JBEP

Journal of Biosciences and Experimental Pharmacology
ISSN-2960-284X

Review Article

Metal Complexes as Chemotherapeutic Agents for the Treatment of Cancer

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Citation: Zubair, T.; Sultana, S.; Majumder, T, J.; Rafi, A. R.; Megh, N. I.; Apu, M. H. H.; Shariare, M. H.; Masum, A.A. Metal complexes as chemotherapeutic agents for the treatment of cancer. *J. Biosci. Exp. Pharmacol.* 2024, ***2(1),*** **01–13.** https://doi.org/10.62624/JBEP00.0007

Academic Editor: Dr. Sazid Md. Sarker

Received date: March 10, 2024
Accepted date: June 26, 2024
Published date: July 15, 2024

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Abstract: Metallic substances have been used for the therapeutic purposes since ancient times. Serendipitous discovery of cisplatin as an anticancer agent apparently initiated the use of metal complexes as chemotherapeutic agents for the treatment of cancer. Later on, many other metal complexes such as gold, silver, ruthenium, arsenic, titanium, manganese, palladium, gallium, aluminum, etc. has been investigated, studied and approved for cancer treatment. Many metal complexes have been synthesized by redesigning existing drug models through metal-ligand exchange or by developing an entirely new drug with enhanced cytotoxic activity and safety profile. Metal-based anticancer drugs offer distinct characteristics over other chemotherapeutic agents. These characteristics include forming DNA adducts, redox activity, photodynamics of metal coordination complexes, selective targeting, protein binding, metal-ligand exchange, structure and bonding. Herein, we have reviewed metal complexes as chemotherapeutic agents, general mechanism of cancer cell killing pathways of metal complex anticancer agents, superiority of metal complexes over other anticancer agents, etc.

Keywords: Cancer, Chemotherapeutic, Metal Complex, Apoptosis, Redox Activity, Photodynamic

1. Introduction

From ancient to modern times, the use of metallic substances for therapeutic purposes has been quite substantial [1][2]. In ancient times, people knew the importance of metallic compounds for therapeutic purposes, and people of different regions and ethnicities used different kinds of metallic compounds. The ancient Chinese, Egyptians, Indians and Assyrians used metal-based compounds to treat diseases and ailments [3]. Now, in this modern age, many metallic compounds are used as anti-cancer agents. For examples, the metal-based anti-cancer drugs Cisplatin [4], Auranofin [5], Zinc Oxide complexes [6], Copper (II) complexes [7], Silver nanoparticles [8], Vanadium compounds [9], Iron Chelators [10] are some of the well-known metal-based compounds used in modern anti-cancer therapy. Currently many studies are being carried out on several metal-based compounds that have potential in cancer therapy. Some of these metallo-drugs are undergoing clinical trials for cancer treatment and tumor detection, whereas some have already approved for cancer treatment.

Metal-based compounds have unique chemical, physical, and biological properties that differentiate them from other anti-cancer drugs as well as provide distinct superiority over other anti-cancer drugs in many cases. Due to their

unique characteristics, metal-based compounds garnered so much attention and interest as therapeutic agents in cancer treatment [11]. Metal coordination complexes such as platinum-based compounds (Cisplatin) can form DNA adducts (ability to covalently crosslink DNA bases and forming intrastrand and interstrand crosslinks) that interfere with DNA repair mechanisms, causing DNA damage, and eventually inducing Type-I programmed cell death, apoptosis in cancer cells [12]. Redox activity (reduction and oxidation reactions) of metal coordination complexes such as copper complex can generate reactive oxygen species (ROS) within the cancer cells and elevate the levels of (ROS) which can lead to DNA damage and eventually cell death [13] [14]. Photodynamics of metal coordination complexes (titanium oxide in aqueous media upon exposure to UV light) is capable of generating reactive oxygen species (ROS), leading to cellular DNA damage and subsequently cell death [15]. Thioredoxin reductase (TrxR), catalyze the anti-oxidative system in cells and prevention of cell death. Selective targeting of metal complexes such as gold complex Auranofin selectively targets and inhibits TrxR which imbalances the intracellular redox state generating ROS and eventually inducing DNA damage and cell death by apoptosis [5]. Palladium (II) complexes can bind to various proteins in a cancerous cell and initiate a cytotoxic event within the cell leading to cellular demise [16]. Metal-ligand exchange properties of ruthenium compounds such as half-sandwich Ru-arene complexes can undergo ligand exchange reactions resulting in a compound that has a specific structure and can selectively target cancer cells and thus ameliorating toxicity against normal cells) [17].

Metal-based compounds can readily lose electrons and become positively charged ions that may interact with biological molecules and make complexes. In human body, metals like iron and copper have crucial functions, such as carrying oxygen and electrons to cells, which help to generate energy. Metals like calcium and magnesium can support the protein and tissues of the body and participate in structural functions. Metals also have functions in our body's metabolic regulations, electrolyte balance and antioxidant defense [18][19][20][21]. In contrast to bioorganic or bio-macromolecular derived drugs, metallic compounds provide a platform for unique metal-based drug designing and molecular modifications. These bioactive metal-based compounds thus enable the formation of bioactive substances with unique and effective mechanisms of action with significantly fewer side effects compared to bioorganic substrates [22][23].

This article reviews the general mechanism of action of metal-based drug compounds, their various types with summarized FDA-approved and under clinical trial drugs, their advantages and superiority over bioorganic substrates and the advancement of metal-based drugs. This paper has also reported pharmacological actions such as anticancer activity on different cell lines, side effects, and cancer cell death rates. Lastly, the paper gives an idea about the future perspective of metal-based drugs.

2. Advantages and Superiority of Metal-based Compounds

Metal-containing carbon-based compounds such as carboplatin [26] and non-carbon-based compounds such as cisplatin [12] have several benefits over purely carbon-based organic molecules in synthesizing novel therapeutic drugs. These benefits stem from their capacity to organize ligands in a three-dimensional arrangement, allowing the functionalization of groups that may be tuned to specific molecular targets [41][42]. Metal-based complexes provide a rich environment for developing a range of different molecular structures that bestow a broad spectrum of coordination numbers, geometries, and kinetic characteristics that are not possible with carbon-based compounds [43][44]. Transition metals' partly filled d orbitals give unique electrical characteristics that might serve as valuable probes in creating anticancer drugs [45]. The oxidation state of a metal is also a significant factor in the design of coordination compounds because it allows for participation in biological redox chemistry and influences the optimum dosage and bioavailability of the drug supplied [46][47]. Furthermore, the capacity to perform ligand-exchanged reactions allows metals to interact and coordinate with biological molecules, as the widely used medication cisplatin [41]. Most noteworthy is the development of radiopharmaceuticals that exploit the radioactive characteristics of metals, which are extensively utilized in detecting cancer and other therapeutic purposes [48].

2.1 Diverse mode of action:

Metal-based anticancer drugs frequently have many modes of action, including DNA binding, the production of reactive oxygen species (ROS) by redox-active and biocatalyst mechanism, the photodynamic and the photoactivated mechanism in which again ROS are formed, and targeting the cellular signaling transduction pathways. All these mechanisms of action eventually lead to the crosslinking of DNA, cell cycle arrest, cytotoxicity and apoptosis [49].

2.2 Selectively targeting organelles

Metal-based compounds are flexible structures with a high degree of versatility due to their diverse oxidation states, coordination geometries, and the broad spectrum of organic ligands linked to the metal core. Ligand functionalization can affect cellular absorption, accumulation, and biomolecule targetability. Modifying the ligands may adjust the metal core's photophysical, electrochemical, and spectroscopic characteristics. This enables them to target the cell's internal and external components [50]. Intracellularly, metal-complex drugs can bind to nucleic acids, mitochondria, endoplasmic reticulum, and ribosomes. Anticancer medicines, such as Au(I) (phosphine), can increase the reactive oxygen species (ROS) within the cells and can directly target mitochondrial and nucleic acid functioning, providing considerable advantages over typical chemotherapy treatments, which cause mitochondrial failure indirectly by using damaged DNAs to create apoptosis-initiating signals [51]. Extracellularly, metal-complex drugs can bind to cell membranes and cell receptors, such as the coupling of the metal-complex ruthenium polypyridyl subunits and Epidermal Growth Factor Receptor 1 (EGFR)-inhibiting 4-anilinoquinazoline ligands results in a class of highly active dual-targeting anticancer drugs that can induce apoptosis [52].

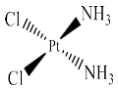
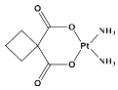
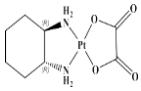
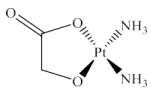
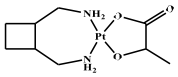
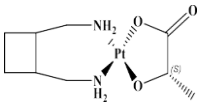
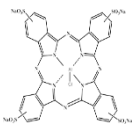
2.3 Enhanced bioavailability and stability of metal-based drugs

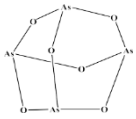
Metal-based anti-cancer drugs have more stability and solubility than organic compounds, which increases their therapeutic efficiency, and minimizes dosing frequency. Coordination bonds as a connection between the metal and its ligands allows the formation of a stable structure non-susceptible to hydrolysis and other degenerative mechanisms, giving the chemical compound stability in different physiological states. This is because it enables the development of prodrugs and controlled release formulations such as oxaliplatin that are not susceptible to fast degradation compared to drugs such as cisplatin to allow for close and flexible monitoring of the drug’s activity in the body. Furthermore, the solubility of the metal-based complexes is another factor that minimizes the degradation of the drug before it gets to the target organs so that a higher proportion of the drug administered has the maximum effect [53][54].

3. Positive Side Effects of Metal-based Anticancer Drugs

While the main target of the metal-based anticancer drug is to prevent the cancer cell proliferation and growth, some metal-based drugs are designed in a way that they exhibit positive auxiliary action While the main target of metal-based anticancer drugs is to prevent cancer cell proliferation and growth, some metal-based drugs are designed in a way that exhibits positive auxiliary actions.

Table 1. Examples of Some Approved Metal-based Drug

Metal- Based Drug Structure	**Mechanism of Action**	**Cancer Target**	**FDA/Country Approved**	**References**
 Cisplatin (Platinol)	Crosslink of DNA Bases, DNA Damage, Apoptosis	breast, testicular, ovarian, and cervical cancers	FDA Approved	[12],[24]
 Carboplatin (Paraplatin)	Crosslinks DNA, prevents DNA\replication, cell division arrest	Ovarian Cancer	FDA Approved	[25][26][27]
 Oxaliplatin (Eloxatin)	DNA damage, DNA and RNA synthesis arrest, Apoptosis	Metastatic Colorectal Cancer	FDA Approved	[28][29][30]
 Nedaplatin (Aqupla)	cross links of guanine bases, cell division arrest, Apoptosis	Small lung Cancer	Approved in Japan	[31][32][33]
 Lobaplatin (D-19466)	Cytotoxicity and induced apoptosis	Gastric Cancer cells	Approved in China	[34][35][36]
 Lobaplatin (1,2-Diammino-l- methylcyclo butane- platinum (II)- lactate)	Formation of DNA adducts and cell apoptosis	Gastric Cancer cells and small cell lung cancer	Approved in China	[35][37]
 Photosens (Sulfonated Aluminum Phthalocyan ine)	Photodynamic treatment, under the presence of oxygen kills cancer cells by generating ROS	Lungs, breasts, bladder, pharynx and larynx	FDA Approved	[38][39]

 Arsenic Trioxide (ATO)	Demise of cancer stem-like cells, inducing caspase dependent and independent apoptosis	A549 Lung cancer cells	FDA Approved	[40]

3.1 Anti-metastatic property of metal-based anticancer drug

Selenosemicarbazone Complexes with Metals is an example of a drug that shows an anti- metastatic effect, which is the drug's ability to prevent the proliferation of cancer cells and metastasize in other parts of the body. Manja Zec *et al.* reported the modulation of matrix- metalloproteinase 2 and 9 (MMP-2 and MMP-9) activity in cancer cell lines by metal complexes with 2-formylpyridine-selenosemicarbazone. It was seen that when the HeLa cell lines were treated with the ligands, the activity and growth of the MMP-2 dropped significantly compared to the non-treated cell. While the main target of metal-based anticancer drugs is to prevent cancer cell proliferation and growth, some metal-based drugs are designed in a way that exhibits positive auxiliary actions [55].

3.2 Anticancer potential of immunomodulatory metal-based drugs

Some metal-based anticancer medications can affect the immune response, possibly assisting the body in recognizing, destroying, and regulating cancer cells within the body. This immunomodulatory impact of the medication can supplement its cytotoxic potential, making it considerably more effective. Some anticancer metal medicines based on platinum, ruthenium, copper, and gold have been found to affect cancer and tumour cells via Immunogenic-Cell Death (ICD). These metal-based medicines enhance tumour-specific immune response and induce IFN-γ mediated immune response, including cytotoxic T cells (CTLs) and γδ T cells that eliminate remaining tumour cells [56].

3.3 Radiosensitization of metal-based anticancer drugs

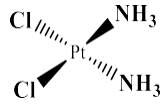
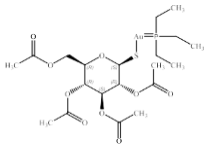
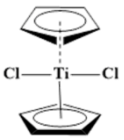
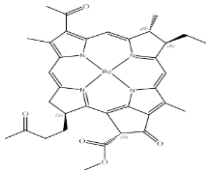
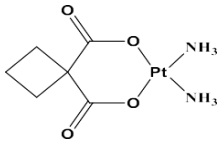
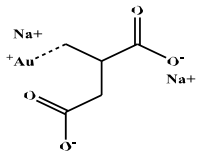
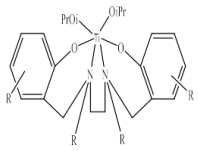
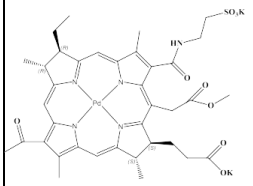
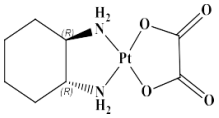
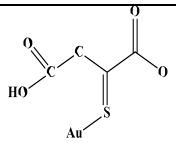
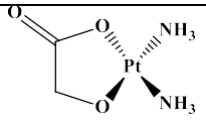
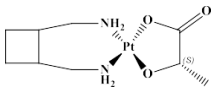
It has been found that some metal-based drugs can increase the sensitivity of cancer or tumour cells to radiotherapy, thus increasing its efficiency. Some platinum complexes such as cisplatin, oxaliplatin and carboplatin are used in chemotherapy and chemo-radiotherapy, and it has been found that they have radiosensitizing and synergistic effects for ionizing radiation. For instance, Kobayashi *et al*. found that when chloroterpyridine platinum (PtTC) bound to plasmid DNA were placed in an aqueous solution, it could enhance the X-ray-induced breaks in DNA [57].

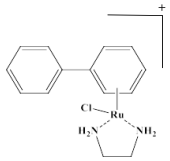
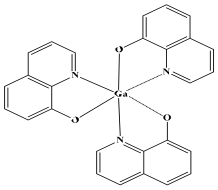
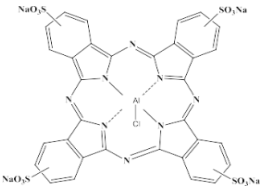
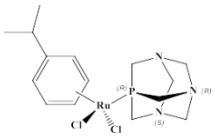
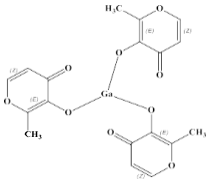
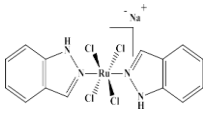
4. Categories of Potential Anti-Cancer Metal Complexes Based on the Metal Used

Due to their unique chemical characteristics and possible therapeutic uses, metal complexes have garnered much attention in anti-cancer research. Anti-cancer drug complexes can be divided into groups according to their metal ion. Effective anti-cancer drugs that bind to DNA and cause apoptosis are platinum-based complexes like carboplatin and cisplatin, which have been investigated and utilized extensively. Similarly, chemicals like RM-175 [49][58] and KP1019 [59] showed specific toxicity against cancer cells, demonstrating the promising anti- cancer effect of ruthenium complexes. Likewise, to generate innovative drugs and offer a variety of mechanisms of action, other transition metals such as iron, copper, and gold have also been investigated for their anti-cancer effects [60][61]. Gold complexes like auranofin [62], sodium aurothiomalate [63], and aurothiomalate have shown promising results in their anti-cancer activity in clinical trial phases. Palladium and Titanium complexes like WST09 [64] and WST11 [64][65], Titanocene dichloride [66] and Titanium (IV) Salan [67], respectively, have shown cytotoxic effects, giving rise to the hope of being used as an anti-cancer agent. Palladium complexes WST09 and WST11 are already approved for clinical use in the European Union, Norway, and Iceland

[64] and are marketed in Russia, Israel, Mexico, the EU, and EEA [64][65], respectively. The FDA has already approved the aluminium complex Photosens (Sulfonated Aluminum Phthalocyanine), which is out for clinical use [38][39]. The logical and proper design, synthesis and use of the anti-cancer metal complexes holds great promise in the selective and targeted cancer therapy.

Table 2. Categories of metal complexes based on metal used

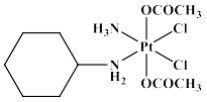
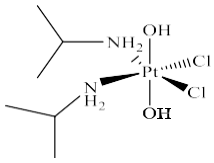
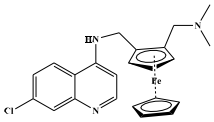
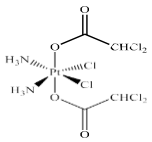
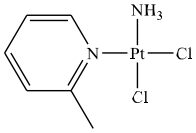
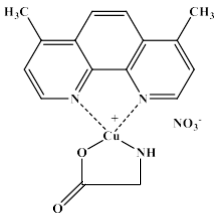
Platinum Complex	Gold Complex	Titanium Complex	Palladium based
 Cisplatin [12]	 Auranofin [62][68]	 Titanocene dichloride [66]	 Palladium bacteriopheophorbide [64]
 Carboplatin [25][26]	 Sodium aurothiomalate [63]	 Titanium (IV) Salan [67]	 Padeliporfin/ WST11 [64][65]
 Oxaliplatin [28][29]	 Aurothiomalate [63][69]		
 Nedaplatin [32]			
 Lobaplatin (1,2-Diammino- l-methylcyclobutane- platinum (II)-lactate) [34]			

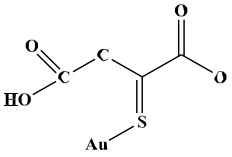
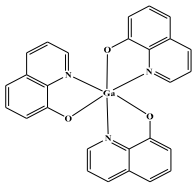
Ruthenium Complex	Gallium Complex	Aluminum Complex
 RM-175 [49][58]	 Gallium tris-8-quinolinolate/ KP46 [70][71]	 Photosens (Sulfonated Aluminum Phthalocyanine) [38][39]
 RAPTA-C/ Ruthenium (II) [Ru-(arene)Cl2PTA] PTA - 1,3,5-triaza-7-phosphaadamantane [72]	 (3-Hydroxy-2-methyl-4H-pyran-4-onato) gallium/(Gallium tris-maltolate) [68] [73]	
 KP1019 [49][59]		

5. Metal Complexes Currently Undergoing Clinical Trial

The first metal-based anticancer drug, cisplatin was discovered in 1960 and after that went through rigorous clinical trials to be first approved in 1978 [74]. Currently, cisplatin is the most widely used anticancer drug for the treatment of advanced ovarian cancer, testicular cancer, and bladder carcinoma [75][76]. Nowadays, many drugs are being studied for their anticancer properties, and of them the metal-based anticancer drugs seem to be very promising for their potential anticancer properties, though comparatively only a few selected metal-based anticancer drugs have been approved by FDA and other regulatory authorities. Currently many metal-based drugs are undergoing in vitro and in vivo study as well as clinical trials. **Table 3** highlights some of the Metal-based anticancer drugs undergoing different phases of clinical trial.

Table 3. Metal complexes currently undergoing clinical trial

Name and Drug Structure	Mechanism of Action	Cancer Target	FDA/Country Approved	References
 Satraplatin	binds to the DNA of cancer cells, alters the structure of the DNA, inhibiting cell division	Lung, Ovarian, Prostate Cancer	Phase III clinical trial	[77][78][79]
 Iproplatin	DNA damage by redox activity, inhibit cell division, Apoptosis	Epidermoid carcinoma of the head and neck, ovarian cancer	Phase III clinical trial	[80][81]
 Ferroquine	Inhibits the formation of hemozoin, generates ROS, negatively regulates Akt kinase and hypoxia-inducible factor-1**α** (HIF-1**α**)	Prostate cancer	Phase II clinical trial	[60][61]
 Mitaplatin	Damages Nuclear DNA and mitochondria, Apoptosis	Lung, Epidermoid carcinoma of the head and neck	Phase II clinical trial	[11][82]
 Picoplatin/AMD 473/ JM473/ZD0473	Binds with DNA, interfere with DNA replication and transcription, Apoptosis	Lung, Ovarian cancer	Phase II/III clinical trial	[83][84]
 Casiopeina	DNA damage, inhibit cell division, Apoptosis	Human Carcinomas, lymphomas	Phase I clinical trials	[85]

 Aurothiomalate	Inhibition of T-cell, Deactivation of CD4+T, Apoptosis	squamous cell carcinoma, large cell carcinoma, adenocarcinoma	Phase I clinical trials	[63][69]
 Gallium tris-8- quinolinolate/ KP46	Ga^{3+} ions bind to ribonucleotide reductase enzyme, disrupt DNA replication, Apoptosis	Lung Cancer	Phase II clinical trials	[70][71]

6. Conclusion

Metal-based anti-cancer drug possesses a potential area in the field of cancer therapies. Distinct physicochemical and biological characteristics of metal-based drugs, such as their capacity to target specific biological processes and coordination geometries, allow for a more customized approach to cancer treatment. These chemicals, ranging from platinum-based chemotherapeutics like cisplatin to developing prospects like ruthenium and gold complexes, have exceptional anticancer potential. The addition of metal-based medications to the oncological arsenal represents a significant move towards precision medicine, opening up new pathways for tailored and targeted therapy. As research progresses, the synergy between metallodrugs and traditional treatments may pave the way for more successful and acceptable cancer medicines, bringing up closer to a future in which cancer is battled with more precision and efficacy. However, possible toxicity and resistance of metal complexes may require more study and development of metal-based anticancer drugs.

Statement and Declarations
Conflict of Interest: The authors declare no competing conflict of interest.
Funding: This work received no external funding/financial aid from any organization.
Ethical Approval: Not applicable.
Informed Consent: Not applicable.
Authors Contribution: T. Zubair conceived the idea and wrote the manuscript. A. Masum read and revised the manuscript and supervised the works.
Acknowledgments: We thank our collaborators and co-workers for their contribution and relentless support.

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