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Metal Coordination Complexes in Antimicrobial Therapy: Advances Against Drug-Resistant Pathogens

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ABSTRACT

The rapid emergence and global dissemination of antimicrobial-resistant (AMR) pathogens have become one of the most serious public health challenges of the twenty-first century. The excessive use and misuse of antibiotics in human medicine, veterinary practice, and agriculture have accelerated the evolution of multidrug-resistant bacteria, fungi, and other pathogenic microorganisms, reducing the effectiveness of conventional antimicrobial therapies. Consequently, the development of novel antimicrobial agents with unique mechanisms of action has become an urgent research priority. Metal coordination complexes have emerged as promising therapeutic candidates because of their structural diversity, tunable physicochemical properties, and ability to interact with multiple microbial targets simultaneously. Coordination compounds containing silver, copper, zinc, cobalt, ruthenium, iron, nickel, and gold exhibit broad-spectrum antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria, fungi, and drug-resistant pathogens. Their antimicrobial mechanisms include disruption of microbial cell membranes, DNA binding, enzyme inhibition, reactive oxygen species generation, interference with protein synthesis, and inhibition of biofilm formation. Recent advances in medicinal inorganic chemistry, ligand engineering, nanotechnology, and targeted drug delivery have further enhanced the therapeutic potential of metal coordination complexes while minimizing toxicity toward host tissues. This review discusses the chemistry of metal coordination complexes, antimicrobial mechanisms, activity against multidrug-resistant pathogens, current biomedical applications, challenges, and future perspectives in combating antimicrobial resistance.

Keywords: *Metal coordination complexes, Antimicrobial therapy, Drug-resistant pathogens, Antimicrobial resistance, Bioinorganic chemistry.*

1. Introduction

Antimicrobial resistance (AMR) has emerged as one of the greatest threats to global health, food security, and sustainable development. The increasing prevalence of multidrug-resistant (MDR) bacteria, extensively drug-resistant (XDR) pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacterales* (CRE), multidrug-resistant *Pseudomonas aeruginosa*, and resistant fungal pathogens has significantly reduced the effectiveness of existing antimicrobial drugs. The widespread misuse and overuse of antibiotics in clinical medicine, livestock production, and agriculture have accelerated microbial evolution, resulting in pathogens capable of surviving previously effective therapeutic agents. The discovery of new conventional antibiotics has declined considerably over recent decades, while resistance continues to expand globally. Consequently, researchers have focused on alternative antimicrobial strategies capable of overcoming existing resistance mechanisms [1]. Among these approaches, metal coordination complexes have attracted considerable attention because of their broad-spectrum antimicrobial activity, multiple molecular targets, and reduced susceptibility to conventional resistance pathways.

Coordination complexes consist of a central metal ion surrounded by organic or inorganic ligands that donate electron pairs to form stable coordinate covalent bonds. The biological properties of these complexes are determined by the nature of the metal center, ligand structure, oxidation state, coordination geometry, lipophilicity, and overall molecular stability [2]. Unlike traditional antibiotics that frequently target a single biochemical pathway, metal coordination complexes can simultaneously interfere with microbial membranes, DNA, proteins, metabolic enzymes, and oxidative stress pathways. This multitarget mechanism substantially decreases the probability of resistance development [3]. Numerous transition metals including silver, copper, zinc, cobalt, iron, ruthenium, nickel, manganese, gallium, and gold have demonstrated remarkable antimicrobial activity when incorporated into appropriately designed coordination complexes. Recent advances in nanotechnology, computational chemistry, molecular docking, and ligand engineering have further accelerated the development of highly selective metal-based antimicrobial agents with improved pharmacological properties and reduced toxicity.

This review summarizes recent advances in the design, classification, antimicrobial mechanisms, biomedical applications, challenges, and future prospects of metal coordination complexes for combating drug-resistant microbial infections.

2. Fundamentals of Metal Coordination Chemistry in Antimicrobial Therapy

Coordination chemistry involves the formation of complexes in which metal ions are bonded to surrounding ligands through coordinate covalent interactions. These ligands may include nitrogen-containing heterocycles, amino acids, Schiff bases, peptides, phosphines, sulfur-containing compounds, carboxylates, or naturally occurring phytochemicals. The coordination environment determines the stability, electronic properties, redox behavior, solubility, and biological activity of the resulting complex.

Metal ions possess unique chemical properties that distinguish coordination compounds from purely organic antimicrobial agents [4]. Many transition metals can exist in multiple oxidation states, undergo reversible redox reactions, and participate in electron transfer processes essential for antimicrobial activity. Furthermore, coordination complexes exhibit variable molecular geometries that enable selective interactions with diverse biological macromolecules. Ligands also play a critical role in determining biological performance. Appropriate ligand selection enhances membrane permeability, improves stability under physiological conditions, increases microbial selectivity, and reduces toxicity toward mammalian cells. Schiff base ligands, bipyridine derivatives, phenanthrolines, amino acids, peptides, and plant-derived polyphenols have been widely investigated because they enhance antimicrobial potency while providing structural versatility for rational drug design. Compared with conventional antibiotics, coordination complexes often exhibit broader antimicrobial spectra because they attack multiple cellular targets simultaneously.

This multifactorial mechanism reduces the likelihood of resistance development and provides effective activity against numerous multidrug-resistant pathogens.

3. Classification of Metal Coordination Complexes Used in Antimicrobial Therapy

Metal coordination complexes used in antimicrobial research can be classified according to their central metal ions. Silver complexes represent one of the oldest and most extensively investigated antimicrobial agents owing to their potent bactericidal activity and relatively low resistance rates. Silver ions interact with microbial membranes, proteins, respiratory enzymes, and DNA, leading to irreversible cellular damage. Silver coordination compounds have demonstrated excellent activity against MRSA, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and numerous other clinically important pathogens.

Copper coordination complexes have attracted increasing attention because copper participates naturally in biological redox reactions [5]. Copper complexes generate reactive oxygen species through redox cycling, disrupt membrane integrity, inhibit essential enzymes, and damage microbial DNA. Their broad-spectrum activity extends to bacteria, fungi, viruses, and biofilm-associated microorganisms. Zinc coordination complexes exhibit antimicrobial activity primarily through enzyme inhibition, membrane destabilization, and interference with microbial metabolism. Because zinc is an essential trace element with relatively low toxicity to humans, zinc complexes have gained considerable interest for pharmaceutical and biomedical applications. Other transition metal complexes including cobalt, iron, nickel, manganese, ruthenium, gallium, gold, and palladium also demonstrate significant antimicrobial properties. Ruthenium complexes possess favorable pharmacological characteristics, including selective microbial targeting and relatively low toxicity, whereas gold complexes exhibit potent inhibition of thiol-containing enzymes involved in microbial metabolism. Gallium complexes interfere with iron metabolism by mimicking ferric ions, thereby inhibiting bacterial growth and biofilm formation.

Table 1: Major Metal Coordination Complexes Used in Antimicrobial Therapy

Metal Ion	Representative Complexes	Major Antimicrobial Mechanisms	Target Microorganisms
Silver (Ag)	Silver-Schiff base complexes	Membrane disruption, DNA damage	Gram-positive and Gram-negative bacteria
Copper (Cu)	Copper(II) complexes	ROS generation, enzyme inhibition	MDR bacteria and fungi
Zinc (Zn)	Zinc coordination complexes	Enzyme inhibition	Bacteria and fungi
Ruthenium (Ru)	Ruthenium polypyridyl complexes	DNA interaction, oxidative stress	Drug-resistant bacteria
Gold (Au)	Gold phosphine complexes	Thiol enzyme inhibition	Bacteria and fungi
Gallium (Ga)	Gallium coordination complexes	Iron metabolism disruption	Biofilm-forming bacteria

4. Mechanisms of Antimicrobial Action of Metal Coordination Complexes

Metal coordination complexes exhibit antimicrobial activity through multiple complementary mechanisms, making them effective against a wide range of pathogenic microorganisms, including multidrug-resistant bacteria and fungi. Unlike conventional antibiotics that generally target a single cellular process, metal complexes simultaneously interfere with several essential biological pathways, thereby reducing the likelihood of resistance development. One of the primary mechanisms involves disruption of the microbial cell membrane [6]. Many metal complexes interact electrostatically with negatively charged phospholipids present on bacterial cell surfaces, causing increased membrane permeability, leakage of intracellular components, and eventual cell lysis.

Silver and copper complexes are particularly effective in damaging membrane integrity, resulting in rapid bacterial death. Another important mechanism is DNA interaction. Several coordination complexes penetrate microbial cells and bind to DNA through covalent interactions, intercalation, or groove binding. This interaction inhibits DNA replication, transcription, and cell division, ultimately preventing microbial proliferation. Ruthenium, copper, cobalt, and platinum complexes have demonstrated significant DNA-binding affinity, leading to irreversible damage of genetic material. Reactive oxygen species (ROS) generation also plays a critical role in antimicrobial activity [7]. Transition metals such as copper and iron undergo redox cycling that produces hydroxyl radicals, superoxide anions, and hydrogen peroxide.

These reactive species oxidize proteins, lipids, nucleic acids, and cellular membranes, inducing oxidative stress beyond the microorganism's antioxidant defense capacity. Coordination complexes additionally inhibit numerous enzymes involved in microbial metabolism. Gold complexes inhibit thiol-containing enzymes, while gallium complexes interfere with iron-dependent enzymes by mimicking ferric ions. Other complexes inhibit respiratory enzymes, ATP synthesis, protein biosynthesis, and metabolic pathways essential for microbial survival. Biofilm inhibition represents another valuable property of metal coordination complexes. Biofilms protect microorganisms from antibiotics and host immune responses. Several coordination compounds prevent biofilm formation by interfering with bacterial adhesion, quorum sensing, and extracellular polymeric substance production, thereby enhancing antimicrobial efficacy.

Table 2: Major Antimicrobial Mechanisms of Metal Coordination Complexes

Mechanism	Biological Effect
Cell membrane disruption	Leakage of cellular contents and cell death
DNA binding and damage	Inhibition of DNA replication and transcription
Reactive oxygen species generation	Oxidative damage to proteins, lipids, and DNA
Enzyme inhibition	Suppression of essential metabolic pathways
Protein denaturation	Loss of enzyme and structural protein function
Biofilm inhibition	Prevention of microbial attachment and colonization
Iron metabolism disruption	Nutrient deprivation and inhibition of bacterial growth

5. Activity Against Drug-Resistant Pathogens and Biofilms

The increasing prevalence of antimicrobial resistance has intensified research into metal coordination complexes because of their effectiveness against pathogens that no longer respond to conventional antibiotics.

Numerous studies have demonstrated that coordination compounds exhibit potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant *Enterobacterales* (CRE), multidrug-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum β-lactamase-producing bacteria. Silver coordination complexes possess broad-spectrum antimicrobial activity and remain effective against many antibiotic-resistant bacterial strains. Copper complexes similarly demonstrate remarkable activity through oxidative stress induction and membrane disruption. Ruthenium and gallium complexes have shown encouraging results against resistant Gram-negative bacteria, particularly those capable of forming persistent biofilms. Biofilms present a major clinical challenge because microorganisms embedded within these structured communities exhibit resistance to antibiotics, disinfectants, and host immune defenses. Biofilm-associated infections commonly occur on medical implants, urinary catheters, prosthetic joints, heart valves, and chronic wounds [8]. Metal coordination complexes inhibit biofilm formation by disrupting quorum sensing pathways, reducing microbial adhesion, degrading extracellular polymeric substances, and directly killing sessile microbial cells. In addition to antibacterial activity, several coordination compounds exhibit potent antifungal effects against *Candida albicans*, *Candida auris*, *Aspergillus fumigatus*, and other opportunistic fungal pathogens. Their broad-spectrum activity highlights their potential as multifunctional antimicrobial agents capable of addressing mixed microbial infections.

Table 3: Drug-Resistant Pathogens Targeted by Metal Coordination Complexes

Drug-Resistant Pathogen	Representative Metal Complexes	Major Antimicrobial Effect
MRSA	Silver, Copper, Ruthenium	Cell membrane disruption and DNA damage
VRE	Silver, Gold	Enzyme inhibition and oxidative stress
CRE	Gallium, Copper	Iron metabolism disruption
Pseudomonas aeruginosa	Copper, Silver	Biofilm inhibition and ROS generation
Acinetobacter baumannii	Ruthenium, Silver	DNA damage and membrane disruption
Candida albicans	Zinc, Copper, Gold	Cell membrane damage and enzyme inhibition

6. Nanotechnology and Metal Coordination Complex-Based Drug Delivery

Nanotechnology has significantly enhanced the therapeutic potential of metal coordination complexes by improving their stability, bioavailability, target specificity, and controlled release. Conventional antimicrobial drugs often suffer from poor pharmacokinetics, rapid degradation, limited tissue penetration, and systemic toxicity. Nanocarrier systems overcome many of these limitations by protecting coordination complexes during circulation and promoting their selective accumulation at infection sites.

Liposomes, polymeric nanoparticles, dendrimers, silica nanoparticles, lipid nanoparticles, hydrogels, and metal-organic frameworks have been extensively investigated as delivery platforms for antimicrobial metal complexes. These nanocarriers facilitate sustained drug release, improve intracellular uptake, and reduce toxicity toward healthy tissues [9]. Surface modification with antibodies, peptides, polysaccharides, or other targeting molecules further enhances selective delivery to microbial cells and infected tissues [10]. Recent advances have also led to multifunctional nanoplatforms combining antimicrobial therapy with diagnostic imaging, photothermal therapy, photodynamic therapy, and biosensing technologies.

Such integrated systems provide opportunities for simultaneous pathogen detection and treatment while minimizing antimicrobial resistance. Green nanotechnology has further contributed to this field through the synthesis of environmentally friendly metal nanoparticles using plant extracts, microorganisms, and natural polymers. These biologically synthesized nanomaterials often exhibit enhanced antimicrobial activity and improved biocompatibility while reducing the environmental impact associated with conventional chemical synthesis.

7. Challenges and Future Perspectives

The considerable progress, several challenges remain before metal coordination complexes can achieve widespread clinical application. One of the principal concerns is potential toxicity toward mammalian cells, particularly for complexes containing heavy metals. Careful optimization of ligand structure, metal oxidation state, dosage, and delivery systems is essential to maximize antimicrobial activity while minimizing adverse effects. Pharmacokinetic limitations, including poor aqueous solubility, rapid metabolism, limited bioavailability, and nonspecific tissue distribution, also require further investigation. Long-term safety studies, standardized toxicity assessments, and comprehensive clinical evaluations are necessary before routine therapeutic use [11-13].

Future research should focus on rational ligand design, computational drug discovery, artificial intelligence-assisted molecular modeling, and structure–activity relationship studies to identify highly selective coordination compounds with improved pharmacological properties. The combination of metal complexes with conventional antibiotics may provide synergistic effects that reduce drug dosage and delay resistance development. Furthermore, advances in nanotechnology, targeted drug delivery, and personalized medicine are expected to accelerate the clinical translation of metal-based antimicrobial agents.

8. Conclusion

Metal coordination complexes have emerged as highly promising antimicrobial agents capable of addressing the growing global challenge of antimicrobial resistance. Their unique chemical properties, structural diversity, and ability to target multiple microbial pathways distinguish them from conventional antibiotics and reduce the likelihood of resistance development. Through mechanisms including membrane disruption, DNA damage, enzyme inhibition, reactive oxygen species generation, interference with iron metabolism, and inhibition of biofilm formation, these complexes exhibit potent activity against a broad spectrum of Gram-positive bacteria, Gram-negative bacteria, fungi, and multidrug-resistant pathogens. Significant advances in medicinal inorganic chemistry, ligand engineering, nanotechnology, and targeted drug delivery have expanded the therapeutic potential of metal coordination complexes while improving their selectivity and reducing toxicity. Silver, copper, zinc, ruthenium, gallium, gold, cobalt, and other transition metal complexes continue to demonstrate encouraging antimicrobial efficacy in preclinical investigations, highlighting their promise as next-generation metallodrugs. Nanocarrier-based delivery systems and multifunctional antimicrobial platforms further enhance treatment effectiveness by improving stability, controlled drug release, and site-specific targeting. Nevertheless, challenges related to toxicity, pharmacokinetics, long-term safety, and large-scale clinical validation remain important considerations for future development.

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