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REVIEW ARTICLE

Histidine Metal Complexes in Medicinal Chemistry: Synthesis, Biological Activities and Therapeutic Applications

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ABSTRACT

Histidine is a naturally occurring amino acid which has attracted great attention in medicinal coordination chemistry due to its excellent metal binding properties through the amino, carboxylate and imidazole functional groups. Such coordination properties allow the synthesis of stable and structurally varied metal complexes with tunable physicochemical properties and potentially promising biological activities. Thus, histidine is becoming a promising ligand for the design of new metal-based drugs. This review focuses on recent developments in the synthesis, coordination chemistry, biological activities, and mechanisms of action and biomedical applications of histidine–metal complexes. Special attention is given to Schiff base-derived ligands, transition metal coordination and structure–activity relationships affecting therapeutic activity. Existing data show that histidine–metal complexes exhibit strong anticancer, antimicrobial, antioxidant and photodynamic activities through various mechanisms, including DNA interaction, apoptosis induction, modulation of ROS and enzyme inhibition. Recent advances in nanotechnology, liposomal formulations and targeted drug delivery systems have further improved the stability, bioavailability and therapeutic activity of these complexes. Despite these advances, toxicity, selectivity, pharmacokinetics and clinical translation remain important challenges. Rational ligand design, advanced delivery systems, detailed mechanism studies and extensive preclinical and clinical testing are needed. Histidine–metal complexes show great potential for developing new therapeutic agents.

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1. INTRODUCTION

The metal ions are very important in various biological activities such as enzyme catalysis, electron transfer, biological signaling, gene regulation, and structure maintenance. The importance of metal ions in biological functions has created the field of medicinal inorganic chemistry where researchers use the varied oxidation state, coordination geometry, and redox properties of the metal complexes for their therapeutic applications [1,2]. Introduction of cisplatin marks an important milestone in medicinal chemistry where scientists confirmed the action of metal drugs on biological systems. Researchers have extended their investigations to explore different transition metal complexes such as ruthenium and iridium and copper and gold and silver and palladium and cobalt and

vanadium and many more. Research is conducted on these metal complexes for improving cancer treatment selectivity by overcoming the issue of drug resistance as well as toxicity and finding other medicinal applications of these complexes in treating cancer, infections, inflammation, and molecular diagnostics [1-3]. As evidence grows, the biological activity of a metal complex has been shown not just to rely on the metal itself but on the coordinating ligand as well. The growing use of ligands composed of amino acids can be attributed to their biocompatibility, along with their ability to make a range of compounds used in forming more stable and selective metal complexes [4,5]. Histidine is an interesting naturally occurring amino acid because of its imidazole side chain which offers excellent donor sites for N coordination that can form relatively stable but biologically dynamic coordination complexes. Histidine contains amino, carboxylate and imidazole functional groups that enable it to coordinate with metals in several ways, and can mimic the metal coordination environment of many metalloproteins and metalloenzymes. The features of histidine make it an extraordinary ligand for the preparation of multifunctional metal complexes that exhibit interesting anticancer, antimicrobial, antioxidant, enzyme-inhibitory, imaging and drug delivery abilities [2,3,5].

Despite the advances in the synthesis and biological study of histidine–metal complexes, the information is scattered throughout and depends on the type of metal ion and therapeutic area. The current research provides a detailed summary about histidine metal complexes which includes their coordination chemistry and synthesis methods and their biological effects and structure activity relationships and therapeutic uses and present obstacles and upcoming developments in medicinal chemistry.

1.1 HISTIDINE AS A BIOACTIVE LIGAND IN METAL COORDINATION CHEMISTRY

1.1.1 Structural Features and Coordination Ability of Histidine

Histidine contains three possible coordination sites: the α-amino group, the α-carboxyl group and an imidazole side chain with two nitrogen atoms, and is one of the most versatile naturally occurring amino acids employed in coordination chemistry. This structure can serve multiple purposes as it can accommodate a range of transition metal ions with the help of its nitrogen and oxygen donor atoms, resulting in complexes with various coordination geometries and thermodynamic stability. The electron-rich nitrogen atoms and the desirable acid base properties of the imidazole ring make it the key metal-binding site of histidine. Histidine can function as a monodentate, bidentate, or tridentate ligand, providing the ability to coordinate via the imidazole nitrogen, amino group, or carboxylate group, either singly or together, depending upon the metal ion, pH and ligand environment. This coordination versatility plays a role in the formation of stable chelate rings, while at the same time allowing for dynamic metal exchange under physiological conditions [6]. The amino group and the carboxyl group also give another source of nitrogen and oxygen donor groups to histidine, increasing its coordination potential. Increase in the complex stability, influence on electronic properties and precise modulation of reactivity of the metal center are most useful in designing biologically active metal complexes with rational design [7]. The structural features make histidine an interesting candidate for the preparation of transition metal complexes with enhanced aqueous solubility, controlled coordination geometry and better biological compatibility. As a result, complex of histidine has been widely studied for its pharmaceutical uses such as antimicrobial, anticancer and dermatological formulations [7].

1.1.2 Biological Significance of Histidine-Based Metal Coordination

Histidine is a central component in the biological metal coordination functions, including metal homeostasis, in living organisms. The amino acid histidine shows strong metal ion binding capabilities which include copper and zinc and iron and nickel ions. The protein helps cells keep their metal levels stable through its role in metal ion movement and storage and controlled release which protects cells from metal toxicity [6]. The coordination properties of histidine also allow the synthesis of biomimetic metal complexes that are able to mimic key structural and catalytic elements of nature's metalloenzymes. Such complexes have been a subject of great interest as they mimic enzymatic redox reaction, catalytic transformation and recognition process of the substrates, which can be useful in therapeutic and diagnostic applications. In addition, the recognition and interactions of proteins with metal involve an important role of histidine-mediated metal coordination. The active sites of metalloproteins often involve histidine residues that coordinate to the metal ion and control the catalytic activity and/or interactions with nucleic acids, proteins and other biological targets. The above properties make histidine-based metal complexes ideal for creation of selective bioactive agents with enhanced pharmacological features [1,2]. Together, the special coordination chemistry of histidine is a powerful link between inorganic chemistry and biological function, and therefore makes the continued development of histidine–metal complexes a promising candidate for medicinal applications [2,6].

1.2 SYNTHETIC STRATEGIES AND CHARACTERIZATION OF HISTDINE-METAL COMPLEXES

1.2.1 Schiff Base-Derived Histidine Metal Complexes

One of the most general approaches towards creating histidine-based metal complexes is by the use of Schiff base chemistry, which allows the modification of the structure of the ligand while still retaining the coordination properties of the amino acid. Imine containing ligands formed via condensation reactions of the amino group of histidine with appropriate aldehyde or ketone, show increased chelating capacity and tunability of their electronic properties for coordination with transition metals [8,9]. Structural modification of Schiff bases derived from histidine represents an effective strategy to tune the steric and electronic features, which affects the metal-binding capability, the stability of the complexes and the coordination geometry. The resulting ligand denticity and enhanced ability to form mono-, bi and polynuclear metal complexes of a wide variety of architectural structures is often seen as a consequence of the additional donor atoms or the aromatic substituents present [10,11]. Metallic elements such as Cu(II), Co(II), Zn(II), Ni(II), Ag(I), and Sn(IV) establish connections with the Histidine Schiff base ligand through imine nitrogen, imidazole nitrogen, amino nitrogen, and carboxylate oxygen. As a result, complexes develop square planar, tetrahedral, square pyramidal, and octahedral coordination geometry which dictates the properties of the metal ion [8,10,12]. Modern synthesis methods undergo full characterization via elemental analysis and FT-IR spectroscopy and UV–Vis spectroscopy and NMR spectroscopy (where applicable) and mass spectrometry and magnetic susceptibility determination and thermal analysis and X-ray diffraction of single crystals or powders. Modern researchers resort to computational modeling which includes density functional theory (DFT) and molecular docking to assist them in structural elucidation and coordination mechanisms of metals prediction [13,11]. The total number of possibilities for the diversity of histidine ligands is largely expanded through Schiff base modifications, allowing for many different coordination possibilities when designing new metal complexes [9,11].

1.2.2 Transition Metal Complexes Incorporating Histidine and Amino Acid Ligands

In addition to Schiff bases, many complexes of transition metals have been prepared directly from the natural amino acids such as histidine in order to make use of the inherent biocompatibility and multifunctional coordination properties of the amino acids. These ligands can easily bind a wide variety of transition metals as amino, carboxylate and heterocyclic donor groups and form stable complexes with variable structural features [14,15]. The choice of metal ion is the primary and crucial factor which determines its coordination geometry, electronic structure, and the overall stability of the complex. The complexes with Cu(II), Co(II), Ni(II), Zn(II), Mn(II) and Fe(II) are often found to have octahedral, tetrahedral or square-planar geometries as per the reaction conditions, denticity of the ligands and the coordination number of the metal [16,17,18]. The process entails simple chemical reactions among coordination compounds in water at certain pH and temperature conditions prior to separating the products using crystallization or precipitation techniques by scientists. Scientists confirm successful complex formation through structural characterization which reveals the coordination modes by using spectroscopic methods together with elemental analysis and conductivity tests and magnetic studies and thermal analysis techniques [19,15]. Scientists have started to use mixed ligand methods which combine histidine with other N and O donor ligands to create new molecular structures and different metal binding sites. The methods enable scientists to control the stability of complex molecules and their solubility and physical chemical characteristics while they can test their biological activities through later assessment stages [17,16]. These synthetic approaches together illustrate how histidine and its related amino acid ligands are an extremely versatile class of ligands for the synthesis of structurally diverse transition metal complexes for pharmacologic purposes. Table 1 presents a comparative summary of representative histidine based metal complexes, their coordination modes, synthetic methods and main characterization techniques.

Table (1): Structural Characteristics, Metal Coordination Modes, and Synthetic Approaches of Histidine Metal Complexes

Histidine ligand	Metal ion(s)	Donor atoms	Coordination geometry	Synthetic strategy	Characterization techniques	Reference
Histidine Schiff base	Cu(II), Co(II), Zn(II), Cd(II)	N,N,O	Octahedral / Square planar	Schiff base condensation	FT-IR, UV–Vis, NMR, XRD	Sumathi & Mahadevi (2022) [10]
Histidine derivative	Sn(IV)	N,O	Distorted octahedral	Schiff base synthesis	FT-IR, NMR, MS	Garza-Ortiz *et al.* (2013) [8]
Histidine–glycine mixed ligand	Cu(II)	N,N,O	Square planar	Solution coordination	FT-IR, UV–Vis, elemental analysis	Sultan *et al.* (2023) [12]
Histidine Schiff base	Transition metals	N,N,O	Variable	Schiff base synthesis	DFT, docking, spectroscopy	Sridevi & Madheswari (2023) [13]
Amino acid Schiff base	Ag(I)	N,O	Tetrahedral	Condensation + metalation	FT-IR, UV–Vis	Aftab *et al.* (2022) [9]
Histidine-derived Schiff base	Transition metals	N,O	Variable	Schiff base synthesis	DFT, spectroscopy	Waziri *et al.* (2025) [11]

Histidine is a highly versatile donor and is able to form stable complexes with a number of transition metals due to the presence of its amino, carboxylate and imidazole donor groups as summarized in Table 1. Most complexes reported have an octahedral or a square-planar structure, but also tetrahedral and distorted octahedral structures are found in certain cases depending on the metal ion and ligand architecture. Schiff base derivatization is the preferred synthetic approach as it enables the ligands to be more dentate and diverse, while solution-phase coordination is the main synthetic route for amino acid-based complexes. In addition, spectroscopic, analytical, and computational methods such as FTIR, UV–Vis, NMR, X-ray diffraction, elemental analysis and density functional theory are now routinely used to confirm coordination geometry and to elucidate structure–property relationships. The biological activities to be discussed later are based on the following chemical characteristics of these structures.

1.3 BIOACTIVE PROPERTIES OF HISTIDINE-METAL COMPLEXES

1.3.1 Anticancer Activity

The usefulness of histidine–metals complexes as anticancer drugs has received much attention, due to the variety of mechanisms by which they can act: biologically compatible ligands, together with transition metal centers, provide multiple mechanisms of action different from those of traditional drugs used in chemotherapy. Both the intrinsic properties of coordinated metal ion and the ability of the histidine ligand to affect the stability, cellular uptake and target selectivity determine their antitumor activity [2,20]. Histidine containing metal complexes show cytotoxicity, one of the main mechanisms being their interaction with DNA. Copper, palladium and other transition metal coordination compounds are capable of binding with DNA via different mechanisms such as intercalative and groove binding, which can interfere with DNA replication and transcription and cause irreversible damage to DNA [21,22]. In addition to binding DNA, a large number of histidine complexes mediate the apoptosis by causing dysfunction of mitochondria, activation of caspase-mediated signaling pathways, imbalance of cellular redox status, and production of reactive oxygen species (ROS). The final phase reveals that the induction of oxidative stress leads to cell death programming in different cancer cell lines, and at the same time, tumor growth is suppressed [23,13,24]. The research group implemented molecular docking and DFT to create appropriate computational models which allow researchers to investigate protein binding properties and identify potential molecular targets and

relate structural features to biological activity. The mentioned approaches are integrated with experiments on cytotoxicity analysis to facilitate the rational design of histidine-based metal complexes [22,13]. Scientists have started investigating multifunctional treatment modalities that combine histidine-based metal complexes and targeted delivery systems. Researchers created systems that involve histidine-based metal complexes and active biological substances in order to enhance drug targeting capacities and prolong their blood circulation time. Researchers managed to identify several approaches to synthesize metal-based cancer drugs and they are going to pay attention to this issue in the future [12,25,20].

1.3.2 Antimicrobial and Antibacterial Applications

Owing to the rising prevalence of antimicrobial resistance, there has been a tremendous research effort aimed at the development of metal complexes for alternative treatments. The range of antibacterial and antifungal properties of histidine-containing metal complexes is due to synergism between the metal ions and amino acids as ligands [2,26]. Multiple methods enable these complexes to fight microbes through their ability to break down bacterial cell membranes and block vital enzyme functions and stop DNA and RNA production and modify membrane barriers and create oxidative damage in cells. The process of metal coordination leads to better ligand fat solubility which helps molecules enter cells while boosting their ability to fight bacteria more effectively than free ligands [14,18]. Recently, it has been shown that photoactive complexes of transition metal are able to offer further possibilities for the fight against resistant microorganisms by means of a photodynamic antimicrobial therapy. The metal complexes activate light and then produce ROS to effectively kill bacterial cells without the risk of their development to resistance [27]. Additionally, ruthenium metal complexes fight staphylococcal bacteria through their antimicrobial properties and their ability to prevent biofilm formation which makes them suitable for treating stubborn infections that develop biofilm resistance [28].

1.3.3 Anti-oxidant and PDT Applications

In addition to their direct cytotoxic and antimicrobial activity, histidine–metal complexes have been found to be potential antioxidants and photodynamic therapy agents. Both their redox-active metal centers and their antioxidant properties allow for the regulation of ROS to be used as either an antioxidant or for oxidative damage, depending on the therapeutic goal. Photodynamic therapy (PDT) is one of the fastest-growing fields of medicinal metal complexes. Appropriately designed metal complexes, upon light irradiation, produce singlet oxygen and other ROS that selectively damage malignant or microbial cells with minimal damage to surrounding healthy tissues [29,27]. The coordinated metal ion, ligand environment, electronic structure and photophysical properties all play a key role in the photodynamic efficiency of these complexes. These parameters have been optimised rationally, and more and more efficient photosensitizers have been developed, characterised by their higher photostability, ROS production efficiency, and therapeutic selectivity [2,29]. All these results illustrate that the histidine-based metal complexes are multi-functional therapeutic agents that can combine various therapeutic properties such as anticancer, antimicrobial, antioxidant and photodynamic properties in a single molecular structure, thus increasing their potential in the field of precision medicine [2,27]. The different pharmacological activities and mechanisms of action described for typical histidine–metal complexes are listed in Table 2.

Table (2): Biological Activities and Therapeutic Mechanisms of Histidine–Metal Complexes

Metal complex	Main biological activity	Proposed mechanism	Experimental evidence	Reference
Cu(II)–histidine complexes	Anticancer	DNA cleavage, apoptosis	Cytotoxicity, DNA binding	Leite *et al*. (2016) [21]
Pd(II)–histidine complexes	Anticancer	DNA/BSA interaction, apoptosis	Cell viability, docking	Hashemi *et al.* (2022) [22]
Mixed-ligand transition metal complexes	Anticancer	ROS generation, apoptosis	In vitro cytotoxicity	Chu *et al.* (2021) [23]
Histidine Schiff	Anticancer	Molecular docking,	Cell line studies	Sridevi & Madheswari

base complexes		oxidative stress		(2023) [13]
Cu(II)–histidine/glycine complex	Anticancer	Cytotoxic activity	Biological evaluation	Sultan *et al.* (2023) [12]
Ag complexes	Anticancer	Oxidative stress, apoptosis	Colorectal cancer cells	Teow *et al.* (2026) [24]
Histidine-based transition metal complexes	Antibacterial	Membrane disruption	Antimicrobial assays	Chohan *et al.* (2006) [14]
Mn/Co/Ni amino acid complexes	Antimicrobial	Enzyme inhibition	MIC evaluation	Danhalilu *et al*. (2022) [18]
Ru complexes	Antibiofilm	ROS-mediated bacterial killing	Biofilm inhibition	Andrade *et al.* (2025) [28]
Photoactive transition metal complexes	Photodynamic therapy	Light-induced ROS generation	Gram-positive bacteria	Pei *et al.* (2025) [27]
Metalloporphyrins	Photodynamic therapy	Metal-dependent ROS production	PDT studies	Abbas *et al.* (2023) [29]

Table 2 presents several biological properties observed from the complexes formed between metal ions and histidine molecules, where all the biological properties arise due to the synergistic action of the coordinated metal ion and histidine ligand. Anticancer property is primarily exhibited through DNA binding, apoptosis, and oxidative stress, while the antimicrobial property primarily targets the cell membrane, enzyme inhibition and generation of ROS. Recent developments in PDT science also illustrate the ability to achieve significant improvements in therapeutic selectivity and efficacy by suitably choosing the metal center and the ligand environment. The findings demonstrate that histidine–metal complexes operate through multiple mechanisms which scientists can use to develop new medicines.

1.4 THERAPEUTIC ACTION MECHANISMS

1.4.1 DNA interacts with molecular structure

Therapeutic activity of many histidine–metal complexes is related to their interactions with biomolecules inside the cell, such as nucleic acids. The complexes can bind to DNA via intercalation, groove binding, and electrostatic interactions, which prevents DNA replication, transcription, and cell-cycle progression, depending on the structure of the coordinated metal ion and the ligands [21,22]. The structure of the coordination sphere around the metal center is a key factor in determining the affinity towards DNA and target selectivity. The Histidine derived ligands can influence the electronic properties, stability and steric accessibility of the metal complex, which in turn affects the interaction of the metal complex with any nucleic acids and DNA associated proteins [21,30]. Molecular docking is an indispensable computational method for studying the interaction of histidine–metal complexes with DNA, enzymes and regulatory proteins. The docking analyses can be used in combination with experimental studies to help predict binding modes, key intermolecular interactions, binding affinities, and can be used for structure activity relationship (SAR) analysis. However, the computational approaches have reduced the time taken to carry out rational design and optimization of bioactive histidine-containing metal complexes [22,11,30]. The studies carried out on DNA binding in the laboratory as well as molecular docking on computers give important data regarding the pharmacological properties of histidine-metal complexes to develop specific site drugs [11,22].

1.4.2 Generation of Reactive Oxygen Species and Oxidative Stress

The generation of reactive oxygen species (ROS) represents the most basic reaction mechanism which facilitates the ability of histidine-metal complexes to exert their biological effects. Superoxide anions and hydrogen peroxide, along with hydroxyl radicals, are produced under the regulation of the redox properties of transition metal ions by way of the electron transfer reactions [1,23].The excessive presence of ROS leads to oxidative damage which affects cancer cell DNA and proteins and membrane lipids to produce mitochondrial dysfunction and trigger apoptotic pathways and cause permanent cellular structure damage. The process of redox reaction selection through oxidative stress induction in cancer cells requires appropriate ligand design to protect normal tissue during histidine-containing metal complex application for treatment purposes [24]. The generation of reactive oxygen species is also critical for photodynamic therapy (PDT), a process closely related to the ability of metal complexes. After light activation, photoactive metal complexes have the ability to generate efficiently singlet oxygen and other reactive oxygen species, which mediate the localized cytotoxicity against malignant or microbial cells. This photodynamic response is very dependent on the type of coordinated metal ion and its ligand environment [29]. The dual action of DNA targeting together with ROS-induced oxidative stress explains why histidine–metal complexes produce diverse therapeutic effects through their complementary mechanisms. The research findings help scientists develop new metal-based drugs which will achieve better treatment results through their improved ability to target specific body areas [21].

1.5 MEDICAL DEVICES FOR HUMAN HEALTHCARE APPLICATIONS

The metal complexes have to be effective drugs; which requires the creation of suitable delivery systems that maximize the therapeutic efficacy of the metal complexes. Thus, much research has been directed towards the combination of metal-based therapeutics with high-tech delivery systems that enhance the stability, bioavailability, and controlled delivery of the drug [31,32]. Nanotechnology has proved to be a successful method to overcome many drawbacks related to traditional metal drugs. Metal complexes can be protected from early degradation, have a longer circulation time in the body, are more easily taken up by cells and can be actively or passively targeted to disease sites by using nanostructured carriers. These benefits can help enhance therapeutic success and minimize damage to normal tissue [31]. Silica-based nanocomposites are in fact found to have good potential for the sustained delivery of metal complexes among the various nanocarriers. For instance, diatom-like silica protein nano-composites have been created that allow the encapsulation of ruthenium polypyridyl complexes for the control delivery of the anticancer agents while maintaining the integrity of the nanocomposites and their anticancer properties. These systems deliver prolonged therapeutic exposure and enhance the efficiency of delivery when compared to free metal complexes [31]. Another approach for delivering metal based therapeutics is the liposomal formulation. Liposomes containing iridium (III) complexes have been reported to enhance the stability of the complex in aqueous solution, its accumulation inside the cells, and to substantially enhance the anticancer activity by means of efficient cellular uptake and controlled drug release. Another advantage of liposomal systems is that they can enhance the pharmacokinetic characteristics of the encapsulated metal complex, thereby minimizing nonspecific toxicity [32]. Metal complexes are now being delivered to targeted sites, further expanding the clinical potential of these complexes. An antibody–drug conjugate (ADC) with platinum containing a platinum-based linker allows for targeted delivery of a platinum-containing metal complex to surface antigen-bearing tumor cells, while sparing non-target cells from the same platinum toxicity. This is a significant step towards precision medicine with metal-containing therapeutics [25]. Overall, the development of nanotechnology, liposomal encapsulation and targeted delivery systems have significantly boosted the therapeutic potential of metal complexes by improving their controlled release and tissue selectivity, as well as their pharmacokinetic properties. The potential for further developments of the coordination chemistry with contemporary drug delivery technologies is anticipated to make the clinical translation of next generation histidine–metal complexes easier.

1.6 STRUCTURE-ACTIVITY RELTIONSHIP (SAR) OF HISTIDINE-METAL COMPLEXES

Metal ion complexes with histidine depend on various parameters such as charge and size of metal ion, geometry of complex, structure of the ligand and its electronic characteristics. SAR analysis is one of the vital techniques to facilitate the design of metal-based drugs that possess required biological activity as all of these aspects are crucial for the stability of the complex, cell permeation, its specificity toward the target and biological activity [22,17]. The type of metal ion incorporated into the complex is among the most significant parameters affecting biological activity. Copper (II) complexes' enhanced DNA binding and redox properties would contribute to an increase in their anticancer and antimicrobial properties. However, zinc (II) complexes are less redox-active, yet are biocompatible and less toxic, thus attracting attention in dermatology as well as for application in enzymes.

The complexes of Co (II) and Ni(II), meanwhile, have proved to possess flexible coordination sites applicable in diverse applications like biological ones. Finally, the complexes of Pd (II) and Ag (I) have demonstrated outstanding properties while interacting with biomolecules as well as possessing antimicrobial and cytotoxic activity [9,22,33]. The biological activity is also affected dramatically by the structure of the ligand. Histidine-derived Schiff bases afford greater denticity of the ligand, electronic flexibility, and more efficient coordination with metals and modulation of the physicochemical properties. The addition of extra donor atoms or aromatic groups can still further increase the stability of the complex and the lipophilicity as well as the target affinity, which can lead to an even better therapeutic effect [9,10]. Another important factor in the influence on biological behavior is the coordination geometry. The steric accessibility, electronic distribution and metal-ligand bond strength of the Octahedral, square-planar, tetrahedral and distorted octahedral complexes have direct implications in interactions with DNA, proteins and cellular membranes. Hence, optimizing the coordination geometry has become an interesting methodology to obtain the maximum biological activity at the minimum undesirable toxicity level [22,17]. The pharmacological properties of histidine–metal complexes are also further affected by the nature and position of the substituents in the ligand as they change the electron density, hydrophobicity, and overall stability of the molecule. These structural alterations have implications on the permeability of the cell, the affinity for the metal, the recognition of the biological target and emphasize the importance of rational design of the ligand in the design of next generation medicinal metal complexes [10,33]. In general, the studies revealed that the best biological activity was obtained when the metal ion was correctly incorporated, the histidine derived ligand was properly designed and the coordination geometry was suitable. Hence, further SAR studies are anticipated to lead to the development of more effective, selective and safe histidine–metal complexes.

1.7 CHALLENGES AND PROSPECTS NOW AND IN THE FUTURE

Although remarkable advances have been made in the development of histidine–metal complexes, certain problems remain that restrict the use of these complexes to clinical practice. While the in vitro biological activity of many complexes is good, their efficacy in the clinic is hampered by poor specificity, low bioavailability, unpredictable pharmacokinetics and poor knowledge of long-term safety profiles [1,2]. Toxicity of the metal center and its metabolites are one of the main challenges. Rational design of the ligand can help to make it more biocompatible, mitigate off-target effects, but it is still a challenge to achieve the right balance between therapeutic activity and systemic safety. In other words, in the future, it is very important to pay attention to ligand engineering methods that will ensure higher specificity for the target while reducing off-target effects in healthy tissue [2,5]. The next challenge associated with many metal compounds is that their bioavailability is very low due to poor solubility in water, poor cellular uptake and poor biodistribution or fast metabolism. However, it is possible to mention some advanced techniques of formulation such as nanocarriers, liposomes and targeted drug delivery systems that can solve these issues [3,5]. The shift from lab to clinic also is tough. While many of the studies currently available are devoted to chemical synthesis, structural characterization and in vitro biological evaluation, extensive in vivo studies, pharmacokinetic studies, toxicological studies and well-designed clinical trials are comparatively limited. The importance of SAR studies will be very crucial in the identification of the most promising drug compounds that will undergo clinical trials, as well as experimental methods [1.3]. Future studies will be useful in order to combine coordination chemistry with computational drug design, drug optimization by artificial intelligence, innovative drug delivery systems, and precision medicine strategies to expedite the discovery of safer and more selective histidine metal complexes. These multi-disciplinary approaches, when combined with an improved understanding of the mechanisms involved, should help in the development of next generation therapeutics based on metals that can have improved clinical potential.

2. CONCLUTION

Histidine is one of the most promising bioactive ligands in medicinal coordination chemistry because of its structural uniqueness, versatile coordination properties and good compatibility with living tissues. The amino, carboxylate and imidazole functional groups allow for the creation of structurally diverse metal complexes that are both stable and physiochemically and biologically modifiable. Based on evidence available, the therapeutic potential of the histidine–metal complex is evident for various therapeutic applications like anti-cancer, anti-microbial, anti-oxidant and photodynamic activities. They have multifunctional biological effects, which occur through various mechanisms of action, including DNA interaction; modulation of reactive oxygen species; enzyme inhibition and selective molecular targeting. Their applications and therapeutic efficacy have also been enhanced by developments in the design of new ligands and coordination chemistry. Histidine–metal complexes can be combined with modern technologies for drug delivery such as nanoparticles, liposomes and targeted delivery systems with the aim of

improving the bioavailability, tissue specificity and systemic toxicity of these compounds. The developments of these technologies have greatly enhanced the potential for histidine-based metal complexes as multi-functional therapeutic platforms for next-generation medicinal applications. Although major advances have been made, there are still a few hurdles to be overcome to make these compounds routine clinical practice. The rational design of highly selective complexes, detailed mechanistic studies, systematic structure–activity relationship studies, development of more sophisticated targeted delivery systems, and extensive preclinical and clinical testing are key areas in which further research is needed. Combining these problems in the multidisciplinary research will help to speed up the improvement of safer and more effective histidine–metal complexes for various therapeutic methods.

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