REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: Revised: Accepted:

Bioactive Metal-Schiff Base Complexes: A Review On Antimicrobial And Anticancer Potential

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ABSTRACT
Metal-Schiff base complexes have emerged as a significant class of compounds in coordination chemistry due to their structural versatility and wide range of biological activities. These complexes, formed by the condensation of primary amines with carbonyl compounds, possess chelating properties that enhance the stability and reactivity of metal ions. In recent years, considerable attention has been focused on their bioactivity, particularly their antimicrobial and anticancer potential. The presence of donor atoms such as nitrogen and oxygen in Schiff bases facilitates strong coordination with metal ions, often resulting in improved pharmacological profiles compared to the free ligands or metal salts alone. This review summarises recent advancements in the synthesis, structural features, and biological evaluation of metal-Schiff base complexes. Emphasis is placed on their mechanism of action against microbial pathogens and cancer cell lines, highlighting their mode of interaction with DNA, proteins, and cellular enzymes. The influence of different metal centres, ligand design, and substitution patterns on bioactivity is also discussed. This work aims to provide a comprehensive overview of metal-Schiff base complexes as promising candidates in drug development and encourages further studies for clinical translation.

Keywords: Schiff base, metal complexes, antimicrobial activity, anticancer activity, bioinorganic chemistry, coordination compounds.

1. INTRODUCTION

Metal-Schiff base complexes are a class of coordination compounds that have gained significant attention recently due to their versatile chemical properties, structural flexibility, and remarkable biological activities. These complexes are formed by the coordination of metal ions (such as Cu^{2+}, Zn^{2+}, Fe^{3+}, and Ni^{2+}) to Schiff base ligands, which are synthesised by the condensation of primary amines with carbonyl compounds (salicylaldehyde, benzaldehyde, etc.). The formation of these metal-ligand complexes enhances the metal's stability, reactivity, and bioavailability, making them effective in various therapeutic applications (Patel *et al.*, 2020).

Overview of Metal-Schiff Base Complexes and Their Bioactivity

The bioactivity of metal-Schiff base complexes is attributed to the strong metal-ligand interaction, which enables these complexes to interact with various biological macromolecules such as DNA, proteins, and enzymes. This interaction results in various biological effects, including antimicrobial, anticancer, anti-inflammatory, and antioxidant activities. The coordination chemistry of metal-Schiff base complexes allows the metal ion to participate in redox reactions, ligand exchange, and coordination with biomolecules, facilitating their ability to modulate biological pathways and promote cellular damage (Ahmad *et al.*, 2021).

One of the most significant aspects of metal-Schiff base complexes is their antimicrobial potential, which has been demonstrated in numerous studies. Cu^{2+}-Schiff base complexes, for example, have shown potent bactericidal activity by disrupting the integrity of bacterial cell walls, inhibiting protein synthesis, and causing DNA damage (Gabriele *et al.*, 2022). Similarly, metal-Schiff base complexes have displayed anticancer properties by intercalating into DNA, inhibiting enzyme activity, and inducing apoptosis in cancer cells (Patil *et al.*, 2021). This wide array of bioactivity positions metal-Schiff base complexes as promising therapeutic agents for various diseases, including infections and cancer.

Importance of Antimicrobial and Anticancer Potential in Drug Design

The growing concern over antimicrobial resistance and the need for more effective anticancer therapies have spurred the development of new metal-based drugs. Metal-Schiff base complexes represent an essential class of compounds that address these challenges. Their ability to combine metal ions with bioactive ligands makes them more effective than traditional small-molecule drugs, as they offer improved selectivity, potency, and stability (Yang *et al.,* 2021).

In antimicrobial drug design, the mechanism of action of metal-Schiff base complexes involves metal ions generating reactive oxygen species (ROS), which cause oxidative stress in bacteria and disrupt their membranes and DNA (Rai *et al.,* 2020). These complexes are particularly promising as antibacterial agents against multidrug-resistant (MDR) pathogens, which have become a significant threat to global health. Moreover, the use of transition metals in Schiff base complexes provides an additional mechanism of action by enhancing the DNA-binding affinity, enabling these compounds to cause strand breaks and cell cycle arrest in cancer cells (Zhang *et al.,* 2022).

In anticancer drug design, metal-Schiff base complexes have been found to target specific biomolecules involved in cancer progression. For example, Cu(II) and Ni(II) Schiff base complexes have shown potent cytotoxicity against various human cancer cell lines, including HeLa (cervical cancer), MCF-7 (breast cancer), and A549 (lung cancer). Their mechanisms of action involve DNA binding, ROS generation, and induction of apoptosis (Patel *et al.,* 2021). Importantly, these complexes can be tailored to enhance selectivity for cancer cells, reducing the toxicity to healthy tissues and improving the therapeutic index of the drug.

The metal-Schiff base interaction plays a crucial role in the design of these targeted therapies. The choice of metal ion and the substitution patterns on the Schiff base ligand can influence the bioactivity of the complex, allowing researchers to optimize the efficacy and selectivity of these complexes for both antimicrobial and anticancer applications (Zhang *et al.,* 2022). Advances in ligand design and the use of novel metal ions continue to improve the overall therapeutic potential of these complexes.

2. SYNTHESIS OF METAL-SCHIFF BASE COMPLEXES

The synthesis of metal-Schiff base complexes involves the careful selection of metal ions and ligand synthesis to create complexes with enhanced biological activity, particularly in the contexts of antimicrobial and anticancer therapies. The coordination between metal ions and Schiff base ligands plays a critical role in the resulting complex's stability, bioavailability, and effectiveness against bacteria and cancer cells.

Metal Selection and Ligand Synthesis for Antimicrobial and Anticancer Applications

The choice of metal ion is critical in determining the biological activity of metal-Schiff base complexes. Transition metal ions such as Cu(II), Fe(III), Zn(II), and Ni(II) are commonly selected due to their ability to form stable complexes with Schiff base ligands, their coordination flexibility, and their bioinorganic properties. These metals, particularly Cu(II) and Fe(III), are well-known for their antimicrobial and anticancer potential due to their ability to generate reactive oxygen species (ROS), which can cause oxidative stress, damage cell membranes, and induce apoptosis (Yang *et al.,* 2021; Patel *et al.,* 2021).

Schiff base ligands, which are derived from the condensation reaction between primary amines (such as ethylenediamine, aniline) and carbonyl compounds (like salicylaldehyde, benzaldehyde), are versatile ligands with a strong tendency to coordinate with metal ions. The Schiff base's C=N bond serves as the main coordinating site for the metal ion, and substituents on the aromatic ring (such as hydroxyl, methoxy, or amino groups) can further influence the bioactivity and selectivity of the complex. For instance, hydroxyl groups in the ligand enhance antimicrobial properties by increasing the metal-ligand interaction with bacterial targets, while amine groups can influence the anticancer properties by improving DNA binding and protein interaction (Gabriele *et al.,* 2022; Zhang *et al.,* 2022).

Optimisation of Reaction Conditions to Enhance Biological Activity

Once the metal ion and ligand have been selected, it is essential to optimize the reaction conditions to ensure the formation of stable and biologically active complexes. The synthesis of metal-Schiff base complexes typically involves reacting the metal salt (such as $CuCl_2$, $FeCl_3$, $NiCl_2$) with the Schiff base ligand in a polar solvent (such as ethanol, acetonitrile, or DMF) under reflux or ambient conditions.

Key factors in optimising the synthesis include:

Metal-to-ligand ratio: The stoichiometry of the metal to the ligand is critical to ensuring the formation of stable complexes. A 1:1 or 1:2 ratio of metal to ligand is usually used, depending on the ligand's chelation capacity (Patil *et al.,* 2021).

Solvent choice: The solvent used during synthesis can impact the solubility of both the metal salt and the Schiff base ligand, as well as the coordination environment of the metal ion. For example, ethanol is commonly used due to its ability to dissolve organic and inorganic components, allowing for optimal complexation.

Reaction temperature and time: The reaction is typically carried out under reflux conditions for several hours to promote the condensation of the ligand and the metHal ion, forming the desired metal-Schiff base complex. Higher temperatures can speed up the reaction but may lead to the degradation of sensitive ligands or the formation of unwanted by-products (Kumar *et al.,* 2022).

pH and solvent polarity: The pH of the reaction medium can influence the coordination environment of the metal ion and the ionisation of functional groups in the Schiff base ligand. An acidic or basic environment is sometimes necessary to facilitate the condensation reaction and ensure the optimal binding between the metal and the ligand.

After the reaction, the metal-Schiff base complex is purified using techniques such as recrystallisation or column chromatography to remove any unreacted metal salts or ligands. The final product is then characterised using techniques like UV-Vis spectroscopy, FTIR spectroscopy, NMR spectroscopy, and X-ray crystallography to confirm the complex's coordination geometry, metal-ligand bonding, and stability (Singh *et al.*, 2021).

Enhancing Biological Activity through Structural Modifications

One of the key strategies for enhancing the biological activity of metal-Schiff base complexes is the modification of the Schiff base ligand. Structural modifications can increase the metal-ligand binding strength, improve lipophilicity, and fine-tune the bioactivity for specific therapeutic targets. For example, the introduction of hydrophobic groups on the ligand can enhance the penetration of the complex into cell membranes, increasing its effectiveness against cancer cells (Patel *et al.*, 2021). On the other hand, hydrophilic groups can improve the solubility of the complexes in aqueous environments, making them more suitable for biological applications (Rai *et al.*, 2020).

By carefully optimising the metal-ligand ratio, reaction conditions, and ligand design, metal-Schiff base complexes can be tailored for enhanced antimicrobial and anticancer activities, increasing their potential for use in drug development.

3. STRUCTURAL CHARACTERISTICS OF METAL-SCHIFF BASE COMPLEXES

The structural characteristics of metal-Schiff base complexes are central to their biological activity, as they determine how the complexes interact with biological targets such as DNA, proteins, and cell membranes. The coordination geometry of the metal ion, along with the metal-ligand interactions, plays a significant role in the stability, bioactivity, and therapeutic potential of these complexes, particularly in the context of antimicrobial and anticancer applications. The following subsections detail the coordination geometry and metal-ligand interactions, as well as the influence of structural modifications on the bioactivity of these complexes.

Coordination Geometry and Metal-Ligand Interactions

The coordination geometry of metal-Schiff base complexes refers to the spatial arrangement of atoms surrounding the central metal ion. This geometry is determined by the electronic configuration of the metal ion, its oxidation state, and the ligand's ability to coordinate with the metal. Standard geometries for metal-Schiff base complexes include octahedral, tetrahedral, and square planar, depending on the nature of the metal ion and the coordination environment (Ahmad *et al.*, 2021).

Octahedral Geometry: This geometry is commonly observed for metal ions like Cu(II), Ni(II), and Fe(III), where the metal ion is coordinated by six donor atoms, including nitrogen and oxygen atoms from the Schiff base ligand. The ligand's donor atoms, particularly the imine nitrogen (C=N) and hydroxyl oxygen, coordinate with the metal, enhancing the complex's stability and reactivity.

Tetrahedral Geometry: Some metal-Schiff base complexes, particularly those involving Zn(II), may exhibit a tetrahedral coordination environment, where four ligand atoms coordinate with the central metal ion. This geometry is associated with higher flexibility and solubility, often improving the bioavailability of the complex (Yang *et al.*, 2021).

Square Planar Geometry: Complexes with square planar coordination are commonly observed with Ni(II) and Cu(II) ions, where the metal ion is coordinated by four donor atoms, forming a flat, planar arrangement. This geometry is beneficial for planar intercalation with DNA in anticancer studies, facilitating strand binding and strand breaks (Patel *et al.*, 2021).

The **metal-ligand interactions** in these complexes are primarily governed by **coordinate bonds**, where the metal ion acts as a Lewis acid and accepts electron pairs from the **ligand's donor atoms**. The **coordination bond strength** is critical for the **stability** and **reactivity** of the complex. The nature of the **ligand** (e.g., **hydroxyl**, **amine**, **carboxyl**) also influences the **metal ion's reactivity**, which can enhance the **antimicrobial** and **anticancer** activities (Kumar *et al.*, 2022).

Influence of Structural Modifications on Bioactivity

The structure-activity relationship (SAR) of metal-Schiff base complexes indicates that structural modifications on the Schiff base ligand significantly enhance biological activity, especially in the context of antimicrobial and anticancer applications. Small changes in the ligand's functional groups and substitution patterns can significantly improve the complex's selectivity, potency, and toxicity profile.

Ligand Substitution: Modifications to the functional groups attached to the Schiff base ligand can significantly affect the metal-ligand interaction and, consequently, the bioactivity of the complex. For example, the incorporation of hydroxyl groups on the aromatic ring enhances the antimicrobial activity by improving the metal-ligand bond and increasing the hydrogen bonding with bacterial targets (Ahmad *et al.*, 2021). Similarly, amine groups can enhance the anticancer activity of the complexes by improving DNA binding and increasing cellular uptake (Patil *et al.*, 2021).

Chelation Effect: The chelation of the metal ion by the Schiff base ligand enhances the stability and solubility of the complex, allowing for improved pharmacokinetics. The bidentate or tridentate coordination of the Schiff base ligand, which involves multiple donor atoms, increases the complex's stability, ensuring better bioavailability (Zhang *et al.*,

2022). The Chelation Effect also reduces the toxicity of metal ions by sequestering them in a stable coordination sphere, limiting their free metal ion concentration in the body.

Electronic Modifications: The introduction of electron-donating or electron-withdrawing groups on the Schiff base ligand can alter the electron density around the metal centre, influencing its oxidation state and redox activity. Electron-donating groups, such as methoxy or hydroxyl groups, may enhance the antioxidant properties of the complex. In contrast, electron-withdrawing groups such as nitro or carbonyl groups can enhance DNA binding affinity, making them more effective for anticancer applications (Kumar *et al.,* 2022).

Hydrophobicity and Lipophilicity: Modifying the ligand's hydrophobicity and lipophilicity can improve the membrane permeability of metal-Schiff base complexes, facilitating drug delivery to cancer cells or bacteria. For example, alkyl chain substitutions can enhance lipophilicity, leading to improved cellular uptake and target specificity (Patil *et al.,* 2021).

Macrocyclic Ligands: The use of macrocyclic Schiff base ligands has been shown to significantly increase the complex's stability and biological activity. Macrocyclic ligands form stable chelate rings around the metal ion, which enhances the stability constant and bioactivity. Metal-Schiff base complexes containing tetraaza macrocyclic ligands, for instance, have been shown to exhibit enhanced anticancer and antimicrobial activities due to their high stability and coordination flexibility (Yang *et al.,* 2021).

The coordination geometry of metal-Schiff base complexes, combined with the metal-ligand interactions, is pivotal in determining the biological activity of these complexes. Structural modifications to the Schiff base ligand can further enhance metal-Schiff base complexes' bioactivity, target specificity, and therapeutic potential for both antimicrobial and anticancer applications. The chelating nature of the ligands and the choice of metal ion are crucial for optimising drug efficacy, bioavailability, and reduced toxicity. This highlights the importance of ligand design and metal selection in developing effective therapeutic agents for various medical applications.

4. ANTIMICROBIAL POTENTIAL OF METAL-SCHIFF BASE COMPLEXES

Metal-Schiff base complexes have gained significant attention for their antimicrobial potential, particularly in the fight against multidrug-resistant (MDR) pathogens. The coordination of metal ions with Schiff base ligands enhances the biological activity of the complexes, making them highly effective against Gram-positive and Gram-negative bacteria. The metal ion plays a crucial role in the mechanisms of action by facilitating the interaction of the complex with bacterial cell walls, DNA, and proteins. The following sections elaborate on the mechanisms of action, in vitro antimicrobial activity, and metal ions' role in enhancing these complexes' antimicrobial efficacy.

Mechanisms of Action: Interaction with Bacterial Cell Walls, DNA, and Proteins

The antimicrobial activity of metal-Schiff base complexes primarily involves interactions with bacterial cell walls, DNA, and proteins, disrupting bacterial growth and death. The metal ion plays a crucial role in these interactions, as it facilitates the formation of reactive oxygen species (ROS), which cause oxidative damage to cellular structures.

Interaction with Bacterial Cell Walls: One of the primary modes of action is the disruption of bacterial cell walls. The metal ion interacts with the phosphates and carboxyl groups in the cell wall components, leading to membrane destabilisation. The lipophilic nature of the metal-Schiff base complex also aids in the penetration of the bacterial membrane, making it easier for the complex to cross the lipid bilayer and inhibit cell function (Ahmad *et al.,* 2021).

DNA Interaction: Metal-Schiff base complexes also intercalate into the DNA of bacteria, causing strand breaks and disrupting the DNA replication process. The metal ions enhance the DNA-binding affinity, promoting the formation of coordination complexes between the metal and the nitrogenous bases of DNA, which leads to structural alterations in the helix. These alterations prevent DNA replication and transcription, leading to bacterial death (Yang *et al.,* 2021).

Protein Inhibition: The metal ion can also interact with bacterial enzymes and proteins, inhibiting their activity. For example, protein synthesis can be disrupted by binding to essential amino acid residues in ribosomes or enzymes that regulate cell division. The ability of metal-Schiff base complexes to chelate essential metal ions in bacterial proteins further amplifies their antimicrobial efficacy (Gabriele *et al.,* 2022).

In Vitro Antimicrobial Activity: Testing Against Gram-Positive and Gram-Negative Bacteria

The antimicrobial activity of metal-Schiff base complexes is typically tested using in vitro assays, such as the agar well diffusion method or broth microdilution method, to determine the minimum inhibitory concentration (MIC). These complexes are tested against a wide range of Gram-positive and Gram-negative bacteria to evaluate their effectiveness.

Testing Against Gram-Positive Bacteria: Metal-Schiff base complexes have shown significant activity against Gram-positive bacteria such as Staphylococcus aureus and Bacillus subtilis. The complexes often exhibit lower MIC values for Gram-positive bacteria due to the thicker peptidoglycan layer in their cell walls, which is more readily affected by the disruption caused by the metal-ligand complex (Patel *et al.,* 2021).

Testing Against Gram-Negative Bacteria: Gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa present more challenging targets due to their outer lipid membrane that acts as a barrier to many drugs. However, metal-Schiff base complexes have still demonstrated significant antimicrobial activity against these bacteria. The metal ions enhance the penetration of the complexes through the lipid bilayer by disrupting the outer membrane, leading to cell death (Zhang *et al.,* 2022).

The MIC values for these complexes are often comparable to those of conventional antibiotics, indicating their potent antimicrobial activity. For example, Cu(II)-Schiff base complexes may exhibit MIC values as low as 10-50 µM against Gram-negative bacteria, making them comparable to antibiotics like ampicillin or gentamicin (Kumar *et al.,* 2022).

Role of Metal Ions (e.g., Cu, Zn, Ni) in Enhancing Antimicrobial Efficacy

The metal ion at the centre of the Schiff base complex plays a key role in determining the antimicrobial efficacy of the complex. The metal ion enhances the binding affinity of the Schiff base ligand to the biomolecular targets in the bacterial cell, facilitating stronger interactions that lead to cell death.

Cu(II): Copper is one of the most commonly used metal ions in Schiff base complexes due to its ability to undergo redox reactions, generating reactive oxygen species (ROS) that induce oxidative stress in bacterial cells. The Cu(II) complexes also exhibit strong DNA-binding affinity, causing strand breaks and inhibiting DNA replication. These features make Cu(II) complexes highly effective against Gram-positive and Gram-negative bacteria (Yang *et al.,* 2021).

Zn(II): Zinc ions are less redox-active compared to copper but still play an important role in the antimicrobial efficacy of Schiff base complexes. Zn(II)-Schiff base complexes have shown strong antibacterial activity due to their ability to disrupt bacterial enzymes and proteins. Zinc plays a crucial role in stabilising many enzyme structures, and its disruption by Schiff base complexes impairs bacterial growth (Patil *et al.,* 2021).

Ni(II): Nickel is also an important metal ion in antimicrobial Schiff base complexes. Ni(II)-Schiff base complexes exhibit good activity against bacterial strains due to their ability to interact with bacterial DNA and inhibit protein function. The stability and lipophilicity of Ni(II) complexes also help enhance their penetration into bacterial cells (Kumar *et al.,* 2022).

Metal-Schiff base complexes exhibit remarkable antimicrobial activity through multiple mechanisms, including disruption of bacterial cell walls, DNA binding, and protein inhibition. The metal ion plays a pivotal role in enhancing the bioactivity of these complexes by facilitating reactive oxygen species (ROS) generation and promoting strong interactions with bacterial targets. These complexes are highly effective against both Gram-positive and Gram-negative bacteria, with Cu(II), Zn(II), and Ni(II) ions proving to be the most effective in enhancing antimicrobial efficacy. The ability to tailor the ligand structure and metal coordination in Schiff base complexes offers the potential for developing novel antimicrobial agents to combat drug-resistant pathogens.

5. ANTICANCER POTENTIAL OF METAL-SCHIFF BASE COMPLEXES

The anticancer potential of metal-Schiff base complexes is a subject of intense research, as these complexes offer significant promise for targeted cancer therapy due to their ability to interact with DNA, induce apoptosis, and arrest the cell cycle in cancer cells. The metal ion plays a pivotal role in facilitating these anticancer mechanisms, enhancing the biological activity of the Schiff base ligands. In this section, we will explore the mechanisms of anticancer action, in vitro and in vivo anticancer activity, and the effectiveness of metal-Schiff base complexes in targeting specific cancer pathways.

Mechanisms of Anticancer Action: DNA Binding, Apoptosis Induction, and Cell Cycle Arrest

The anticancer activity of metal-Schiff base complexes is largely attributed to their ability to interact with DNA, leading to strand breaks, cell cycle arrest, and induction of apoptosis in cancer cells. The metal ion plays a crucial role in enhancing the DNA-binding affinity of the Schiff base ligand, promoting intercalation and strand scission, which disrupt the integrity of the DNA molecule.

DNA Binding: Metal-Schiff base complexes are known to intercalate into the DNA helix, causing structural distortions that hinder DNA replication and transcription. The metal ion enhances the ligand's binding affinity for the DNA backbone, facilitating the formation of stable metal-DNA complexes. This interaction can result in strand breaks, topological changes, and DNA damage, which are crucial for the cytotoxic effects of these complexes on cancer cells (Patel *et al.,* 2021).

Apoptosis Induction: One of the primary mechanisms through which metal-Schiff base complexes exert anticancer effects is by inducing apoptosis in cancer cells. Apoptosis, or programmed cell death, is vital for eliminating cancerous cells. Metal-Schiff base complexes induce apoptosis by activating intrinsic and extrinsic apoptotic pathways. The metal ion can generate reactive oxygen species (ROS), which cause oxidative stress, leading to mitochondrial dysfunction and the activation of caspases, key enzymes involved in the apoptotic process. This mechanism has been demonstrated in HeLa (cervical cancer), MCF-7 (breast cancer), and A549 (lung cancer) cell lines, where treatment with metal-Schiff base complexes caused DNA fragmentation, caspase activation, and cell death (Ahmad *et al.,* 2021; Zhang *et al.,* 2022).

Cell Cycle Arrest: Metal-Schiff base complexes also induce cell cycle arrest at specific phases, particularly the G2/M phase, which is crucial for cancer cell division. The metal ion enhances the ability of the Schiff base ligand to interact with cell cycle regulatory proteins, leading to disruption of mitotic progression. By arresting the cell cycle, these complexes prevent cancer cells from proliferating, making them ideal candidates for chemotherapy (Gabriele *et al.,* 2022). Studies have shown that Cu(II) and Ni(II) Schiff base complexes effectively arrest cancer cells at the G2/M phase, thereby inhibiting cell division and inducing cytotoxicity.

In Vitro and In Vivo Anticancer Activity: Evaluation on Human Cancer Cell Lines (e.g., HeLa, MCF-7, A549)

The anticancer activity of metal-Schiff base complexes is typically evaluated through in vitro and in vivo assays. In vitro studies on human cancer cell lines provide valuable insights into the cytotoxicity, selectivity, and mechanisms of action of these complexes. In vivo studies on animal models further confirm the therapeutic efficacy and bioavailability of these complexes.

In Vitro Anticancer Activity: HeLa (cervical cancer), MCF-7 (breast cancer), and A549 (lung cancer) cell lines are commonly used to evaluate the anticancer effects of metal-Schiff base complexes. The MTT assay and cell viability tests are commonly employed to determine the IC_{50} values (the concentration required to inhibit 50% of cell growth) of these complexes. Many metal-Schiff base complexes have exhibited IC_{50} values in the micromolar range, indicating their potent cytotoxicity against cancer cells. For example, Cu(II) and Ni(II) complexes showed significant cytotoxicity against MCF-7 and A549 cell lines, with IC_{50} values in the range of 5–20 µM (Yang *et al.*, 2021; Kumar *et al.*, 2022).

In Vivo Anticancer Activity: In vivo studies using animal models, such as mice or rats, are performed to assess the therapeutic efficacy and toxicity of metal-Schiff base complexes. These studies often involve tumor-bearing models where metal-Schiff base complexes are administered to tumor-bearing mice to evaluate tumor regression, pharmacokinetics, and therapeutic index. In one study, Cu(II)-Schiff base complexes demonstrated significant tumor growth inhibition in Xenograft models (Gabriele *et al.*, 2022). The complexes not only reduced tumor volume but also exhibited minimal toxicity to healthy tissues, making them promising candidates for targeted anticancer therapy.

Effectiveness of Metal-Schiff Base Complexes in Targeting Specific Cancer Pathways

The effectiveness of metal-Schiff base complexes in targeting specific cancer pathways lies in their ability to interact with critical molecular targets involved in cancer progression. These targets include DNA, protein kinases, and metabolic enzymes, which regulate essential processes like cell proliferation, survival, and apoptosis.

DNA as a Target: As discussed earlier, DNA binding is a critical mechanism through which metal-Schiff base complexes exert their anticancer activity. The complexes intercalate into the DNA helix, causing strand breaks and disrupting replication, thereby blocking the proliferation of cancer cells. This mechanism is particularly effective in targeting rapidly dividing cells (Zhang *et al.*, 2022).

Protein Kinases and Enzyme Inhibition: Metal-Schiff base complexes have also shown the ability to inhibit key protein kinases involved in cancer cell signaling pathways, such as PI3K/Akt, MAPK, and mTOR. These pathways regulate processes like cell cycle progression, survival, and angiogenesis. By targeting these pathways, metal-Schiff base complexes can block cancer cell proliferation and induce cell death (Yang *et al.*, 2021).

Metabolic Enzymes: Cancer cells often exhibit altered metabolism to support their rapid growth and survival. Metal-Schiff base complexes have been shown to inhibit metabolic enzymes such as glutaminase and lactate dehydrogenase, which are crucial for the Warburg effect in cancer cells. By inhibiting these enzymes, metal-Schiff base complexes can starve cancer cells of the nutrients they need to proliferate (Kumar *et al.*, 2022).

The anticancer potential of metal-Schiff base complexes is profound, with these complexes exhibiting significant cytotoxicity against a range of human cancer cell lines. Their ability to intercalate into DNA, induce apoptosis, and arrest the cell cycle makes them effective candidates for chemotherapeutic agents. The metal ion, particularly Cu(II), Ni(II), and Zn(II), plays a pivotal role in enhancing the DNA-binding affinity, generating reactive oxygen species (ROS), and targeting specific cancer pathways involved in cell proliferation, survival, and apoptosis. These findings highlight the promise of metal-Schiff base complexes as novel anticancer agents and suggest their potential for development into clinically viable therapies.

6. MECHANISMS OF ANTIMICROBIAL AND ANTICANCER ACTIVITIES

The mechanisms underlying the antimicrobial and anticancer activities of metal-Schiff base complexes are multifaceted, involving molecular interactions, cellular uptake, and the generation of reactive species. The metal ion plays a crucial role in enhancing the biological activity of these complexes, promoting interactions with cellular targets, and contributing to oxidative stress through redox reactions. In this section, we discuss the molecular interactions and cellular uptake of metal-Schiff base complexes, the role of oxidative stress and ROS, and the contribution of metal-ion catalysis to both antimicrobial and anticancer effects.

Molecular Interactions and Cellular Uptake of Metal-Schiff Base Complexes

The interaction between metal-Schiff base complexes and biological macromolecules is central to their antimicrobial and anticancer effects. These complexes typically interact with DNA, proteins, and cell membranes, facilitating their bioactivity.

DNA Binding and Intercalation: The metal ion in the metal-Schiff base complex facilitates the DNA binding by enhancing the coordination between the ligand and the DNA molecule. The planar structure of the Schiff base ligand allows for intercalation between DNA base pairs, disrupting DNA replication and transcription. This binding can result in strand breaks, topological changes, and inhibition of polymerases, contributing to cytotoxicity (Patil *et al.*, 2021). The metal ions also facilitate stronger binding to DNA by interacting with the phosphate backbone, increasing the binding affinity.

Protein Interactions: Metal-Schiff base complexes can also bind to proteins, particularly enzymes involved in cellular functions such as cell division and metabolism. The metal ion plays a key role in disrupting the active sites of enzymes like kinases, proteases, and ribosomal proteins, inhibiting their activity and affecting cell survival (Yang *et al.,* 2021). For example, complexes can interact with ribosomal RNA or cytoskeletal proteins, leading to cell death in microbial and cancerous cells.

Cell Membrane Interactions: The lipophilic nature of metal-Schiff base complexes allows them to penetrate cell membranes. Once inside the cell, the metal ion can interact with intracellular targets, such as enzymes and DNA, contributing to the biological activity of the complex. Metal-Schiff base complexes can also disrupt membrane integrity, leading to membrane fluidity changes and permeabilization, ultimately causing cellular damage (Zhang *et al.,* 2022).

Role of Oxidative Stress and Reactive Oxygen Species (ROS) in Both Antimicrobial and Anticancer Effects

One of the major mechanisms behind the antimicrobial and anticancer activity of metal-Schiff base complexes is the generation of reactive oxygen species (ROS). The metal ions, particularly Cu(II) and Fe(III), catalyze redox reactions, leading to the production of ROS such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH\cdot$). These ROS can cause extensive oxidative damage to biomolecules like proteins, lipids, and DNA, resulting in cell death.

Oxidative Stress in Antimicrobial Activity: In bacteria, ROS generated by metal-Schiff base complexes can cause damage to the cell wall, membranes, and DNA, leading to bacterial cell death. The generation of ROS disrupts the redox balance in bacterial cells, which are less equipped to handle oxidative stress compared to mammalian cells. As a result, metal-Schiff base complexes act as effective antibacterial agents, particularly against drug-resistant strains. The Cu(II)-based complexes, for example, have shown strong antimicrobial activity by inducing oxidative stress in bacteria, causing DNA damage and cellular rupture (Ahmad *et al.,* 2021).

Oxidative Stress in Anticancer Activity: In cancer cells, the generation of ROS by metal-Schiff base complexes induces mitochondrial dysfunction, leading to apoptosis. ROS can activate caspase pathways and damage DNA, initiating programmed cell death. The metal ions, particularly Cu(II) and Ni(II), catalyze the production of ROS, which induces oxidative stress, further enhancing anticancer activity (Patel *et al.,* 2021). ROS-mediated DNA damage is a key mechanism in anticancer therapy, as cancer cells are highly proliferative and more vulnerable to genetic instability induced by oxidative damage.

Metal-Ion Catalysis and Redox Reactions: Contribution to the Overall Activity

The ability of metal-Schiff base complexes to catalyze redox reactions is fundamental to their antimicrobial and anticancer activity. The metal ion acts as a redox center, facilitating the transfer of electrons and the generation of ROS.

Redox Reactions in Antimicrobial Activity: The redox-active metal ions in metal-Schiff base complexes play a crucial role in their antimicrobial action by generating ROS and causing oxidative damage to bacterial cells. The metal ions undergo reduction and oxidation cycles, resulting in the production of highly reactive species such as hydroxyl radicals and superoxide anions. These reactive species can cause damage to cellular macromolecules, leading to cell membrane disruption and DNA fragmentation, thus killing the bacteria (Rai *et al.,* 2020).

Redox Reactions in Anticancer Activity: In anticancer therapy, metal-Schiff base complexes leverage redox chemistry to induce DNA damage, protein inhibition, and mitochondrial dysfunction. The metal ions can catalyze the production of ROS, which results in oxidative stress that induces apoptosis in cancer cells. By inducing DNA strand breaks, cell cycle arrest, and protein degradation, the redox-active metal-Schiff base complexes target key cancer pathways, effectively killing tumor cells (Zhang *et al.,* 2022).

The antimicrobial and anticancer activities of metal-Schiff base complexes are primarily driven by their molecular interactions with cellular targets (such as DNA, proteins, and membranes), oxidative stress, and metal-ion catalysis. The generation of ROS through redox reactions is a key mechanism underlying their bioactivity, leading to cell death via oxidative damage, DNA strand breaks, and cell cycle arrest. By understanding these mechanisms, researchers can design metal-Schiff base complexes with enhanced selectivity, potency, and targeting ability for antimicrobial and anticancer therapies. The metal ion, in particular, plays a pivotal role in the bioactivity of these complexes, and the redox properties of the metal significantly contribute to the overall therapeutic efficacy.

7. STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF METAL-SCHIFF BASE COMPLEXES

The Structure-Activity Relationship (SAR) of metal-Schiff base complexes plays a crucial role in understanding the biological efficacy and selectivity of these complexes for antimicrobial and anticancer applications. The SAR of metal-Schiff base complexes focuses on how modifications in the ligand structure and the coordination environment of the metal ion influence their biological activity, including antimicrobial potency, anticancer effects, and overall toxicity. In this section, we explore the influence of ligand modifications, the correlation between metal coordination and biological activity, and design strategies to improve selectivity and reduce toxicity.

Influence of Ligand Modifications on Antimicrobial and Anticancer Potency

The ligand structure in metal-Schiff base complexes plays a significant role in determining the biological activity of the complex. Structural modifications to the Schiff base ligand can enhance the antimicrobial and anticancer properties of

the complex by improving the metal-ligand interaction, binding affinity for biological targets, and solubility of the complex.

Functional Group Substitution: The presence of electron-donating or electron-withdrawing groups on the aromatic ring or amine side chain of the Schiff base ligand can significantly influence its metal binding properties and biological activity. For example, the introduction of hydroxyl or amino groups can improve the metal-ligand chelation, enhancing the DNA binding affinity and cytotoxicity against cancer cells. These modifications can also influence the antibacterial activity, as they can increase the hydrogen bonding capacity with bacterial targets, thereby improving the antimicrobial potency (Patil *et al.,* 2021; Gabriele *et al.,* 2022).

Aromaticity and Planarity: The planar nature of the Schiff base ligand allows for intercalation into the DNA helix, which is essential for the anticancer activity. Ligands that maintain a planar structure increase the interaction with DNA, thereby enhancing the anticancer effects. Additionally, aromatic rings with electron-donating groups, such as methoxy or hydroxyl, can improve the lipophilicity of the complex, aiding its cell membrane penetration and increasing bioavailability (Zhang *et al.,* 2022).

Chelation and Bidentate/Tridentate Coordination: The ability of the Schiff base ligand to form bidentate or tridentate chelate complexes with the metal ion improves the stability and bioactivity of the complex. Bidentate ligands, which coordinate through two donor atoms (such as amine nitrogen and carbonyl oxygen), increase the stability constant and improve selectivity for biological targets. Tridentate ligands, which provide additional coordination sites, further enhance stability, enabling stronger interaction with biomolecular targets, leading to improved cytotoxicity and antimicrobial efficacy (Kumar *et al.,* 2021).

Correlation Between Metal Coordination and Biological Activity

The coordination of the metal ion with the Schiff base ligand directly influences the biological activity of the complex. The coordination geometry and electronic properties of the metal play a crucial role in determining the metal-ligand bond strength, the DNA-binding affinity, and the overall biological efficacy. Different metals exhibit different redox properties and binding strengths, which contribute to the antimicrobial and anticancer activity.

Metal Selection: The choice of metal ion is critical in determining the bioactivity of metal-Schiff base complexes. For instance, Cu(II) and Ni(II) complexes are widely studied due to their redox activity, which facilitates the generation of reactive oxygen species (ROS) that lead to oxidative stress and cell death in both bacteria and cancer cells. Fe(III) and Zn(II) complexes, on the other hand, exhibit a more structural role, stabilizing the Schiff base ligand and promoting DNA binding (Yang *et al.,* 2021; Zhang *et al.,* 2022).

Coordination Geometry: The coordination geometry of the metal-ligand complex also plays an important role in determining the biological activity. Complexes with octahedral or square planar geometries, typically seen with Cu(II) and Ni(II), are more likely to intercalate into DNA and disrupt cellular processes. The metal ion's coordination environment affects its redox potential and ability to generate ROS, which is critical for antimicrobial and anticancer activity (Gabriele *et al.,* 2022).

Metal Ion Redox Properties: The redox-active metals, such as Cu(II) and Fe(III), generate ROS through redox cycling. These reactive species can induce oxidative damage to cellular macromolecules, particularly DNA, leading to strand breaks and cell death. The redox potential of the metal ion influences its biological activity, with Cu(II) and Ni(II) complexes showing stronger anticancer and antimicrobial properties due to their higher oxidative reactivity (Zhang *et al.*, 2022).

Design Strategies for Improving Selectivity and Reducing Toxicity

To enhance the therapeutic potential of metal-Schiff base complexes while reducing their toxicity, several design strategies can be employed:

Targeted Ligand Design: Modifying the Schiff base ligand to improve selectivity for cancer cells or bacterial targets can help reduce toxicity to healthy tissues. Hydrophilic or charged ligands can improve solubility in aqueous environments, while hydrophobic ligands can enhance membrane penetration. Additionally, functional groups that target specific cancer cell surface receptors or bacterial proteins can improve selectivity (Kumar *et al.,* 2022).

Metal Ion Coordination with Biomolecules: The coordination of metal ions to specific biomolecules within the cancer cells or bacteria can further improve selectivity. For example, incorporating targeting groups (such as peptides or antibodies) into the complex can direct the metal-Schiff base complex to specific cellular sites, reducing off-target effects and improving the therapeutic index (Yang *et al.,* 2021).

Optimisation of Metal-Ligand Ratio: The metal-to-ligand ratio in the complex can also be optimized to ensure the formation of stable, bioactive complexes. This optimisation ensures that the complex is effective while maintaining minimal toxicity to healthy cells. Studies have shown that complexes with a 1:2 metal-ligand ratio often exhibit improved stability and bioactivity (Zhang *et al.,* 2022).

Incorporation of Biocompatible Materials: The design of biocompatible delivery systems, such as liposomes or dendrimers, can enhance the bioavailability of metal-Schiff base complexes while protecting them from rapid metabolism and excretion. This approach allows for targeted delivery of the complexes to tumor sites or bacterial infections, reducing systemic toxicity (Patil *et al.,* 2021).

The Structure-Activity Relationship (SAR) of metal-Schiff base complexes plays a crucial role in optimizing their antimicrobial and anticancer activities. Ligand modifications, metal coordination, and redox properties significantly influence the biological efficacy of these complexes. By modifying the ligand structure and metal ion coordination, researchers can enhance selectivity, improve biological potency, and minimize toxicity, leading to more effective therapeutic agents. The ability to tailor these complexes through SAR studies holds significant promise for the development of novel antimicrobial and anticancer therapies.

8. RECENT ADVANCES IN METAL-SCHIFF BASE COMPLEXES FOR DRUG DEVELOPMENT

Recent advancements in the design and application of metal-Schiff base complexes have significantly enhanced their potential as therapeutic agents. These developments focus on improving bioavailability, stability, and target specificity, as well as exploring innovative delivery systems and clinical applications.

Novel Approaches in Design for Enhanced Therapeutic Potential

Ligand Modification: Incorporating electron-donating or electron-withdrawing groups into Schiff base ligands can modulate the electronic properties of the metal center, enhancing DNA binding affinity and increasing cytotoxicity against cancer cells. For instance, introducing hydroxyl groups has been shown to improve solubility and interaction with biological targets.

Macrocyclic Complexes: The development of macrocyclic Schiff base metal complexes offers advantages in terms of stability and selectivity. These complexes can be designed to target specific biomolecules, reducing off-target effects and improving therapeutic outcomes.

Utilization of Nanocarriers and Liposomal Formulations

Liposomal Encapsulation: Encapsulating metal-Schiff base complexes in liposomes enhances their stability and bioavailability. This approach also allows for controlled release and targeted delivery to tumor sites, improving the efficacy of the therapeutic agents.

Stimuli-Responsive Nanocarriers: Designing nanocarriers that respond to specific stimuli, such as pH or enzyme activity, enables the targeted release of metal-Schiff base complexes at disease sites. This strategy minimizes systemic toxicity and maximizes therapeutic effects.

Clinical Trials and Future Perspectives

Ongoing Clinical Studies: Ruthenium-based Schiff base complexes, such as KP1019 and KP1339, are undergoing clinical trials for the treatment of advanced gastrointestinal cancers. These trials aim to evaluate the efficacy and safety of these complexes in cancer therapy.

Emerging Applications: Beyond anticancer and antimicrobial activities, Schiff base metal complexes are being explored for their potential in treating viral infections and neurodegenerative diseases, expanding their therapeutic scope.

9. TOXICITY AND BIOCOMPATIBILITY OF METAL-SCHIFF BASE COMPLEXES

The toxicity and biocompatibility of metal-Schiff base complexes are critical factors that determine their suitability as therapeutic agents, particularly in the contexts of cancer treatment and antimicrobial therapy. While these complexes exhibit potent biological activity, their toxicity to normal tissues must be carefully assessed to ensure therapeutic safety. In this section, we explore the evaluation of acute and chronic toxicity in animal models, the safety profiles of metal-Schiff base complexes in normal versus cancerous tissues, and strategies to minimize side effects and enhance biocompatibility.

Evaluation of Acute and Chronic Toxicity in Animal Models

The toxicity of metal-Schiff base complexes is typically evaluated through acute and chronic toxicity studies conducted in animal models. These studies help assess the safe dosage range, potential adverse effects, and long-term toxicity of the complexes, which are essential for the development of safe and effective therapeutics.

Acute Toxicity: In acute toxicity studies, metal-Schiff base complexes are administered to animals, usually rodents, at high doses to determine the lethal dose (LD_{50}), which is the dose required to cause 50% mortality. These studies typically involve oral, intravenous, or intraperitoneal administration. For example, in studies on Cu(II) and Ni(II) complexes, the complexes were administered to rats or mice, and their behavioral changes, weight loss, and organ toxicity (especially in the liver and kidneys) were observed. Acute toxicity studies provide essential information on the safety window of metal-Schiff base complexes and help determine whether the complex can be further developed for therapeutic use (Kumar *et al.,* 2021).

Chronic Toxicity: Chronic toxicity studies are conducted by administering lower doses of metal-Schiff base complexes over an extended period (typically several weeks to months). These studies assess the long-term effects of the complexes on various organs, such as the liver, kidneys, and heart, to identify potential organ toxicity or cumulative effects. Chronic toxicity studies also evaluate the potential for carcinogenicity or mutagenicity, particularly in the context of anticancer metal-Schiff base complexes. These studies are essential for understanding how prolonged exposure to the complex may affect normal cells (Zhang *et al.,* 2022).

Safety Profiles of Metal-Schiff Base Complexes in Normal versus Cancerous Tissues

One of the most significant advantages of metal-Schiff base complexes is their ability to selectively target cancer cells while minimizing damage to healthy tissues. The biocompatibility of these complexes in normal tissues and their selectivity for cancer cells are crucial for reducing toxicity during treatment.

Selective Targeting of Cancer Cells: Metal-Schiff base complexes are designed to interact preferentially with cancer cells, exploiting the differential properties of cancerous tissues, such as increased membrane permeability, higher metabolic activity, and altered redox status. For instance, Cu(II) and Ni(II) complexes have been shown to exhibit stronger binding affinity for DNA in cancer cells than in normal cells, leading to selective cytotoxicity. Additionally, the oxidative stress induced by the metal ion (such as the generation of reactive oxygen species (ROS)) is often more effective in cancer cells, which are more vulnerable to oxidative damage compared to normal cells (Ahmad *et al.,* 2021).

Biocompatibility in Normal Tissues: Despite the potent anticancer activity, the safety profile of metal-Schiff base complexes in normal tissues must be carefully monitored. Toxicity to healthy cells can occur due to off-target effects, which may result from overaccumulation of the complexes in non-target tissues or insufficient selectivity for cancer cells. In in vivo studies, Cu(II) complexes have shown negligible toxicity in healthy tissues, including the liver and kidney, when administered at therapeutic doses. However, Ni(II) complexes, while effective in anticancer activity, may induce toxicity in the liver and kidneys, requiring careful dose management (Patil *et al.,* 2021).

Strategies to Minimize Side Effects and Enhance Biocompatibility

Several strategies can be employed to reduce the toxicity of metal-Schiff base complexes and enhance their biocompatibility, making them more suitable for clinical applications:

Ligand Modification: One of the most effective strategies for improving the biocompatibility of metal-Schiff base complexes is through ligand modification. By incorporating functional groups that improve selectivity for cancer cells and reduce toxicity to normal tissues, researchers can optimize the therapeutic index. For example, the addition of hydrophilic groups (such as hydroxyl or amino groups) can enhance the solubility of the complexes, improving their bioavailability while reducing the risk of toxic accumulation in non-target tissues (Yang *et al.,* 2021).

Nanocarrier Systems: Encapsulating metal-Schiff base complexes in nanocarriers such as liposomes, dendrimers, or micelles can significantly enhance their selectivity and reduce toxicity to healthy tissues. These nanocarriers can facilitate targeted drug delivery, ensuring that the complex is delivered primarily to tumor sites or infection sites, while minimizing exposure to normal cells. Nanocarriers can also provide controlled release of the drug, reducing the toxicity associated with peak drug concentrations (Gabriele *et al.,* 2022).

Polymer Conjugation: Conjugating metal-Schiff base complexes with biocompatible polymers can enhance the stability and selectivity of these complexes. Polymer conjugation can help shield the metal ion from premature deactivation in the bloodstream, reducing off-target toxicity. Additionally, polymer-drug conjugates can be designed to exploit the enhanced permeability and retention (EPR) effect in tumors, improving drug accumulation at the tumor site while minimizing exposure to normal tissues (Patil *et al.,* 2021).

Targeted Delivery Using Antibodies or Peptides: The use of antibodies or peptides as targeting moieties can enhance the selectivity of metal-Schiff base complexes for cancer cells. By conjugating the complexes with targeting agents that specifically bind to cancer cell receptors or antigens, the complexes can be directed to tumor tissues, thereby reducing systemic toxicity and improving the therapeutic efficacy.

The toxicity and biocompatibility of metal-Schiff base complexes are key factors that determine their success as therapeutic agents. While these complexes exhibit potent antimicrobial and anticancer activities, careful evaluation of their toxicity profiles is essential to ensure safe and effective treatment. Advances in ligand modification, nanocarrier systems, and targeted delivery strategies are crucial for improving the therapeutic index of these complexes, enhancing their selectivity for cancer cells or bacteria, and minimizing side effects on healthy tissues. As the development of metal-Schiff base complexes continues, further research into their toxicity, biocompatibility, and targeting capabilities will be critical for advancing their clinical applications.

10. CHALLENGES IN DEVELOPING METAL-SCHIFF BASE COMPLEXES AS THERAPEUTIC AGENTS

Despite the significant potential of metal-Schiff base complexes as therapeutic agents, their development faces several challenges. These challenges include issues related to metal ion toxicity, bioaccumulation, stability in physiological environments, and the ability to overcome resistance mechanisms in both bacteria and cancer cells. Addressing these challenges is crucial for the successful translation of metal-Schiff base complexes into clinically viable drugs. In this section, we will discuss the limitations associated with metal ion toxicity, the stability concerns of these complexes, and the need to overcome resistance mechanisms in therapeutic settings.

Limitations Related to Metal Ion Toxicity and Bioaccumulation

One of the major challenges in developing metal-Schiff base complexes for therapeutic use is the toxicity of the metal ions at higher concentrations. While the metal ion enhances the bioactivity of the Schiff base complex, it can also lead to toxicity if uncontrolled accumulation occurs in healthy tissues. Certain metal ions, particularly Cu(II), Fe(III), and Ni(II), are known to induce oxidative stress, leading to damage in liver, kidney, and neural tissues, which can limit their use as therapeutic agents (Patil *et al.,* 2021).

Metal Ion Toxicity: In the case of Cu(II) complexes, while these complexes show promising anticancer and antimicrobial properties, excess copper accumulation in cells can lead to cellular damage, as copper ions are known to catalyze the production of reactive oxygen species (ROS). The accumulation of ROS can damage cell membranes, DNA, and proteins, resulting in cell death. Similarly, Fe(III) and Ni(II) complexes, if not properly controlled, can cause toxicity due to their redox properties, leading to metal ion overload and subsequent organ toxicity (Kumar *et al.*, 2022).
Bioaccumulation: Bioaccumulation of metal-Schiff base complexes in tissues can also be a concern, particularly for metals like copper and iron, which are involved in essential biological functions. Prolonged exposure to these complexes might result in bioaccumulation in the liver, kidneys, or brain, potentially causing long-term toxicity. In anticancer therapy, metal ion bioaccumulation can limit the selectivity and efficacy of metal-Schiff base complexes, as they may affect healthy and cancer cells. As a result, the dosage and delivery system of these complexes must be carefully optimised to avoid toxic side effects (Gabriele *et al.*, 2022).

Stability Concerns in Physiological Environments
Another significant challenge for developing metal-Schiff base complexes is their stability in physiological environments, such as blood circulation or extracellular fluid. Metal-Schiff base complexes must retain their structural integrity and biological activity in the presence of physiological ph, temperature, and biological fluids, which can degrade or alter the stability of the complex.
Instability in Biological Fluids: Metal-Schiff base complexes are susceptible to hydrolysis or ligand exchange reactions, especially under conditions found in biological fluids. For example, at physiological ph (7.4), some metal ions may undergo hydrolysis, forming hydroxides that may not have the same bioactivity as the original complex. Additionally, ligand exchange reactions can lead to the loss of the Schiff base ligand, reducing the complex's therapeutic potential (Zhang *et al.*, 2022).
Lack of Solubility: Solubility of the metal-Schiff base complexes in aqueous environments is another critical issue. Poor solubility can affect the bioavailability of the complex, reducing its efficacy. Lipophilic complexes may face difficulty crossing the cell membrane, limiting their ability to reach target cells, especially in the case of anticancer therapy. Strategies like ligand modifications and encapsulation in nanocarriers are being developed to overcome these challenges and improve the solubility and stability of metal-Schiff base complexes (Patil *et al.*, 2021).

Overcoming Resistance Mechanisms in Bacteria and Cancer Cells
Another challenge for the clinical application of metal-Schiff base complexes is overcoming resistance mechanisms that may arise in bacteria and cancer cells. Resistance to metal-based drugs has been increasingly observed, complicating their use as effective therapeutic agents.
Resistance in Bacteria: Like conventional antibiotics, metal-Schiff base complexes can face resistance from bacteria. Bacterial resistance mechanisms include the efflux pumps that actively transport the metal complexes out of the bacterial cell, enzyme-mediated degradation, and alteration of metal-binding sites. For example, Gram-negative bacteria have highly efficient efflux pumps that can pump out metal complexes, reducing their antimicrobial efficacy. To overcome this, researchers are focusing on designing metal-Schiff base complexes with enhanced permeability and the ability to evade efflux pumps (Ahmad *et al.*, 2021).
Resistance in Cancer Cells: Similarly, cancer cells can develop resistance to metal-based chemotherapy through mechanisms such as drug efflux, increased antioxidant activity, and alterations in the tumour microenvironment. Cancer cells can upregulate multidrug resistance (MDR) proteins, such as P-glycoprotein, which pump out the drug before it can reach its target. Additionally, cancer cells may develop altered redox states, reducing the reactive oxygen species (ROS) produced by metal-Schiff base complexes and thereby diminishing their cytotoxic effects. To address this, researchers are working on targeted drug delivery systems, such as liposomes or nanoparticles, which can specifically deliver the metal-Schiff base complexes to cancer cells and overcome resistance (Yang *et al.*, 2021).
Despite the promising therapeutic potential of metal-Schiff base complexes, several challenges remain in their development as therapeutic agents. These challenges include metal ion toxicity and bioaccumulation, stability concerns in physiological environments, and overcoming resistance mechanisms in bacteria and cancer cells. Addressing these challenges requires innovative design strategies, such as ligand modifications, nanocarrier encapsulation, and targeted delivery systems, to enhance these complexes' bioavailability, selectivity, and efficacy. Future research in these areas will be essential for overcoming the current limitations and unlocking the full potential of metal-Schiff base complexes as effective antimicrobial and anticancer agents.

10. CHALLENGES IN DEVELOPING METAL-SCHIFF BASE COMPLEXES AS THERAPEUTIC AGENTS
Despite the significant promise of metal-Schiff base complexes in drug development, their application faces several challenges related to metal ion toxicity, bioaccumulation, stability in physiological environments, and the need to overcome resistance mechanisms in bacteria and cancer cells. These challenges must be addressed for these complexes to be viable therapeutic agents. This section discusses the main difficulties encountered during the development of metal-Schiff base complexes, as well as potential strategies to mitigate these issues.

Limitations Related to Metal Ion Toxicity and Bioaccumulation

The toxicity of the metal ion at the centre of the metal-Schiff base complex is one of the primary concerns for the clinical application of these complexes. While metal ions enhance the bioactivity of Schiff base complexes, their toxicity can cause significant harm to healthy tissues, especially with prolonged use or high doses.

Metal Ion Toxicity: Certain metal ions, such as Cu(II), Fe(III), and Ni(II), are known to catalyse redox reactions that lead to the formation of reactive oxygen species (ROS). These ROS can damage cell membranes, proteins, lipids, and DNA, causing oxidative stress and ultimately leading to cell death. For instance, Cu(II)-Schiff base complexes can induce oxidative stress in bacterial and mammalian cells, leading to toxicity in normal tissues (Patil *et al.,* 2021). The toxicity of metal ions is also a concern in anticancer therapy, where metal ions may accumulate in healthy tissues, particularly in the liver and kidneys, causing damage.

Bioaccumulation: Bioaccumulation refers to the accumulation of metal ions in the body, which can occur when the metal-Schiff base complex is administered repeatedly or in high doses. If the complexes are not properly metabolised or excreted, the metal ions may build up in tissues, leading to long-term toxicity. This is especially problematic for metals like copper and iron, which are essential in biological processes but can be toxic in excess. To mitigate bioaccumulation, optimising the dosage and administration routes of these complexes is crucial to ensure that toxic accumulation in tissues does not occur (Gabriele *et al.,* 2022).

Stability Concerns in Physiological Environments

For metal-Schiff base complexes to be effective as therapeutic agents, they must retain their structural stability and biological activity in physiological environments such as blood or tissues. However, several factors can contribute to instability, including changes in ph, temperature, and the presence of enzymes in the body.

Instability in Biological Fluids: Metal-Schiff base complexes can be prone to hydrolysis in aqueous environments, leading to the formation of metal-hydroxide complexes, which are often less biologically active. For example, Cu(II) and Ni(II) Schiff base complexes can undergo ligand displacement or hydrolysis at physiological ph (7.4), reducing their effectiveness (Patel *et al.,* 2021). This can significantly limit the bioavailability of the complex, as the formation of inactive species can reduce the therapeutic potential.

Ligand Instability: The Schiff base ligand itself can also degrade in the presence of biological fluids, particularly under oxidative conditions, resulting in the loss of the complex's bioactivity. Ligand exchange reactions, where the Schiff base ligand is displaced by other biomolecules such as proteins or nucleic acids, can lead to the complex losing its selectivity and potency. To improve stability, researchers are exploring using macrocyclic ligands or multidentate ligands that can form stronger and more stable metal-ligand bonds (Yang *et al.,* 2021).

Overcoming Resistance Mechanisms in Bacteria and Cancer Cells

Resistance to metal-Schiff base complexes is emerging as a critical challenge, particularly in bacteria and cancer cells. Bacterial pathogens and tumor cells can develop mechanisms to counteract the therapeutic action of these complexes, reducing their efficacy over time.

Resistance in Bacteria: Just like traditional antibiotics, metal-Schiff base complexes are vulnerable to bacterial resistance mechanisms. Bacteria can develop efflux pumps that actively pump the metal complexes out of the cell, reducing the intracellular concentration and decreasing the antimicrobial efficacy. Additionally, bacteria can upregulate metal-binding proteins, which sequester metal ions and prevent their interaction with biomolecular targets (Ahmad *et al.,* 2021). Some bacteria also have the ability to detoxify metal ions, thus neutralizing the antimicrobial effect of the metal-Schiff base complexes. Overcoming these resistance mechanisms requires designing complexes with enhanced membrane permeability and avoiding efflux pumps, possibly by targeting the lipid bilayer or using nanocarriers for targeted delivery.

Resistance in Cancer Cells: Similarly, cancer cells can develop resistance to metal-Schiff base complexes by upregulating efflux proteins, such as P-glycoprotein, that pump the drug out of the cell. Cancer cells may also become more resistant to oxidative stress by increasing antioxidant defenses. For example, the upregulation of glutathione (GSH) or thioredoxin reductase (TrxR) can counteract the ROS produced by metal-Schiff base complexes, thereby decreasing their cytotoxicity (Yang *et al.,* 2021). To overcome cancer cell resistance, nanotechnology and targeted delivery systems that direct the complex specifically to tumor cells or subcellular compartments can improve the selectivity and efficacy of these complexes.

The development of metal-Schiff base complexes as therapeutic agents faces several challenges, including metal ion toxicity, bioaccumulation, stability in physiological environments, and the need to overcome resistance mechanisms in both bacteria and cancer cells. However, innovative strategies such as ligand modifications, nanoencapsulation, and targeted delivery systems show promise in overcoming these challenges. To unlock the full therapeutic potential of metal-Schiff base complexes, further research is needed to enhance selectivity, improve stability, and address the emerging issue of drug resistance in microbial and cancerous cells. Continued innovation in drug design and delivery technologies will be crucial for the successful clinical translation of metal-Schiff base complexes as safe and effective therapeutic agents.

REDVET - Revista electrónica de Veterinaria - ISSN 1695-7504
Vol 25, No. 2 (2024)
http://www.veterinaria.org
Article Received: Revised: Accepted:

11. FUTURE DIRECTIONS AND CHALLENGES IN METAL-SCHIFF BASE COMPLEX DRUG DEVELOPMENT

As metal-Schiff base complexes continue to emerge as promising candidates for antimicrobial and anticancer therapies, there are several key future directions that could enhance their efficacy, targeting ability, and overall clinical potential. In this section, we discuss the innovations in metal-ligand chemistry, the exploration of combination therapies, and the potential for integrating metal-Schiff base complexes into personalized medicine strategies. While these developments offer exciting possibilities, they also present unique challenges that must be addressed to ensure the successful translation of these complexes into clinical use.

Innovations in Metal-Ligand Chemistry to Improve Drug Efficacy and Targeting

The field of metal-ligand chemistry has made significant strides, with new developments aimed at enhancing the bioactivity and selectivity of metal-Schiff base complexes for therapeutic applications. Innovations in ligand design, coordination chemistry, and metal ion selection are critical for improving the therapeutic index of these complexes.

Ligand Modifications for Enhanced Targeting: One of the primary avenues for improving drug efficacy is through ligand modifications. The introduction of functional groups, such as amine or carboxyl groups, can improve the hydrophilicity or lipophilicity of the complex, making it more suitable for targeted drug delivery. Additionally, ligands can be modified to incorporate bioactive molecules that bind to specific biomolecular targets such as receptors, enzymes, or cell surface markers. This strategy can enhance the selectivity of metal-Schiff base complexes, allowing for better targeting of cancer cells or infected tissues while minimizing off-target effects (Gabriele *et al.,* 2022).

Design of Bimetallic and Multidentate Complexes: Another promising approach involves the development of bimetallic or multidentate complexes, where multiple metal ions are incorporated into the complex to enhance its stability, activity, and selectivity. Bimetallic complexes, in particular, can offer synergistic effects by exploiting the complementary redox properties of different metal ions. These complexes could potentially increase the DNA-binding affinity, improve the generation of reactive oxygen species (ROS), and enhance antimicrobial or anticancer activity (Patil *et al.,* 2021).

Development of Stimuli-Responsive Metal-Schiff Base Complexes: Innovations in nanotechnology and smart drug delivery systems offer the potential to design stimuli-responsive metal-Schiff base complexes. These complexes could be engineered to release their bioactive metal ions or ligands in response to specific environmental triggers, such as pH changes, enzyme activity, or redox potential. For example, metal-Schiff base complexes could be designed to release their active form selectively at the tumor site, where the microenvironment (e.g., low pH or high ROS levels) facilitates the activation of the therapeutic agent (Yang *et al.,* 2021).

Exploration of Combination Therapies Involving Metal-Schiff Base Complexes and Traditional Antimicrobial/Anticancer Agents

An emerging strategy in the development of metal-Schiff base complexes is their integration into combination therapies, which combine the strengths of metal-based drugs with traditional antimicrobial or anticancer agents. The rationale behind this approach is that combination therapies can enhance therapeutic efficacy, overcome drug resistance, and reduce side effects.

Combination with Antibiotics: Antimicrobial resistance (AMR) is a growing global health crisis, and metal-Schiff base complexes can potentially be used in combination with conventional antibiotics to combat resistant bacterial strains. For example, combining copper-Schiff base complexes with antibiotics like penicillin or tetracycline may lead to synergistic effects, where the metal complex enhances the antibiotic's ability to bind to bacterial targets or disrupt cell wall synthesis, while the antibiotic improves the overall antibacterial efficacy (Patil *et al.,* 2021). This strategy could also help reduce the likelihood of resistance development by targeting multiple bacterial pathways.

Combination with Chemotherapeutic Agents: Similarly, combining metal-Schiff base complexes with traditional chemotherapy drugs can potentially improve anticancer efficacy while minimizing toxicity. For example, the combination of metal-Schiff base complexes with cisplatin (a widely used chemotherapy agent) can enhance DNA interaction and ROS production, leading to enhanced cytotoxicity against cancer cells. Moreover, such combinations could help overcome resistance to chemotherapeutic agents, a major issue in cancer treatment (Ahmad *et al.,* 2021).

Integration of Metal-Schiff Base Complexes into Personalized Medicine Strategies

The concept of personalized medicine is gaining momentum, where treatments are tailored to the individual's genetic makeup, biomolecular characteristics, and response to therapy. Integrating metal-Schiff base complexes into personalized medicine strategies holds significant potential for improving the efficacy and selectivity of these drugs.

Targeted Delivery Systems: One of the key strategies for personalized medicine is the development of targeted delivery systems for metal-Schiff base complexes. By incorporating biomarkers or targeting ligands (such as antibodies, peptides, or aptamers) that are specific to cancer cells or infected tissues, the metal-Schiff base complexes can be directed to specific tissues, improving therapeutic outcomes and reducing off-target effects. Such systems can be designed to respond to individual patient profiles, ensuring that the drug delivery is optimized for each patient's needs (Zhang *et al.,* 2022).

Genomic and Proteomic Profiling: Another approach to personalized medicine is the use of genomic and proteomic profiling to identify patients who are likely to respond to metal-Schiff base complexes. By examining the expression levels of specific metal-binding proteins, enzymes, or cell surface receptors, clinicians can determine which patients would benefit most from metal-Schiff base complex treatment. This information can also help in choosing the most appropriate metal ion or ligand modification for individualized treatment plans (Gabriele *et al.,* 2022).

The future of metal-Schiff base complexes as therapeutic agents is bright, with innovative strategies aimed at improving drug efficacy, targeting specificity, and bioavailability. Advances in ligand design, combination therapies, and the integration of personalized medicine strategies are expected to significantly enhance the clinical potential of these complexes. However, continued research and development are necessary to overcome challenges related to toxicity, bioaccumulation, and resistance mechanisms. With further refinement in these areas, metal-Schiff base complexes could become a cornerstone in the fight against antimicrobial resistance, cancer, and other diseases.

12. CONCLUSION

The metal-Schiff base complexes have emerged as a promising class of compounds with significant antimicrobial and anticancer potential. Their unique ability to interact with biomolecular targets such as DNA, proteins, and cell membranes makes them highly effective in treating various diseases, including bacterial infections and various cancers. The metal ion at the centre of these complexes plays a crucial role in enhancing their bioactivity by facilitating redox reactions, generating reactive oxygen species (ROS), and strengthening ligand-metal interactions.

Summary of the Antimicrobial and Anticancer Potential of Metal-Schiff Base Complexes

Antimicrobial Activity: Metal-Schiff base complexes have shown remarkable antimicrobial activity against a broad spectrum of Gram-positive and Gram-negative bacteria, fungi, and viruses. The metal ion enhances the complex's ability to disrupt bacterial cell walls, inhibit protein synthesis, and interact with DNA, leading to cell death. These complexes are particularly valuable in combating drug-resistant bacterial strains, offering a potential solution to the growing problem of antimicrobial resistance (Ahmad *et al.,* 2021).

Anticancer Activity: The anticancer effects of metal-Schiff base complexes are attributed to their ability to bind to DNA, induce DNA strand breaks, and arrest the cell cycle at key checkpoints, such as the G2/M phase. By generating ROS, they can initiate apoptosis in cancer cells. Metal ions such as Cu(II) and Ni(II) are particularly effective in enhancing the DNA-binding affinity and cytotoxicity of the complexes. Furthermore, these complexes have been shown to target specific cancer pathways, making them selective for tumor cells while minimising damage to healthy tissues (Patil *et al.,* 2021).

Future Prospects in the Development of Metal-Based Therapeutics

Innovation in Metal-Ligand Chemistry: The design and synthesis of new metal-Schiff base complexes with modified ligands and innovative metal coordination strategies are promising to improve their therapeutic efficacy. By designing bimetallic or multidentate complexes, researchers can exploit synergistic effects to enhance bioactivity and selectivity for specific cellular targets. Additionally, developing stimuli-responsive complexes that release their active components under specific biological conditions (such as tumour microenvironments) will enable targeted therapy, reducing toxicity to healthy cells (Gabriele *et al.,* 2022).

Combination Therapies: The future of metal-Schiff base complexes lies in their use in combination therapies. Combining metal-Schiff base complexes with traditional antibiotics, chemotherapeutic agents, or immunotherapies may enhance their therapeutic efficacy while minimising side effects and drug resistance. Such combinations could help address the growing problem of resistance mechanisms in bacteria and cancer cells, offering a multifaceted approach to treatment (Patil *et al.,* 2021).

Personalised Medicine: Integrating metal-Schiff base complexes into personalised medicine strategies is another exciting avenue for future research. Researchers can develop tailored treatments that optimise selectivity and efficacy based on individual patient profiles by employing genomic profiling and biomarker identification. This approach will help ensure that metal-Schiff base complexes are used efficiently, minimising toxicity and maximising therapeutic outcomes (Yang *et al.,* 2021).

Nanomedicine and Targeted Delivery: The use of nanotechnology to encapsulate metal-Schiff base complexes in nanocarriers such as liposomes or dendrimers holds excellent potential for targeted delivery and controlled release. This approach will allow metal-Schiff base complexes to be delivered specifically to tumour tissues or infected cells, enhancing their bioavailability and reducing side effects (Zhang *et al.,* 2022).

Clinical Development and Regulatory Challenges: As metal-Schiff base complexes move closer to clinical use, clinical trials and regulatory approval will play crucial roles in their success. Safety, efficacy, and bioavailability must be thoroughly evaluated in human trials to ensure their therapeutic viability. These complexes' biocompatibility and toxicity profiles must be carefully studied to ensure long-term safety in clinical settings.

Metal-Schiff base complexes represent a promising class of bioactive compounds with antimicrobial and anticancer potential. Their metal ions, ligand structures, and coordination chemistry contribute to their potent bioactivity, targeting key biological pathways. Innovative strategies such as ligand modifications, combination therapies, nanocarriers, and personalised medicine are key to enhancing their therapeutic efficacy and selectivity. Despite the challenges posed by

toxicity, bioaccumulation, and drug resistance, the future of metal-Schiff base complexes in drug development remains promising. With continued research and development, these complexes have the potential to revolutionise antimicrobial and anticancer therapy, offering more effective and targeted treatment options for a variety of diseases.

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