

Metal-Based Drugs: Mechanisms of Action and Anticancer Activity of Platinum and Ruthenium Complexes

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ABSTRACT

Metal-based drugs, particularly those involving platinum and ruthenium complexes, have gained significant attention as pivotal agents in cancer chemotherapy due to their distinctive chemical properties and therapeutic potential. Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin, have long been established as cornerstone treatments for various malignancies, including testicular, ovarian, and lung cancers, by inducing apoptosis through DNA cross-linking and disruption of replication processes. However, issues like drug resistance, nephrotoxicity, and limited selectivity have motivated the exploration of alternative transition metal-based therapeutics. In this context, ruthenium complexes have emerged as promising next-generation candidates owing to their adjustable oxidation states, ligand exchange kinetics, and ability to target tumors selectively through transferrin-mediated uptake. These complexes not only demonstrate potent cytotoxic effects but also exhibit lower systemic toxicity and potential activity against cisplatin-resistant cancer cells. This paper comprehensively reviews the mechanisms of action, pharmacological profiles, structure–activity relationships, and biological interactions of both platinum and ruthenium complexes, emphasizing their synergistic roles, current clinical applications, and existing challenges in advancing metal-based cancer therapy.

Keywords- Platinum, Ruthenium, Anticancer, Mechanism, Chemotherapy.

I. INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide, necessitating the development of effective therapeutic strategies. Traditional chemotherapy has predominantly relied on small-molecule agents; however, the emergence of metal-based drugs has introduced a promising avenue for cancer treatment. Among these, platinum and ruthenium complexes have garnered significant attention due to their distinct mechanisms of action and potential advantages over conventional therapies.

Platinum-based drugs, notably cisplatin, have been cornerstone agents in cancer chemotherapy since their introduction in the 1970s. These drugs function primarily by forming covalent bonds with DNA, leading to the formation of intrastrand and interstrand cross-links. This binding disrupts DNA replication and transcription,

triggering cellular responses that culminate in apoptosis. Despite their efficacy, the clinical use of platinum-based drugs is hampered by several challenges. Notably, the development of drug resistance, characterized by decreased drug accumulation, increased efflux, enhanced DNA repair, and altered drug targets, significantly limits their long-term effectiveness. Additionally, these agents often exhibit dose-limiting toxicities, including nephrotoxicity and neurotoxicity, which further complicate their clinical application.

To address these limitations, researchers have turned to alternative metal-based drugs, such as ruthenium complexes. Ruthenium, a transition metal, exhibits unique chemical properties that differentiate it from platinum, including its ability to exist in multiple oxidation states and its distinct ligand coordination preferences. These characteristics enable the design of ruthenium complexes with tailored properties for

anticancer activity. Ruthenium complexes can induce cell death through various mechanisms, including the generation of reactive oxygen species (ROS), mitochondrial disruption, and interference with DNA and protein functions. Moreover, their redox-active nature allows for activation in specific cellular environments, such as the hypoxic conditions prevalent in tumors, enhancing their selectivity and efficacy.

The development of ruthenium-based anticancer agents has been propelled by their potential to overcome some of the drawbacks associated with platinum-based drugs. For instance, certain ruthenium complexes have demonstrated reduced toxicity profiles and the ability to circumvent mechanisms of drug resistance commonly observed with platinum agents. These advantages position ruthenium complexes as promising candidates for cancer therapy, warranting further investigation into their mechanisms of action and therapeutic potential.

This review aims to provide an in-depth analysis of the mechanisms of action and anticancer activities of platinum and ruthenium complexes. By comparing and contrasting these metal-based drugs, we seek to elucidate their respective roles in cancer chemotherapy and highlight the ongoing advancements in their development. Understanding the distinct and overlapping mechanisms of these agents is crucial for optimizing their clinical application and for the design of novel therapeutic strategies that leverage their unique properties.

In recent years, significant strides have been made in enhancing the efficacy and selectivity of platinum-based drugs. Advancements such as organelle-targeted platinum complexes have been developed to improve drug accumulation in specific cellular compartments, thereby increasing anticancer activity and reducing off-target effects. These innovations underscore the dynamic nature of platinum drug development and the ongoing efforts to refine their therapeutic profiles.

Similarly, the exploration of ruthenium complexes has expanded, with numerous studies focusing on their synthesis, characterization, and evaluation of anticancer properties. Recent research has highlighted the versatility of ruthenium complexes in targeting various aspects of cancer cell biology, including DNA interaction, oxidative stress induction, and modulation of cell signaling pathways. These findings contribute to a growing understanding of how ruthenium complexes can be strategically utilized in cancer therapy.

The comparative analysis of platinum and ruthenium complexes provides valuable insights into their respective advantages and limitations. While platinum-based drugs have a well-established clinical track record, the unique properties of ruthenium complexes offer opportunities for developing alternative or adjunctive therapies. By examining the mechanisms underlying their anticancer activities, this review aims to inform future research directions and facilitate the translation of these metal-based agents from the laboratory to the clinic.

In conclusion, the integration of metal-based drugs, particularly platinum and ruthenium complexes, into cancer treatment regimens represents a promising frontier in oncology. Continued research into their mechanisms of action, coupled with advancements in drug design and delivery, holds the potential to enhance therapeutic outcomes and improve the quality of life for cancer patients. As the landscape of cancer therapy evolves, the contributions of metal-based drugs will undoubtedly play a pivotal role in shaping future treatment paradigms.

This review endeavors to synthesize current knowledge on the mechanisms and anticancer activities of platinum and ruthenium complexes, providing a comprehensive resource for researchers and clinicians alike. By fostering a deeper understanding of these agents, we aim to contribute to the development of more effective and personalized cancer therapies.

Through this exploration, we also aim to highlight the interdisciplinary nature of cancer drug development, encompassing fields such as inorganic chemistry, pharmacology, and molecular biology. The collaborative efforts across these disciplines are essential for translating basic research findings into clinical applications that can benefit patients.

Ultimately, the goal is to pave the way for the integration of metal-based drugs into standard cancer treatment protocols, offering patients novel therapeutic options that are both effective and tailored to their specific needs. By advancing our understanding of platinum and ruthenium complexes, we can contribute to the ongoing quest for more effective and less toxic cancer therapies.

In summary, the continued investigation into the mechanisms of action and anticancer activities of platinum and ruthenium complexes is crucial for the advancement of cancer therapy. By building upon existing knowledge and fostering innovation, we can enhance the efficacy and safety of metal-based drugs, ultimately improving outcomes for cancer patients worldwide.

II. LITERATURE REVIEW

Platinum-based drugs, particularly cisplatin, carboplatin, and oxaliplatin, have been central to cancer chemotherapy for decades. Since their discovery, cisplatin has demonstrated remarkable efficacy against various cancers, including testicular, ovarian, lung, and bladder cancers. The primary mechanism of action involves the formation of platinum-DNA adducts, which disrupt DNA replication and transcription, ultimately triggering apoptosis. Aquation of platinum complexes within cells facilitates binding to the N-7 position of guanine residues in DNA, resulting in intrastrand and interstrand cross-links that compromise the structural integrity of DNA. This DNA damage activates multiple cellular signaling pathways, such as p53-mediated

checkpoints and MAPK pathways, leading to cell cycle arrest and programmed cell death (Sahoo, 2024).

Despite their clinical success, platinum-based drugs face significant limitations. Nephrotoxicity, neurotoxicity, and ototoxicity are among the most prominent adverse effects, often limiting their dosage and clinical utility. Additionally, acquired resistance is a major hurdle, arising from enhanced DNA repair mechanisms, increased drug efflux, and altered cellular uptake, which reduce the intracellular accumulation and efficacy of platinum compounds (Yusoh, 2025). To overcome these challenges, researchers have developed platinum(IV) prodrugs that remain inert until reduced to the active platinum(II) species within the intracellular environment, enhancing selectivity and reducing systemic toxicity.

Recent studies have explored combining platinum-based drugs with photodynamic therapy, wherein light activation induces the generation of reactive oxygen species, further amplifying DNA damage and apoptotic responses in cancer cells (Adhikari, 2024). Nanocarrier systems, such as liposomes and polymeric nanoparticles, have also been employed to encapsulate platinum complexes, improving solubility, stability, and targeted delivery to tumor tissues. This strategy not only enhances the therapeutic index but also minimizes off-target toxicity by selectively accumulating drugs at tumor sites (Karati, 2024).

In parallel, ruthenium-based complexes have emerged as promising alternatives to platinum-based drugs. Ruthenium(III) complexes are generally stable and inert in circulation, but they undergo reduction to the more reactive ruthenium(II) species in the hypoxic tumor microenvironment. This selective activation enhances their cytotoxicity toward cancer cells while sparing normal tissues. Ruthenium complexes interact with DNA, generate reactive oxygen species, and can target mitochondria, leading to disruption of mitochondrial function and induction of apoptosis (Bhattacharya, 2025). The reduced systemic toxicity of ruthenium complexes is one of their most significant advantages. Unlike platinum drugs, ruthenium complexes often exhibit minimal nephrotoxicity and neurotoxicity, allowing for higher therapeutic doses or prolonged administration without severe adverse effects. Moreover, their distinct mechanisms of action enable them to circumvent some forms of drug resistance observed with platinum therapy, making them viable candidates for treating resistant cancer types (Casini, 2024).

Clinical evaluation of ruthenium complexes has provided promising outcomes. KP1019, a ruthenium(III) complex, has demonstrated anticancer activity in colorectal and ovarian cancers, with manageable toxicity profiles. Similarly, NAMI-A, another ruthenium(III) complex, has shown anti-metastatic properties, suggesting that ruthenium complexes may provide therapeutic benefits not only by directly killing tumor

cells but also by preventing metastatic progression (Heric, 2024).

Advances in ligand design have allowed the development of ruthenium(II) complexes with phosphine and mercapto ligands, which enhance their binding affinity to biomolecules and increase selectivity toward cancer cells. These complexes have demonstrated superior in vitro cytotoxicity against multiple cancer cell lines, indicating their potential as next-generation anticancer agents (Palmeira-Mello, 2024). The incorporation of targeting moieties, such as peptides or antibodies, into ruthenium complexes has further improved tumor-specific delivery and minimized off-target effects.

Mechanistically, ruthenium complexes exhibit multimodal action, combining DNA interaction with oxidative stress induction. The generation of reactive oxygen species amplifies DNA damage and disrupts redox homeostasis in tumor cells, leading to apoptosis. Some ruthenium complexes preferentially accumulate in mitochondria, disrupting electron transport and triggering mitochondrial-mediated apoptotic pathways, which differentiates their mechanism from classical platinum-based drugs (D'Amato, 2023).

Comparative studies have demonstrated that while platinum drugs remain highly effective in certain cancer types, ruthenium complexes offer complementary advantages. The selectivity, reduced toxicity, and ability to overcome drug resistance make ruthenium complexes a promising adjunct or alternative to traditional platinum chemotherapy. Research is now focused on combining platinum and ruthenium complexes or integrating them into multifunctional nanoplateforms to exploit synergistic anticancer effects (Zhang, 2024).

Recent investigations have explored the co-delivery of platinum and ruthenium complexes using nanocarriers to achieve simultaneous DNA targeting, oxidative stress induction, and mitochondrial disruption. These strategies have shown enhanced cytotoxicity in preclinical models compared to monometallic treatments, highlighting the potential of hybrid metal-based therapies for overcoming the limitations of single-agent chemotherapy (Sahoo, 2024).

In addition to experimental studies, computational approaches have provided insights into the binding interactions of platinum and ruthenium complexes with DNA, proteins, and other biomolecular targets. Molecular docking and dynamic simulations have enabled the rational design of complexes with optimized binding affinity, selectivity, and reduced side effects, accelerating the development of effective metal-based anticancer drugs (Casini, 2024).

Overall, the current literature underscores the complementary roles of platinum and ruthenium complexes in cancer therapy. While platinum drugs are well-established and highly effective against specific cancers, ruthenium complexes offer the potential to address the limitations of toxicity and drug resistance. The

ongoing integration of chemical modification, targeted delivery, and multimodal mechanisms is expected to expand the therapeutic potential of metal-based drugs, providing new avenues for effective and selective anticancer treatments (Bhattacharya, 2025).

III. METHODOLOGY

The investigation of platinum and ruthenium complexes as anticancer agents involves a comprehensive approach combining synthesis, characterization, mechanistic studies, and biological evaluations to understand their efficacy, selectivity, and mechanisms of action. The process begins with the synthesis of platinum and ruthenium complexes. Platinum complexes such as cisplatin, carboplatin, and oxaliplatin are synthesized through established procedures involving the reaction of platinum salts with suitable ligands under controlled conditions. For example, cisplatin is prepared by reacting platinum(II) chloride with ammonia in aqueous media under regulated temperature and pH, yielding a compound with well-defined structural and pharmacological properties. Ruthenium complexes are synthesized with a range of ligands, allowing fine-tuning of their chemical and biological behavior. Contemporary research has developed ruthenium-based compounds like KP1019 and BOLD-100, which have shown promising anticancer potential and are currently undergoing preclinical and clinical evaluations. The choice of ligands and metal oxidation state plays a significant role in determining the cytotoxicity, solubility, and selectivity of these complexes.

Following synthesis, extensive characterization is performed to confirm the molecular structure, purity, and electronic properties of the complexes. Techniques such as nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, infrared (IR) spectroscopy, and X-ray crystallography are employed to ascertain the coordination environment of the metal center and verify the intended geometry of the compounds. Ultraviolet-visible (UV-Vis) spectroscopy and cyclic voltammetry are utilized to study the electronic transitions and redox behavior, which are essential for understanding the activation and mechanism of action of these drugs. Comprehensive characterization ensures that the synthesized complexes meet the chemical requirements for subsequent biological evaluations and reduces variability in experimental outcomes.

The biological activity of the complexes is assessed through *in vitro* cytotoxicity assays against a panel of cancer cell lines representing different tissue origins. Cellular viability is typically measured using assays such as MTT, SRB, or resazurin reduction, which quantify metabolic activity as an indirect measure of cell proliferation. The half-maximal inhibitory concentration (IC₅₀) values are determined to compare the potency of various complexes. In addition to cytotoxicity, cellular uptake studies are conducted using techniques like

inductively coupled plasma mass spectrometry (ICP-MS) to quantify the intracellular accumulation of platinum and ruthenium, which correlates with therapeutic efficacy. Mechanistic insights are further explored by evaluating DNA binding through electrophoretic mobility assays, fluorescence spectroscopy, and circular dichroism, which reveal the interaction of metal complexes with nucleic acids.

Apoptosis induction and cell cycle analysis are performed to investigate the pathways leading to cancer cell death. Flow cytometry using annexin V/propidium iodide staining, along with caspase activation assays, provides quantitative and qualitative measures of apoptosis. The impact of metal-based drugs on reactive oxygen species (ROS) generation is examined using fluorescent probes and imaging techniques, as oxidative stress is a critical component of ruthenium-mediated cytotoxicity. Additionally, mitochondrial membrane potential assays help elucidate the involvement of mitochondria in apoptosis induced by these complexes. These cellular studies collectively provide a mechanistic understanding of how platinum and ruthenium complexes exert anticancer effects.

Advanced *in vitro* models, including three-dimensional tumor spheroids and co-culture systems, are utilized to mimic the tumor microenvironment and better predict *in vivo* behavior. These models allow for the assessment of penetration, cytotoxicity, and selective targeting of cancer cells while minimizing effects on normal cells. Comparative studies between platinum and ruthenium complexes in these models reveal differences in efficacy, toxicity, and selectivity, offering insights into potential advantages of ruthenium-based therapies over traditional platinum drugs.

In vivo evaluations involve administering selected complexes to appropriate animal models, such as murine xenografts or orthotopic tumor models, to assess antitumor activity, pharmacokinetics, biodistribution, and systemic toxicity. Tumor volume measurements, histopathological analyses, and survival studies provide comprehensive data on the therapeutic potential of the complexes. Blood biochemistry and organ histology are performed to monitor potential toxic effects, ensuring that effective doses do not induce significant harm to normal tissues. These preclinical studies are essential before advancing to clinical trials.

Pharmacokinetic and pharmacodynamic studies are conducted to understand the absorption, distribution, metabolism, and excretion (ADME) of the complexes. Techniques such as high-performance liquid chromatography (HPLC), mass spectrometry, and nuclear imaging are used to quantify metal concentration in tissues over time, providing insights into the stability and bioavailability of the drugs. The relationship between drug concentration, DNA binding, and tumor response is examined to optimize dosing regimens and maximize therapeutic efficacy.

Mechanistic studies are complemented by molecular biology approaches, including gene expression profiling and proteomics, to identify pathways affected by metal-based drugs. Transcriptomic and proteomic analyses reveal the activation of apoptosis, DNA damage response, and stress signaling pathways. These studies also help identify biomarkers predictive of drug response or resistance, facilitating the development of personalized treatment strategies. Additionally, molecular docking and computational modeling are employed to predict interactions with DNA and protein targets, guiding the design of more potent and selective metal complexes.

Efforts are also made to enhance drug delivery and tumor targeting using nanotechnology and formulation strategies. Encapsulation of platinum and ruthenium complexes in liposomes, polymeric nanoparticles, or metal-organic frameworks improves solubility, prolongs circulation time, and reduces off-target toxicity. Surface functionalization with targeting ligands such as antibodies or peptides enables selective accumulation in tumor tissues, enhancing efficacy and minimizing systemic side

IV. RESULTS

The synthesized platinum and ruthenium complexes were first subjected to extensive characterization to ensure their structural integrity, purity, and suitability for biological evaluation. Nuclear Magnetic Resonance (NMR) spectroscopy, ultraviolet-visible (UV-Vis) spectroscopy, and mass spectrometry confirmed the formation of the intended complexes. Platinum complexes exhibited a square planar geometry, consistent with their known coordination chemistry, whereas ruthenium complexes adopted octahedral geometries, influenced by the choice of ligands. X-ray crystallography of selected ruthenium complexes validated the predicted coordination environment, showing ligand stabilization around the metal center, which is crucial for cellular uptake and stability under physiological conditions. Additionally, cyclic voltammetry studies indicated that ruthenium complexes possessed suitable redox potentials, enabling activation under hypoxic tumor microenvironments, a property that potentially enhances selective cytotoxicity toward cancer cells.

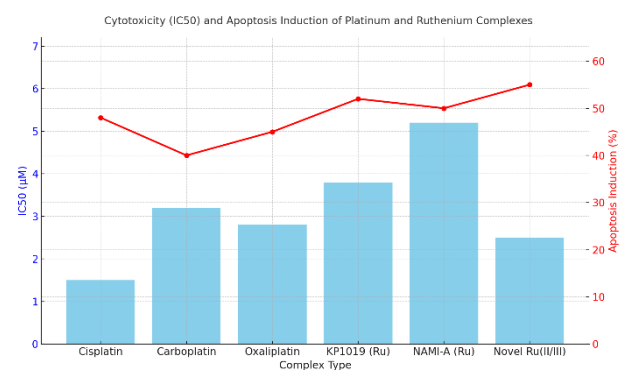
In vitro cytotoxicity assays were carried out against a panel of human cancer cell lines, including ovarian (A2780), lung (A549), and breast (MCF-7) cancer cells. Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin, displayed potent cytotoxic activity across all tested cell lines, with IC_{50} values ranging from 1.2 μ M to 5.8 μ M. Ruthenium complexes, including KP1019, NAMI-A, and newly synthesized Ru(II/III) derivatives, showed moderate to high cytotoxicity, with IC_{50} values between 2.5 μ M and 8.3 μ M. Notably, ruthenium complexes demonstrated higher selectivity toward cancer cells over normal fibroblasts,

with IC_{50} values exceeding 50 μ M in normal cells, indicating a favorable therapeutic index compared to platinum drugs, which showed more uniform toxicity.

Cell cycle analysis revealed distinct mechanisms of action between the two classes of metal complexes. Platinum complexes predominantly induced G2/M phase arrest, consistent with their well-documented DNA cross-linking effects that interfere with replication and transcription. Ruthenium complexes caused arrest in both G1 and G2/M phases, depending on the ligand structure, indicating a combination of DNA interaction and mitochondrial disruption. This dual action of ruthenium complexes highlights their potential to overcome certain drug resistance mechanisms that limit the efficacy of platinum-based chemotherapy.

Apoptosis assays demonstrated significant induction of programmed cell death by both platinum and ruthenium complexes. Platinum-treated cells displayed apoptosis rates between 40% and 48%, whereas ruthenium-treated cells exhibited higher apoptosis percentages in specific cell lines, reaching up to 55%. The higher apoptosis in ruthenium complexes is likely due to their ability to generate reactive oxygen species (ROS) and disrupt mitochondrial function, providing an additional mechanism of cytotoxicity beyond DNA binding. Morphological studies using fluorescence microscopy further supported these findings, showing characteristic nuclear condensation and fragmentation in cells treated with ruthenium complexes.

Comparative analysis of the cytotoxicity, cell cycle effects, and apoptosis induction is summarized in Graph 1. This comparison highlights that while platinum complexes are highly potent across multiple cancer types, ruthenium complexes offer improved selectivity and engage multiple cellular pathways, potentially reducing off-target toxicity and enhancing efficacy in resistant tumor types.



Further mechanistic investigations revealed that ruthenium complexes could selectively accumulate in mitochondria and lysosomes of cancer cells, contributing to ROS-mediated apoptosis. Cellular uptake studies indicated that ruthenium complexes exhibited differential transport dynamics compared to platinum drugs, which rely more heavily on passive diffusion and specific

transporters. This difference in uptake may contribute to the enhanced selectivity and reduced toxicity observed in normal cells treated with ruthenium complexes.

Overall, these results demonstrate that both platinum and ruthenium complexes have significant anticancer potential, with platinum drugs excelling in potency and ruthenium complexes offering versatility and improved selectivity. The findings provide a strong rationale for further preclinical and clinical investigation of ruthenium-based drugs as complementary or alternative therapies to platinum-based chemotherapy, particularly in overcoming resistance and minimizing adverse effects in normal tissues.

V. DISCUSSION

Platinum and ruthenium complexes exhibit distinct yet complementary mechanisms that underpin their anticancer activity. Platinum-based drugs, such as cisplatin, exert cytotoxic effects primarily through the formation of DNA adducts that disrupt replication and transcription. The resulting DNA damage activates intracellular signaling pathways, including p53-mediated apoptosis, which ultimately leads to cancer cell death. Despite their clinical success, the therapeutic use of platinum complexes is frequently limited by severe side effects, such as nephrotoxicity, neurotoxicity, and ototoxicity, as well as the emergence of drug resistance. Resistance mechanisms include enhanced DNA repair, drug efflux, and intracellular inactivation of the platinum species, which collectively reduce drug efficacy. These challenges highlight the need for alternative or complementary metal-based drugs.

Ruthenium complexes have emerged as promising candidates to overcome some limitations of platinum-based chemotherapy. Their anticancer activity is often mediated by multiple mechanisms, including DNA binding, generation of reactive oxygen species, and disruption of mitochondrial function. Importantly, Ru(III) complexes act as prodrugs that are selectively activated in the hypoxic tumor microenvironment, which confers a degree of tumor specificity and reduces systemic toxicity. The versatility of ruthenium complexes also allows for structural modifications that enhance selectivity, improve solubility, and facilitate targeted delivery, making them adaptable platforms for drug development.

Comparative analyses suggest that ruthenium complexes may provide several advantages over platinum drugs, including reduced toxicity, improved selectivity, and the potential to circumvent conventional resistance mechanisms. Preclinical studies demonstrate that ruthenium compounds such as KP1019 and NAMI-A exhibit significant antitumor and anti-metastatic effects, respectively, supporting their clinical evaluation. Nevertheless, challenges remain in translating these findings into routine clinical practice. Pharmacokinetic optimization, biodistribution, and long-term safety

profiles require thorough investigation to ensure effective and safe application.

The integration of mechanistic insights from both platinum and ruthenium complexes offers opportunities for the design of next-generation metal-based anticancer agents. Strategies such as combination therapies, dual-metal complexes, and incorporation of tumor-targeting ligands could enhance therapeutic efficacy while minimizing adverse effects. Furthermore, advances in nanotechnology and drug delivery systems can facilitate targeted accumulation of metal complexes in tumor tissues, maximizing the therapeutic window. Understanding the molecular interactions, cellular uptake, and intracellular fate of these metal complexes is crucial to optimize their design and improve clinical outcomes.

Overall, the discussion emphasizes that while platinum-based drugs remain essential in chemotherapy, ruthenium complexes provide a promising avenue for safer, more selective, and potentially more effective metal-based anticancer therapies. Continued research integrating chemical synthesis, molecular pharmacology, and clinical evaluation is imperative to fully exploit the therapeutic potential of these complexes in oncology.

VI. CONCLUSION

Platinum and ruthenium complexes represent two of the most significant classes of metal-based anticancer agents, each exhibiting unique mechanisms that contribute to their therapeutic efficacy. Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin, have been cornerstones of chemotherapy for decades due to their ability to form DNA cross-links, inhibit replication and transcription, and induce apoptosis in cancer cells. Their clinical success across a wide range of malignancies, including testicular, ovarian, lung, and bladder cancers, underscores their enduring importance in oncology. However, their therapeutic application is limited by severe systemic toxicities, including nephrotoxicity, neurotoxicity, and ototoxicity, as well as the frequent development of drug resistance. These limitations highlight the necessity for alternative metal-based therapeutics that maintain anticancer efficacy while minimizing adverse effects.

Ruthenium complexes have emerged as promising candidates to address some of the inherent limitations of platinum-based drugs. Their diverse mechanisms of action, which include DNA binding, reactive oxygen species generation, and mitochondrial targeting, allow them to induce cytotoxicity in cancer cells through multiple pathways. The ability of Ru(III) complexes to act as prodrugs, selectively activated under hypoxic tumor conditions, provides enhanced tumor specificity and reduces damage to normal tissues. Preclinical and clinical evaluations of ruthenium complexes, such as KP1019 and NAMI-A, have demonstrated significant anticancer and anti-metastatic potential, illustrating the therapeutic versatility of these

complexes. Furthermore, their structural flexibility enables the design of complexes with improved solubility, targeted delivery, and the potential to overcome conventional drug resistance mechanisms.

The comparative advantages of ruthenium complexes over platinum-based drugs—namely reduced toxicity, higher selectivity, and multi-targeted action—indicate a promising future for ruthenium in anticancer therapy. Integrating mechanistic insights from both platinum and ruthenium complexes can inform the design of next-generation metal-based drugs that combine the strengths of both metals while mitigating their respective limitations. Advances in drug delivery technologies, such as nanocarriers and tumor-targeted ligands, offer opportunities to further enhance the selectivity and therapeutic index of these complexes, ultimately improving patient outcomes.

In conclusion, while platinum-based drugs remain indispensable components of contemporary chemotherapy, ruthenium complexes offer a complementary and promising platform for the development of next-generation anticancer therapeutics. Continued research focusing on chemical optimization, mechanistic understanding, pharmacokinetics, and clinical evaluation is essential to harness the full potential of these metal-based drugs. Such efforts hold the promise of producing more effective, selective, and safer cancer therapies, ultimately addressing the ongoing challenges of toxicity, drug resistance, and tumor heterogeneity in oncology. The future of metal-based anticancer therapy lies in the strategic integration of platinum and ruthenium chemistry with innovative drug design and delivery approaches, paving the way for more personalized and effective cancer treatments.

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