International Journal of Chemistry, Mathematics and Physics (IJCMP)
[Vol-9, Issue-4, Oct-Dec, 2025]
https://dx.doi.org/10.22161/ijcmp.9.4.1
ISSN: 2456-866X

Theoretical Assessment of Metal–Drug Complexes for Enhanced Antimicrobial Activity: Mechanisms and Conceptual Frameworks

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Received: 29 Aug 2025; Received in revised form: 26 Sep 2025; Accepted: 01 Oct 2025; Available online: 06 Oct 2025

Abstract— *The need for innovative approaches in drug development is underscored by the increasing compromise in the efficacy of conventional antimicrobial agents due to the increased rise of resistance. Metal-drug complexes (MDCs), created by coordinating medicinal molecules with transition metals such as iron, copper, zinc, and silver, are a promising way to increasing antibacterial activity via several mechanisms. This paper presents a theoretical assessment of the impact of metal coordination on pharmacological behavior, based on coordination chemistry concepts and bioinorganic frameworks. It focuses on variations in solubility, stability, membrane permeability, and target affinity. Mechanistic pathways encompass the regulation of drug pharmacokinetics via enhanced metabolic stability and controlled release, the promotion of charge transfer that improves interaction with microbial membranes, and the inhibition of enzymes through competitive chelation of essential metal cofactors. Computational approaches such as density functional theory (DFT), ligand field theory, molecular docking, and thermodynamic simulations are highlighted for their importance in predicting the structural, electrical, and binding properties of MDCs. These methodologies allow for a structured design approach by simulating interactions between microbial targets and metal ions in physiological situations, leading the development of selective and effective antibacterial treatments. Chelation by endogenous competitors is reversible, supporting microbial specificity. Theoretical models indicate that MDCs may function as slow-release formulations and exhibit broad-spectrum antimicrobial activity, especially against resistant strains that contain distinct metalloenzyme cofactors. This conceptual framework provides a foundation for the expeditious experimental validation and targeted drug development in antimicrobial research, positing metal coordination chemistry as a versatile platform to circumvent the shortcomings of conventional antibiotics in addressing antimicrobial resistance. The synergistic application of mechanistic understanding and computational design provides an enormous avenue for the discovery of novel metallo-antimicrobials with improvements in therapeutic properties.*

Keywords— ***Metal–drug complexes, Antimicrobial mechanisms, Transition metals, Chelation, Enzyme inhibition***

I. INTRODUCTION

The swift emergence and proliferation of AMR studies jeopardize current therapeutics and exacerbate the global burden of infectious diseases, rendering this issue a significant global health concern. Because of this, advanced microbial defenses are a big problem for traditional antimicrobial agents. This means that new drugs and new ways to avoid resistance pathways are needed. One of the important approaches that has recently gained attention is the coordination of metal ions with pharmaceutical agents to create MDCs. These kinds of complexes had better antimicrobial effects because of different bioinorganic chemistry-based ways. These kinds of complexes take advantage of metals' unique chemical and biological properties, such as their different oxidation

states, coordination geometries, redox activity, and catalytic ability, to make drugs work better, be more specific, and have a better overall pharmacodynamic profile [1, 2, 3]. Thus, metallo-drugs comprising an extremely diverse class of metal-containing compounds have an equally significant medical history. Generally described to be agents with anticancer effects, platinum-based compounds obtain such name due to possessing platinum and therefore are cytotoxic agents considered useful in chemotherapy for tumors via DNA crosslinking. Transition metals are being used as agents in disrupting microbial integrity and biochemical pathways in addition to their accepted use in oncology. Some studies claim that they can be used instead of or along with antibiotics that are already available. The fundamental principle is that coordination chemistry alters the essential physicochemical characteristics of the parent drugs, including lipophilicity, solubility, redox properties, and their interactions with microbial membranes and enzymes. Changes can make them better at getting through membranes, sticking to targets, and staying stable in the body [4, 5, 6, 7, 8, 9]. The creation of MDCs is essentially a use of metal–ligand coordination. Transition metals interact or coordinate with donor atoms from pharmaceutical ligands like nitrogen, oxygen, and sulfur. This leads to the formation of stable chelates or coordination compounds. The drug complexation process can change the way molecules are arranged and how electrons are distributed in the original drug, which can change how it works in the body and how specific it is. Theoretical frameworks, such as ligand field theory and frontier molecular orbital concepts, offer computational approaches to anticipate the effects of changes in the metal coordination environment, ligand geometry, or oxidation states on the electronic characteristics and reactivity of complexes. This type of knowledge is considered fundamental to rational drug design and optimization [10]. Several pathways facilitate the antimicrobial enhancement associated with MDCs. The inhibition of enzymes via chelation represents a vital mechanism; numerous essential microbial enzymes are classified as metalloenzymes, necessitating specific metal ions for their catalytic activity or structural stability, including kinases and transaminases. MDCs possess the ability to compete for metal binding sites, which effectively inhibits enzymatic activity and disrupts essential biochemical processes. Moreover, interactions that involve charge transfer mediated by the metal center could potentially increase binding affinity or allow for movement across charged and polar biological membranes, thus enhancing the intracellular delivery of the drug. Chelated drugs often exhibit enhanced lipophilicity, which is associated with an increased ability to traverse lipid bilayers, consequently improving bioavailability [11, 12, 13]. Moreover, coordination chemistry enables the adjustment of drug pharmacodynamics through mechanisms such as controlled and gradual release, in addition to depot effects. This results in an extended duration of the drug in target tissues and a decrease in the frequency of dosage administration. Metal ions integrated into complexes can directly interact with microbial or viral targets through binding to essential sites or inducing conformational alterations, thus enhancing antimicrobial effectiveness. This approach provides advantages in addressing resistant bacteria dependent on advanced metal homeostasis and enzymatic modifications [3, 7]. Theoretical and computational techniques are essential for enhancing understanding and directing experimental verification. This study employs ligand field theory and DFT to probe the electronic structures and stabilities of the proposed complexes, while molecular docking predicts the binding affinities of MDCs with biological receptors and enzymes, a key step in drug design. Thermodynamic modeling further clarifies the distribution and competition of endogenous metals under physiological conditions, essential for evaluating specificity and efficacy in vivo [10,11]. Since the reactivity of metal complexes influences host toxicity, selecting antimicrobials with minimal harm is critical. Assessing reversibility in chelation-driven mechanisms, particularly the displacement by ions such as Mg(II), is therefore central to predicting biological outcomes. Integrating coordination chemistry, mechanistic bioinorganic models, and computational simulations, this work establishes a theoretical framework for systematically enhancing antimicrobial activity through metal–drug coordination. By consolidating existing literature with these approaches, it provides a conceptual basis for experimental efforts aimed at developing metallo-antimicrobials to combat resistant infections. The selection of transition metals (iron, copper, zinc, silver) alongside classical pharmaceuticals (sulfonamides, tetracyclines) exemplifies a highly pragmatic application of this methodology.

II. THEORETICAL FRAMEWORK

Metal–Ligand Coordination Principles

MDCs arise from the fundamental interactions between metal ions and drug molecules through coordination bonds, typically involving donor atoms such as nitrogen, oxygen, or sulfur from the drug ligands. The processes of chelation and complex formation alter key physicochemical properties of the drug, such as solubility,

chemical stability, and membrane permeability, which together govern pharmacokinetic and pharmacodynamic responses. Chelation enhances lipophilicity, often resulting in improved medication penetration across hydrophobic biological membranes, thus facilitating intracellular delivery. Variations in the oxidation state and coordination geometry of metal ions markedly affect the electronic environment surrounding the drug, thereby altering the complex's interactions with biological targets, including enzymes and ribosomal machinery, as well as its engagement with biological transport systems that facilitate cellular uptake and distribution. Computational frameworks such as ligand field theory and frontier molecular orbital (FMO) analysis help to predict electronic and structural effects, providing mechanistic insight into the reactivity and selectivity profiles of diverse MDCs. These strategies are critical for facilitating rational design by relating changes in the organizing environment to predicted biological activities [14].

Mechanistic Pathways

Enzyme Inhibition by Chelation

A primary mechanism through which MDCs demonstrate antimicrobial effects is via chelation-mediated inhibition of enzymes. Microbial enzymes, including transaminases, kinases, and various metalloenzymes, depend on the presence of bound metal ions to maintain their structural integrity and facilitate catalytic activity. Drug complexes that coordinate with metal ions have the ability to competitively bind to enzymatic metal sites, which in turn inhibits the enzyme activity essential for microbial metabolism and survival. Copper (II) complexes of sulfonamide drugs demonstrate a notable ability to inhibit the biosynthesis of tetrahydrofolic acid, which serves as a crucial cofactor in bacterial metabolism, exhibiting greater efficacy compared to the free drug ligands. This competitive chelation disrupts enzymatic pathways and interrupts essential metal ion homeostasis, a weakness often exploited in bacterial resistance mechanisms [12].

Charge Transfer and Membrane Transport

Metal complexes contribute to improved antimicrobial activity via charge transfer interactions, which increase the drug's ability to interact with the polar or charged elements of biological membranes. These metal complexes, which contain some well-known antibiotics like tetracyclines and ethambutol, are more active in living things than the free drugs. People have said that charge transfer processes that happen with metal ions help microbes stick to surfaces and grow inside cells. This chelation usually makes the complex more lipophilic than the free drug, which makes it easier for the drug to get through the lipid bilayers. This increase in permeation is meant to attack the pathogens inside cells and the processes that move drugs out of cells, which often makes the drug less effective [11].

Modulation of Drug Pharmacodynamics

Some principles of coordination chemistry might be able to change how drugs work by using controlled-release mechanisms or depot effects. When forming MDCs, they may form adducts of sufficient stability to prolong the systemic circulation or the maintenance of the drug in targeted tissues. This slows down the rate at which the complex is excreted, which keeps therapeutic drug levels stable at lower doses or less frequent dosing. The long-doze setting of a drug may also lower the usual toxicity that comes from the drug's peak concentration. Second, the metal center can also directly improve how well drugs bind to microbial or viral targets by changing the shape of the drug so that important functional sites interact with each other in a way that makes it more specific or more likely to bind to the target. This actually makes the antimicrobial spectrum bigger because it changes the way the drug works by changing the target or making it less likely to bind to the drug [5].

III. CONCEPTUAL METHODOLOGY

Computational Simulations

This text endeavors to examine computer simulation methodologies relevant to the design and comprehension of MDCs with enhanced antimicrobial characteristics. So, DFT calculations and ligand field theory together make a very solid quantum chemical method that can guess the molecular structures, electronic properties, and thermodynamic stabilities of possible drug-metal complexes. So, DFT lets you optimize molecular structure and figure out electronic parameters like charge distribution, binding energies, and frontier molecular orbitals (HOMO-LUMO). These factors are essential for establishing reactivity and selectivity profiles in a biological context. Ligand field theory, on the other hand, gives us distance by looking at how the oxidation states and coordination environments of metal ions affect electronic transitions and the stability of complexes. This makes it much easier to predict how biological interactions will work [15]. Even if docking simulations are still just theoretical exercises without any experimental proof, they will still be very useful tools. The in silico binding studies forecast the affinity and orientation of MDCs at target sites, potentially bacterial ribosomes or viral entry proteins, and elucidate potential

binding modes at atomic resolution. Candidate complexes undergo in silico screening to assess their capacity to competitively inhibit enzymatic or receptor functions, resulting in subsequent synthetic and biological evaluations. Thermodynamic modeling enhances this methodology by forecasting the distribution of competing and dominant species under physiological pH conditions, taking into account competitive equilibria with endogenous metal ions like magnesium (Mg^2+). It is crucial to ascertain bioavailability and specificity by identifying the species that are likely to persist as dominant in vivo, thereby affecting antimicrobial activity [16].

Reaction Pathway Mapping

Using computer predictions to map out reaction pathways that show different ways that MDCs can have some antimicrobial effects creates mechanistic paths. These mechanisms may involve competition with metal-dependent enzymes via chelation, charge transfer–mediated adsorption to microbial membranes, or alterations in receptor–ligand binding through metal association. For example, metal binding can block essential enzymatic sites needed for antimicrobial action, while charge transfer interactions may enhance adsorption and translocation across charged microbial membranes, facilitating intracellular drug delivery.

Hypothesis Articulation and Applications

A hypothesis applies to putative mechanistic theoretical implications speculating on the action of metal coordination in antimicrobial drug efficacy. Initially, human speculation states that metal coordination brings about a modification in the pharmacokinetic and pharmacodynamic disposition of the drugs vis-à-vis membrane transport, target-binding affinity, or resistance to metabolic degradation (H1). Transition metals, i.e., Fe, Cu, Zn, or Ag, acting through coordination, enhance the lipophilicity properties of drugs. On applying this principle, lipophilicity would allow drugs to pass through the membranes and enter into the cytoplasm inside. This property also changes the electronic and steric structure of drugs, which makes them interact more strongly with specific targets. In fact, these complexes may not be broken down or metabolized, which would make them more bioavailable a nd extend their therapeutic effects [17]. The alternative hypothesis (H2) suggests that antibacterial action through chelation can be inhibited by competing for endogenous metal ions, such as Mg (II). This method would stop microbes from growing while keeping the host's integrity intact. Endogenous ions inside biological systems can displace exogenous metal complexes by competing for identical binding sites, thereby creating a natural regulatory mechanism for the activity and selectivity of MDCs. Reversibility supports the hypothesis of an antimicrobial effect, aimed specifically at any disruption in microbial metal homeostasis or metal availability in the environment [3]. These proposed hypotheses offer a foundational theoretical framework for the systematic design of contemporary antimicrobial agents characterized by customized pharmacokinetic behaviors and specificity profiles. The first step in making slow-release drug formulations that keep therapeutic levels of the drug in the body for a long time is to stabilize MDCs and then control the release of both the metal and the drug. This means you don't have to take the medicine as often. Metal coordination chemistry also gives us new ways to make broad-spectrum antimicrobial agents that can effectively kill bacteria that are resistant to drugs, especially those that use unique metalloenzyme cofactors or metal-dependent virulence factors to avoid traditional drugs. Modeling research has shown that the effectiveness of MD combinations will always be different. Instead, it will depend on how microbial metal homeostasis activities work with the ions that are already in the body and how they compete with them. In microbial environments, the interaction between metal complexes and native metal ions may affect how drugs are taken up by cells, how they interact with their targets, and how well they work as antimicrobial agents. So, all of these biochemical factors should be taken into account when planning future treatments. This conceptual framework aims to enable accurate antimicrobial therapy based on bioinorganic chemistry, focusing on the creation of novel approaches to address antimicrobial resistance by modifying drug efficacy through metal interactions.

IV. DISCUSSION

From a mechanistic standpoint, this theoretical framework has clarified multiple pathways by which metal–drug coordination chemistry may enhance antimicrobial activity, aiming to stimulate further experimental and clinical investigations. So, metal complexes can change the way drugs look and work in ways that make them better than regular drugs. These advantages include enzyme inhibition through chelation, modified membrane permeability via charge transfer mechanisms, along with the modulation of pharmacokinetics through alterations in drug stability and bioavailability. This study thoroughly investigates the various factors that affect the design of precision antimicrobial drugs. Metal coordination is one of the most important ways that metal complexes that kill bacteria can stop enzymes from working. Bacteria need

metalloenzymes to stay alive. They need certain metal ions to do their jobs or stay in shape. These are kinases, transaminases, along with dehydrogenases that work jointly to make the chain that helps us breathe. The MDC that binds in competitive inhibition at active sites does so by chelating the metal ion cofactors or directly coordinating with amino acid residues. The enzyme stops working and can't do the metabolic steps that cells need to do their jobs. Copper (II) and silver(I) complexes are examples of interference because they bind to important enzymatic metals or protein sites and stop bacterial proteases and disrupt respiratory electron transport. The versatility of metal complexes, particularly their ability to create three-dimensional configurations that align with enzyme active sites, improves selectivity and effectiveness compared to uncoordinated drugs [18]. Moreover, the coordination of metals confers a strategic advantage by interfering with the metal homeostasis in microorganisms. Certain complexes function by displacing essential metal ions, including zinc and magnesium, from the active sites of enzymes or bacterial transport proteins, thereby exploiting weaknesses in metal-dependent bacterial processes. The processes involved in replacement not only hinder enzyme function but also create imbalances in metal ions that negatively affect bacterial survival, thereby increasing the efficacy of antimicrobial agents. The dual mechanism involving direct enzyme binding and metal ion displacement is essential to understanding the low tendency for resistance development in metallo-antimicrobials. This presents a notable contrast to traditional antibiotics, which typically focus on a singular biochemical pathway [19]. A significant pathway involves the alteration of membrane permeability via charge transfer interactions. Complexes formed between metals and drugs demonstrate improved interactions with charged microbial membranes through non-covalent electrostatic and charge-transfer forces, thereby promoting adsorption and aiding in the translocation across lipid bilayers. The process of complexation frequently enhances the lipophilicity of drugs, thereby facilitating their passage across membranes and promoting intracellular accumulation relative to the parent compounds. Nonetheless, these augmented penetrations are essential for intracellular pathogens and the resistance challenges associated with efflux pumps. Some metal complexes can also cause oxidative stress by forming reactive oxygen species (ROS) or changing the membrane potential through electron transfer. This means that oxidative stress is another way that bacteria can be killed [20]. On the other hand, pharmacokinetic benefits are other aspects of metal coordination that change how drugs work. Drugs could have a longer half-life if they form stable metal complexes. This would keep them from breaking down too quickly and being cleared by the kidneys. This would keep the drugs at a therapeutic level for a longer time. Controlled release might lower the amount of medicine needed and the number of times it needs to be given, which would lower systemic toxicity and make it easier for patients to follow their treatment plan. The coordination geometry and electronic properties are also very important because they affect how well the drug works in the body and should therefore lower the risk of side effects. This is because they have a big effect on how drugs are taken up and broken down. Recent progress in this area uses metal–ligand interactions to achieve targeted pharmacological control. This is an example of how chemical and biological sciences can come together through coordination chemistry [10]. The dominant viewpoint maintains that computational techniques are crucial for clarifying intricate mechanisms and decisively guiding the progress of metallodrugs. Density Functional Theory (DFT) and ligand field theory approaches offer essential understanding of electronic structure, stability, and reactivity. As a result, these methods let us guess how changes in the oxidation state of metals, the coordination number, and the ligand environment will affect biological activity. Molecular docking simulations allow for in silico screening of target binding in terms of both affinity and specificity. This makes it easier to do synthetic trial and error by choosing complexes that are more likely to work in the lab. Thermodynamic modeling forecasts species distribution and ligand-exchange equilibria in physiological conditions, yielding essential insights into the stability of complexes along with their competition with endogenous ions like magnesium and zinc. Using these computer programs to study coordination chemistry in a systematic way has made metallo-antimicrobial design a formal scientific field [16]. There are still many problems with using MDCs in real life, even though there are some promising signs. Because metals are reactive and found in all biological systems, it is important to reduce host cytotoxicity and stop the buildup of unwanted metals while still keeping antimicrobial specificity. One effective strategy to achieve this goal may involve the creation of complexes featuring reversible coordination or even controlled release mechanisms activated by microbial microenvironments. Also, understanding how endogenous ions compete with and displace other ions and how metal homeostasis changes among pathogens makes it easier to develop species-selective targeting activities. The enhancements in delivery systems and formulations, including nanoparticle conjugates and prodrug strategies, facilitate the resolution of various pharmacological challenges, thereby augmenting clinical applicability [21].

V. CONCLUSION

The theoretical investigation conducted in the study regarding MDCs positions them as significant contenders in the realm of advanced antimicrobial agents, adept at tackling the escalating global challenge of drug resistance. When coordinated, metals significantly alter the pharmacokinetic and pharmacodynamic properties of conventional drugs concerning membrane permeability, target affinity, and metabolic process stability. These enhancements stem from the distinctive chemical characteristics of transition metals, including their varying oxidation states, coordination geometries, and redox reactivities. These traits make it possible for antimicrobial action to happen in a lot of different ways.

The primary mechanisms identified include enzyme inhibition via chelation, wherein metal complexes vie for the binding of metal ions or residues on enzymes critical to microbial metabolic pathways, thereby obstructing essential biochemical functions. Another way is to change how permeable membranes are by moving charges around. This makes it easier to get drugs into cells and makes them work versus pathogens that are resistant to many drugs. Another mechanism that has been looked at is controlled release through metal complexes. This can make drugs last longer in the body and lower their toxicity by keeping therapeutic levels in the blood with fewer doses. Theoretical and computational chemistry methods, such as DFT, ligand field theory, molecular docking, and thermodynamic modeling, are necessary for the logical design and improvement of these complexes. We can use these methods to make educated guesses about how stable a structure will be, what its electronic properties will be, how strongly it will bind to other molecules, and even how species will balance out in normal conditions. This helps us make our experiments better and speed up the translation process. These results provide important information about how MDCs and naturally occurring metal ions interact with each other, which affects selectivity and efficacy. In prior investigations concerning metals, copper, silver, zinc, and iron demonstrated significant antimicrobial characteristics alongside acceptable safety profiles, positioning them as promising candidates for therapeutic advancement. Enhancements in drug repurposing, combination therapy, and bioconjugation-based targeted drug delivery have significantly augmented the clinical applications of MDCs. This has made it possible to develop more precise antimicrobial therapies that can fight off new ways that bacteria can become resistant. The flexibility of metals' coordination strategies makes them attractive mechanistic tools for broadening antimicrobial options. Still, it is a big task to make sure that these metal-based antimicrobial agents work better in real-life situations. The safety of the host, systemic toxicity, and nonspecific metal accumulation necessitate advanced chemical design and delivery strategies. To fully realize the therapeutic potential of MDCs, more interdisciplinary research that combines inorganic chemistry, microbiology, pharmacology, and nanotechnology is needed. Given all of the above, coordination chemistry is a very comprehensive and adaptable framework for designing antimicrobial agents with better effectiveness, specificity, and pharmacological properties. MDCs have established themselves as potential candidates for effective treatment of infectious diseases through various mechanisms, including enzyme targeting, modulation of membrane interactions, and enhancement of pharmacokinetics. The combination of theoretical, computational, and experimental approaches has created a strong set of tools for finding new drugs that can help with the growing problem of antimicrobial resistance and improve antibacterial outcomes around the world.

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