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Metal Complexes as Antimicrobial, Antiviral and Antiparasitic Agents

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ABSTRACT

Metal complexes have demonstrated multifaceted utility, serving as potent antimicrobial, antiviral and antiparasitic agents due to their diverse properties and mechanisms of action against drug-resistant pathogens. Cobalt (III) complexes to copper (II) compounds have showcased remarkable efficacy against a variety of microbial adversaries. They exhibit broad-spectrum activity, targeting viruses, bacteria, fungi, and protozoa with equal fervour. Notably, cobalt (III) complexes like the CTC series have shown promise as antiviral agents, particularly in inhibiting the replication of the herpes simplex virus and other viral strains. Similarly, copper (II) complexes have displayed potent antiparasitic properties, effectively combating parasites such as *Trypanosoma cruzi*, the causative agent of Chagas disease. As the threat of antimicrobial resistance looms large, the exploration of metal complexes offers a ray of hope in the quest for effective treatments. This review explores the unique properties of these metal complexes and their application as antimicrobial, antiviral and antiparasitic agents. Furthermore, the review discusses the proposed mechanism of action of metal complexes as they interact with drug-resistant microbes.

Keywords: metal complexes, antimicrobial, antiviral, anti-parasitic

INTRODUCTION

The treatment of infectious diseases is a major challenge due to emerging infections and the rise of multi-drug resistant pathogens a phenomenon called antimicrobial resistance (AMR). This 'silent pandemic' dates back to penicillin discovery. Since then, researchers are actively searching for novel compounds and nano-technological materials to combat resistant pathogens and mitigate the global burden of antimicrobial resistance[1]. Despite the discovery of various strong antimicrobials, the increase in antimicrobial resistance still calls for new classes of antimicrobial agents with unique mechanisms of action. This is because antimicrobial resistance has been primarily linked to the constant evolution of microbes. This evolution process has been accelerated by the excessive or improper use of antimicrobials and inadequate infection control in healthcare centres.

Infections caused by drug-resistant pathogens have become a significant cause of illness and deaths worldwide as it is reported that pathogenic diseases worldwide account for nine million

deaths annually[2]. According to recent updates from the Infectious Diseases Society of America, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species are identified as the most concerning pathogens, particularly; methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and fluoroquinolone-resistant *P. aeruginosa*, which are showing a rapid increase in infection rates. Treatment failures with these resistant strains often lead to high mortality rates[3]. To combat the high mortality rates, medical professionals have resorted to using 'last resort' antibiotics such as carbapenems. Unfortunately, cases of resistance to 'last resort' antibiotics are also increasing leaving the world susceptible to incurable infections.

Metal-based antimicrobial substances hold immense promise in combating antimicrobial resistance among pathogens. These substances leverage the unique properties of metals to effectively target and eliminate resistant microbes[4]. Metal ions and their binding components are integral to a multitude of biological processes, exerting significant influence on cellular functions and organismal physiology. For example, Calcium (Ca^{2+}), magnesium (Mg^{2+}), zinc (Zn^{2+}), copper (Cu^{2+}), iron (Fe^{2+}), and manganese (Mn^{2+}) ions play essential roles in biological processes within the nucleus. These ions are present in detectable amounts and are bound to DNA and RNA in the cells[5]. According to Claudel and co-workers[6] metal atoms are soluble in biological fluids because they easily lose electrons and generate positively charged ions. Their electron deficiency allows them to interact easily with electron-rich biomolecules like DNA and proteins, influencing catalytic mechanisms or stabilizing their structures. Coordination complexes and organometallics offer diverse oxidation states, coordination numbers, and geometries, leading to numerous structures. By understanding biological processes, tailored metal–ligand combinations can be designed for specific interactions. These combinations have been utilized to inhibit enzymes, label proteins, image cells, probe bio-macromolecules, alter bioavailability, and act as MRI contrast agents. Moreover, the versatility of metal–ligand combinations allow for the design of entities with various properties like charge, solubility, and chemical reactivity. These complexes offer diversity in medicinal chemistry, especially as antimicrobial agents combating drug-resistant diseases. Their strategic manipulation through rational design holds immense promise for the development of innovative therapeutic drugs and diagnostic probes. Iron is predominantly stored in the body as ferritin, an iron-binding protein, with significant reserves in the liver, bone marrow, and spleen. The cellular levels of iron are controlled by iron-responsive element binding proteins IRP1 and IRP2. **Figure 1** illustrates a basic outline of iron absorption, distribution, and recycling in the body which is an example of metal ion interaction with proteins[7].

Metals have been proven through multiple studies to target multiple cellular sites within microbial cells, including the cellular membrane, genetic material, and reactive oxygen species-mediated cellular processes. This contrasts with organic antibiotics, which usually target particular biochemical pathways such transcription, translation, replication, and enzymatic activities. The broad-spectrum activity of metals against microbial cells makes them promising candidates for combating antibiotic-resistant microbes[8].

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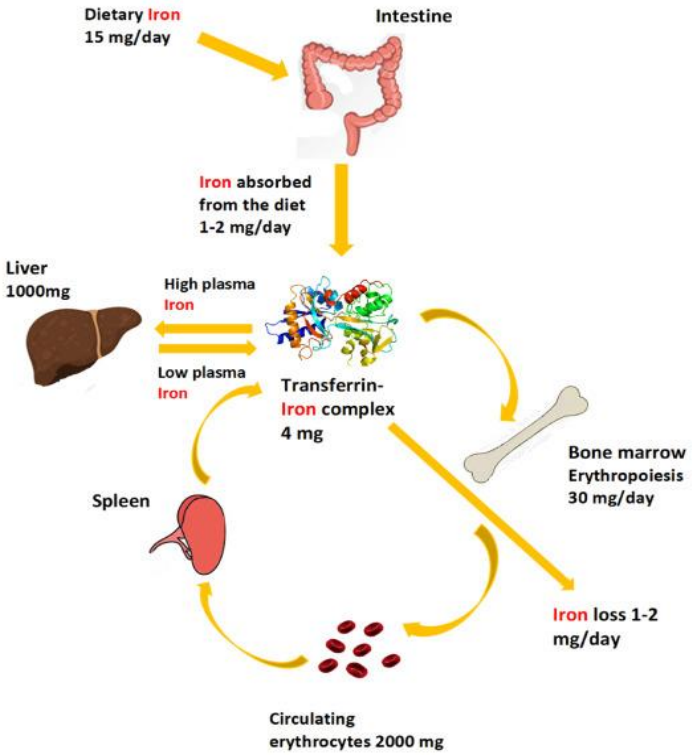

Figure 1: A simple scheme of iron absorption, distribution and recycling in the body.

Antimicrobials are medical compounds that are used to treat or prevent infections by destroying microorganisms or inhibiting their growth. These agents inhibit relevant microorganisms by interfering with vital processes within the cell, such as the production of macromolecules, functioning of cellular enzymes, or the overall integrity of cellular structures like the cell wall and/or cell membrane. The history of antimicrobial therapy has been a journey of discovering drugs effective against microbial species resistant to existing treatments. These drugs have saved lives and reduced illness burdens when used to treat severe infections or prevent them in certain situations. However, as many antimicrobials are derived from microorganisms, some microbial strains have evolved to resist them by inactivating or becoming impermeable to these drugs. Antibiotic resistance for instance presents a major global health threat, as bacteria have developed resistance to all antibiotics currently used in clinical practice, and there are only a limited number of new drugs being developed. It's crucial to comprehend the molecular mechanisms bacteria employ to resist antimicrobial agents. This understanding helps identify global trends in resistance and enhances the utilization of existing drugs. Additionally, it aids in designing new medications less prone to resistance development and innovative strategies to tackle resistance effectively[9]. Due to their innate ability and tendency to defend themselves against these substances, microorganisms tend to develop resistance to antimicrobial substances. The resistance occurs when antimicrobials are not able to enter microbial cells due to the differences in their chemical properties or changes in the structure of the microbe's membranes which then acts as a barrier [9]. Resistance can be acquired from external factors such as misuse of antibiotics and/or wrong prescriptions or internal factors such as genetic changes through spontaneous mutations or by transfer of resistance genes from other microbes. Other contributing factors include mechanisms like antibiotic inactivation, alterations in the target sites of antibiotics, reduced membrane permeability, and

the presence of efflux pumps that expel drugs from the microbial cells. This review presents literature on the development and potential application of metal complexes in eliminating different types of bacteria, antiviral and antiparasitic agents.

Metal Complexes as Antimicrobial Agents

Over the years, the emergence of antimicrobial resistance has posed a significant threat to human health, which led to the exploration of alternative routes of therapeutic strategies. Reports indicate a continuous rise in the prevalence of drug-resistant strains, contributing to widespread health concerns worldwide. Notable examples include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and numerous other drug-resistant human pathogens prevalent in regions such as Europe and the United States[10]. Sharma and co-workers[11] reported that Paracelsus, a Swiss physician, used silver compounds internally and externally to treat wounds which as a tradition in the medicinal world is still being applied today as these compounds show the ability to harm or kill different types of bacteria (Gram positive and Gram negative) and fungi. For instance, silver sulfadiazine (**Figure 2**) creams (silvazine and flamazine) are used to treat wound infections[11].

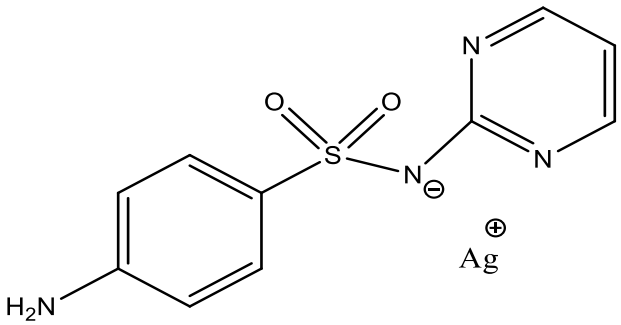

Figure 2: Silver sulfadiazine.

Silver has been proven to cause structural changes and interact with nucleic acids in the bacterial cells [12]. A study by Feng[11], it demonstrated that upon treatment of *E.coli* and *S. aureus* with silver ions (Ag^{+}) morphological changes occurred as the membrane surrounding the cytoplasm separated from the cell wall. The mechanism of action of silver and its complexes still needs further investigations. However, silver complexes have possess cytotoxic properties against gram-positive and gram-negative bacteria as well as fungi as it has strong affinity to thiol (sulfhydryl, SH) groups in bacterial cells in structural or enzymatic proteins. The efficacy of palladium complexes against resistant microorganisms has also been documented in scientific literature. For instance, the Pd (II) complex of tetracycline has demonstrated remarkable potency against tetracycline-resistant bacterial strains, such as *E. coli*. This complex exhibited a sixteen-fold increase in effectiveness compared to the parent compound. Similarly, the Pd (II) flubendazole complex (**Figure 3**) of doxycycline has shown twice the potency against microorganisms compared to doxycycline alone[13].

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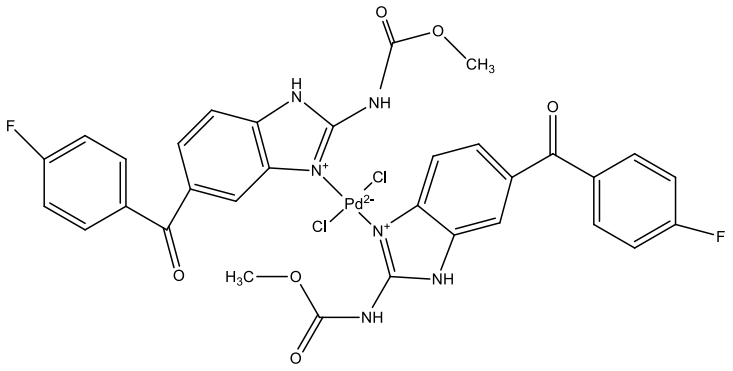

Figure 3: Pd(II) flubendazole complex of doxycycline.

Additionally, tin complexes have exhibited antimicrobial activity, including organotin (IV) complexes containing N-alkylisatin bisthiocarbonohydrazones and isatin. Copper ions, known for their antifungal effects, have also been studied extensively for their antimicrobial potential. Metal complexes also demonstrate activity against a wide range of fungi through unique inhibitory mechanisms. For example, the coumarin complex, along with its associated metals like copper, cobalt, nickel, and zinc, displays antifungal properties against several fungal species including *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani*, and *Candida glaberata*[14]. Metal complexes of coumarin containing ligands with nitrogen (**Figure 4**) and oxygen donor systems were proven to poses inhibitory characteristics relevant to these fungal species as they inhibited their enzymatic activities in a study, which then destroyed their existence[14].

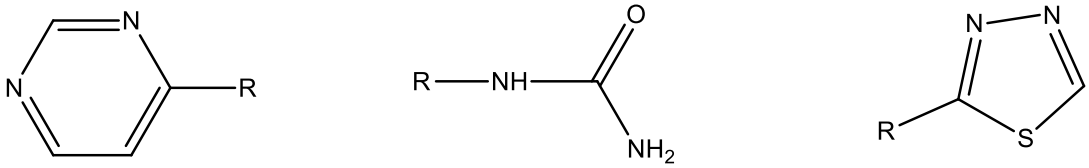

Figure 4: Ligands used for in-vitro antifungal activity.

Schiff bases have been investigated for their potential in various biological and therapeutic applications, making them promising candidates for drug development or as biological samples. These applications include their use as anti-bacterial agents, antifungal agents, antiviral agents, anti-inflammatory agents, anti-tumor agents, anti-cancer agents, and anti-diabetic agents[15]. Schiff base ligands play a pivotal role in modern coordination chemistry, as metal complexes of Schiff bases represent some of the most extensively studied coordination compounds. The ligand functions as a monobasic ligand, coordinating *via* three species: the oxygen of the carbonyl group in the enol form (—C═O—), the nitrogen atom of the azomethine —C═N—) group, and the phenolic –OH group. The ligands are synthesized by condensing primary amines with carbonyl compounds one example is (**Figure 5**) with an octahedral geometry for the Co(II), Ni(II), and Cu(II) complexes[16].

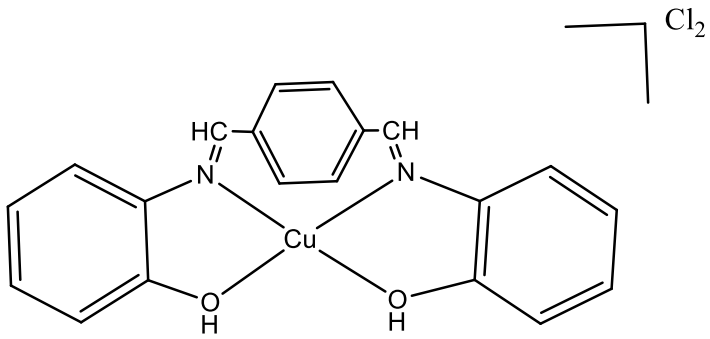

Figure 5: Copper (II) Complex with Schiff base.

Metal Complexes as Antiviral Agents

Viral diseases are ubiquitous worldwide and can range in intensity from minor ailments to life-threatening infections, as demonstrated by the recent Covid-19 pandemic. Despite significant advancements in biomedical sciences, viral infections continue to pose a significant challenge to global health[17]. Vaccination programs have played a crucial role in eradicating or significantly reducing the burden of numerous diseases. For instance, smallpox was successfully eradicated in 1979 and the incidence of poliomyelitis, a paralytic disease, has been greatly reduced due to vaccination efforts[18]. However, despite these successes, there are still several viral pathogens for which effective vaccines are not yet available[19]. According to Domingo and co-workers[20], viruses can emerge due to multiple factors, including alterations in the host, environment, or vector. New pathogenic viruses can arise in humans from existing human viruses or from animal viruses. Over the last few decades, several viral diseases that emerged have become established in human populations worldwide. Some well-known examples include the SARS coronavirus, West Nile virus, monkeypox virus, Hantavirus, Nipah virus, Hendra virus, Chikungunya virus, and the ongoing threat of pandemic influenza viruses, particularly those of avian or swine origin[20].

The course of viral infections is determined by complicated reactions between the virus and the host biological systems. All viruses require a host cell to synthesise their proteins. As a result, all viruses proliferate in a remarkably identical manner. The virus must first connect to the cell before entering the cytoplasm. The genome is released from the protective capsid and, either in the nucleus or in the cytoplasm, it is transcribed, and viral mRNA controls protein synthesis in a generally well-regulated manner. Finally, the virus replicates its genome and, along with viral structural proteins, forms new virions that are expelled from the cell[19]. Each of the steps mentioned here provides a potential target for inhibition. Drugs which inhibit viral attachment or entry have been challenging to discover. Galdiero and co-workers[19] further showed that targeting the initial stages of virus entry presents an appealing strategy for therapeutic intervention because inhibitors can act extracellularly, making them relatively accessible. This approach could be enhanced by a single drug simultaneously targeting multiple entry points, leading to a more effective therapeutic compound. Furthermore, there is potential for the development of broad-spectrum antiviral agents capable of combating viruses from various families. Such agents could serve as first-line treatments for unexpected viral epidemics or pandemics in the future. Only one entrance inhibitor, enfuvirtide (T-20), a synthetic peptide that blocks the HIV gp41 envelope protein to stop fusion, had received FDA approval by 2011[19]. In a research by De Castro and co-workers [17] nearly 90 compounds have received approval for clinical use, primarily targeting treatments against a range of viral infections including hepatitis

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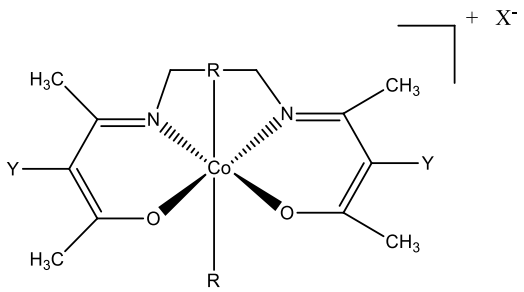
B (HBV), hepatitis C (HCV), herpes simplex (HSV), influenza, cytomegalovirus (CMV), and human immunodeficiency virus (HIV). Antiviral drugs are primarily classified into several categories, including DNA polymerase inhibitors, reverse transcriptase inhibitors, protease inhibitors (PI), and other types of antiviral drugs (OT). Additionally, antiviral medications are not strain-specific like vaccines are, which means they can also work against novel virus strains, particularly during pandemics.

In recent studies, there has been a discovery of Co (III) complexes formed with both mono and polydentate ligands, which exhibit both antiviral and antibacterial activities [21]. The most common form of ligand utilised in stabilising the cobalt (III) ion in aqueous solutions is the chelating N, O donor ligand. Cobalt (III) complexes generated from this ligand donor set have been shown to have antibacterial or antiviral properties. Among the classes with potential are the CTC complexes (Charge-transfer-complexes) (**Figure 6**), which are made up of a chelating Schiff-base, imidazole, and 2-methylimidazole. CTC class of drugs have been used in a rabbit eye model infected with Herpes Simplex Virus Type 1 (HSV-1), and all complexes demonstrated inhibition of HSV-1 replication in vitro. Remarkably, strong antiviral activity was observed with concentrations as low as 5 μg/mL [21].



1a: Y = H; R = amine; X = Cl
1b: Y = Cl; R = amine; X = Cl
1c: Y = H; R = imd; X = Cl
1d: Y = H; R =2-mimd; X = Br

Figure 6: Structure of CTC-type Cobalt (III) complex. imd = imidazole and 2-mimd = 2-methylimidazole.

Even though the exact mechanism of action of the CTC complexes has yet to be fully understood, it has been proposed that their molecular target is the herpes virus's maturational protease, a serine protease rich in the amino acid histidine (**Figure 7**) [21]. According to Takeuchi and co-workers [22] CTC complexes are known for their high affinity for nitrogenous donors like histidine residues. It's plausible that they bind at the axial position and potentially inhibit an enzyme vital for viral replication[21]. Supporting this, evidence suggests that the interaction with axial histidine is crucial. For instance, a cobalt(III) chelate complex with an imidazole ligand already in the axial position (1c, CTC-82) was found to be inactive against HSV-1[20]. Furthermore, CTC-96 (1d) has been shown to inhibit membrane fusion events, preventing virus entry, as evidenced by its inhibition of plaque formation by VSV (vesicular stomatitis virus) and VZV (varicella-zoster virus) [23].

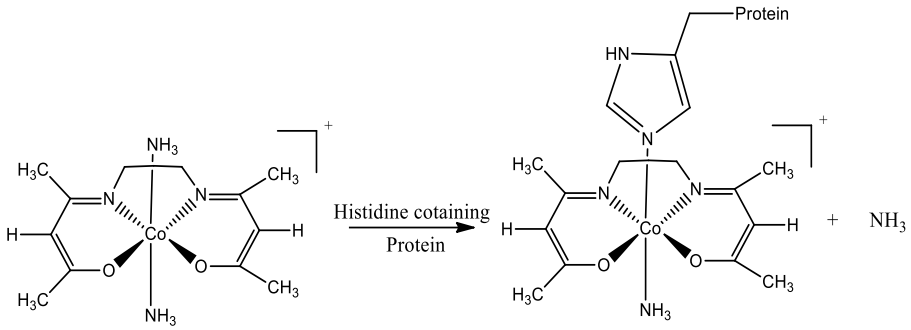


Figure 7: Interaction of a histidine containing protein with CTC complexes.

Takeuchi and co-workers[22] documented the synthesis of CTC-96, while Redox Pharmaceutical Corporation manufactured and distributed the therapeutic formulation DoxoviTM (**Figure 8**). CTC compounds were also discovered to inhibit Sp1, a DNA-binding zinc finger protein, suggesting that they could be used to treat human immunodeficiency virus type 1 (HIV-1) [22].

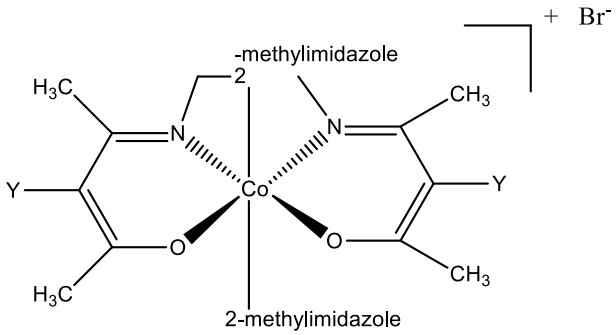


Figure 8: The general structure of Doxovi™, CTC-96

Metal Complexes as Antiparasitic Agents

It's been well known over the world for several years that parasitic diseases are of great concern globally [24]. Among other parasites, protozoan parasites, which are single-celled eukaryotic organisms representing a diverse and polyphyletic group are known to cause majority of diseases worldwide especially in underdeveloped countries. These protozoan parasites include Trichomonas vaginalis, Plasmodium falciparum, Giardia intestinalis, Trypanosoma cruzi and Leishmania Mexicana and are well known to cause significant diseases in humans, the diseases they cause are accountable for approximately 500 million fatalities worldwide [25]. Work by Utzinger and co-workers [26], stated that the transmission methods of these protozoan parasites vary, reflecting their diverse ecological life cycles. Some are carried by insects acting as vectors, such as *Plasmodium* species (which cause malaria), *T. brucei* (the agent behind human African trypanosomiasis, or HAT), *T. cruzi* (the cause of Chagas disease), and various *Leishmania* species (responsible for leishmaniasis). On the other hand, parasites like *E. histolytica* (which leads to amebiasis), *Cryptosporidium parvum* (causing cryptosporidiosis), *Cyclospora cayetanensis* (associated with cyclosporiasis), and *Giardia lamblia* (responsible for giardiasis) are transmitted through the consumption of contaminated food or water tainted with faecal matter. This wide array of transmission modes reflects the complex interactions between these parasites, their hosts, and the environment [26]. Various metal complexes target different parasites, with protozoa being among them. New antibiotic drugs have been developed to combat parasitic diseases such as giardiasis, leishmaniasis,

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malaria, trichomoniasis, and trypanosomiasis. Trypanosomiasis, also known as Chagas disease, is classified by The World Health Organisation (WHO) as one of the potential fatal neglected tropical diseases which is caused by the flagellate protozoa *Trypanosoma cruzi* which enters the human bloodstream through injection by triatominae bugs in their trypomastigote form [27]. *T. cruzi* infection has two phases: acute and chronic. During the acute phase, which typically lasts 3 to 4 months after parasite entry, patients often show no symptoms. However, there's a high level of circulating parasites in the blood, making direct diagnosis possible. The chronic phase follows as the immune response reduces parasite levels. In this phase, IgG antibodies are present, and parasite levels are low and sporadic, requiring amplification methods for detection [28]. The clinical treatment currently available for chagas disease relies on drugs that were developed decades ago, such as benznidazole or nifurtimox. According to Guedes and co-workers [29] clinical trials involving nifurtimox and benznidazole (**Figure 9**) have demonstrated their limited efficacy in preventing the progression of chronic Chagas disease. Additionally, these drugs are associated with a range of toxic side effects [29].

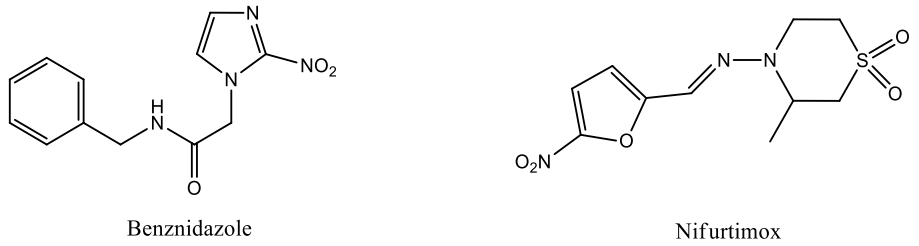

Figure 9: Structures of some of the available anti-trypanosomal drugs.

The identification of new compounds with higher activity and reduced toxicity holds the potential to broaden treatment options, including for patients without evident clinical symptoms or whose manifestations require more sophisticated medical assessments for detection[26]. New antiparasitic medications against trypanosomiasis are developed by evaluating various complexes, such as Co (II) or Cu (II) with triazole derivatives, Pt (II) or Pd (II) with thiosemicarbazones, Ru (II) with lapachol or thiosemicarbazones, and vanadium with polypyridyl ligands. These investigations examine how complexes affect parasite targets such as cysteine proteases, HGPRTs, and DNA [29]. Recent studies have reported the survival of *T. cruzi* when exposed to benznidazole (BZ), even when using genetically modified parasites that overexpress different DNA repair proteins [30]. These investigations have highlighted that this drug induces double-stranded DNA breaks in the parasite, thereby supporting its mechanism of action through the formation of reactive oxygen species (ROS), particularly hydroxyl radicals[30]. The significance of ROS in *T. cruzi* infections has been underscored, as high levels of ROS are detrimental to the parasite. However, it was also noted that when ROS production was inhibited in the host cell, a significant reduction in the proliferation of wild-type parasites was observed[27]. For these reasons, Portes and co-workers[26] explored oxindolimine–metal complexes (**Figure 10**) as potential antiparasitic agents due to their ability to generate reactive oxygen species (ROS) and their notable antitumor properties. In their report these complexes demonstrated efficacy in inducing oxidative damage to DNA and mitochondria, in addition to inhibiting selected proteins. Given these promising characteristics, they investigated their potential as antiparasitic agents. The complexes used for this study are shown below. All of the metal complexes demonstrated efficacy against the trypomastigote forms of parasites, surpassing the activity of the free ligands. Specifically, complexes 1 and 2 exhibited the highest

activity within the series. Interestingly, copper (II) complexes outperformed the corresponding zinc (II) complexes with the same ligand, suggesting that the ability of copper compounds to generate reactive oxygen species (ROS) may contribute to their superior performance[27].

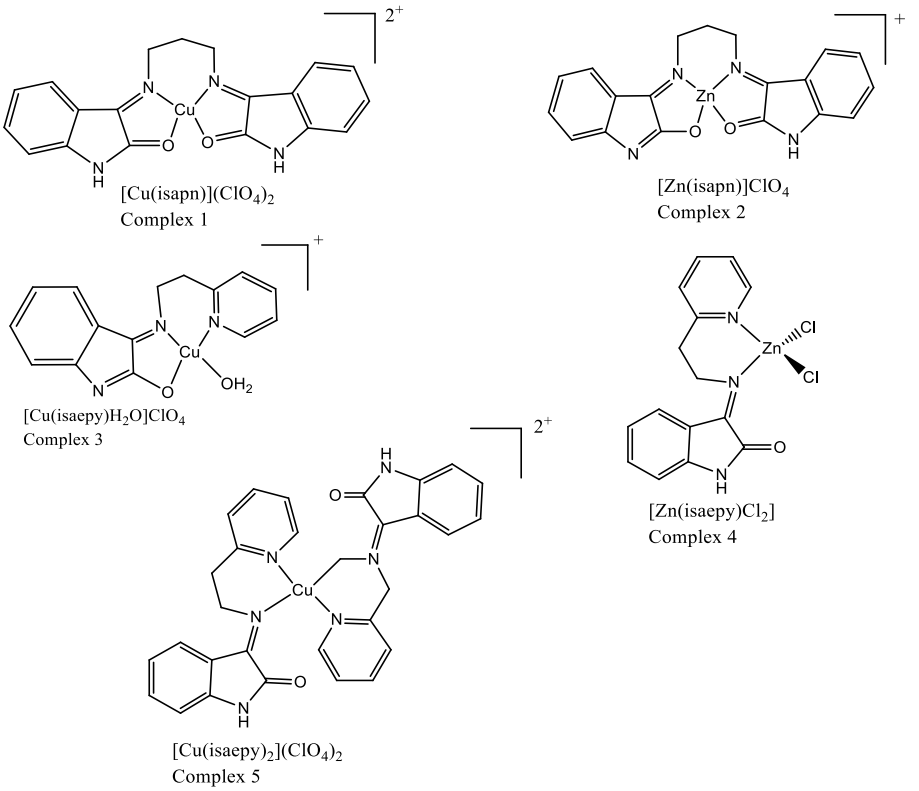

Figure 10: Structures of the oxindolimine-metal complexes.

CONCLUSION

The fight against antimicrobial resistance demands innovative solutions, and metal complexes are stepping up as potential game-changers. With their distinct ways of working and ability to tackle a wide range of pathogens, these complexes offer hope for overcoming the challenges posed by drug-resistant microbes. When it comes to battling viruses, metal complexes show real promise. For instance, the CTC series. These cobalt (III) complexes have caught researchers' attention for their ability to take on herpes simplex virus and other viral nasties. They could pave the way for new antiviral treatments that work differently from traditional options. But it's not just viruses that metal complexes are taking on. They're also showing potential in the fight against parasitic diseases, especially those caused by protozoa. With diseases like trypanosomiasis on the radar, these complexes offer fresh hope for treatments that could make a real difference in neglected tropical disease hotspots. In the grand scheme of things, exploring metal complexes as antimicrobial agents is opening up exciting new possibilities. Their unique qualities and wide-ranging effectiveness mean they could be key players in turning the tide against drug-resistant infections and helping the community at large stay one step ahead of infectious diseases worldwide. The use of metal complexes, with further investigations and refinements, has the potential to revolutionize the field of antimicrobial therapy and safeguard global health.

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Conflicts of Interest
There are no conflicts of interests.

References
1. Rizzotto, M. (2012). Metal complexes as antimicrobial agents. A search for antibacterial agents, 10, 45651

2. Wang, S., Zeng, X., Yang, Q., & Qiao, S. (2016). Antimicrobial peptides as potential alternatives to antibiotics in food animal industry. International journal of molecular sciences, 17(5), 603.

3. Li, F., Collins, J. G., & Keene, F. R. (2015). Ruthenium complexes as antimicrobial agents. Chemical Society Reviews, 44(8), 2529-2542.

4. Liang, X., Luan, S., Yin, Z., He, M., He, C., Yin, L., Zou, Y., Yuan, Z., Li, L., & Song, X. (2018). Recent advances in the medical use of silver complex. European Journal of Medicinal Chemistry, 157, 62-80.

5. Anastassopoulou, J., & Theophanides, T. (1995). The role of metal ions in biological systems and medicine. In Bioinorganic Chemistry: An Inorganic Perspective of Life (pp. 209-218). Springer.

6. Claudel, M., Schwarte, J. V., & Fromm, K. M. (2020). New antimicrobial strategies based on metal complexes. Chemistry, 2(4), 849-899.

7. Jomova, K., Makova, M., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., Rhodes, C. J., & Valko, M. (2022). Essential metals in health and disease. Chemico-biological interactions, 367, 110173.

8. Di Martino, P. (2022). Antimicrobial agents and microbial ecology. AIMS microbiology, 8(1), 1.

9. Darby, E. M., Trampari, E., Siasat, P., Gaya, M. S., Alav, I., Webber, M. A., & Blair, J. M. A. (2023). Molecular mechanisms of antibiotic resistance revisited. Nature Reviews Microbiology, 21(5), 280-295. https://doi.org/10.1038/s41579-022-00820-y

10. Baig, M. I. R., Kadu, P., Bawane, P., Nakhate, K. T., Yele, S., Ojha, S., & Goyal, S. N. (2023). Mechanisms of emerging resistance associated with non-antibiotic antimicrobial agents: a state-of-the-art review. The Journal of Antibiotics, 76(11), 629-641.

11. Sharma, B., Shukla, S., Rattan, R., Fatima, M., Goel, M., Bhat, M., Dutta, S., Ranjan, R. K., & Sharma, M. (2022). Antimicrobial Agents Based on Metal Complexes: Present Situation and Future Prospects. International Journal of Biomaterials, 2022, 6819080. https://doi.org/10.1155/2022/6819080

12. Feng, Q. L., Wu, J., Chen, G. Q., Cui, F., Kim, T., & Kim, J. (2000). A mechanistic study of the antibacterial effect of silver ions on Escherichia coli and Staphylococcus aureus. Journal of biomedical materials research, 52(4), 662-668.

13. Guerra, W., de Andrade Azevedo, E., de Souza Monteiro, A. R., Bucciarelli-Rodriguez, M., Chartone-Souza, E., Nascimento, A. M. A., Fontes, A. P. S., Le Moyec, L., & Pereira-Maia, E. C. (2005). Synthesis, characterization, and antibacterial activity of three palladium (II) complexes of tetracyclines. Journal of Inorganic Biochemistry, 99(12), 2348-2354. https://doi.org/https://doi.org/10.1016/j.jinorgbio.2005.09.001

14. Rehman, S. U., Chohan, Z. H., Gulnaz, F., & Supuran, C. T. (2005). In-vitro antibacterial, antifungal and cytotoxic activities of some coumarins and their metal complexes. Journal of Enzyme Inhibition and Medicinal Chemistry, 20(4), 333-340.

15. El-Gammal, O. A., Mohamed, F. S., Rezk, G. N., & El-Bindary, A. A. (2021). Structural characterization and biological activity of a new metal complexes based of Schiff base. Journal of Molecular Liquids, 330, 115522.

16. Abo-Aly, M. M., Salem, A. M., Sayed, M. A., & Aziz, A. A. (2015). Spectroscopic and structural studies of the Schiff base 3-methoxy-N-salicylidene-o-amino phenol complexes with some transition metal ions and their antibacterial, antifungal activities. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 136, 993-1000.

17. De Castro, F., De Luca, E., Benedetti, M., & Fanizzi, F. P. (2022). Platinum compounds as potential antiviral agents. Coordination Chemistry Reviews, 451, 214276.

18. Henderson, D. A. (1987). Principles and lessons from the smallpox eradication programme. Bulletin of the World Health Organization, 65(4), 535.

19. Galdiero, S., Falanga, A., Vitiello, M., Cantisani, M., Marra, V., & Galdiero, M. (2011). Silver nanoparticles as potential antiviral agents. Molecules, 16(10), 8894-8918.

20. Domingo, E. (2010). Mechanisms of viral emergence. Veterinary research, 41(6).

21. Chang, E. L., Simmers, C., & Knight, D. A. (2010). Cobalt complexes as antiviral and antibacterial agents. Pharmaceuticals, 3(6), 1711-1728.

22. Takeuchi, T., Böttcher, A., Quezada, C. M., Meade, T. J., & Gray, H. B. (1999). Inhibition of thermolysin and human α-thrombin by cobalt (III) Schiff base complexes. Bioorganic & medicinal chemistry, 7(5), 815-819.

23. Schwartz, J. A., Lium, E. K., & Silverstein, S. J. (2001). Herpes simplex virus type 1 entry is inhibited by the cobalt chelate complex CTC-96. Journal of Virology, 75(9), 4117-4128.

24. Nash, T. E. (2014). Parasitic Diseases that Cause Seizures: Parasitic Diseases that Cause Seizures. Epilepsy Currents, 14(2_suppl), 29-34.

25. Lee, S.-M., Kim, M.-S., Hayat, F., & Shin, D. (2019). Recent advances in the discovery of novel antiprotozoal agents. Molecules, 24(21), 3886.

26. Utzinger, J., Becker, S. L., Knopp, S., Blum, J., Neumayr, A. L., Keiser, J., & Hatz, C. F. (2012). Neglected tropical diseases: diagnosis, clinical management, treatment and control. Swiss medical weekly: official journal of the Swiss Society of Infectious Diseases, the Swiss Society of Internal Medicine, the Swiss Society of Pneumology, 142.

27. Portes, M. C., Ribeiro, G. A., Sabino, G. L., De Couto, R. A. A., Vieira, L. Q., Alves, M. J. M., & Da Costa Ferreira, A. M. (2023). Antiparasitic Activity of Oxindolimine–Metal Complexes against Chagas Disease. Inorganics, 11(11), 420.

28. Lopez-Albizu, C., Rivero, R., Ballering, G., Freilij, H., Santini, M. S., & Bisio, M. M. C. (2023). Laboratory diagnosis of Trypanosoma cruzi infection: a narrative review [Review]. Frontiers in Parasitology, 2. https://doi.org/10.3389/fpara.2023.1138375

29. Guedes, P. M. d. M., Fietto, J. L. R., Lana, M. d., & Bahia, M. T. (2006). Advances in Chagas disease chemotherapy. Anti-Infective Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Infective Agents), 5(2), 175-186.

30. Rajao, M. A., Furtado, C., Alves, C. L., Passos-Silva, D. G., De Moura, M. B., Schamber-Reis, B. L., Kunrath-Lima, M., Zuma, A. A., Vieira-da-Rocha, J. P., & Garcia, J. B. F. (2014). Unveiling benznidazole's mechanism of action through overexpression of DNA repair proteins in Trypanosoma cruzi. Environmental and molecular mutagenesis, 55(4), 309-321.

31. Docampo, R. (1990). Sensitivity of parasites to free radical damage by antiparasitic drugs. Chemico-biological interactions, 73(1), 1-27.

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