useful for creating of new nanomedicine for healing bacterial infections.

In recent years, the development of phyto-assisted metallic nanoparticles and their combinations with commercial antibiotics are getting more attention due to their potential for antimicrobial, cytotoxic, and wound healing activities [16].

Benefits of Platinum in Combination

Synergistic effect: Platinum nanoparticles and antibiotics enhance each other's effects, resulting in lower doses required and a reduced risk of side effects. An interesting investigation was done by Nishanthi R, et al. [17]. They synthesized AgNPs, AuNPs, and PtNPs using the aqueous rind extract of *Garcinia mangostana* as a reducing agent. Later on, these nanoparticles were combined with different antibiotics: penicillin G, gentamycin, methicillin, streptomycin, azithromycin, vancomycin, clotrimoxazole, and ciprofloxacin, and then tested against famous pathogens: *Bacillus* sp. and *Staphylococcus* sp. (gram-positive) and *Klebsiella* sp. and *Pseudomonas* sp. (gram-negative). The surprising results were that antibiotics that were before ineffective when used alone in inhibiting bacterial growth, now demonstrated significantly enhanced antimicrobial action when combined with metal nanoparticles. Amongst the metal nanoparticles, gold nanoparticles showed a 100% increase in antibacterial activity, at the same time silver and platinum nanoparticles demonstrated increases of 87.5% and 37.5%, respectively.

Overcoming resistance: Some platinum compounds can disrupt the defense mechanisms of resistant bacteria, making them more susceptible to antibiotics. Evidence of this were again demonstrated in the research of Nishanthi R, et al. [17] for the combination of streptomycin with the three NPs, which showed the most potent synergistic effect when used against streptomycin-resistant *Bacillus* sp.

Anti-biofilm development action: Platinum-based materials can inhibit the formation of bacterial biofilms, which are an important factor in chronic infections and antibiotic resistance. A lot of bacterial species can organize into a biofilm by building a protective extracellular matrix, limiting the efficacy of the host immune system and antibiotic therapies to kill the bacteria [18]. Thus, biofilm formation often results in persistent infections and treatment failure [19].

A major clinical problem nowadays is the biofilm formation on orthopedic implants. In a lot of cases, this leads to periprosthetic joint infection and unsuccessful treatment. In the study of van Hoogstraten SWG, et al. [20], statistically significant antibacterial effects were found for the Ag as a positive control, the Pt–Cu coating against *S. aureus*, and for Ag against *E. coli*. This research has shown the potential of Pt-based coatings, but of course, the coating composition must be further characterized to create a more stable antibacterial coating beneficial for high-loaded implant surfaces.

It is worth mentioning that there still are some challenges with the effective application of platinum-based drugs. These challenges could be connected to reduced drug uptake, increased efflux, and apoptosis pathway inactivation. Zhou XH, et al. [21] managed to develop two prodrugs, Pt-DHA and Pt-BisDHA, that have dual capability preferential accumulation in chemo resistant cancer cells and ferroptosis activation – and that enables Pt-DHA to reverse platinum resistance *in vitro* and *in vivo* effectively. It is obvious that overcoming platinum resistance should be of great importance from a developmental point of view. A significant weakness in the development of phyto-nanoantibiotics include limited *in vivo* investigations, not enough long-term cytotoxicity data, and the absence of standardized synthesis protocols that address the stability, reproducibility, and scalability of such compounds, complicating their clinical trial development [16].

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, it is clear that the problem with antimicrobial resistance cannot be solved solely by the development of new antibiotics. Antibiotics themselves have a lot of challenges to overcome because of their overuse or improper use in clinical facilities or misuse by the patients themselves. Platinum shows promising properties for constructing metallodrugs, but that helpful application of such therapeutic agents is still not explored enough. Taken together, the above-mentioned findings strongly support the urgent need to investigate new pathways of manipulating antimicrobial drugs and platinum (in the form of nanoparticles or coordination complexes) together in order to create effective and more potent antimicrobial compounds.

Overall, there is an inspiring perspective for the development of metal-based antimicrobial agents where the metals are in the form of nanoparticles or coordinated ions. However, communities and countries as a whole should place greater emphasis on these scientific developments so that this research area can progress further in the interest of human health. There should be joint efforts among developers, researchers, clinicians, industry specialists, and regulatory organizations in order to unravel the potential of greener novel antibiotics for multifunctional therapies, overcoming setbacks and liabilities in the development process, and later on in the preclinical phases, clinical trials, commercialization of the new products.

Author contributions:

Developing a concept: Nedelina Kostadinova, collecting data: Nedelina Kostadinova, Krum Kafedjiiski, Valentina Belcheva; writing: Nedelina Kostadinova, Krum Kafedjiiski; data curation: Pavlina Teneva, Dobrilina Yarkova. Final editing of the manuscript: Nedelina Kostadinova.

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Address for correspondence:
Assoc. Prof. Nedelina Kostadinova, Ph.D.
Department of Health care, Medical college at Trakia University-Stara Zagora;
9, Armeiska Str., Stara Zagora, Bulgaria.
E-mail: nedelina.kostadinova@trakia-uni.bg,