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Bioactive Transition Metal Complexes: Mechanistic Insights And Applications Against Antibiotic-Resistant Pathogens

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Abstract

The increasing diversity and escalating drug resistance of bacterial pathogens have significantly compromised the efficacy of conventional antimicrobial agents, creating formidable challenges in modern infection control. Transition metal complexes (TMCs) have emerged as promising antimicrobial candidates due to their structural versatility, ability to adopt multiple oxidation states, and capacity to coordinate with a wide range of ligands. These complexes interact with bacterial membranes, disrupt enzymatic processes, induce oxidative stress, and target biomolecules such as DNA and proteins. Metals such as copper, silver, iron, and zinc exhibit enhanced antimicrobial properties when coordinated with stable ligand frameworks. Their propensity to generate reactive oxygen species (ROS) contributes to potent bactericidal activity against multidrug-resistant (MDR) strains. This review explores mechanisms, ligand design, therapeutic potential, applications, and future perspectives of TMCs in combating antibiotic resistance.

Keywords: Metal complexes; Bioactivity; multidrug-resistant; Antibacterial activity

1. Introduction

Antibiotic resistance has intensified globally due to excessive antibiotic use and rapid bacterial adaptation (Frei, 2020). Mechanisms such as enzymatic degradation, efflux pumps, biofilm formation, and horizontal gene transfer accelerate the spread of resistant strains, including MRSA, VRE, ESBL-producing *E. coli*, and carbapenem-resistant *Pseudomonas* (Lemire et al., 2013). The diminishing effectiveness of traditional antibiotics necessitates innovative antimicrobial strategies. Transition metal complexes (TMCs) have gained attention because their mechanisms differ significantly from those of conventional antibiotics, making them less prone to resistance development (Li & Liu, 2021). Their tunable redox properties, diverse geometries, and adaptable ligand systems enable multitarget activity, including membrane disruption, enzyme inhibition, and ROS generation (Chohan et al., 2006). Advances in coordination

chemistry have led to complexes with enhanced stability, solubility, and biological activity (Andrejszki & Erwin, 2021). Ligand engineering enables fine control over pharmacokinetics and facilitates selective interaction with bacterial cells. TMCs often exploit bacterial metal transport systems, allowing efficient intracellular delivery (Zhang & Zhao, 2019).

In recent years, attention has shifted toward exploring the multifaceted antimicrobial pathways offered by TMCs as a viable alternative to conventional antibiotics. Many pathogenic bacteria rely on metal ions as cofactors for essential biochemical processes, creating unique opportunities for metal-based agents to interfere with microbial homeostasis (Foster et al., 2022). By disrupting metalloproteins, inhibiting metalloenzymes, or replacing native metal ions with cytotoxic alternatives, TMCs can trigger metabolic collapse in resistant bacteria. Furthermore, metal complexes can generate localized oxidative stress through controlled ROS production, damaging nucleic acids, membranes, and proteins in a manner that bacteria find difficult to counter (Zhao et al., 2020). The structural versatility of these complexes also allows researchers to design ligands with targeted lipophilicity, charge distribution, and steric properties that enhance membrane permeability and improve cellular uptake.

Importantly, several metal complexes have demonstrated broad-spectrum activity against MDR strains while showing relatively low toxicity to mammalian cells, emphasizing their therapeutic potential (Norden et al., 2021). The synergistic combination of redox activity, ligand modulation, and metal-center reactivity positions TMCs as one of the most promising classes of next-generation antimicrobial agents. Given their unique chemical and biological characteristics, TMCs represent a rapidly expanding frontier in combating antibiotic resistance and addressing the global MDR crisis.

2. Importance of Transition Metal Complexes in Antimicrobial Research

Transition metal ions play fundamental roles in biological redox reactions, enzymatic regulation, and structural stabilization (Frei, 2020). When incorporated into coordination complexes, their antimicrobial potency often surpasses that of the metal ion or ligand alone due to synergistic effects (Chohan et al., 2006). The following features contribute significantly to their antimicrobial effectiveness:

- Variable oxidation states permitting participation in redox-driven antimicrobial pathways (Lemire et al., 2013).
- Flexible coordination environments that enable interactions with DNA, proteins, and membranes (Li & Liu, 2021).
- Tunable lipophilicity and electron density through ligand modification (Andrejszki & Erwin, 2021).
- Multimodal antibacterial activity that reduces the likelihood of resistance development (Frei, 2020).

These features make TMCs valuable candidates in the search for next-generation antimicrobial agents.

3. Mechanisms of Antibacterial Action of Transition Metal Complexes

Metal complexes exhibit multiple antibacterial mechanisms, often acting simultaneously, which contributes to their effectiveness against MDR pathogens.

3.1 Membrane Disruption

Many metal complexes are cationic and lipophilic, facilitating interactions with negatively charged bacterial membranes. This results in membrane destabilization, leakage of cytoplasmic contents, and loss of membrane potential (Lemire et al., 2013).

3.2 DNA Binding and Cleavage

Complexes with aromatic ligands such as phenanthrolines or bipyridines can intercalate into DNA, inhibiting replication and transcription (Li & Liu, 2021). Redox-active metals such as Cu(II) and Fe(III) may cleave DNA through ROS formation (Zhang & Zhao, 2019).

3.3 Enzyme Inhibition

Certain complexes inhibit metalloenzymes involved in essential bacterial functions. For instance, Zn(II) complexes disrupt enzymatic pathways by replacing native metal cofactors (Zhou & Wong, 2022).

3.4 ROS Generation

Copper and iron complexes often produce ROS via redox cycling, leading to oxidative damage of proteins, lipids, and nucleic acids (Frei, 2020).

3.5 Protein Dysfunction

Silver and copper complexes interact with thiol groups in bacterial enzymes, causing protein denaturation and metabolic collapse (Lemire et al., 2013).

Table 1. Mechanisms of Action of Major Transition Metal Complexes

Metal	Mechanism	Targets	Example
Copper	ROS generation	DNA, enzymes	Cu(II)-Schiff base
Silver	Protein denaturation	Thiol proteins	Ag(I)-NHC
Iron	Fenton reaction	DNA, oxidative pathways	Fe(III)-phenanthroline
Zinc	Enzyme inhibition	Metalloenzymes	Zn(II)-imidazole

4. Transition Metal Complexes as Antibacterial Agents

4.1 Copper Complexes

Cu(II) complexes show significant antibacterial activity due to their redox cycling and ability to generate ROS (Chohan et al., 2006). Schiff base ligands enhance activity by increasing lipophilicity and membrane permeability.

4.2 Silver Complexes

Ag(I) complexes demonstrate broad-spectrum antibacterial properties. Their affinity for thiol-containing proteins allows effective inhibition of bacterial enzymes (Nunes et al., 2020).

4.3 Iron Complexes

Fe(II)/Fe(III) complexes utilize bacterial iron acquisition systems for selective uptake, inducing oxidative stress via Fenton-type reactions (Zhang & Zhao, 2019).

4.4 Zinc Complexes

Zn(II) complexes disrupt bacterial metalloenzymes and maintain lower toxicity toward mammalian cells (Zhou & Wong, 2022).

4.5 Cobalt and Nickel Complexes

These complexes often engage in DNA binding and redox interactions, exhibiting potent antibacterial effects depending on ligand design (Andrejszki & Erwin, 2021).

Table 2. Antibacterial Activities of Selected Metal Complexes

Complex	Ligand Type	Target Bacteria	Mechanism
Cu(II)-Schiff base	Schiff base	*E. coli, S. aureus*	ROS, membrane disruption
Ag(I)-NHC	NHC	*P. aeruginosa*	Protein denaturation
Fe(III)-phenanthroline	N-donor	*K. pneumoniae*	Oxidative stress
Zn(II)-imidazole	N-donor	*B. subtilis*	Enzyme inhibition

5. Ligand Design in Metal-Based Antibacterial Agents

Designing ligands to control the biological behavior of metal complexes is central to developing effective antimicrobial agents. Ligand properties such as lipophilicity, denticity, aromaticity, and electron-donating strength influence complex stability, redox behavior, and membrane permeability (Frei, 2020). Chelating ligands form stable metal–ligand rings that resist dissociation under physiological conditions (Chohan et al., 2006). Aromatic heterocycles like phenanthrolines enhance DNA-binding ability through intercalation (Li & Liu, 2021). Macrocyclic ligands provide exceptional stability and can be functionalized for pathogen-specific targeting (Andrejszki & Erwin, 2021). Modern ligand engineering incorporates bioactive fragments to create hybrid complexes with synergistic antimicrobial effects.

6. Applications and Therapeutic Potential

Transition metal complexes demonstrate broad applicability across clinical, biomedical, and industrial domains. They exhibit strong activity against MDR strains, including biofilm-forming pathogens that are difficult to eradicate using conventional antibiotics (Lemire et al., 2013). Their potential use in medical device coatings, wound dressings, and drug delivery systems highlights their relevance in infection prevention (Nunes et al., 2020). Metal complexes can synergize with classical antibiotics, enhancing their efficacy against resistant pathogens (Frei, 2020). Nanocarrier-based delivery platforms including

liposomes, polymeric nanoparticles, and MOFs further improve selectivity and reduce toxicity (Zhang & Zhao, 2019).

7. Challenges and Future Perspectives

Despite promising results, several barriers hinder the clinical translation of metal complexes. Potential toxicity, limited in vivo stability, and incomplete mechanistic understanding require further investigation (Li & Liu, 2021). Advances in spectroscopic and computational tools will improve mechanistic insights and enable rational drug design. Future work should focus on engineering complexes with enhanced biocompatibility, pathogen-selective activation, and improved pharmacokinetics (Andrejszki & Erwin, 2021). Development of advanced nanocarriers may provide safe and targeted delivery systems, expanding the therapeutic potential of metal-based antibacterial agents.

8. Conclusion

Transition metal complexes represent a promising class of antibacterial agents capable of addressing the growing challenge of MDR bacterial infections. Their multitargeted mechanisms, redox activity, and ligand tunability distinguish them from conventional antibiotics. Continued interdisciplinary research in ligand design, nanotechnology, and mechanistic studies will be crucial for their successful clinical development. Moreover, the ability of metal complexes to bypass traditional resistance pathways such as efflux pumps, target site modification, and enzymatic degradation gives them a significant therapeutic advantage. Their capacity to interfere with essential bacterial processes, including DNA replication, membrane integrity, protein folding, and metal-ion homeostasis, highlights their versatility as antimicrobial agents. Integrating metal complexes with nanocarrier systems or hybridizing them with existing antibiotics may enhance drug delivery, reduce systemic toxicity, and combat resistance through synergistic action. Developing standardized biological assays and understanding long-term environmental impacts will also be essential for responsible therapeutic deployment. Overall, transition metal complexes hold immense potential as next-generation antimicrobial candidates. With sustained research efforts and strategic innovations, they may play a transformative role in global strategies designed to combat antibiotic resistance and restore the effectiveness of antibacterial therapy.

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