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A Review of Anticancer Activities of Ruthenium-Based Complexes

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Abstract
The therapeutic effectiveness of platinum-based chemotherapeutic agents like cisplatin and carboplatin and oxaliplatin gets restricted because they cause serious side effects and patients develop drug resistance and these drugs fail to target cancerous cells. Researchers have conducted extensive studies to identify transition metal alternatives to existing treatments because ruthenium complexes show strong potential as candidates for medicinal inorganic research. The distinct biochemical characteristics of ruthenium enable it to produce better drug effects because of its two oxidation states and its octahedral shape and its ligand movement abilities that mimic biological mechanisms and its ability to mimic iron when it binds to transferrin. Recent studies demonstrate that anticancer agents operate through multiple pathways which include DNA intercalation and mitochondrial disruption-based apoptosis and redox-dependent cell death and tumor metastasis control. The selectivity of ruthenium activation to hypoxic tumor conditions increases its therapeutic ratio. NAMI-A and KP1019 and their derivatives like KP1339 have shown positive preclinical and clinical outcomes in their battle against metastatic cancer and drug-resistant cancer cell lines. This review examines the current state of research on ruthenium-based treatments by showing their various mechanisms of action and their new structural developments and their growing use as advanced metallodrugs for cancer therapy.

Keywords: *Ruthenium complexes, Anticancer mechanism, Platinum drug resistance, Metallodrugs, Clinical development*

I. Introduction

Cancer remains one of the top global death causes which results in millions of annual deaths despite progress in both diagnosis and treatment. The complex and diverse nature of cancer biological systems results in different patient responses to standard treatment methods which creates an immediate requirement for new chemotherapy drugs that show better target accuracy and lower body side effects and higher success rates against difficult-to-treat tumors. Platinum-based chemotherapy drugs including cisplatin and carboplatin function as the fundamental treatment method because their powerful cytotoxic properties work through DNA crosslinking and apoptosis activation. The drug's square-planar coordination structure together with its high electrophile properties creates major problems including nephrotoxicity and neurotoxicity and hematological adverse effects. Platinum-based drugs cause resistance development in multiple tumors which creates a major obstacle for achieving successful long-term treatment results.

Recent years have witnessed a shift in research focus toward transition metal-based alternatives which have made ruthenium complexes the most important compounds for study in medicinal inorganic chemistry. Ruthenium displays multiple chemical properties and various biological characteristics which scientists use to develop anticancer drugs through its combination of these two aspects.

- **Octahedral Geometry:** Ruthenium six coordination sites generate structural changes which allow chemists to control three chemical properties through their specific modifications of ligand environments. The geometric design of this structure enables researchers to add bioactive ligands and targeting elements which improve the accuracy of medical treatments.
- **Activation by Reduction:** The body uses normal tissues which contain ruthenium(III) complexes as prodrugs because their inactive state remains until hypoxic and acidic tumor conditions convert them into active ruthenium(II) forms. The process of "activation by reduction" allows the body to protect itself from dangerous effects while delivering specific drug activation to cancer cells.
- **Iron Mimicry:** Ruthenium uses its chemical resemblance to iron to access native metal-transport systems which include transferrin-based metal absorption. The overexpression of transferrin receptors in fast-growing cancer cells enables ruthenium complexes to gather in cancerous tissues which improves tumor targeting and treatment effectiveness.

The distinct properties of ruthenium-based drugs provide a strong basis for developing next-generation metallodrugs which will solve the main problems that exist in platinum-based cancer treatments.

II. Classification of Ruthenium Complexes

2.1 Ruthenium(III) Compounds

The complexes show lower toxic effects compared to their counterparts because their kinetic stability prevents most ligand exchange process. The system maintains its stability which enables bloodstream movement while maintaining minimal contact with other body parts until it enters the tumor microenvironment. The most notable example is NAMI-A (). NAMI-A shows almost no ability to kill primary tumor cells in vitro which makes it different from standard chemotherapy drugs. Its main strength actually exists in its strong ability to prevent tumor cells from spreading. The process stops metastatic spreading by controlling how cancer cells stick to surfaces and how they move and spread through tissues while it also controls how blood vessels develop through its effects on the extracellular matrix. Researchers began to develop second-generation derivatives because the drug showed positive results during Phase I trials but stability problems and primary tumor treatment limitations stopped its development process. The KP1019 complex and its sodium salt NKP-1339 which operates with better water solubility show strong treatment effects against primary solid tumors which include colorectal cancers. The compounds follow a different biochemical mechanism because they create strong bindings to serum proteins that include albumin and transferrin which lead to their concentration in cancer tissues. The process results in major endoplasmic reticulum (ER) stress which activates the mitochondrial pathway for programmed cell death. NKP-1339 has demonstrated a controllable safety record through its clinical studies which establishes it as one of the leading ruthenium drug candidates available today.

2.2 Ruthenium(II) Arene Complexes

Organometallic ruthenium(II) complexes display a common geometric pattern which researchers refer to as "piano-stool" geometry. In this configuration, the ruthenium center connects to a hydrophobic -arene "seat" through three "legs" that use different ligands which include halides and phosphines. The structural arrangement operates with multiple functions because the arene ring maintains the oxidation state while its lipophilic surface enables better entry through cellular membranes.

The RAPTA series, particularly RAPTA-C (), represents a breakthrough in this category. The complexes use 1,3,5-triaza-7-phosphaadamantane (PTA) ligand which creates pH-dependent solubility for the molecule. The RAPTA compounds function as anti-metastatic drugs which exhibit lower systemic toxicity than NAMI-A thus making them suitable for combination treatment approaches.

Polypyridyl Complexes have become popular as a method to perform Photodynamic Therapy (PDT) treatments. The complexes which use bipyridine or phenanthroline ligands exhibit strong luminous output together with prolonged excited state duration. The substances produce reactive oxygen species (ROS) through intersystem crossing which occurs when users expose them to particular light wavelengths. The method enables doctors to remove cancerous cells while keeping damage to surrounding healthy tissue at minimal levels which solves the "selectivity" crisis present in current chemotherapy treatments.

III. Mechanisms of Action

The anticancer activity of ruthenium complexes operates through multiple cellular targets and biochemical pathways because the complexes do not produce their effects through a single molecular pathway. The ability of the multi-target system to operate multiple functions creates benefits that exceed the capabilities of traditional platinum-based drugs because platinum-based drugs depend on their main mechanism which directly modifies DNA through alkylation. The biological macromolecules interact with ruthenium compounds because of the metal's ability to create dynamic chemical bonds while maintaining stable but reactive chemical connections. Recent studies have shown that these complexes disrupt cellular growth by establishing mechanisms which include their DNA binding capabilities and their capability to cause mitochondrial damage and their power to create oxidative stress and their selective inhibition of enzymes.

3.1 DNA Binding and Damage

DNA serves as a major target inside cells for various ruthenium-based medications. The broader DNA interaction spectrum of ruthenium complexes exists because they differ from cisplatin which creates intra- and inter-strand cross-links between guanine residues that result in DNA distortion and replication arrest.

- **Intercalation:** Ruthenium complexes which contain large planar aromatic ligands like 1,10-phenanthroline and 2,2′-bipyridine demonstrate the ability to intercalate between stacked DNA base pairs. The intercalative binding mode causes double helix stabilization, but it disrupts vital processes such as replication and transcription, which results in cell growth inhibition.
- **Electrostatic and Groove Binding:** The positively charged Ru^II complexes establish electrostatic interactions with the negatively charged phosphate backbone of DNA while they also bind to the minor and major grooves of DNA, which results in different binding site preferences that depend on the ligand design and charge distribution.

- **G-Quadruplex Stabilization:** Some Ru^II polypyridyl complexes establish stronger binding relationships with G-quadruplex structures than with any other target. The structural stabilization of these complexes prevents telomerase from functioning which results in telomere extension being blocked and cancer cells losing their ability to become immortal. The research has focused on this pathway because it shows specific preference for cancer cells that undergo fast proliferation.

3.2 Mitochondrial Dysfunction and Apoptosis

Mitochondria function as primary cellular sites for ruthenium activity, which extends beyond its nuclear target sites. The positively charged RuII complexes with their medium lipophilicity properties show a tendency to build up inside the mitochondrial matrix, which carries a negative electrical charge. The complexes which enter cells create a disruption of the mitochondrial membrane potential (Δψ_m) which results in mitochondrial swelling and the release of cytochrome c and the start of the intrinsic apoptotic pathway.

The released cytochrome c interacts with Apaf-1 to form the apoptosome complex which activates both caspase-9 and downstream effector caspase-3 to produce programmed cell death. The cancer cells lose their ability to produce ATP while their metabolism becomes disrupted because ruthenium compounds block their mitochondrial respiration by stopping vital electron transport chain enzymes. The selective mitochondrial targeting leads to specific cell death because cancer cells possess higher mitochondrial membrane potential and greater metabolic requirements than normal cells do.

3.3 Oxidative Stress (ROS Generation)

Cancer cells require a supplementary critical mechanism for the generation of reactive oxygen species (ROS). Ruthenium complexes facilitate redox cycling, transitioning between Ru^II and Ru^III states; this property allows them to initiate electron transfer reactions. Consequently, these reactions convert molecular oxygen into superoxide anion (O_2^-) and other ROS.Cancer cells experience oxidative stress when their ROS production reaches uncontrolled levels, which leads to damage of cellular DNA and proteins and lipids that exceeds their antioxidant defense mechanisms. The oxidative stress condition results in redox imbalance, which subsequently leads to cellular death through either apoptosis or necrosis.

The malignant cells already function at higher baseline ROS levels which means that ruthenium exposure will lead to increased oxidative stress that pushes them beyond their oxidative limit while not causing major damage to healthy tissues. The development of redox-active ruthenium therapeutics through ROS-mediated cytotoxicity represents a valuable research direction that targets the metabolic weaknesses of cancer cells.

The three processes of DNA interaction and mitochondrial damage and ROS production work together in different ways because of their complementary nature to demonstrate how ruthenium complexes can disrupt cancer cell survival pathways, which creates a solid base for future development of new metallodrugs with multiple action mechanisms.

Mechanism	Specific Action	Biological Outcome
DNA Binding	Intercalation between base pairs and stabilization of G-quadruplex structures.	Inhibits telomerase activity; curtails cancer cell immortality.
Mitochondrial Targeting	Preferential accumulation within the mitochondrial matrix and disruption of membrane potential ($\Delta\psi_m$).	Triggers Cytochrome C release and the Caspase-3/9 apoptotic cascade.
Redox Modulation	Catalytic redox cycling between Ru^{II} and Ru^{III} states.	Generates excessive ROS (superoxide); induces oxidative stress past the cellular threshold.
Enzyme Inhibition	Coordination to key enzymes (e.g., thioredoxin reductase, topoisomerase II).	Disrupts essential metabolic pathways and cellular signaling.
Iron Mimicry	Strong binding affinity toward serum transferrin and albumin.	Increases selectivity by exploiting the high iron demand of malignant cells.

Table 1: *Multi-Modal Mechanisms of Ruthenium Activity, Source: Author Generated*

IV. Current Clinical Challenges and Future Perspectives

The progression of ruthenium-based complexes, from their initial identification to clinical trials, underscores the capacity of transition metals as efficacious frameworks for the creation of anticancer therapeutics. Three primary candidates exemplify both the clinical promise and the persistent obstacles inherent in the utilization of ruthenium compounds.

- **NAMI-A:** NAMI-A, a complex of ruthenium(III) with imidazolium, is currently being studied in Phase II clinical trials for patients with metastatic lung cancer.
  This compound exhibits anti-metastatic properties through a tripartite mechanism: it alters the extracellular matrix, inhibits angiogenesis, and impedes the motility of cancer cells.The product showed positive results in preclinical testing but its commercial development faced challenges because it demonstrated weak effects on solid tumors and had difficulties with its formulation.

- **KP1019:** The chemical compound indazolium trans-[Ru^III (IndH)(Ind)_2 Cl_4] better known as KP1019 completed its Phase I trials which studied its effects on multiple solid tumors including colorectal cancer and pancreatic cancer. The mechanism of the drug works by creating endoplasmic reticulum (ER) stress which leads to mitochondrial dysfunction followed by cell death through apoptosis. The drug KP1019 showed good tolerability and targeted cancerous tissue but it could not maintain stability in normal body conditions. The researchers developed the sodium salt derivative KP1339 which showed better solubility and entered later clinical trials because of its improved drug absorption properties.
- **TLD1433:** TLD1433, a Ru^II-based photosensitizer, is a novel photodynamic therapy (PDT) agent presently undergoing Phase II clinical trials for non-muscle-invasive bladder cancer. When this compound is exposed to light, it produces singlet oxygen and other reactive oxygen species. This process helps to destroy cancer cells while protecting healthy tissues.The achievement demonstrates how effective ruthenium compounds become when used together with light-based treatment methods.

Compound	Coordination State	Primary Structure / Ligands	Clinical Status
NAMI-A	Ru^{III}	Imidazolium trans-tetrachloro(dimethylsulfoxide)(imidazole)ruthenate(III)	Phase II
KP1019	Ru^{III}	Indazolium trans-tetrachlorobis(1H-indazole)ruthenate(III)	Phase I
NKP-1339	Ru^{III}	Sodium salt derivative of KP1019	Phase I/II
RAPTA-C	Ru^{II}	Organometallic p-cymene complex with PTA (1,3,5-triaza-7-phosphadamantane) ligand	Pre-clinical
TLD1433	Ru^{II}	Polypyridyl photosensitizer complex	Phase II

Table 2:Comparative Profile of Clinical Ruthenium Candidates, Source: Author Generated

4.1 Overcoming Solubility and Delivery

Ruthenium drugs face multiple challenges which must be resolved before they can become common treatment options despite their positive preliminary results. A major challenge for researchers is the drug's poor water solubility. This property makes it difficult to deliver the drug through injections and also limits how well the body can absorb it.

The majority of ruthenium complexes show hydrophobic properties because their large aromatic ligands create extensive coordination, which leads to their quick elimination or aggregation from living organisms.

Researchers are now focusing on developing better drug delivery systems and new drug formulations which will enhance drug effectiveness. Scientists increasingly use nanocarrier systems which include liposomes and polymeric nanoparticles and dendrimers and carbon nanotubes to create controlled release systems which improve the solubility of ruthenium drugs and direct their delivery to tumor locations. The nanocarriers utilize the Enhanced Permeability and Retention (EPR) effect, which enables therapeutic macromolecules to build up in tumors through their permeable blood vessels and their blocked lymphatic systems.

The research focuses on bioconjugation techniques, which involve linking ruthenium with peptides and nucleic acid segments, to develop methods which increase target specificity and support dual theranostic applications.The development of future ruthenium-based drugs depends on their implementation through multimodal therapeutic design which unites three separate treatment methods into one comprehensive system. The process of ligand optimization which focuses on stability and reactivity evaluation now uses in silico modeling together with quantum chemical analysis as its main guiding methods for rational drug discovery. The combination of ruthenium with other therapeutic metals through hybrid formulations delivers synergistic advantages by activating different cellular pathways in the body.

The clinical translation of ruthenium complexes NAMI-A KP1019 and TLD1433 has established benchmarks for their development but researchers need to resolve issues with solubility and delivery before they can proceed. The combination of nanotechnology with targeted bioconjugation will enable the development of new ruthenium-based drugs which will deliver safe and effective anticancer treatments that destroy primary tumors and metastatic cancer cells.

V. Conclusion

Ruthenium-based complexes establish a new standard for metallodrug development because they introduce advanced anticancer treatments which operate through multiple mechanisms instead of using conventional cytotoxic agents. Ruthenium complexes work differently than traditional platinum-based drugs, which mainly kill cells by linking DNA. They also bind to DNA, target mitochondria, change oxidation-reduction reactions, & inhibit enzymes.The biochemical diversity of this system provides strong antitumor

power while maintaining safe toxicity levels because it activates only in tumor environments which experience hypoxic conditions and acidic environments.

Ruthenium pharmacology has evolved beyond basic coordination chemistry toward the development of multifunctional intelligent systems which execute precision oncology treatment. The current research focuses on creating delivery systems which utilize nanocarriers to deliver photoactivated ruthenium agents and bioconjugated complexes that react to biological signals. The new technologies enable specific area activation of treatments which reduces overall body exposure while increasing their effectiveness against tumors. The new method combines computational modeling with spectroscopic analysis to enable scientists to design ligands efficiently while they prepare for preclinical studies which help them move potential treatments to clinical testing.

The future work establish hybrid theranostic platforms which can provide both diagnostic and therapeutic functions through a single molecular system. Ruthenium chemistry offers transformative potential for cancer treatment because it delivers targeted methods which physicians can control while producing lower toxicity effects that meet current medical standards.

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