The Role of Metal-Based Drugs in Medicinal Chemistry: Applications and Challenges

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Abstract

Metal-based drugs are important classes of new drugs in current medicinal chemistry with some different therapeutic profiles compared to organic compounds. This review considers these drugs used in oncology, antimicrobial therapy, and neurodegenerative disease focusing on the cytostatic and antimicrobial effects, the action mechanisms, and problems related to chemotherapy. Information about toxicity, resistance and stability issues is provided together with ideas on how to manage specific difficulties. The review further taps into recent studies and points future of drug design and advanced nanotechnology-based drug delivery techniques.

Keywords*: Metal-Based Drugs, Medicinal Chemistry, Therapeutic Efficacy, Drug Resistance and Toxicity*

Introduction

Metal complexes have caused a major shift in drug design with possibilities in the treatment and management of numerous diseases, including cancer, bacterial and viral infections, and neurodegenerative disorders. The uniqueness of metallodrugs is in exploiting the flexibility of the coordination chemistry of the metallic ions such that various activities that are otherwise impossible in organic chemistry are attainable. Thus, these mechanisms permit metal-based drugs to interact with biological targets in ways that organic derivatives cannot. Typical instances are coordinating to biomolecules, catalyzing redox reactions, and generating redox species that can perturb cell signaling (Borutzki *et al*.,2023).

One of the greatest success stories in this area is the anticancer drugs based on platinum as cisplatin, carbo-platinum, and oxaliplatin. These drugs have been very successful in causing havoc through DNA crosslinking, with cancer cell replication, and apoptosis of cancer cells. Likewise, silver and copper complexes are significant research findings as treatments for increasing antibiotic resistance (Mujahid *et al*., 2023; Mateo & Jiménez, 2022). Other uses include gold-containing compounds as anti-inflammatory agents and metal-binding agents for neurological diseases like Alzheimer's since malfunctioning metal ions contribute to the disease (Aili *et al*., 2023; Chiang, 2024).

However, these success stories should not belie the fact that the administration of metal-based drugs is not problem-free. The three major obstacles to the application of metal complexes in cancer treatment are their off-target toxicity, the emergence of drug resistance, and the instability of the complexes under physiological conditions. To solve these problems, solutions must incorporate advances in inorganic chemistry, molecular biology, and nanotechnology, as Ni, 2022 have proposed.

Table 1. Timeline of Synthetic Drug Formulation and the Evolution of Metal-Based Drugs in Medicinal Chemistry (Kostova, 2023).

Period	Milestone/Event	Significance
Ancient Medicine	Use of gold, silver, and mercury in traditional medicine	Antimicrobial and anti-inflammatory applications; early evidence of metal therapeutic use.
19th Century	Fowler’s Solution (Potassium Arsenite)	Arsenic compounds used for diseases like syphilis; notable for their severe toxicity.
Early 20th Century	Paul Ehrlich’s "Magic Bullet" (1907)	Development of Salvarsan, the first synthetic drug targeting syphilis; introduced targeted therapy.
	Discovery of Sulfa Drugs (1932)	Revolutionized antimicrobial therapy, setting a precedent for synthetic drugs.
Mid-20th Century	Antibiotics Era (1940s)	Mass production of penicillin encouraged the development of synthetic analogs and antibiotics.
	Discovery of Cisplatin (1965)	Platinum-based drug targeting DNA; approved in 1978 for cancer treatment.
Late 20th Century	Development of Platinum Drugs	Introduction of carboplatin and oxaliplatin to overcome resistance and toxicity issues.
	Gold-Based Drugs	Auranofin approved for rheumatoid arthritis; modulates immune responses.
	Ruthenium Complexes	Explored for their tumor-targeting capabilities and redox activity.
Early 21st Century	Metal Drug Diversification	Expanded use of metals like ruthenium, copper, and gold in anti-cancer and antimicrobial fields.

	Neurodegenerative Disease Therapies	Chelation therapy for Alzheimer's and Parkinson's; mitigates oxidative stress and amyloid formation.
	Nanotechnology	Introduction of nanoparticles for drug delivery, improving stability and reducing toxicity.
2020s and Beyond	Advanced Ligand Design	Rational ligand design improves specificity and reduces side effects of metal-based drugs.
	Exploration of Novel Metals	Metals like manganese and molybdenum investigated for unique therapeutic applications.
	Combination Therapies	Integration of metal-based drugs with organic drugs to overcome resistance mechanisms.
	AI in Drug Design	Accelerates discovery of novel metal-drug compounds and optimizes clinical development.

Applications of metal-based drug

Anticancer Application

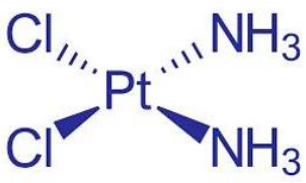
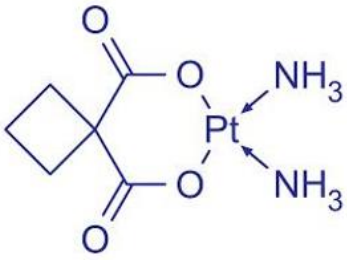
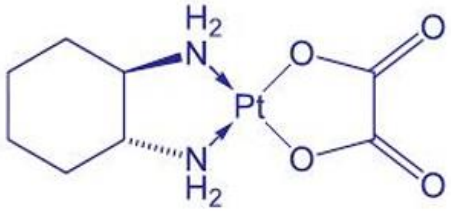
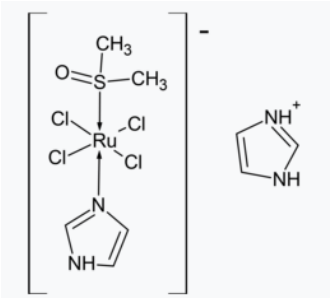
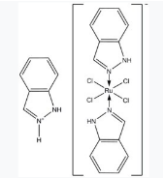
Platinum-based chemotherapeutics, including cisplatin, carboplatin, and oxaliplatin, are also no stranger to chemotherapy regimens and have been used for decades in the treatment of multiple tumor types including testis, ovary, and lung (Havasi *et al*., 2023). These drugs act by these purines bases of DNA covalently bound to intra- and interstrand cross links. This interaction then suppresses DNA replication and transcription and finally causes apoptosis (Arole, 2023). Nevertheless, Pt-based drugs have many limitations including nephrotoxicity, neurotoxicity, and acquired resistance caused by DNA repair, efflux of drug, or detoxification via glutathione (Stanković *et al.*, 2020).

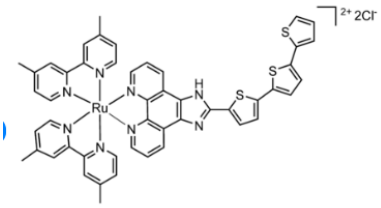
To address these disadvantages, researchers shifted their focus to a class of ruthenium-based compounds due to the distinct pharmacological characteristics of these agents. Due to their lower toxicity towards the entire organism and healthy/tumoral tissues, [(O, N) NAMI-A and (O, O) KP1019] metal-based complexes are appealing metallodrugs for anticancer drug discovery.

They also specifically accumulate in the cancer cells themselves thus making them more effective to cancer. This selectivity includes properties like redox activity, a high ability to poor iron in cellular processes, and specific targeting under the tumor hypoxic and acidic environment (Alessio & Messori, 2019). In addition, specific drugs with a basis of ruthenium could be targeting proteins and enzymes, which extends the anticancer application range.

Unlike platinum-based drugs, certain resistance patterns may not influence ruthenium complexes in tumor cells, according to some studies. Some coordinated ruthenium death agents, for example, inhibit alternative non-canonical signaling pathways, leading to cell death either by ROS-induced oxidative-stress or by altering mitochondrial activity. (Lv *et al*., 2024). Similarly, its structural modularity, in which a variety of ligands can be inserted into the Ru center, allows for the selective delivery of this drug but also co-delivery with other anticancer drugs.

Table 2. Structural Comparison of Platinum-Based and Ruthenium-Based Drugs

Drug Type	Example	Chemical structure	Structure Description
Platinum-Based	Cisplatin		- Central Pt atom with two amine (NH_3) groups in a cis configuration. - Two chloride (Cl^-) ions act as leaving groups.
	Carboplatin		- Central Pt atom with two amine (NH_3) groups. - A bidentate cyclobutane dicarboxylate ligand stabilizes the structure.
	Oxaliplatin		- Central Pt atom. - Bidentate oxalate ($C_2O_4^{2-}$) and R, R-diaminocyclohexane ligands enhance stability and activity.
Ruthenium-Based	NAMI-A		- Central Ru atom. - Four chloride (Cl^-) ligands. - One dimethyl sulfoxide (DMSO) ligand. - One imidazole (Im) ligand.
	KP1019		- Central Ru atom. - Four chloride (Cl^-) ligands. - Two indazole (In) ligands for improved stability and targeting.

	TLD1433		- Central Ru^{2+} ion. - Ligands typically include polypyridyl groups designed for photodynamic therapy. - Exploits redox activity and ligand diversity for cancer treatment.

Antimicrobial Agents

The efforts to optimize the antimicrobial characteristics of silver, copper and zinc have been carried out with the knowledge that metal ions have been used for ages and act according to their proclivity to interact with the microbial cell components thus hampering vital processes. For instance, the silver ions may adsorb to the bacterial enzymes or most likely the proteins (the thiol groups) to inactivate them thus result in the cell arrest. Silver ion is also adhered to microbial DNA and inhibits replication and transcription. Mechanistically, copper ions catalyze redox cycling in biological systems, generating reactive oxygen species (ROS) that damage cell membranes, proteins, and nucleic acids (Zhang *et al.*, 2022). Zinc also changes the functionality of the enzyme by replacing its necessary cofactors, and destabilizes membrane stability (Liu *et al*, 2022).

As a more recent development, the use of nanotechnology has enhanced the antibacterial properties of these metals. For example, silver nanoparticles (AgNPs) are also investigated for their effectiveness against multiple drug-resistant microorganisms.

AgNPs can enter bacterial cells more easily than bulk silver due to a greater surface area-to-volume ratio and, thus, release ions in bacterial cells (Streich *et al*., 2023). Moreover, their coordinated multi-hop action, ROS generation, membrane-N disruption, and protein damage make it harder for bacteria to develop resistance, unlike conventional antibiotics.

Copper and zinc nanoparticles have also shown good antimicrobial properties when applied to the surface layers of various medical items so that no biofilm and thus nosocomial infection can form (Uthra *et al*., 2024). These nanoparticles can be engineered to incorporate functional groups in order to enhance their stability as well as functionalized moieties to enable one to target a delivery of their particular therapeutic payload in the case of biomedical applications.

It includes: To provide an example of such mechanisms, and applications: - one can use tabular format to show the relative efficacy of silver, copper, and zinc ions and, their nanoparticles against the same pathogens as above. Additionally, still, it might be concerned with planar aim pictorial of the pathways of cell-viability in which silver nanoparticles act on the bacterial cells to have improved multi-dimensional understandings like clarification.

Table 3. Antimicrobial Efficacy of Metal-Based Drugs

Metal-Based Drug	Metal	Mechanism of Action	Target Pathogens	MIC (µg/mL)	Comparison to Conventional Antibiotics	References
Cisplatin	Platinum (Pt)	Forms intrastrand and interstrand DNA cross-links, leading to DNA damage and cell death	*Escherichia coli*, *Staphylococcus aureus*	0.5–2.5	More effective than some conventional antibiotics in DNA-targeting mechanisms	Rosenberg *et al*., 1965
Silver Nanoparticles	Silver (Ag)	Disrupts microbial cell membranes, interacts with enzymes and DNA	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*	0.1–10	Highly effective against multi-drug resistant strains	Marambio-Jones & Hoek, 2010
Carboplatin	Platinum (Pt)	DNA cross-linking and inhibition of replication	*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*	2–5	Less effective than cisplatin but with lower toxicity	Reedijk, 1999
NAMI-A	Ruthenium (Ru)	Inhibition of DNA replication and apoptosis induction through reactive oxygen species	*Escherichia coli*, *Staphylococcus aureus*	0.3–1	Comparable to broad-spectrum antibiotics, with less toxicity	Alessio *et al*., 2004
KP1019	Ruthenium (Ru)	DNA intercalation, generation of reactive oxygen species	*Salmonella enterica*, *Candida albicans*	0.5–2.0	More effective than some antibiotics, especially against resistant strains	Hartinger *et al*., 2006

		leading to cell death				
TLD1433	Ruthenium (Ru)	Photodynamic therapy (PDT) – generation of ROS upon light activation, killing microbial cells	*Staphylococcus aureus*, *Escherichia coli*	0.2–5	More effective than traditional PDT agents in bacterial eradication	McFarland *et al*., 2018
Gold Nanoparticles	Gold (Au)	Disrupts bacterial membranes and inhibits enzyme activity	*Staphylococcus aureus*, *Escherichia coli*	1–10	Comparable to conventional antibiotics, with reduced cytotoxicity	Dykman & Khlebtsov, 2012
Zinc Sulfate	Zinc (Zn)	Inhibits bacterial enzyme function and disrupts DNA replication	*Pseudomonas aeruginosa*, *Streptococcus pneumoniae*	1–3	Generally, less potent but used as a supplement in therapeutic regimens	Prasad, 2009

Neurodegenerative Disease Management

Chelation treatment and metal focus compounds for the restoration of iron and copper are seen as lucrative approaches for managing neuropathic diseases including Alzheimers and Parkinsonism. In these disorders, disturbances of metal ion homeostasis cause oxidative stress, inflammation and accumulation of misfolded protein such as amyloid-beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease as suggested by Sensi *et al*., 2009.

Such dysregulation for instance results to the production of ROS through Fenton like reactions, hence increasing the oxidative stress in neurons. Some chelators like deferoxamine have been recommended to treat iron–induced oxidative stress to slow down the development of neurodegenerative changes (Devos *et al*., 2014). Likewise, either a deficiency or excess of copper is reported to have a relation with increase in oxidative stress and amyloid formation in Alzheimer's disease. Several metal-based compounds such as clioquinol and PBT2 have also evidenced metal replenishment/ homeostasis and reduction of oligomer formation besides enhancing the solubility of amyloid proteins (Adlard *et al*., 2008).

Other current investigations have also examined the role played by Zinc in controlling Amyloid-beta deposition and Tau hyperphosphorylation, making Zinc-targeting treatments compatible with Iron and Copper chelation therapies (Bush and Tanzi, 2008). These results suggest that the strategy by which distinct

gallium chelators exert their effects on the multiple facets of inflammation might afford improved therapeutic results.

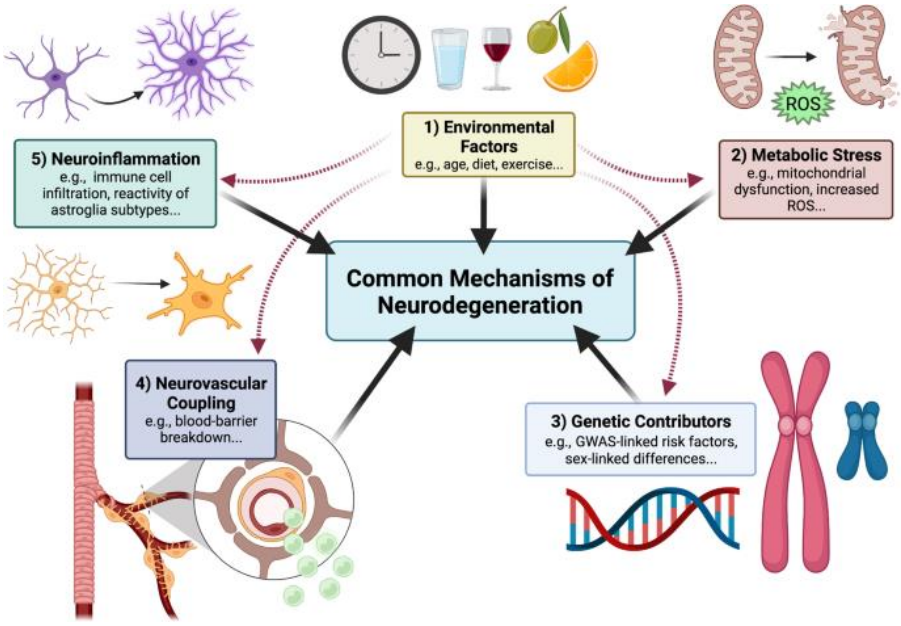


Figure 1. The role of neuroinflammation and metabolic stress in neurodegenerative diseases (Wareham *et al*.,2022).

Anti-inflammatory and Antimalarial Drugs

This immunomodulating activity accounts for the utility of many gold compounds, especially auranofin, as experimental therapeutics in rheumatoid arthritis. Auranofin: The mechanism is believed to be multifaceted with multiple processes that occur in concert leading to the anti-inflammatory and immunosuppressive effect. The mechanism of action of the gold drugs occurs mainly by inhibiting the thioredoxin reductase, an enzyme responsible for reducing thioredoxin as part of the cellular redox system. A recent example is a study by Hoffner *et al.,2018* that demonstrated how this inhibition changes cellular oxidant states, which can greatly impact inflammatory states. Auranofin's ability to modulate oxidative stress is especially relevant when one considers RA, where increased oxidative stress leads to tissue damage and chronic inflammation (Rigobello *et al*., 2005).

Inhibition of pro-inflammatory cytokines (such as tumor necrosis factor-alpha (TNF-a) and interleukin-1 beta (IL-1)), is an important part of the mechanism of action of auranofin. 3. These cytokines act as bookends in the pathogenesis of RA, mediating synovial inflammation and joint destruction (Chikanza *et al*., 2000). Auranofin prevents chronic inflammation in RA which is a vicious cycle which promotes the production of these cytokines (Furst, 1983).

The gold ions in auranofin also directly inhibit the function of immune cells. They prevent the synthesis of certain proteins that promote part of the inflammatory cascade and thus decrease the inflammatory response (Roder & Thomson, 2015). Such a broad effect on the cell-mediated immune system reflects auranofin's effectiveness for chronic inflammatory processes such as RA.

In fact, recent studies have unveiled further uses for auranofin outside of RA.

Auranofin has been reported in studies to cause the production of reactive oxygen species (ROS) in different cell types, such as platelets and T-cells (Gromer *et al*., 1998). This ROS induction results in overall cellular stress and sometimes apoptosis, which could have a role in why its use is limited in other diseases, such as specific cancers (Marzano *et al.*, 2007). Surprisingly, auranofin has also shown promise in metabolic conditions. Current research conducted on obese mice demonstrates that auranofin enhances insulin sensitivity and rectifies several obesity-related issues, such as hepatic steatosis and hyperinsulinemia (Kim *et al*., 2019). Moreover, the effects seem to be mediated through the accumulation of auranofin in the white adipose tissue and its influence on leptin levels, which represent an unexplored area of treatment for metabolic disorders.

Since they are antimalarials and they utilize the iron-bound drugs, they take advantage of the fact that malaria has very distinct metabolic pathways, especially when in its intraerythrocytic form. These compounds must interact with iron to form free radicals that are extremely deadly to the Plasmodium (Meshnick *et al*., 1996). Such a mechanism increases antimalarial efficacy and combats the evolution of drug resistance by perturbing core processes necessary for parasite survival, (O'Neill *et al.*, 2010). Their dual role as anti-inflammatory agents and as antimicrobials point to other disease class crossovers as this drug repositioning possesses. It increases the arsenal of therapeutics, but in doing so, it expedites drug discovery by taking advantage of existing safety and pharmacokinetic data.

Table 4. Comparison of Gold-Based Drugs and Iron-Complexed Antimalarial Drugs (Marcelino *et al.*,2017)

Drug Type	**Example Drug**	**Therapeutic Target**	**Mechanism of Action**	**Clinical Application**	**Advantages**	**Limitations**
Gold-Based Drugs	Auranofin	Immune system, specifically targeting macrophages and T-cells	- Inhibits thioredoxin reductase (TR) enzyme, disrupting redox homeostasis. - Modulates immune response and inflammation.	- Treats rheumatoid arthritis (RA) by reducing inflammation. - Potential for use in cancer and autoimmune disorders.	- Effective in treating autoimmune diseases with relatively low toxicity. - Promotes immune system modulation.	- Limited use outside autoimmune conditions. - Requires careful monitoring due to potential toxicity.
Iron-Complexed Antimalarial Drugs	Artemisinin-based compounds (e.g., Artemether, Artesunate)	Parasite metabolism and heme detoxification in Plasmodium species.	- Inhibits heme polymerase, causing the accumulation of toxic heme inside malaria parasites,	- Primary treatment for malaria, especially Plasmodium falciparum. - Combats drug-resistant	- Highly effective against malaria, including multidrug-resistant strains. - Rapid action in	- Risk of resistance development. - Potential side effects like neurotoxicity and hepatotoxicity with long-term use.

			leading to cell death.	malaria strains.	clearing parasites.	
Iron-Complexed Antimalarial Drugs	Ferrous sulfate (combined with antimalarial agents)	Iron regulation in parasitic metabolism.	- Iron is chelated to interfere with parasite enzyme activity. - Synergistic action with antimalarial drugs to improve therapeutic outcomes.	- Used as adjunctive therapy for malaria, especially in anemic patients.	- Effective in combination therapy. - Enhances the action of other antimalarial drugs.	- Ineffective as a monotherapy. - Can contribute to iron overload in patients with chronic conditions.

Mechanisms of Actions

DNA Binding and Crosslinking

An important class of platinum chemotherapeutics is cisplatin; whose toxicity stems primarily from binding to DNA as intrastrand and interstrand cross-links. Hydrolysis, the first step upon cisplatin entry into the cell, produces an active species as chloride ligands are replaced by water molecules. This activated complex can react with purine bases, with particular preference for the guanine and adenine deoxynucleosides (Zacharioudakis, and Rodriguez, 2023).

This typically results in interstrand crosslinking between two neighboring guanine bases or between guanine and adenine, which induces severe displacement of the DNA helix. These structural changes disrupt normal physiological cellular processes like DNA synthesis and transcription which lead to cell cycle arrest and apoptosis (Semlow and Walter, 2021). Another subset of DNA lesions that can occur are interstrand crosslinks (ICLs) which occur at slightly less of a frequency then covalent modifications but they exacerbate the issue by preventing the mechanical unwinding of DNA which serves to increase cytotoxicity (Housh *et al*., 2021).

Cisplatin induces DNA damage and elicits three main cellular outcomes, one of which is the activation of the p53 apoptotic pathway, leading to increased antitumor activity (Hirata *et al*., 2021). Nonetheless, the effectiveness of the drug is often decreased through factors like increased DNA repair, drug efflux from cells, and conversion to inactive forms through interaction with glutathione (Yang *et al*., 2006).

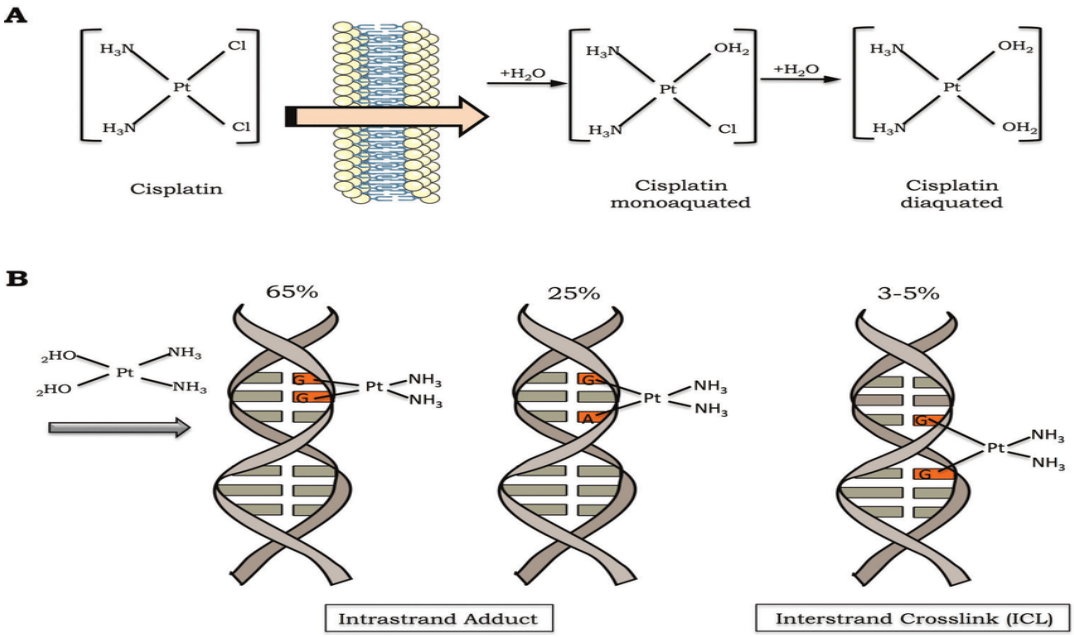


Figure 2. The chemical mechanism of cisplatin activation and DNA crosslinking could provide a clear visual representation of its molecular interactions. (García-González and Rodríguez, 2018)

Table 5. Comparative Analysis of DNA Lesions and Their Cellular Consequences

Type of DNA Lesion	Description	Biological Consequences
Intrastrand Crosslinks	Covalent bonds between nucleotides on the same DNA strand	Distorts DNA structure, impedes replication and transcription
Interstrand Crosslinks	Covalent bonds between nucleotides on opposite DNA strands	Blocks DNA strand separation, severely inhibits replication and transcription
Base Modifications	Chemical alterations to DNA bases (e.g., oxidation, alkylation)	Mutagenic if unrepaired, can lead to mispairing during replication
Single-Strand Breaks (SSBs)	Break in one strand of the DNA double helix	Interferes with replication, can lead to double-strand breaks if unrepaired
Double-Strand Breaks (DSBs)	Breaks in both strands of DNA	Highly cytotoxic, can lead to chromosomal rearrangements and cell death if mis repaired

Abasic Sites	Loss of a DNA base, leaving the sugar-phosphate backbone intact	Blocks replication and transcription, potentially mutagenic
Cyclobutane Pyrimidine Dimers (CPDs)	Formation of covalent bonds between adjacent pyrimidines	Distorts DNA structure, blocks replication and transcription
6-4 Photoproducts (6-4 PPs)	Linkage between carbon atoms of adjacent pyrimidines	Severely distorts DNA helix, blocks replication and transcription

Oxidative Stress Induction

The generation of reactive oxygen species (ROS) in co-metal complexes is well documented as a part of their cytotoxic and antimicrobial action. With respect to complex formation, numerous transition metal complexes such as copper, iron, and ruthenium release redox reactions in surrounding cell environments that result in the generation of radical species such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•) (Sadler & Guo, 1998; Bouraguba *et al.*, 2024). These ROS are often stimulated by the presence of iron or copper ions, which can accelerate ROS production and increase overall toxicity (SSRN, 2023). These ROS induce oxidative stress, as they, among other effects, change the structure and properties of lipids, proteins, and DNA. Lipid peroxidation impairs membrane function and integrity while protein oxidation inactivates proteins important in metabolic processes within the human body. Furthermore, ROS cleaves DNA strands, modifies bases, and interferes with replication and transcription, inducing apoptosis of cancer cells or killing microbes (Wang *et al.*, 2019; Piotrowski *et al.*, 2021).

For example, the disturbance of cellular redox homeostasis caused by metal complexes especially those based on Cu (II) complexes will increase the level of oxidative stress in cancer cells, which induces the cytotoxicity significantly in cancer cells but has less effects on normal cells with low concentration of glutathione (GSH) (Ding *et al.*, 2024). For example, copper and iron complexes utilize Fenton-like reactions to facilitate ROS production, while ruthenium complexes mainly generate ROS under hypoxic conditions, like those of tumor cells. This selective action enhances the suitability of Ru-based drugs for drug-targeted cancer chemotherapy (Brabec & Kasparkova, 2019). In accordance, selective anticancer activity of some ruthenium (II) complexes has been reported through the induction of apoptosis, cell cycle arrest, and ROS accumulation via the selective inhibition of thioredoxin reductase (TrxR) (Piotrowski *et al.*, 2021).

Similarly, silver complexes and nanoparticles have been shown to exert antimicrobial effects via ROS release, leading to membrane disruption, metabolic impairment, and ultimately cell death (Durán *et al.*, 2016). Metal complexes possess the capability to manufacture ROS and perturb cellular redox balance, which has prompted interest in their usage as a potential future source of antimicrobial and anticancer agents [23,24]. For example, several copper (II) complexes have been discovered to trigger robust ferroptosis-dependent immunogenic cell death responses and target in vivo tumor growth in animal models (Ding *et al.*, 2024).

It is to be noted that, the efficacy of the metal complexes varies greatly depending on the specific ligands and cellular environments. Others, for instance, alternate Cu-ligand complexes that were highly catalytic

for production of ROS in vitro, did not show increased antimicrobial or cytotoxic activity in cellular studies, underscoring how established results in vitro can fail to predict behavior in biological systems (Bouraguba *et al*., 2024).

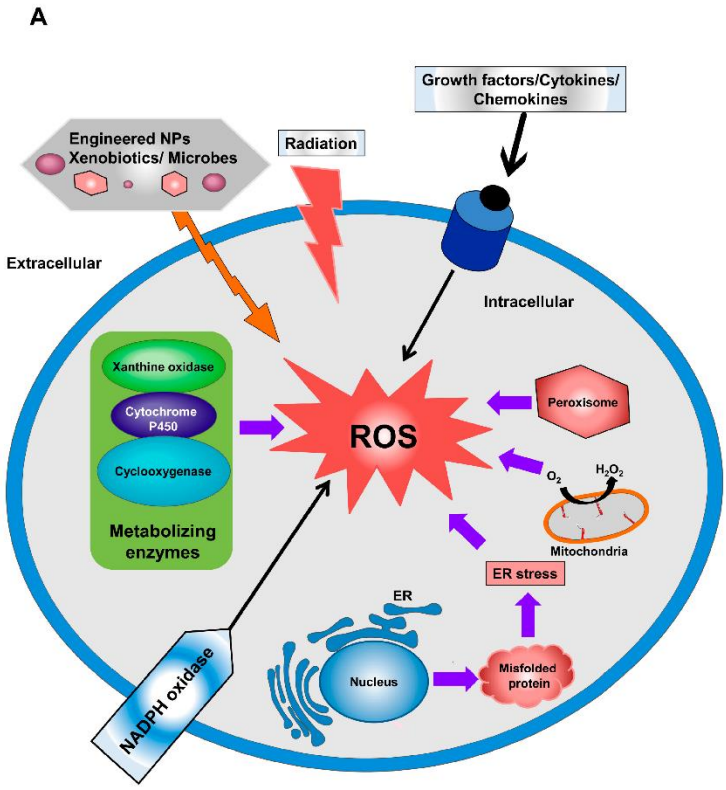


Figure 3. The ROS generation mechanism by metal complexes and their effects on cellular components could visually represent the multi-targeted action of ROS. (Abdal Dayem, *et al*., (2017)

Enzyme Inhibition

Many metal ions, including copper and zinc, have antimicrobial effects because the ions interfere with crucial enzymes in microorganisms, affecting fundamental metabolic processes in pathogens. Copper ions, for example, bind with thiol groups in proteins, distorting their structure and function, and attacking enzymes essential to cellular processes (Kostova, 2006). In bacteria, copper can interfere with enzymes involved in energy-producing processes, such as cytochrome c oxidase, as well as enzymes involved in the synthesis of biomolecules, such as nucleotides and amino acids (Grass *et al*., 2011). These effects translate into metabolic dysfunction by interfering with microbial enzyme function and growth, ultimately leading to cell death.

Similarly, it is well documented that zinc can chelate and suppress certain important bacterial enzymes, including those required for cell wall synthesis and DNA replication (Nies, 2003). Zinc, based on its ability to bind with metal cofactors, displaces these factors from the active site of enzymes, thereby altering their catalytic properties. Additionally, zinc is documented to participate in the regulation of bacterial resistance mechanisms, including the control of genes involved in processes such as metal homeostasis and oxidative stress response (Turner *et al*., 2006).

Such disruptions contribute to the bactericidal impact of zinc-based antibacterial agents.

By targeting microbial enzymes without significantly affecting human enzymes, metal ions can be used to design antimicrobial therapies with low toxicity. These metal ions, their complexes, and nanoparticles are being increasingly investigated as alternatives or complements to antibiotics, particularly in light of the growing problem of antibiotic resistance (Lemire *et al*., 2013).

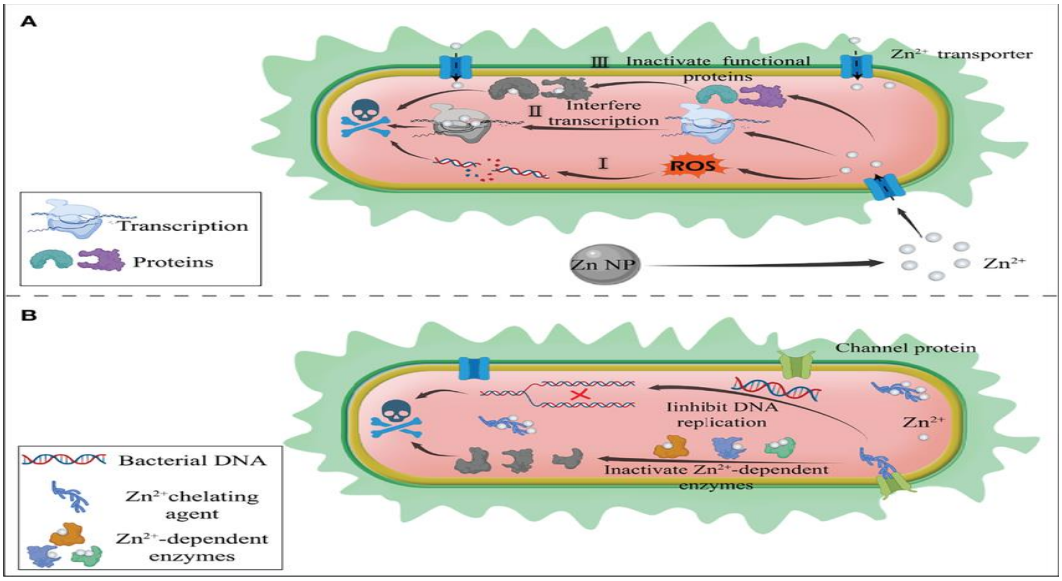


Figure 4. The inhibition of microbial enzymes by copper and zinc ions could visually depict their interaction with key metabolic enzymes in bacteria. (Khan and Ali 2022).

Challenges in Development

Toxicity

Metal-based drugs, however, have several disadvantages, including lack of selectivity, high toxicity, and broad activity within the organism. Compared to purely organic drugs, which can be designed to target specific molecular targets with high selectivity, metal-based drugs often act on a broad set of biological molecules due to the versatile coordination chemistry of metal ions (Sadler & Guo, 1998). For example, cisplatin, a platinum-based drug, is highly effective in attacking DNA in cancer cells but can also interact with other cellular biomolecules, such as proteins and lipids, leading to potentially damaging effects. These non-specific interactions are responsible for severe side effects, including nephrotoxicity, neurotoxicity, and hepatotoxicity (Wheate *et al*., 2010).

Similarly, other metal-containing compounds, such as gold or ruthenium complexes, can interact with cellular components other than their intended targets. For instance, gold-containing drugs like auranofin, used as immune modulators in rheumatoid arthritis (RA), may disrupt normal cellular functions, leading to side effects such as gastrointestinal complaints or hematologic alterations (Shaw *et al*., 2012).

The relatively broad activity of metal-based drugs underscores the need for continued efforts to improve their selectivity. Current approaches include designing metal complexes with specific ligands that target only tumor cells or inflamed tissues, as well as developing drug delivery systems that home in on particular cell receptors to minimize harm to healthy cells and tissues (Bae *et al*., 2013). Additionally, the use of nanotechnology to encapsulate metal drugs in nanoparticles is being explored to enhance their bioavailability and reduce their impact on healthy tissues (Johnstone *et al*., 2016).

Table 6. Comparative Toxicity Profiles of Metal-Based Drugs

Drug Type	Major Toxicities	Severity	Mechanism of Toxicity	Selectivity
Cisplatin	Nephrotoxicity	High	ROS generation, DNA damage	Low
	Ototoxicity	High	Cochlear cell damage, mtDNA platination	Low
	Neurotoxicity	Moderate	Peripheral nerve damage	Low
	Myelosuppression	Moderate	Bone marrow suppression	Low
Auranofin	Gastrointestinal	Moderate	Thioredoxin reductase inhibition	Moderate
	Hematological	Low	Immune cell modulation	Moderate
Ruthenium Complexes	Nephrotoxicity	Low	ROS generation	High
	Neurotoxicity	Low	Mitochondrial dysfunction	High

Resistance

Long-term application of metal-based drugs has been found to be ineffective due to the development of resistance in both cancer cells and pathogenic microorganisms. In the case of cisplatin for cancer treatment, tumor cells quickly develop resistance to the drug. Several mechanisms contribute to this resistance: increased DNA repair capacity, enhanced efflux of the drug out of cancer cells, and alterations in drug transport into cancer cells (Wheate *et al*., 2010). Cancer cells may also overexpress proteins such as multidrug resistance-associated proteins (MRPs) or P-glycoprotein, which pump platinum drugs out of the cells, reducing intracellular accumulation to levels insufficient to kill the tumor cells (Kruh & Belinsky, 2003). Additionally, changes in DNA repair mechanisms, such as the upregulation of ERCC1, enable cancer cells to repair DNA damage caused by platinum-based drugs, promoting survival (Shaw *et al*., 2014). Similarly, in antimicrobial therapy, resistance to metal-based compounds, including silver, copper, and zinc-based drugs, has emerged. Some bacterial pathogens have developed mechanisms to protect themselves from toxic levels of metal ions. These mechanisms include the transport of metal ions out of the

cell via carrier proteins, binding of metal ions with intracellular chelating molecules, and enzymatic conversion of metal ions into less toxic forms (Lemire *et al*., 2013). Moreover, biofilm formation, a well-known tactic of microbes in chronic infections, can enhance the neutralization of metal-based antimicrobial agents. Chronic biofilms hinder drug penetration due to their thick extracellular matrix, which prevents metal-based drugs from reaching the bacteria (Høiby *et al*., 2010).

The development of resistance in both cancer chemotherapy and antimicrobial therapy highlights the urgent need to find new strategies to overcome or delay resistance. These strategies may include the synthesis of second- and third-generation metal-based drugs with improved pharmacokinetic profiles, the use of metal-based drugs in combination with other agents to prevent the establishment of resistance mechanisms, and the application of nanotechnology for targeted drug delivery to minimize interactions with non-target cells or components (Santos *et al*., 2017). Furthermore, the discovery of new ruthenium (Ru) complexes has shown promise, as they do not produce cross-resistance like platinum (Pt) drugs due to their distinct mechanisms of action (Brabec & Kasparkova, 2019).

Table 7. Resistance Mechanisms in Metal-Based Drugs and Their Impact on Therapeutic Outcomes

Metal-Based Drug	**Resistance Mechanisms**	**Impact on Therapeutic Outcomes**
Platinum (e.g. cisplatin)	- Reduced cellular accumulation via decreased influx or increased efflux	Decreased drug efficacy and tumor cell survival
	- Increased detoxification systems	Reduced formation of platinum-DNA adducts
	- Enhanced DNA repair processes	Diminished cytotoxicity
	- Elevated apoptosis threshold	Reduced cancer cell death
	- Autophagy induction	Potential cytoprotective effect
	- ABCB1 export and EGFR gene expression	Reduced intracellular drug concentration
Silver	- Efflux pumps	Decreased antimicrobial efficacy
	- Altered membrane permeability	Reduced silver ion uptake
	- Enzymatic detoxification	Neutralization of silver's antimicrobial effects
Copper	- Copper homeostasis systems (e.g. ATP7A/B)	Reduced intracellular drug accumulation
	- Sequestration in vesicles	Decreased cytotoxicity
	- Upregulation of copper efflux pumps	Reduced antimicrobial efficacy
Gold (e.g. auranofin)	- Thioredoxin reductase inhibition	Potential development of resistance in bacteria
	- Altered cellular redox balance	Reduced therapeutic efficacy

Stability and Bioavailability

In contrast to organic compounds, the degradation of metal compounds in physiological media represents one of the challenges in the design of metal-based drugs. Such degradation can result in a significant reduction in the drug's efficacy. Metal complexes are typically labile in vitro as there are a few notable exceptions and they are sensitive to variations in pH, the chelating capacity of proteins and nucleic acids, and enzymatic effects. As an example, cisplatin (a commonly used platinum compound) does hydrolysis upon dissolving in aqueous solutions, yielding reactive platinum species capable of interacting and binding to cellular components (Rosenberg *et al*., 1965). But that also means a drug is subject to premature degradation, which lessens both its bioavailability and therapeutic value. In addition, cytotoxic metal ions (for example, Au, Ag, and Pt) liberated from the NPs can nonspecifically chelate with healthy tissues, thereby having systemic toxicity (Wheate *et al*., 2010).

Likewise, gold, ruthenium, copper, and other metal complexes suffer from stability problems since they can participate in ligand exchange-based deactivation pathways yielding inactive or stable species.

The ability of the drug to be oxidized or reduced in the bloodstream will also affect its efficacy; ruthenium complexes, which are being studied for anticancer activity, are a class of drugs currently being investigated (Brabec & Kasparkova, 2019). Copper-loaded compounds are one of the most common antimicrobials, but they can break down into less effective forms or have interactions that minimize their action within the more complex environment associated with cell membranes (Kostova, 2006).

To address these stability concerns, this has led researchers to focus more on the design of new stable metal complexes in physiological settings. These strategies include using stronger ligands to protect the metal from early degradation and creating delivery systems for the drug, such as nanoparticles or liposomes, that contain metal-based drugs and are only released at the target (Bae *et al*., 2013). A different strategy is to synthesize prodrugs that are inactivated until they arrive at the target site, such as tumor cells or bacterial biofilms, where they become activated (Cai *et al*., 2014). In addition, the fine-tuning of a series of new metal complexes with enhanced stability and pharmacological traits has been made possible through breakthroughs in computational chemistry and molecular modeling. Regulation of coordination chemistry can lead to attenuation of degradation and increased therapeutic activity (Santos *et al*., 2017).

Economic Constraints

Despite the progress made in the development of new metal-containing drugs, the application of potent metals for therapeutic use continues to be limited by extreme economic challenges. These challenges arise due to the high costs involved in the synthesis and characterization of metal complexes, especially for precious metals (e.g. platinum, gold and ruthenium). For instance, platinum-based agents such as cisplatin involve a series of multistep syntheses of complex platinum salts and precise activation conditions, making

them intrinsically costly (Wheate *et al*., 2010). This tighter supply of raw materials, coupled with the high costs of these materials, creates more financial pressure (Johnstone *et al*., 2016).

Methods for characterization, such as X-ray crystallography, nuclear magnetic resonance (NMR), and mass spectrometry, play an essential role in confirming structural integrity and therapeutic activity of metal-based entities. Unfortunately, not only are these techniques time-consuming, but they are also expensive, greatly inflating drug development costs (Sadler & Guo, 1998). The huge expenses deter people from using such advanced analytical methods as inductively coupled plasma mass spectrometry (ICP-MS) during the experimental phase (Hambley, 2007). These compounded costs usually make metal-based drugs commercially infeasible for bulk production.

Another big hurdle is scaling up production. Laboratory metal complex synthesis protocols are often deemed unsuitable for industrial production, owing to stringent purity and specialized formulations required to ensure stability and efficacy (Alessio *et al*., 2017). Such R&D, in turn, is also dissuaded due to the small commercial market for metal-based drugs targeting rare diseases (Hartinger *et al*., 2011).

In response to these limitations and within the context of an economic crisis, researchers are looking for alternative strategies. Replacing platinum with less expensive transition metals, such as ruthenium and copper, that have similar therapeutic applications, has shown potential (Brabec & Kasparkova, 2019; Tisato *et al*., 2010).

Similarly, improvements in green chemistry, from eliminating toxic solvents by switching them for biodegradable alternatives to optimizing catalytic processes are also employed as cost- and ecoefficient solutions (Sheldon, 2018).

New manufacturing technologies such as continuous flow synthesis and high-throughput screening are transforming the field. Continuous flow systems improve reproducibility and decrease waste generation, and high-throughput techniques accelerate the generation of viable metal-based drug candidates (Baumann & Baxendale, 2015; Blay *et al*., 2020). Such developments could overcome economic limitations and enable sustainable and scalable policies, opening avenues for the production of metal-based therapeutics.

Future directions

Thus, the most pressing promises of metal-based drugs regarding their materialization in the field of medicinal chemistry and their ability to unlock what can be achieved with modern tools and approaches. Innovative strategies. There are several areas that are particularly promising in moving the true therapeutic potential of these compounds forward.

Nanotechnology: Drug Delivery in Nanotechnology

Nanotechnology has demonstrated its potential leading to breakthroughs in novel drug delivery technologies supporting diverse therapeutic areas. Among these, one of the most promising advancements made in recent years is the targeted delivery of metal-based drugs (Farokhzad & Langer, 2006). Various nanocarriers like liposomes, dendrimers and polymeric micelles have been synthetized with a purpose to load metal-based drugs to overcome the barriers of poor solubility, low stability and systemic toxicity (Torchilin, 2005; Svenson & Tomalia, 2005; Gaucher *et al*., 2010). Such carriers can be bio-functionalized with ligands, antibodies or receptor to exploit active targeting of specific tissue sites such as tumours or inflamed tissue by overexpressed surface biomarker (Davis *et al*., 2010; Byrne *et al*., 2008). e.g. tumors possess the enhanced permeability and retention (EPR) effect that allows passive accumulation of nanocarriers at the tumor site, while active targeting enhances site specificity (Maeda *et al*., 2000).

The systemic exposure is considerably lessened by nanoencapsulation of metal-based drugs in nanocarriers thus minimizing off-target toxicity which is of prime concern for such compounds, for example, cisplatin and other metallotherapeutics (Bae *et al*., 2013). Mechanisms for the controlled release of a therapeutic agent can also improve therapeutic precision by allowing for modulation of the dose or extending the pharmacokinetic profile (Cabral *et al*., 2011). This strategy is especially favorable for metal-containing therapeutics that exhibit a narrow therapeutic index (the ratio between the toxic and therapeutic dose) in that it facilitates the relation between toxicosis and therapeutic void (Duncan, 2006). Nanoparticle engineering has also developed stimuli-responsive designs like pH or enzyme-triggered release to increase spatiotemporal control of drug delivery (Alexis *et al*., 2008). Taken together, these innovations highlight the power of nanotechnology to surmount the constraints associated with traditional metal-based drug formulations.

Ligand Engineering

Ligand design is an integral aspect of modern medicinal inorganic chemistry, allowing the formation of metal-based drugs with greater specificity and selectivity (Sadler, 1991). One strategy to reduce off-target toxicity and enhance therapeutic efficacy is to engineer ligands that specifically bind diseased tissues without acting on healthy tissues (Farrell, 2015). This enables researchers to modulate the reactivity and binding affinity of the metal complexes to a given biological target through changing the ligand denticity, stereochemistry or electronic properties in the metal ion coordination environment (Schatzschneider, 2011). For instance, cationic platinum (II) or ruthenium (II) complexes decorated with tumor-targeting ligands selectively concentrate in cancer cells via receptor-mediated endocytosis, resulting in reduced systemic toxicity (Ang *et al*., 2005; Meggers, 2007).

This strategy is also applicable to antimicrobials, using ligands that mimic natural substrates of microbial enzymes, allowing selective inhibition of pathways in pathogens (Santos *et al*., 2017). Moreover, redox-active ligands provide stabilization of the metal-center in defined oxidation states, which facilitates target interactions under physiological conditions (Jakupec *et al*., 2008). By ensuring more efficient ligand-metal binding interactions, researchers enhance the local concentrations of effective drugs at diseased sites, gradually elevating the therapeutic index of metal-based therapies (Dyson & Sava, 2006). These developments highlight the power of the rational ligand design approaches to address shortcomings that traditional metallodrugs face.

Investigating Other Transition Metals

While platinum-containing compounds are still the mainstay of metal-based chemotherapy, there has been a growing interest in the design of theragnostic based on different transition metals like manganese (Mn), molybdenum (Mo), or zirconium (Zr). When some of these metals were also found to exhibit unique physicochemical properties, distributions, and the ability to be incorporated into novel complexes capable of new therapeutic mechanisms which would distinguish them from those of platinum itself (Johnstone *et al*., 2016). Various metal species such as cobalt (Co) have been studied for their redox-active capacity and antioxidant potential for the attenuation of oxidative stress involved in neurodegenerative diseases (Finkelstein *et al*., 2013; Simões *et al*., 2020). Manganese-based systems exhibiting catalase-mimetic activity are also being investigated and are neuroprotective in preclinical models of Parkinson's disease (Santini *et al*. 2014).

Molybdenum complexes, especially those built from sulfur-rich ligands, display antineoplastic and antimicrobial properties by mechanisms not related to the classical formation of Pt (II)-DNA adducts. And for instance, Mo-Schiff base compound exhibits disrupted enzymatic pathways in cancer cells or microbial

pathogens and thus a lower probability of cross-resistance with respect to platinum drugs (Kostova, 2006; Romanski *et al*., 2011).
Zirconium (IV) has been exploited comparatively less, although the stability and tunable ligand exchange kinetics of its coordination compounds haves also observed in a promising role in targeted radiotherapy and server as photodynamic therapy agents (Gasser *et al*., 2017).
Researchers attempt to expand the armamentarium of metals and obtain candidates of higher efficacy and with less off-target toxicity. Exploring non-platinum metals also solves the limitations such as cisplatin resistance and cumulative nephrotoxicity, that is, it may provide options for refractory cancers and infectious diseases (Hartinger *et al*., 2011).

Metal-Based Drugs Combination Therapies

Combination therapies, defined as the administration of metal-based drugs with other therapeutic agents, have emerged as a way to overcome drug resistance and augment therapeutic effect (Tardi *et al*., 2009). Chemotherapy, targeted therapy or immunotherapy can be combined with metal-based drugs to produce additive or synergistic effects and thus overcome the disadvantages of monotherapy (Shen *et al*., 2012). As an example, platinum-based compounds such as cisplatin and DNA repair inhibitors, including poly (ADP-ribose) polymerase (PARP) inhibitors, target cancer cells' ability to repair platinum-mediated DNA damage, which can also overcome a major resistance mechanism (Lord & Ashworth, 2017).
Metal-antibiotic combinations in antimicrobial therapy utilize multiple pathways to kill pathogens, lowering the chances of resistance development. In one case, the β-lactam antibiotic ceftazidime was sampled with cobalt (III) complexes to boost membrane permeability in Gram-negative bacteria (Frei *et al*., 2020). In the similar manner, the combination of silver nanoparticles with vancomycin exhibited significant activity against methicillin-resistant Staphylococcus aureus (MRSA) through dual targeting of biofilm formation and cell wall biosynthesis (Ejidike & Ajibade, 2015).
Combination regimens also allow dose reduction of individual agents to minimize the systemic toxicity and maintain the therapeutic outcomes. For example, synergetic interactions between the ruthenium polypyridyl complexes and paclitaxel enable lower doses of both agents to exhibit similar tumor suppression in breast cancer models (Levina *et al*., 2017). This is in harmony with the National Cancer Institute's focus on rationale drug combinations for maximal patient safety and efficacy (Baylin & Jones, 2016).

Conclusion

Metal-based drugs constitute a radical class of drugs that has positively impacted the treatment of variety of diseases such as infective diseases, cancerous diseases, and even neurological diseases. Unlike conventional organic drugs whose formulation presents challenges due to the complexity of biological systems, these drugs take advantages of the coordination chemistry of metal ions in dealing with these systems. However, several obstacles greatly prevented the clinical uses of metal-based drugs, such as toxicity, resistance as well as stability of the drugs involved.
Research in this area is still active and much progress is being made to overcome these limitations due to promising use of metals for better and safer metal-based therapies.
Recent developments in material engineering and nanotechnology create a prospect for enhancing drug delivery and appropriate targeting of metal pharmaceuticals. With improved formulations, researchers are trying to reduce the side effects and size of doses that can cause adverse consequences in the body's internal

metabolism. For example, in nanotechnology, metal nanoparticles and nanocarriers can be produced to accurately deliver the drug at the targeted site, including tumor or infected tissues, thereby increasing drug effectiveness and minimizing toxicity to healthy tissues. This approach also enables the control release in such a way that it is active only in the place of action; a factor that reduces side effects and improves the result of the treatment containing metal-based drugs. In addition, by using new advanced materials and smart drug delivering systems, this problem of drug resistance can be solved. Metal-based drugs are being tested alongside other drugs to increase the chances of overcoming resistance mechanisms including chemotherapy drugs, antibiotics and inhibitors of resistance pathways. These strategies also help to improve the efficacy of metal-based drugs as well as minimize potential feedback that is inevitable with long-term use of metal-based drugs. Besides these technological changes, research into other new metal molecules including ruthenium, copper, manganese has opened up further uses of metal-based drugs. These other metals may introduce novel therapeutic properties with minimalism of side reactions rather than first-line metals such as platinum. Still expanding the variety of metal ions which could be used for therapeutic purposes, the scientists provide more opportunities for metal-based therapies, including the ability to adjust these approaches to various treatment situations.

Thus, it is for this reason that, notwithstanding the fact that there are problems to work on, active developments in material science, nanotechnology, and metal chemistry create a great potential for the use of metal-based drugs as essential tools in the treatment of complicated diseases. Over time with more research and development work, these drugs will not only be safer and more effective. However, it will also be instrumental in meeting future healthcare needs since they, too, have adapted to the system.

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