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"Unlocking The Therapeutic Power Of Metal Complexes: A Review Of Recent Discoveries"

*[1]Ms. Pooja S. Kothekar, *[2]Ms. Ruchi S. Shivhare, *[3]Dr. Sanjay P. Wate, *[4]Dr. Sachin W. Lohe

Assistant professor, Assistant professor, Principal, HOD

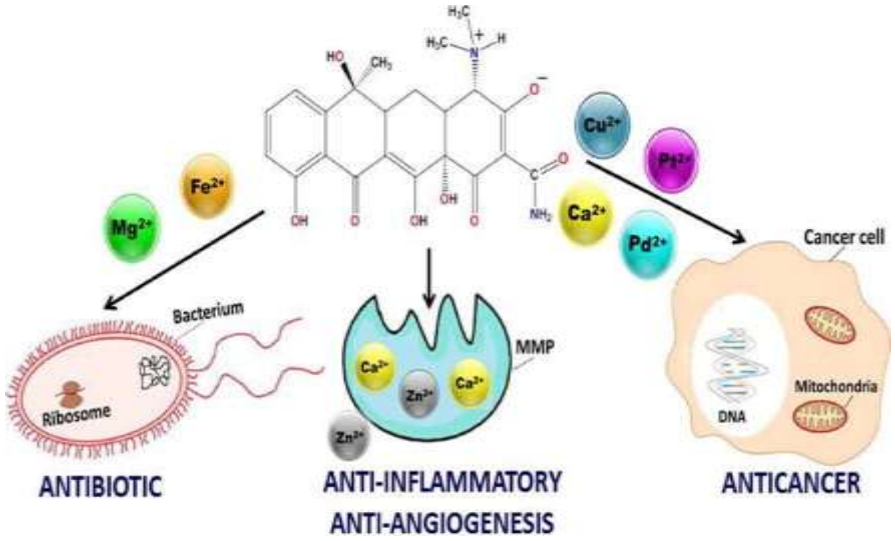
Pharmaceutical Chemistry

Anurag college of pharmacy warthi, Bhandara, India

Abstract: The therapeutic potential of metal complexes has garnered significant attention due to their diverse properties and applications. This review consolidates recent discoveries involving metal complexes, focusing on the therapeutic aspects of d-block elements (Fe, Ni, Cu, Zn, Tc, Ru, Rh, Ir, Pt, Au), lanthanides, actinides, and bismuth complexes. The study highlights the use of various ligands-monodentate, bidentate, and multidentate-as well as organometallic compounds. Key properties such as color, photophysical characteristics, magnetism, reactivity, biological activity, and catalytic behavior are discussed. The findings underscore the versatility of metal complexes in therapeutic applications, showcasing their potential in advancing medical treatments and diagnostics.

INTRODUCTION:

Metal complexes are formed by a central metal atom or ion, known as the coordination center, surrounded by bound molecules or ions called ligands. There are numerous possible combinations of metals and ligands. In the studies, ten d-block elements (Fe, Ni, Cu, Zn, Tc, Ru, Rh, Ir, Pt, and Au) were included, as well as complexes of lanthanides and actinides in two studies. Bismuth complexes were the only main group elements studied. Various versatile ligands were used in these contributions, including monodentate (N-, P-, O-, S), bidentate (N, N-, O, O-, N, S-), and multidentate examples. Some studies also included organometallic compounds. Metal complexes have a broad range of properties, such as color, photophysical characteristics, magnetism, reactivity, biological activity, catalytic behavior, and structure.(1)

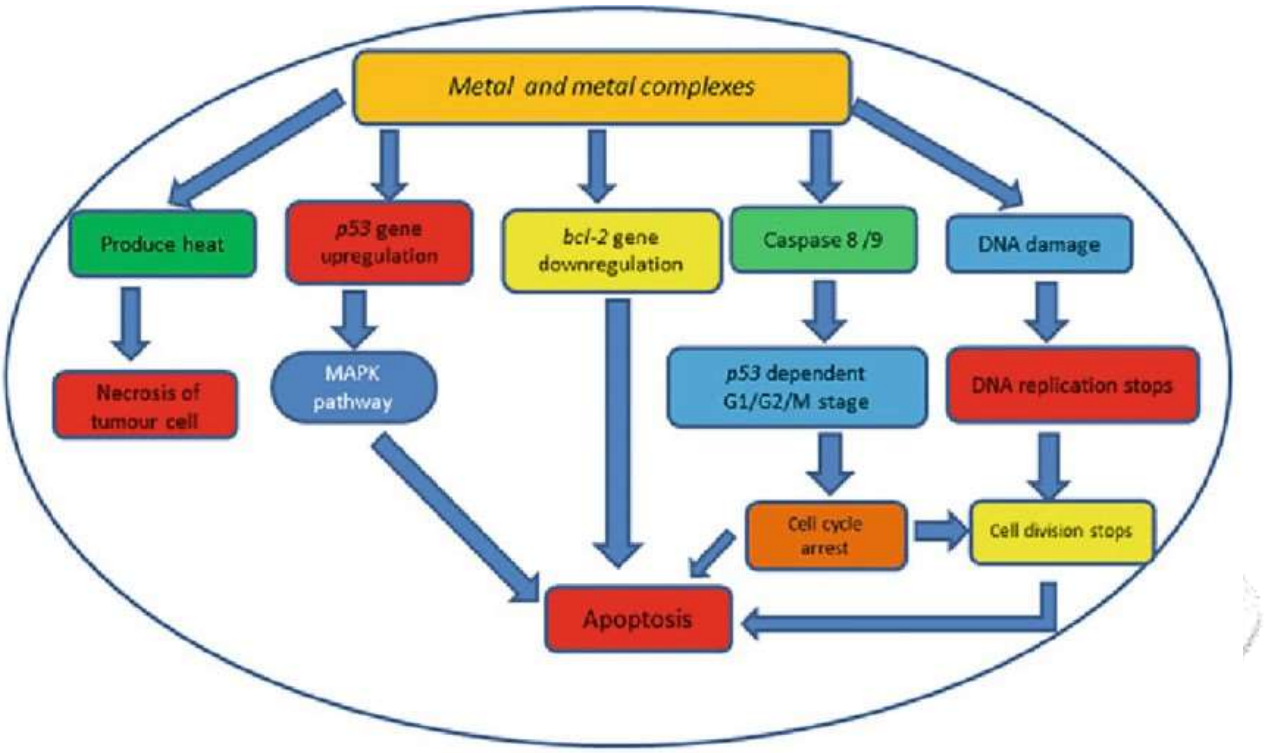


Chemistry of transition metal

The properties of d-block transition metals differ considerably between the first (3d) and the second series metals (4d), although the differences in properties among the second and third series (5d) metals are not as pronounced. The metallic radii of elements from scandium, Sc, to copper, Cu, (166 to 128 pm) are significantly smaller than those of yttrium, Y, to silver, Ag, (178 to 144 pm) or those of lanthanum, La, to gold, Au, (188 to 146 pm). Furthermore, metal compounds of the first series transition metals are rarely 7-coordinate, whereas transition metals from the second and third series may be 7-9 coordinates. Transition elements are metallic elements that have incomplete d or f shells in the neutral or cationic states. They are also referred to as transition metals and make up 56 of the 103 elements. These transition metals are classified into d-block metals, which consist of 3d elements from Sc to Cu, 4d elements from Y to Ag, and 5d elements from Hf to Au, and f-block metals, which consist of lanthanoid elements from La to Lu and actinoid elements from Ac to Lr. Simple substances of transition metals have properties characteristic of metals, meaning they are hard, good conductors of heat and electricity, and melt and evaporate at high temperatures. Although they are used widely as simple substances and alloys, we typically encounter only iron, nickel, copper, silver, gold, platinum, or titanium in everyday life. However, molecular complexes, organometallic compounds, and solid-state compounds such as oxides, sulfides, and halides of transition metals are used in the most active research areas in modern inorganic chemistry.[(2)]

Transition metal complexes are cationic, neutral, or anionic species in which a transition metal is coordinated by ligands. These metals exhibit different oxidation states and can interact with various negatively charged molecules. Advances in inorganic chemistry have provided better opportunities to utilize metal complexes as therapeutic agents. The mode of action of metal complexes on living organisms differs from that of non-metals and these complexes display a great diversity in their action. Medicinal inorganic chemistry can exploit the unique properties of metal ions for designing new drugs, leading to clinical applications such as the use of cisplatin for cancer treatment. Transition metal complexes offer a diversity of action, serving not only as anti-cancer agents but also as anti-inflammatory, anti-infective, and anti-diabetic compounds. Developing transition

metal complexes as drugs is a challenging task requiring considerable effort to obtain compounds of interest. Despite their limitations and side effects, transition metal complexes remain widely used as chemotherapeutic agents, making a substantial contribution to medicinal therapeutics. Furthermore, transition metal complexes play important roles in catalysis, materials synthesis, photochemistry, and biological systems, exhibiting diverse chemical, optical, and magnetic properties.[3]



Complexes of Gold:

Gold forms complexes with various metals such as copper, vanadium, ruthenium, rhodium, nickel, palladium, iron, cobalt, and others. Some of these complexes, including palladium(II), nickel(II), and copper(II), show promise in cancer treatment. Additionally, arsenic trioxide, a metalloid compound, is approved for medical use. Research shows that metal complexes have a wide-ranging potential against cancer compared to small organic molecules, mainly due to their ability to change properties by selecting the right oxidation state. Furthermore, the choice of ligand significantly impacts solubility, reactivity, and biological activity.

Chrysotherapy, which involves the use of gold(I) compounds in medicine, has been known since ancient times. The early twentieth century was crucial for "gold chemistry" as Koch discovered the use of potassium gold(I)-cyanide as an anti-tuberculosis agent, while Forestier found that gold(I) complexes could treat rheumatoid arthritis. Later, the Food and Drug Administration approved auranofin, a gold(I) complex, as an oral anti-arthritic drug. Other gold(I) compounds like aurothiomalate and aurothioglucose were also used as anti-arthritic agents. Research into gold(III) compounds has revealed promising anti-inflammatory, antiparasitic, and anticancer activities.

Gold complexes primarily interact with enzymes containing cysteine or selenocysteine, and some exhibit autophagy or interact with topoisomerase I or the ubiquitin-proteasome system. The square-planar geometry of gold(III) complexes, similar to cisplatin, makes them potential antitumor drugs. Studies have shown that these complexes can combat tumors resistant to cisplatin treatment and have substantial cytotoxic effects against solid cancer tumors without systemic toxicity. Additionally, gold(III) complexes show potential in preventing cancer, HIV, bronchial asthma, and acting as antimicrobial agents.

However, their rapid hydrolysis and reduction to Au(I) or Au(0) indicate their instability. Evidences from literature suggest DNA-independent activation of some gold(III) complexes, while others bind to DNA, leading to potential cytotoxic activities. Based on this information, we have decided to write a review covering the interactions of novel gold(III) complexes with small biomolecules, DNA, model proteins, such as bovine serum albumin (BSA), their kinetic properties, and biological activity supported by computational calculations.

Biological Targets for Gold Complexes

The study of potential anticancer activity of different transition metal ion complexes primarily considers their interactions with small biomolecules such as amino acids, peptides, nucleosides, nucleotides, and further explores the interactions with DNA and proteins. In this regard, interactions with L-methionine (L-Met), L-histidine (L-His), guanine (Guo), guanosine-5′-monophosphate (5′-GMP), inosine (Ino), and inosine-5′-monophosphate (5′-IMP) are crucial and should be highlighted. These interactions depend on the redox properties, electrophilicity, and kinetic lability of the complexes. At times, the reactivity of the nucleophiles indicates deactivation of the complexes.

Cytotoxic Activity of Gold Complexes

The cytotoxicity and selectivity of different transition metal ion complexes on various cancer cells play a key role in the design and development of new potential anticancer agents. At the beginning of the twenty-first century, a gold(III) porphyrin complex with satisfying physiological stability was reported as a promising anticancer agent with IC50 values in the range of 0.73–0.11 μM. Studies against normal and cisplatin-resistant ovarian cancer have shown the ability of the gold(III) porphyrin complex, in vitro and in vivo, to exceed cisplatin resistance without affecting health. Furthermore, carbamate-based Au(III) complexes were used for animal experiments and, based on the observed data of clinical studies, gave promising results of good anticancer effects. All these facts have contributed to the assumption that gold(III) complexes have different modes of action compared with platinum antitumor active compounds. The potential activity was estimated by 3-(4,5-dimethythiazol-. 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test on different cell lines (A549, A375,

and LS-174, 4T1 and CT26, MDA-MB-231, HCT-116, MRC-5, MCF-7, HT-29, HepG2 and NHDF, HeLa) for complexes. [4]

The cytotoxic property of gold complexes has recently garnered attention, possibly due to the challenges observed with the clinical use of platinum compounds. Gold(III) complexes, as an emerging class of metal complexes, exhibit potential antitumor properties as an alternative to cisplatin. These complexes are designed to be highly effective, less toxic, and selectively bind to the active site of enzymes. The selectivity of gold(III) complexes to thiol-containing enzymes such as thioredoxin reductase (TrxR) makes them attractive for designing compounds that can selectively bind to residues in the active site of the enzyme. Various forms of gold(III) complexes have been synthesized, and their anticancer activity has been evaluated against cancer cell lines.[5]

In addition, some gold(I) compounds, known for their anti-inflammatory and immunosuppressive properties in the treatment of rheumatoid arthritis, have been considered for their potential anticancer activity. Studies have shown that gold(I) compounds inhibit tumor cell proliferation in vitro, but their in vivo effectiveness is limited. The similarity of gold(III) to platinum(II) and the investigation of its anticancer activity have led to the synthesis of new, stable gold(III) compounds using ligands with nitrogen atoms as donor groups. These studies have shown that the interaction of gold(III) complexes with DNA, the target of platinum(II) complexes, is not as strong as that of platinum drugs, suggesting a different cytotoxic mechanism. Recent reports have also indicated that new gold(III) dithiocarbamate derivatives exhibit cytotoxicity comparable with, and even greater than, cisplatin toward human tumor cell lines in vitro. These derivatives act quickly, inhibit DNA and RNA synthesis, and show minimal cross-resistance with cisplatin, suggesting a different mechanism of action.[6]

Complexes of Copper:

Copper has significant biochemical effects in the human body, either as an essential trace metal or as part of various externally administered compounds. Research has shown the multifaceted role of copper in biological systems, especially in its involvement in human diseases. Current studies focus on copper homeostasis and its relationship to iron metabolism, as well as the role of copper in biological processes related to human physiology and pathology. There is also growing interest in copper complexes due to their potential use as antimicrobial, antiviral, anti-inflammatory, antitumor agents, enzyme inhibitors, or chemical nucleases. Several Cu(II) complexes of NSAIDs have been prepared and structurally characterized, exhibiting enhanced anti-inflammatory and antiulcerogenic activity, along with reduced gastrointestinal toxicity compared to the uncomplexed drug. These complexes are a class of potential anti-inflammatory drugs with reduced side effects, and their mode of action is attributed to their marked superoxide dismutase (SOD)-mimetic activity. Other research focuses on the potential chemotherapeutic properties of copper-based compounds, with the speculation that the degradation of viral nucleic acid may occur after the intervention of copper ions. Additionally, the study and development of Cu complexes could contribute to the design and production of antiviral and

antibacterial materials, capable of deactivating HIV or H1N1 viruses and antibiotic-resistant bacteria. Copper plays a crucial role in human health and disease. Copper in food (organic copper) is processed by the liver and transported and sequestered safely. Inorganic copper, such as that in drinking water and copper supplements, largely bypasses the liver and enters the free copper pool of the blood directly, potentially posing toxicity risks as it may penetrate the blood/brain barrier.

Copper is associated with various health disorders including:

1. Oxidative-Stress-Related Disorders
2. Aceruloplasminemia
3. Wilson's Disease
4. The Menkes Disease
5. Alzheimer's Disease
6. Inflammation
7. Cancer[7]

Although copper has a long history of medical applications, research into copper coordination compounds as potential antiproliferative agents has only been conducted in the last few decades, especially after the discovery of cisplatin, which is widely used as an anticancer drug. Copper is considered to be less toxic than non-essential metals due to its role as an essential cofactor in numerous enzymes and physiological processes. Over the years, a wide variety of copper complexes have been tested as cytotoxic agents and have demonstrated antitumor activity in in vitro tests (on cultured cancer cell lines) and a few in vivo experiments (on murine tumour models). The well-established coordination chemistry of copper, often enriched by its flexible redox behaviour, provides significant potential for the design of more potent and less toxic copper-based antiproliferative drugs. Most of the investigated compounds belong to the family of copper(II) complexes, with either five-coordinate environments comprising distorted square pyramidal and trigonal bipyramidal geometries, or distorted six-coordinate octahedral arrays. While the majority of these agents are mononuclear species, there are a few distinct examples of dimeric compounds that exhibit remarkable antitumor activity. Notably, there are tetrahedral copper complexes containing soft tertiary phosphines or aromatic amines (e.g., phen, bipy) as donor ligands that display antiproliferative activity in the sub-micromolar range. Various synthetic strategies have been explored to enhance the antitumor efficacy, including efforts to improve the hydrophilic character of copper compounds to ensure suitable solubility in physiological conditions, thereby enhancing bioavailability and reducing in vivo toxicity. There is ongoing debate around attempts to correlate the antitumor activity of copper compounds with the copper oxidation state, coordination number, and geometry. Correlations, if they exist, are yet to be substantiated. However, given that the intracellular trafficking of copper(I) species might be favoured concerning the internalization of copper compounds due to the primary role of the hCtr1 system, a specific monovalent metal transporter, in driving the copper transport machinery at the plasma membrane in mammalian cells, further research in this area is warranted. Initially, copper complexes were tested with a vision towards behaviour analogous to cisplatin, and consequently, their interaction with nucleic acids was

extensively investigated. However, it has become clear over time that copper compounds can act through different mechanisms. In addition to DNA binding, intercalation, and cleavage activity, SOD mimetic activity, as well as the generation of ROS through redox cycling, have been described. These intracellular molecular events generally trigger cancer cell death through an apoptotic mechanism. Furthermore, the downregulation of antiapoptotic proteins (Bcl-2 and Bcl-XL) has been observed in human cancer cells treated with copper compounds. More recently, a non-apoptotic form of programmed cell death (pyroptosis) has been evidenced in human cancer cells treated with both copper(I) and copper(II) complexes.[8]

Copper complexes have been found to exhibit cytotoxic properties, which work differently from the widely used platinum compound cisplatin. These complexes have varying activities depending on the type of ligand attached to them. Investigations into the cytotoxic effects of copper-based complexes have been based on the assumption that endogenous copper may be less toxic to normal cells than to cancer cells. However, copper can still competitively bind to sites that would otherwise be occupied by other metals due to its redox activity. It's an essential cellular element necessary for many biological pathways and serves as a cofactor in enzyme catalytic processes. The role of copper in angiogenesis has been a matter of contention, and the overall role of metals in this process is still under scrutiny. The antiproliferative effects of these complexes have been evaluated, and all four complexes exhibited good cytotoxicity against cancer cell lines. Those with salicylate as an auxiliary ligand showed better anticancer activity. The enhanced activity of the most effective complex may be due to the presence of a Schiff base complex and a nonsteroidal anti-inflammatory drug[5].

Copper complexes play a significant role in the active sites of numerous metalloproteins in biological systems and also have potential applications for various catalytic processes in living organisms. They are involved in bioinorganic and medicinal chemistry and have been found to interact with biological systems, exhibiting antineoplastic, antibacterial, antifungal, and anticancer activity[9].

Copper is also implicated in Creutzfeldt-Jakob (prion) disease, and recent studies have highlighted the roles of copper, iron, and zinc as contributors to both amyloid Ab assembly in vitro and the neuropathology of Alzheimer's disease[10].

Complexes of Cadmium:

The biological interest in cadmium lies in its potential to seriously disrupt the metabolism of living organisms, leading to acute or chronic intoxication. Cadmium is considered toxic, and though the exact molecular mechanism of its toxicity is not fully understood, it is known to form complexes with biochemical ligands in living organisms, disrupting their biological functions. Therapeutic strategies for cadmium detoxification involve administering external ligands that can compete with biological ligands, mobilizing the cadmium for elimination. Cadmium's toxicity varies depending on the types of ligands it forms complexes with. It has an affinity for easily oxidizable soft ligands, especially when the chelate effect comes into play. For the study of cadmium complexes relevant to biological systems, chelating agents such as adenosine 5’-triphosphate (ATP),

amino acids, nitrogenated bases, dithiocarbamates, thiolates, and vitamins were considered. Structural studies of cadmium(II) complexes with amino acids have been focused on essential α-amino acids, with only a few of them having been structurally studied in the solid state. Similarly, research on cadmium complexes with vitamins and derivatives is limited, with relatively few known solid phase structures for these complexes. Given the d10 state of the Cd2+ ion, it is expected that the coordination chemistry of this metal ion is dominated by coordination to four two-electron donors. Ligands containing thiolate or carboxylate groups are of particular interest due to their relevance in the field of cadmium detoxification by chelation[(11)]

Complexes of Platinum:

Platinum-based anticancer drugs are often used in chemotherapy, but they can lead to serious side effects and drug resistance. There is a growing interest in enhancing these drugs' effectiveness by modifying them with bioactive molecules, targeting groups, photosensitizers, fluorophores, or nanomaterials. This modification aims to improve tumor selectivity, reduce systemic toxicity, increase cellular accumulation, overcome drug resistance, visualize drug molecules, achieve synergistic anticancer effects, and add extra functionality to the drugs. Various strategies are being used to modify platinum complexes, including conjugation with bisphosphonates, peptides, receptor-specific ligands, polymers, nanoparticles, magnetic resonance imaging contrast agents, metal chelators, or photosensitizers. These modifications are driven by the need for targeted drug delivery, theranostic purposes, and treatment or prevention of Alzheimer's disease. The rationale behind these modifications is explained at the molecular or cellular level, taking into account the requirements for diagnosis, therapy, and visualization of biological processes. Platinum complexes, besides their antitumor activity, also possess other biological activities, such as enzymatic activity, antibacterial activity, antimycobacterial activity, and anti-amyloid activity. These complexes display inhibitory activity against the aggregation of amyloid-β peptide (Aβ), which may have implications for the treatment or prevention of Alzheimer's disease. The versatility of platinum complexes has led to the exploration of new possibilities by modifying them with bioactive molecules or nanomaterials, resulting in the development of multifunctional platinum complexes, such as targeted anticancer drugs and detectable theranostic agents. This summary highlights the achievements in functionalizing platinum complexes over the past 5 years, outlining strategies for targeted drug delivery, real-time imaging, and anticancer or anti-Alzheimer's therapy[(12)].

The structure-activity relationships of platinum coordination compounds show that only those compounds with cis geometry can block cell growth. Cisplatin, the most active complex, has been found to exhibit antitumor activity, while its trans isomer has no such activity. Many derivatives of cisplatin also inhibit growth, and these compounds have at least one N-H group, which is responsible for important hydrogen-bond donor properties, either in the approach of the biological target or in the final structure. Most well-known platinum anticancer complexes have the general formula cis-[PtX2(NHR2)2], in which R represents an organic fragment and X represents a leaving group, such as chloride or (chelating bis)carboxylate. Many other active Pt(II) compounds

are now known, even with trans geometries, and these will be discussed later. The development of cisplatin as a successful antitumor drug is often seen as a prototypical success story. The large number of patients who have been cured after cisplatin treatment of cancer is impressive. However, the fact that the precise mechanism of action remains elusive has resulted in great interest in metal DNA binding generally and the binding properties of cisplatin and its analogs in particular. As a consequence, cisplatin chemistry has provided fertile ground for exciting bioinorganic chemistry research. It is very important to note that similar coordination complexes from other groups of metals do not yield active compounds. The key factor explaining why Pt is most useful clearly relates to ligand-exchange kinetics. An important property of platinum coordination compounds is that the Pt-ligand bond, which has the thermodynamic strength of a typical coordination bond, is much weaker than (covalent) C-C, C-N, or C-O single and double bonds. However, the ligand-exchange behavior of Pt compounds is quite slow, giving them high kinetic stability and resulting in ligand-exchange reactions taking minutes to days, rather than microseconds to seconds for many other coordination compounds. Another unusual phenomenon deals with the preferred ligands for Pt ions. Pt(II) has a strong thermodynamic preference for binding to S-donor ligands. For that reason, one would predict that platinum compounds would perhaps never reach DNA, with many cellular platinophiles (S-donor ligands, such as glutathione, methionine) acting as competing ligands in the cytosol. Finally, the so-called kinetic trans effect should be mentioned, which is responsible for ligand-exchange reactions on metal ions. The effect is most pronounced for Pt(II) compounds, where it has been studied in great detail. The rule can be quite simply formulated as: ligands located trans to another ligand with a strong trans effect (such as many soft ligands) are more rapidly substituted than ligands in cis positions. Despite the success of cisplatin, however, it lacks selectivity for tumor tissue, which leads to severe side effects, including renal impairment, neurotoxicity, and ototoxicity (loss of balance/hearing), which are only partially reversible when the treatment is stopped. With long-term or high-dose therapy, severe anemia may develop. To address these problems, modified versions of cisplatin, leading to second and third generation platinum-based drugs have been synthesized over the past 30 years. Several platinum complexes are currently in clinical trials, but some of these new complexes have not yet demonstrated such significant advantages over cisplatin. The second-generation platinum drug carboplatin, [Pt(C6H6O4)(NH3)2], has fewer toxic side effects than cisplatin and is more easily used in combination therapy. Its low reactivity allows a higher dose to be administered. Carboplatin is mainly used in ovarian cancer treatment, while oxaliplatin is known to be most effective in colon cancer treatment. More recent developments have shown that spontaneous (intrinsic) drug resistance may develop in certain tumors, which is one of the main limitations when treating patients. Such resistance is easily detected in tumor cell lines, allowing for the rapid screening of new drugs. As a result, a new group of compounds with different amines and lacking the classical cis-diamine structure with two leaving groups has evolved during the last decade. These compounds are often considered the so-called third-generation drugs. Combining drugs with different modes of action often synergizes their effects, so scientists will continue to probe the various metallopharmaceutical mechanisms in the hope that together they might yield an even wider range of effective chemotherapeutic agents. Combination therapy could be the way forward in the fight

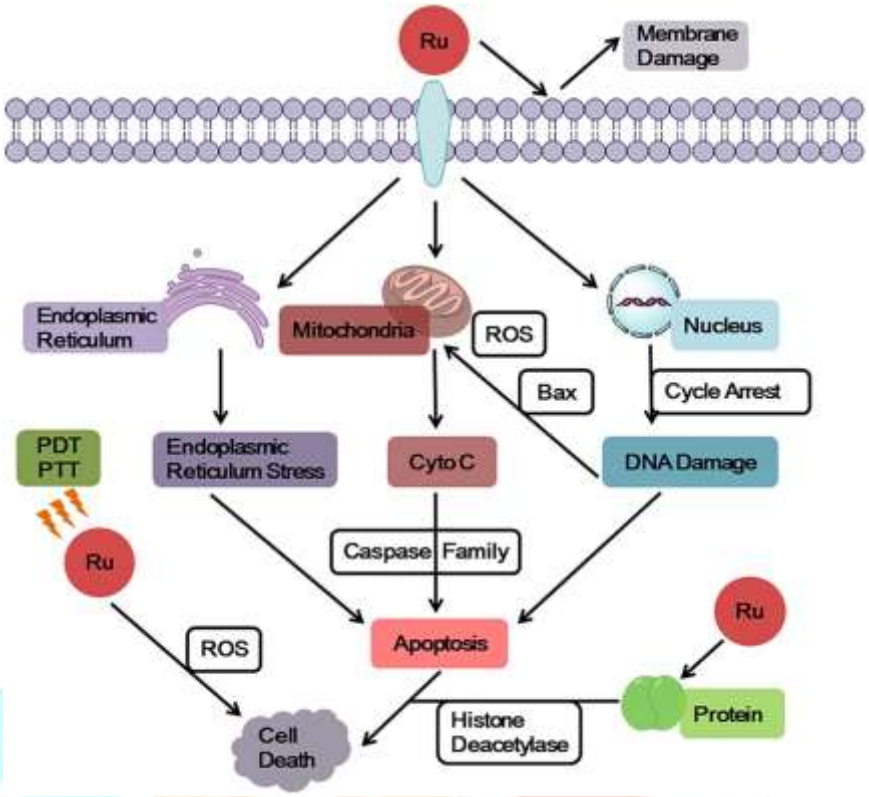
against cancer. Platinum-Based Anticancer Agents: Besides cisplatin, the second-generation drug, carboplatin (diamine[1,1-cyclobutanedicarboxylato(2-)]-O,O´-platinum (II)) has been introduced into oncotherapy. The observed pharmacokinetic differences between cisplatin and carboplatin primarily depend on the slower rate of conversion of carboplatin[13].

Recent Progress in the Field: The reactivity of platinum(IV) complexes with biomolecules and the clinical development of platinum(IV) complexes have been previously reviewed. Reports continue to surface about platinum(IV) complexes of platinum(II) analogues or biomolecules, but rarely do these yield complexes with new cytotoxicity profiles. Oxidation does not necessarily guarantee improved stability. For example, Battle et al. recently demonstrated that the generation of the platinum(IV) version of the clinical drug cisplatin did not confer stability due to steric bulk around the platinum(IV) center destabilizing the higher oxidation state [14].

Cisplatin has become one of the most frequently used and effective cytostatic drugs for treating solid carcinomas. Other metal compounds containing platinum, other platinum metals, and even non-platinum metals have been shown to be effective against tumors in humans and experimental tumors in animals. These compounds include maingroup metallic compounds of gallium, germanium, tin, and bismuth, early-transition metal complexes of titanium, vanadium, niobium, molybdenum, and rhenium, and late-transition metal complexes of ruthenium, rhodium, iridium, platinum, copper, and gold. Several platinum complexes and four non-platinum metal anti-tumor agents have entered early clinical trials [15].

Complexes of Ruthenium:

Research on drugs based on ruthenium compounds is a rapidly developing field in medicinal chemistry and medicine, particularly in the development of chemotherapeutics that have minimal side effects and are resistant to drug resistance. Ruthenium complexes show promise compared to other metal-based drugs such as cisplatin, carboplatin, and oxaliplatin. Two Ru(III) compounds, KP1019 and NAMI-A, have entered phase II clinical trials as anticancer compounds.



The specific mechanism of action of Ru(III) complexes is not fully understood. The initial hypothesis was based on the "activation by reduction" mechanism, which suggests that Ru(III) complexes act as prodrugs that can be reduced to Ru(II) active species in the hypoxic (therefore reducing) environment of cancer cells. Ru(II) complexes have been synthesized and investigated for their antiproliferative properties.

Bifunctional Ru(II) complexes such as RAPTA showed antimetastatic properties and low toxicity. For example, RAPTA-C has been shown to reduce the growth of lung metastases in mice bearing breast carcinoma. RAPTA-C also inhibited cell proliferation in vitro by arresting cells in the G2/M phase of the cell cycle and inducing apoptosis. It is believed that these Ru(II) complexes may have antiangiogenic activity.

In general, RAPTA compounds seem to work via molecular targets other than DNA, suggesting a different mode of action from classical platinum anticancer drugs. The mechanism of action of the RAPTA complexes may involve interactions with critical intracellular or extracellular proteins. For example, RAPTA compounds inhibit specific cysteine proteases involved in cancer development and angiogenesis.

The aim of the present study was to evaluate the angiostatic effects of RAPTA complexes in a series of in vitro bioassays. RAPTA-C and RAPTA-T, as well as two new ruthenium compounds bearing the DAPTA ligand, DAPTA-C and DAPTA-T, were characterized for their effect on angiogenesis of endothelial cells (EC). These compounds were also evaluated in the chicken embryo chorioallantoic membrane (CAM) model to study the rate and efficacy of angiogenesis inhibition in vivo.

The influence of the ruthenium(II) compounds was also evaluated in the CAM model by monitoring their influence on the regrowth of blood vessels after application of angio-occlusive photodynamic therapy. The

results demonstrate that ruthenium compounds possess an intrinsic angiostatic activity, making them attractive for further clinical development[16].

Ruthenium has been receiving a lot of attention as a potential foundation for new compounds to treat cancer. Over the last two decades, there has been a significant increase in research papers focusing on the synthesis of ruthenium anticancer drugs. The interest in ruthenium compounds is evident from the number of review papers discussing their properties and highlighting the differences compared to platinum and other transition metal compounds. The interest in ruthenium-based compounds was sparked in the mid-1980s by a few research groups. Since then, many scientists have been exploring this field due to the unique properties attributed to ruthenium-based compounds. These properties suggest the potential for developing innovative anticancer drugs that could overcome the limitations of existing platinum drugs, such as limited activity and toxicity. However, despite the extensive research, there are no clear guidelines for developing effective ruthenium compounds with innovative mechanisms for targeting cancer cells or overcoming the limitations of platinum drugs. The existing data on the properties of these compounds is highly varied, and there is a lack of convincing information on their mechanisms of action. The future research in this area should focus on understanding the relationships between the activity of ruthenium compounds and their targets in order to design more selective and effective complexes. Using proteomic techniques, rather than genomic studies, may help in understanding how these agents interact with cancer cells. Proteomic approaches, particularly those associated with mass spectrometry and multidimensional chromatography, may also help identify where ruthenium ions bind inside the cell. Understanding the targets of ruthenium compounds is crucial for designing new chemical entities that can effectively target tumor or metastatic cells. One existing example of promising characteristics is NAMI-A, which has demonstrated the unique property of effectively stopping lung metastases. Understanding the mechanisms of action of such compounds is essential for the rational design of anticancer agents. The accumulated knowledge on the chemical reactivity of ruthenium compounds could significantly contribute to the proteomic approach and aid in understanding the role of the metal in targeting molecules responsible for cancer malignancy[17].

Ruthenium compounds have shown potential as drug candidates, although they differ from existing platinum-based drugs. Their antitumor potential was established over two decades ago. However, their cytotoxic profile was not well explored initially, possibly due to their different mode of action compared to cisplatin. These compounds offer the potential of reduced toxicity and better tolerance in vivo, attributed to ruthenium's ability to mimic the binding of iron to serum transferrin. This exploits the body’s mechanism of nontoxic delivery of iron. Ruthenium compounds have several advantages over platinum-based complexes, including stability in various oxidation states under physiological conditions and different coordination geometries. In recent years, numerous research groups have explored ruthenium compounds for their ability to inhibit tumor growth. Their cytotoxicity is generally related to their ability to bind to DNA, although exceptions exist. Some ruthenium compounds inhibit DNA replication, induce mutagenic effects, and reduce RNA synthesis. Notably, three

promising ruthenium(III) complexes—NAMI-A, KP1019, and NKP-1339—have entered clinical trials. NAMI-A interferes with tumor cell interactions with the extracellular matrix, suggesting potential effects against metastasis. Clinical trials have evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of these compounds. The redox activities of KP1019 and NPK-1339 align with the proposed mode of action of ruthenium compounds, involving disturbance of cellular redox balance, induction of G2/M cell cycle arrest, blockage of DNA synthesis, and induction of apoptosis. Additionally, their high tumor targeting potential may be based on the delivery to tumor sites by serum proteins and activation in the reductive tumor milieu. The administration of KP1019 and NKP-1339 intravenously and their interaction with serum proteins are significant in this context. Research has demonstrated a strong binding affinity of these compounds to proteins in the bloodstream, particularly to albumin and transferring[18].

Complexes of Iron:

A promising approach in developing anticancer drugs involves targeting the molecular pathways that support the survival and spread of cancer cells. Copper and iron are essential metals that play key roles in the rapid growth of cancer cells, and several chelators have been studied to reduce the availability of these metals in the cells. This review explores the significant contributions of copper and iron to cancer progression and spread, and evaluates selected copper and iron chelators that show promise as anticancer drugs. It also discusses efforts to enhance the delivery, effectiveness, and tumor response of these chelators, including a transmetallation strategy for targeting both copper and iron. Additionally, it describes analytical tools for measuring copper and iron levels and tracking these metals in cells, tissues, and the body to assess the effectiveness and specificity of chelators for cancer treatment.

The Role of Fe in Cancer: The human body contains iron (Fe), which is essential for various cell functions such as oxygen transport, energy metabolism, and DNA synthesis. Fe exists in different forms in the body and its ability to convert between ferrous and ferric forms is crucial for these biological functions. The body strictly regulates the absorption, storage, and distribution of Fe to maintain balance, as an imbalance can be harmful. Fe is ingested in heme and nonheme forms and gets converted to Fe(II) during digestion. It is then released into the blood circulation by a transmembrane protein called ferroportin 1 (Fpn1). Serum transferrin (sTf) can efficiently bind with Fe(III), so Fe needs to be oxidized for sTf to be taken up. In enterocytes, Fe oxidation occurs through an enzyme called hephaestin. Improperly sequestered Fe or excessive accumulation of labile Fe pool can lead to overproduction of reactive oxygen species (ROS) through Fenton chemistry, which can cause cell damage and disease. This can play a role in cancer and its progression. Certain Fe chelators have been found to reduce tumor growth by regulating the cell cycle, angiogenesis, or the suppression of metastases. These chelators are designed to bind and regulate extracellular Fe(III) and intracellular Fe(II)/Fe(III) in cancer cells. Fe(II) and Fe(III) chelators considered for anticancer applications can be categorized based on their

ligands' capability of binding to Fe ions. There have been numerous studies on Fe chelators, and their role in suppressing cancer is providing insights for future anticancer therapies[19].

Complexes of Nickel:

Complexes of diimino-functionalized ligands are commonly used as catalysts for a wide variety of reactions. Salen ligands are prepared by condensing two equivalents of salicylaldehyde derivatives with diamines. Chiral versions of these ligands are typically accessed using chiral 1,2-diamines[20].

MDA-MB-231 cells were plated in a 96-well plate and treated with Cu(EtDTC)2, Zn(EtDTC)2, or Ni(EtDTC)2 for 24 hours, as indicated. DMSO was used as a solvent control. After the treatment, the medium was removed, and MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide) (1 mg/ml PBS) was added to each well. The cells were then incubated at 37°C for 4 hours to allow for complete cleavage of the tetrazolium salt by metabolically active cells. Next, MTT was removed and 100 µl of DMSO was added, followed by colorimetric analysis using a multilabel plate reader at 560 nm (Victor3; PerkinElmer (Wellesley, MA, USA)). Cu(EtDTC)2 and Zn(EtDTC)2 were equally potent, inhibiting about 90% of cell proliferation at both concentrations used, while Ni(EtDTC)2 inhibited less than 10% of cell proliferation at 10 µM and about 20% at 20 µM. This study shows the inhibition of Breast Cancer MDA-MB-231 Cell Proliferation[21]

Complexes of Cobalt:

The use of transition metals in medicine has advanced significantly in recent years. Cobalt derivatives, such as Doxovir, have shown promising antiviral activity. Studies have suggested that cobalt complexes interact with proteins and can be used to improve the therapeutic efficacy of bioactive small molecules. Additionally, Co(III) complexes can be used as prodrugs capable of undergoing bioreduction to produce a bioactive agent. Lastly, redox activation of Co(III) to generate complexes that act as effectors of biological activity has been demonstrated[22].

Complexes of Tin:

Tin compounds fall into two main classes: inorganic tin salts and organotin compounds. Both are widely used in various industrial applications. Inorganic tin compounds have some commercial use in dental treatments, such as tin(II) fluoride being more effective than sodium fluoride for protecting dental enamel and reducing dental mottling fluorosis. Tin compounds are also used as catalysts for silicone rubbers and in radiopharmaceuticals[23].

Complexes of Zinc:

The treatment of infectious diseases is challenging due to emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Antibiotic resistance is a major concern as bacteria can develop resistance through mutation or acquiring antimicrobial resistant genes. This resistance reduces the effectiveness of antibiotics, leading to the need for new antimicrobial agents. Developing new medicines is costly and time-consuming. Efforts are underway to develop cost-effective, shorter routes of synthesis for effective anti-infective agents against bacteria and fungi. Initial screening of compounds has shown promising results with respect to biological assays against Gram-positive bacteria and fungi[(24)]

Complexes of Magnase:

Manganese (Mn) is a vital trace metal that serves as a cofactor for enzymes. Mn-containing complexes, especially SOD mimics, have high antioxidative potential and are being investigated for cancer prevention and anti-aging properties. Mn complexes exhibit diverse redox chemistry, with compounds like Mn-porphyrin having oxidation states ranging from +2 to +5. SOD mimics based on various ligand systems have shown promise in inhibiting tumor growth and preventing cancer[(25)].

Complexes of Silver:

In recent decades, silver complexes have been researched for their strong antibacterial properties. They are more effective than silver salts, active at low concentrations, and have low toxicity. Studies have shown silver complexes with Ag-O and Ag-N bonds have broader antimicrobial activity. This research focuses on the preparation and characterization of five potential antibacterial agents: AgIbu, AgNap, AgMef, AgAsp, and AgSal[(26)].

Cancer is a condition caused by genetic abnormalities in somatic cells, leading to the growth of abnormal cell clones. The term "cancer" refers to any disease characterized by an accumulation of cells, which can be caused by excessive cell proliferation or the failure of cells to undergo apoptosis in response to normal signals. There are various types of malignancies, with the most common being lung, breast, colon and rectum, stomach, prostate, liver, cervix, and esophagus cancers. Additionally, Ag(I) mixed ligand complexes have shown significant anticancer activity against Ehrlich's ascites tumor cells[(27)].

Complexes of Bismuth and Antimony:

The interest in dithiocarbamate complexes of bismuth and antimony is sustained due to various reasons. These include their structural diversity, unique application as biological agents/catalysts, and use in materials and surface chemistry. Bismuth and antimony, both in Group 15 of the Periodic Table, have been used as Lewis acids in various organic syntheses. These compounds have been extensively used in catalysis and as drug candidates, resulting in the synthesis of medicinally useful compounds. Bismuth compounds have been used to treat medical disorders for over two centuries, and antimony-based compounds have been used in the treatment of leishmaniasis, but accompany severe side effects related to toxicity[(28)].

Results

The review systematically analyzes the therapeutic properties of metal complexes formed with ten d-block elements, lanthanides, actinides, and bismuth. The studies reveal the following key results:

1. D-Block Elements

- Iron (Fe): Notable for its role in oxygen transport and potential in treating anemia.

- Nickel (Ni): Demonstrates catalytic properties useful in drug synthesis.

- Copper (Cu): Exhibits antimicrobial and anticancer activities.

- Zinc (Zn): Vital for enzyme function and has potential in wound healing.

- Technetium (Tc): Utilized in diagnostic imaging due to its radioactive properties.

- Ruthenium (Ru): Shows promise in targeting cancer cells and improving drug delivery.

- Rhodium (Rh): Effective in catalyzing biochemical reactions.

- Iridium (Ir): Investigated for its role in radiotherapy.

- Platinum (Pt): Widely used in chemotherapy, particularly in cisplatin-based treatments.

- Gold (Au): Exhibits anti-inflammatory and anticancer properties.

2. Lanthanides and Actinides:

- These complexes are explored for their luminescent properties and potential in imaging and therapy.

3. Bismuth: - Known for its antimicrobial effects and use in treating gastrointestinal disorders.

4. Ligand Versatility:

- Monodentate, bidentate, and multidentate ligands contribute to the stability and reactivity of metal complexes, enhancing their therapeutic efficacy.

5. Organometallic Compounds:

- Show diverse applications in medicine, including targeted drug delivery and imaging.

Conclusion

The review underscores the extensive therapeutic potential of metal complexes across various applications. The diversity in metal types and ligands significantly impacts the properties and effectiveness of these complexes. The study highlights the successful integration of d-block metals, lanthanides, actinides, and bismuth in therapeutic contexts, demonstrating advancements in medical treatments and diagnostics. The broad range of properties—ranging from biological activity to catalytic behavior—positions metal complexes as crucial components in future therapeutic strategies. Continued research and development in this field are essential for harnessing the full potential of metal complexes, potentially leading to novel therapies and improved clinical outcomes.

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