A BRIEF IDEA OF METAL COMPLEXES IN MEDICINAL CHEMISTRY: CURRENT STATUS AND FUTURE PROSPECTIVE

Abstract

Recent clinical research has brought attention to the rising incidence of drug resistance to well-established treatments. Antibiotics and drug resistance in particular have posed a severe threat to human health. Metal complexes have long been important in the development of medical science. Many chemical substances employed in medicine lack an entirely organic method of action, and for activation or biotransformation, the metal salt is necessary, either directly or indirectly. Metallo medicines have long attracted the interest of researchers due to their improved theranostic action through altering the pharmacological properties of the complexes towards biological receptors. Metal complexes, which have a high medical value, have already been shown to have a wide range of pharmacological actions by regulating a variety of molecular targets. They make effective chelating ligands for metal coordination because heterocyclic rings contain heteroatom(s), phenolic oxygen, carbonyl, hydroxyl, and/or heteroatom(s). Basically, the metal complexes of ferrocenyl chalcones and bidentate chalcone/Schiff base analogues have demonstrated tremendous promise. This chapter intends to draw attention to current data supporting the use of chalcone as a preferred scaffold in medicinal chemistry. For medicinal and bioinorganic chemists, understanding chelating mode, their stoichiometric properties, and mode(s) of action may be helpful in designing and developing novel, and economically advantageous metal complexes for a variety of biomedical applications.

Keywords: Metal complexes, Medicinal chemistry

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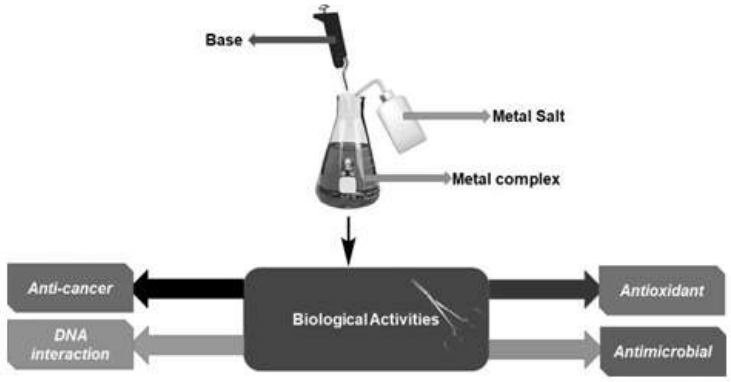
I. INTRODUCTION

In recent years metal and metallic pharmaceuticals are essential in the healthcare industry.1 Numerous medical disorders, including neoplasms (transition metal)2, hyperglycemia (oxovanadium)3 rheumatoid arthritis (gold compounds)4 inflammation (copper or bivalent metals)5 infections (silver-containing drugs)6 and maniac depression (lithium compounds)7, are being prevented or treated with them. Compared to non-complexed compounds, metal complexes have gained a lot of attention in medicinal chemistry over the past decade. Recent studies have shown that some drugs' active ingredients lack a fully organic method of action and must thus be activated by metal ions, directly or indirectly.8 For the bulk of biological functions, trace metals like Cu, Fe, Zn, Ni, etc. are necessary. The condition of the metal ions and how they act within the body are associated to a number of diseases or physiological abnormalities as well as ageing.9 Metal cofactors are necessary for the appropriate folding of nearly 30–40% of proteins, including the metallo enzymes, into an active three-dimensional (3D) structure. Medicinal Chemistry is very popular in modern science. The topic of "metals in medicine" was presented at international conferences like the International Conference on Bioinorganic Chemistry (ICBIC) and the European Conference on Bioinorganic Chemistry (EUROBIC). In July 2002, the first Metals in Medicine Gordon Research Conference, was held in Biology filed. The metal in medicine was expanded in very well known journal like Chemical Reviews, Coordination Chemistry Reviews, and Metal Ions in Biological Systems.

Cisplatin, Indazolium trans-[tetrachlorobis(1H- indazole)ruthenate(III)] (KP1019 or FFC14A) are a few well-known metallo pharmaceuticals for cancer chemotherapy.10 Gaur et al. synthesized two ruthenium chalcone complexes, cis,fac- [RuCl(DMSO-S)3(L)] , and investigated their intercalating potential. Specifically, (L=1-(2-hydroxyphenyl)-3-(4-chlorophenyl) Bis-chalcone (L) and cis,fac-[RuCl2(DMSO-S)3(DMSO-O)] coordinate to generate [Ru2(L)(DMSO)6Cl2] (2) and [Ru2(L)(DMSO)6Cl2] (1), respectively. Nitrogen, Oxygen, Sulfur, Phosphorous, and other ligands containing electron donor heteroatoms form coordination bonds with the metal ion.11 Inorganic metal complexes are expected to exhibit different pharmacokinetic and pharmacodynamic features after interacting with biological receptors because to a wide range of coordination site and liganding behavior.12 Many metal complexes are well-known antibiotics that have demonstrated enhanced outcomes against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) as a result of their special characteristics.13.

It has been discovered that the quinoline group of antibiotics' complexes, including ciprofloxacin, norfloxacin, and tetracycline, have increased activity in comparison to the antibiotic alone. Tetracycline's Pd(II) complex is sixteen times more effective than the tetracycline-resistant bacterial strain E. coli HB101/pBR322 while doxycycline's Pd(II) complex is twice as effective as doxycycline against resistant strains.14 The goal of the current chapter is the overview of metal complex and their effect on biomedical and biochemistry filed.



Scheme 1: Schematic diagram of metal complex activities

II. SCOPE OF CHAPTER

1. **Metal Complexes:** Synthesis, properties and application, Since Alfred Werner won the chemistry Nobel Prize in 1913 for developing coordination chemistry and octahedral shape of transition metal complex. Various chalcone metal complexes have been synthesized, characterized, and biologically screened, according to recent research. Chalcones are excellent metal chelators because of their distinctive structural characterization. Metal chalcone complexes are synthesized by chalcone ligand in some organic solvent. Due to their numerous applications in (bio-)imaging15, theranostics. photophysics16, catalysis17, etc., many chalcone metal complexes have gained significant notoriety during the past ten years. Due to their enhanced pharmacological properties, these metal complexes have gained significant importance in biomedical chemistry.18 Notion and Tweedy's chelation theory can be used to explain why chelates' pharmacological actions have improved. The lipid membrane that encircles the cell favors the passage of only lipid-soluble elements, in accordance with the overtone idea of cell permeability. Liposolubility is one of the major variables regulating antibacterial activity because of this. Due to the orbital overlap of the ligands and partial sharing of the metal ion's positive charge with the donor groups during chelation, the polarity of the metal ion is lowered to a higher extent. Additionally, the complexes can more easily penetrate lipid membranes thanks to the delocalization of the p-electrons over the entire chelate ring.

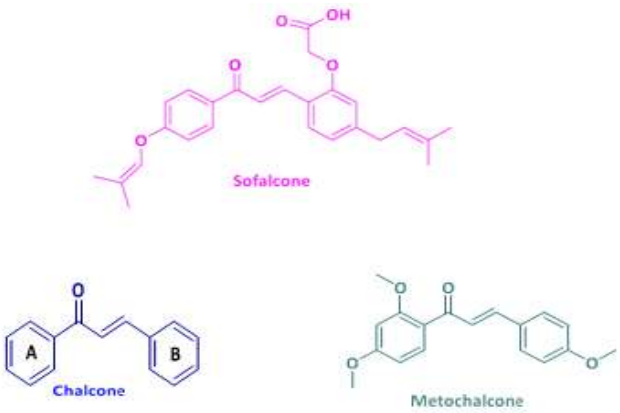
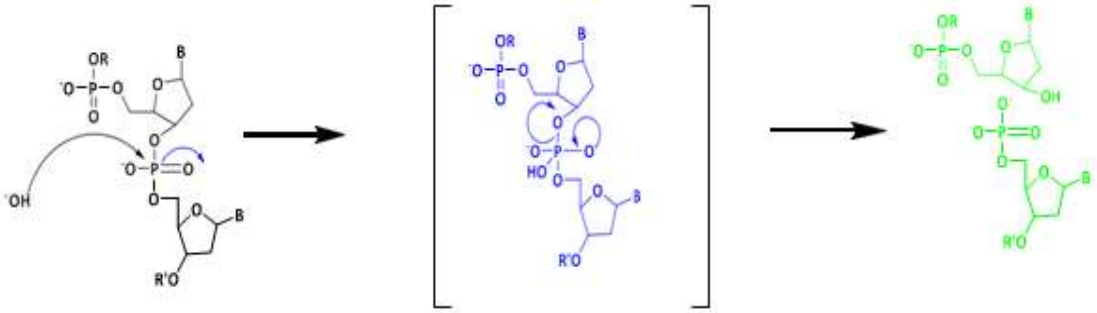


Figure 1: Schematic diagram of sofalcone, chalcone and metochalcone

2. **Amphiphilic Metal Complexes Binding to Bio Molecules:** Understanding how physiologically active compounds interact with Deoxyribonucleic acid (DNA) and proteins is crucial to understanding their mode of action. The fundamental issues with amphiphilic complexes are how much metallo surfactants differ from their non-amphiphilic analogues in terms of their DNA or protein binding characteristics, and how can aggregation in solution affect the binding affinity towards these biomolecules.19



Scheme 2: General mechanism of hydrolytic DNA cleavage

3. **Metal Complex For Anti-Cancer Drug Agent**: Metal complexes have recently attracted a lot of interest in bioinorganic medicinal chemistry because of their ability to chelate or coordinate with a number of metals and exhibit modulatory effects on a variety of anti-cancer targets. Several powerful and less toxic coordinated complexes with promising anticancer action were recently synthesized employing chalcone scaffold (Figure. 2). In a study, Gaur et al. synthesized two ruthenium chalcone complexes, [Ru2(L)(DMSO)6Cl2] and [RuCl(DMSO-S)3(L)](L = 1-(2-hydroxyphenyl)-3-(4-chlorophenyl) propenone) (1) and (2), respectively, and investigated their intercalating potential. Both freshly produced complexes demonstrated a remarkable capacity to intercalate and firmly adhere to the DNA groove. The calf-thymus DNA sequence d(ACCGACGTCGGT)2 and the complex interacted through electrostatic and hydrogen bonding interactions. The complex effectively cleaves the super-coiling of the pBR322 plasmid DNA and binds through the main groove of the DNA, according to the nuclease activity. Comparatively, complex (2) showed similar DNA binding, but the contact was determined to be stronger with the minor groove.20,21

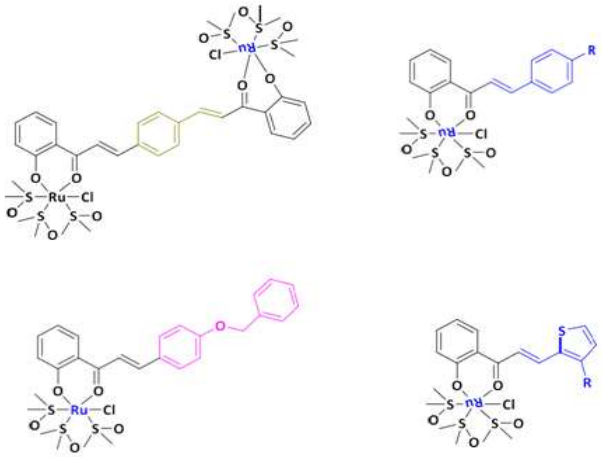
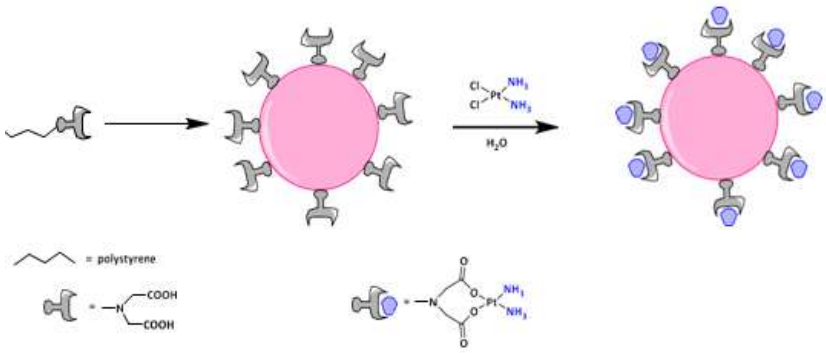


Figure 2: Schematic diagram of chalcone complex for anti-cancer agent

4. **Anticancer Activity:** Cisplatin is one of the most effective anticancer drug agent. There are numerous instances when cisplatin has been added to a micellar system and studied in vitro and in vivo. For instance, block copolymer micelles that were covalently cross-linked by cisplatin demonstrated decreased nephro- and neurotoxicity in rats.22 Clinical trials are being conducted on a few micellar and liposomal systems, most of which are composed of polymers containing cisplatin or oxaliplatin derivatives linked to them. Due to their block structure, the polymers used are typically already amphiphilic by nature and cannot be attributed to the traditional metallo surfactant structure.23 There are other potential options as listed below, however, research beyond in vitro, i.e. in vivo, have not yet been published for other amphiphilic complexes. Since ruthenium has been discussed as a platinum substitute in anticancer treatment, such as when coordinated to DMSO and imidazole like in NAMI-A, it is of special importance in this context.24



Scheme 3: Cisplatin-derived micelles for anticancer therapy

5. **Reported Metal Chalcone Complexes:** For several metals in the periodic table, their ligand behavior and their derivatives have been described. In accordance with its organization, we start beryllium and magnesium then move on to other transition metals like Fe, Ru, Co, Ni and Cu as well as some P-block metal named as Ga and Te. We observed that the few transition metals like Co, Ni, Cu, Zn play important roles in biological science. In comparison to the remaining transition metals and rare earth metals, there are much fewer well-described metal complexes.25

III. EXPERIMENTAL SECTION

1. **Synthesis of Transition Metal Complex:** The transition metals are very good chelators because of their size, charge, functional group as well as thermal and oxidative properties. In order to synthesized chalcone metal complexes, it is necessary to react the metal and metal salt in an organic solvent and the ion acceptors are soluble in methanol, ethanol and acetonitrile.26

In terms of concentration, pH, temperature, ligand metal ratio, inert atmosphere will be applied for synthesis of metal complexes. The complex can be produced in one of two ways: one by refluxing via stir condition and secondly via crystallization procedure. The more popular technique is still reflux synthesis. The pH was adjusted by a metal ion before the chalcone was added to the solution to aid in deprotonation. Dropwise additions of metal ions are then made from a solution, maintaining the ligand-metal ratio (typically

2:1). Many chalcone independently dissociable proton molecules they behave as weak polyprotic acids, pH is a key factor in the formation of complexes. Though it also largely relies on the metal ion, the ideal pH for the production of the majority of metal chalcone complexes is somewhere about 6. Chalcones exist in a protonated state at a pH below 3, which is not conducive to metal complexes. At higher pH values (more than 8), as is often the case with the metal complexation reaction, the deprotonated form of the chalcone predominates in favor of complexation, however there is a risk of metal hydroxide precipitation at high pH. The metal chalcone complexes usually contain two chalcone molecules due to steric considerations. However, 3:1 ligand metal ratio is the best way to the formation of metal complex.27

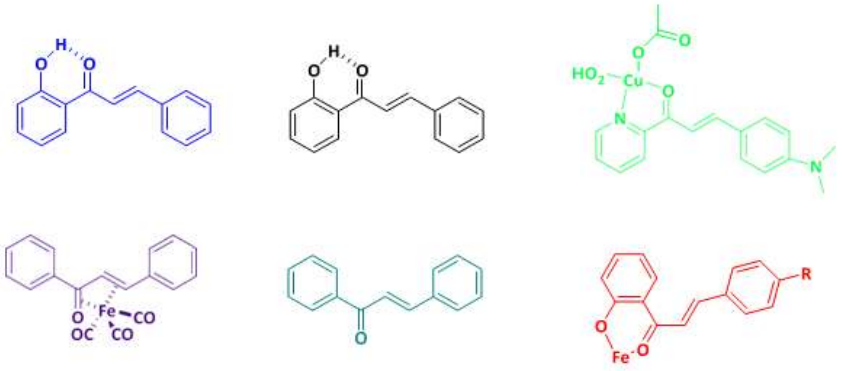


Figure 4: Chalcone metal complex

2. **Structural Characterization Of Metal Complexes:** The primary analytical techniques used for the characterization of metal complexes are elemental analysis and spectroscopic approaches such IR, UV-Vis spectroscopy, XRD, 1H and 13C NMR, and mass spectrometry.28 The 13C NMR spectra is not any time fruitful for characterization of metal complex due to just display of carbon spectra of free ligand. It has been investigated the nature of the complexation and determined site coordination Job's plot is required. In addition, various methods have been used, including thermogravimetry29,30 to confirm the thermal stability of complex. X-ray structural analysis to elucidate the structure and configuration of the end result.31

Figure 5: Characterization of chalcone metal complex

IV. APPLICATION

Metal complexes are the novel area of study. In terms of the quantity of publications, metal complexes of chalcones with anticancer properties is most active research in biological science. For instance, Ru-chalcone compounds have demonstrated the ability to suppress the growth and proliferation of tumors as well as cancer cells, with strong selective in-vitro cytotoxicity against ovarian cancer cells and act as a novel anticancer agent. On the basis of the finding, ruthenium chalcone complexes may hold significant promise for the development of novel, non- classical anticancer medications. The antioxidant and antibacterial properties of scavenging free radicals are demonstrated in conjunction with metal ions like zinc or copper that have further relevant uses. In this situation, chalcone complexation is essential to increase the stability of metal ions through the membrane.32 However, some compounds' poor water solubilities make them unsuitable for biological purposes. Adding extra hydrophilic groups to the chalcones skeleton would be a logical strategy. No metal-chalcone complex has reached the point of clinical trials for medicinal uses, in part due to limited solubility, and investigations are still in the in vitro stage. Overall, it is necessary to improve the synthesis processes for metal complexation to have greater control over the structures that are produced, and it is also important to pay more attention to structural characterization in order to open the door to understanding their mode of action. Only a small number of potential pathways, including those backed by well- known theories like the chelation theory, have been put up to account for a particular bioactivity33. The question of whether and how the metal complexation is related to the frequently observed enhanced activity is still unanswered because none of these pathways have been properly investigated. Because of this, it looks extremely desirable to continue fine-tuning the biological activities by meticulous ligand design at the current stage of study. It is possible to derive important aspects affecting the biological activity of metalchalcone complexes through critical analysis of the facts reported here, which may be useful for future considerations.34

1. **Electronic Stability of Transition Metal Complex:** The stability of the complex is increased and its polarity is decreased by a suitable distribution of the electron densities of the metal and ligand, encouraging the translocation of the polar metal that is protected by the intact complex across the membrane. When combined with electron-deficient chalcone ligands, the transition metals with more electrons, such Cu(II), are usually more stable. The contrary is also true. Chalcone ligands with extended coplanar p-systems have been found to increase the lipophilicity of metal complexes, however this may have an impact on the final coordination geometry, raising the overall polarity.

2. **Crystal Field Energy:** Highly potent chalcone ligands with significant electron delocalization corresponding to the low energy molecular orbitals form stable low-spin complexes, which are usually square planar structures. Similar to this, excessively high complexes irreversibly bind their target sites.

3. **Unpaired Electron:** In comparison to comparable diamagnetic complexes, paramagnetic compounds having copper (Cu) and cobalt (Co) show greater antioxidant and biocidal activities. Similar results are obtained by giving unpaired, highly reactive metal electrons into the relevant high energy molecular orbitals in various chalcone complexes which are low crystal field stabilized.

4. **Metal complexes overview in Medicinal Chemistry:** Several different similar chemicals were developed and assessed shortly after cisplatin was first used in clinical settings. Two cis coordinated leaving groups in neutral Pt (II) complexes with square-planar geometry have been identified as crucial structural elements for anticancer action.35 Complexes made of gold (III) have long been sought after as cancer prevention measures. Numerous gold (III) complexes have shown intriguing anticancer properties, but their limited medical potential has long been a problem. A number of physiologically stable gold (III) complexes with notable in vitro and in vivo anti-cancer properties were created by Che et al.36 According to research, a panel of cancer cell lines were sensitive to the [Au (TPP)] Cl (H2TPP = tetraphenylporphyrin) complex, which demonstrated strong in vitro anticancer activity

Table 1

Sl. No.	Metal Complex	Mechanism of action	Medicinal use
1	Platinum (Pt)	a) Apoptosis induction of cisplatin by cellular absorption, aquation/activation, DNA platination, and cell processing. b) cytoplasm's acidification, ER stress, disruption of RNA transcription, suppression of crucial oncogenic proteins, and loss in metabolic adaptability by cisplatin.[37]	Compounds based on platinum have a particular impact on head and neck tumours. It is believed that these coordination complexes function to cross-link DNA in cancer cells.[38]
2	Gold (Au)	a) **Immunomodulation**: The gold salts are thought to bind with albumin and then be absorbed by immune cells, where they are thought to cause anti-mitochondrial actions and ultimately cell death. b) **Suppression of cell proliferation**: Gold compounds can inhibit the proliferation of certain immune cells, particularly T cells, which are involved in the inflammatory response in RA (Rheumatoid Arthritis) c) **Induction of apoptosis**: Gold compounds have been shown to induce apoptosis in specific immune cells, including activated T cells. By promoting the elimination of pathogenic immune cells, gold compounds may help regulate the immune response in RA.[39]	The term "chrysotherapy" refers to the application of gold formulations in medicine, particularly for the relief of joint pain and the management of inflammatory conditions like rheumatoid arthritis.[40]

3.	Lithium (Li)	a) Inhibition of glycogen synthase kinase-3 (GSK-3) b) Modulation of neurotransmitter systems by influencing cell membrane characteristics, cell membrane transport and ion distribution, neurotransmitter modulation, and intracellular signalling.[41]	Li_2CO_3 can be used to prevent the onset of manic-depressive symptoms, bipolar disorder and conditions.[38]
4.	Zinc (Zn)	a) cell proliferation and tissue repair. b) Impair immune function and increase the susceptibility to infections, including herpes.[42]	Applying zinc topically can help heal wounds. Herpes can be treated with zinc oxide (Zn^{2+}).[38]

V. CONCLUSION AND FUTURE PROSPECTIVE

This chapter presents the first thorough overview of the emerging and growing subject of metal complexes. The primary group metals, transition metals, and various chalcone complexes that include them are listed along with their biological activities. We describe novel synthetic methods for the synthesis of stable and crystallisable metal chalcone complexes. This book chapter focuses on effective and potential applications of metal chalcone complexes in the biomedical field, which are produced by the synergistic interaction of intrinsic metal and chalcone characteristics and typically improve biological activities. The use of metal-chalcone complexes as potent reactive oxygen species scavengers and superior antioxidants may open up new possibilities for chalconoids. Additionally, certain metal chalcone complexes have been observed to have antiviral/anti-HIV and antibacterial properties.

This chapter focuses on the current status and future prospective biochemistry applications of metal complexes, which comes about as a result of the synergistic interaction between the inherent metal and chalcone features, typically boosting the biological activities. The use of metal-chalcone complexes as potent reactive oxygen species scavengers and superior antioxidants may open up new possibilities for chalconoids.

For several metal chalcone complexes, additional antiviral/anti-HIV and antibacterial characteristics have been discovered, suggesting that these substances may become "multi-anti" agents like the chalcone itself in future. The therapeutic usage of metal complexes is currently an unknown field of study and may be helpful to create new therapeutic medicines.

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