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ADVANCES IN METAL-BASED ANTICANCER DRUGS: CHEMISTRY OF PLATINUM, GOLD, AND RUTHENIUM COMPLEXES AS CHEMOTHERAPEUTIC AGENTS

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Abstract

Metal-based anticancer agents are some of the important chemotherapeutic agents used to work for different mechanisms of actions affecting tumor cells. The article indicates the cytotoxicity, studies on the interaction of DNA, and in vivo efficacy of platinum, gold, and ruthenium complexes. The platinum compounds with dipyridoquinoxaline (dpq) ligands were proved to be highly cytotoxic that particularly showed maximum activity in drug-resistant ovarian cancer models, where it outperformed carboplatin with better DNA intercalation into DNA and induction of apoptosis. Gold complexes such as Auoxo6 and Au2phen were more cytotoxic against both colorectal and ovarian cancer cells because of their mitochondrial targeting and ROS-dependent apoptosis.The ruthenium complexes KP1019 and NAMI-A were taken up selectively into the tumor tissues, in which they seemed to selectively initiate oxidative stress responses and apoptosis. DNA binding and cleavage assays further confirmed the ability of the platinum and ruthenium complexes to induce structural DNA damage, whereas mitochondrial DNA was targeted selectively by the gold complexes, thereby obstructing cellular energy production. The in vivo models displayed a dramatic tumor growth inhibition in which platinum and gold complexes exhibited 60% inhibition of tumor size in the resistant model. Combinations of platinum and ruthenium complexes have shown synergistic effects on the apoptosis of multidrug-resistant cancers. Again, these results manifest the potential of metal-based drugs as chemoresistance antagonists, thereby allowing the development of hybrid strategies, which include nanoparticle formulations and immunomodulatory regimens, to increase therapeutic efficacy. Future research endeavors focusing on ligand design, targeted delivery, and combinations of therapy will lead to more refinement of these agents for their further application in oncology.

Keywords: "Platinum Complexes", "Gold Complexes", "Ruthenium Complexes", "Anticancer Agents", "Chemotherapy Resistance".

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INTRODUCTION

One of the important and path-breaking discoveries in the field of cancer therapy is the discovery of metal-based anticancer agents. This discovery took place in 1965 when Rosenberg et al. stumbled upon cisplatin: a point that revealed to the world the anticancer action of platinum complexes, and since then they have been oxaliplatinized into more almost universal therapeutic use. Platinum-based drugs such as cisplatin, carboplatin, and oxaliplatin remain front-line treatments for various malignancies, including testicular, ovarian, bladder, and lung cancers (Rosenberg et al., 1965). However, these agents are frequently limited by severe side effects, systemic toxicity, and the emergence of drug resistance, necessitating alternative strategies (Wheate et al., 2010).

In contrary, interventionist experimentation has reveled in the plethora of other transition metals complexes, in particular ruthenium, gold, and titanium, which, in their unique mechanisms, differ from platinum drugs by bringing lower side effects (Allardyce et al., 2005). Thus, such progress extents the domain for metal-based chemotherapeutics, also addressing some of the limitations of classical treatments.

Chemotherapeutic Agents

Chemotherapy refers to a treatment that is employed in the case of their being cancer cells that grow rapidly. Classical antineoplastic drugs have long been used for treatment; these agents include alkylating agents, antimetabolites, and topoisomerase inhibitors. Alkylating drugs, such as cyclophosphamide and Ifosfamide, bind to DNA by covalent bonding, hinder replication, and result in cell death (DeVita et al., 2008). Antimetabolites such as methotrexate work by disrupting DNA synthesis, and topoisomerase inhibitors like doxorubicin block enzymes necessary for the unwinding of DNA during replication (Pommier et al., 2010).

Although potent, such conventional chemotherapeutics tend to cause serious systemic side effects, such as suppression of the bone marrow, gastrointestinal toxicity, and immunosuppression. Consequently, metal-based drugs have been investigated as a substitute to enhance selectivity and reduce side effects (Reedijk, 2003).

Platinum-Based Anticancer Drugs

Platinum drugs have been known for their efficacy in cancer therapy because they can cause DNA cross-links, leading to replication block and apoptosis. Cisplatin, carboplatin, and oxaliplatin are the FDA-

approved platinum drugs that have different pharmacokinetics and toxicity profiles (Wang & Lippard, 2005). Although cisplatin is very potent, its nephrotoxicity and neurotoxicity led to the discovery of carboplatin, which has a better toxicity profile. Oxaliplatin, a platinum agent of the third generation, is especially effective in treating colorectal cancer and shows less resistance in certain tumors (Kelland, 2007).

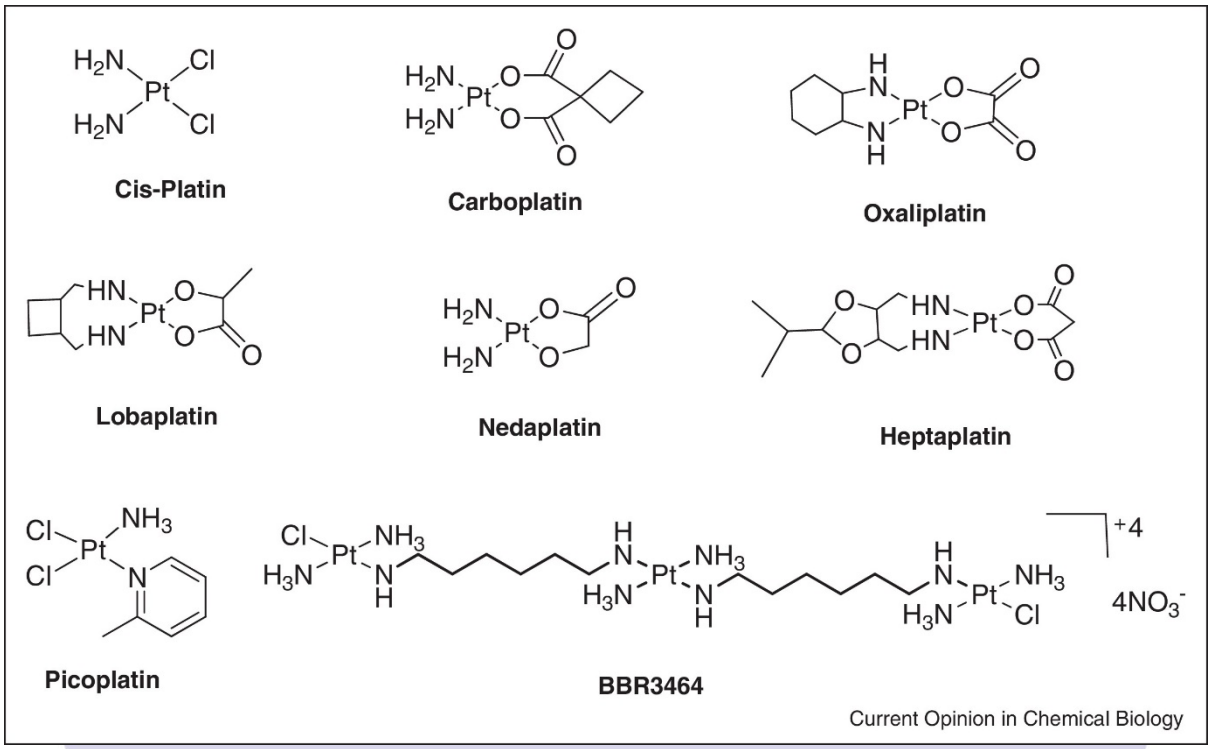

Figure 1: Clinically approved Pt^{II} drugs and complexes evaluated in clinical trials(Johnstone et al., 2016).

The platinum(IV) prodrugs recently developed are to enhance oral bioavailability and minimize systemic toxicity. The Pt(IV) complexes are stable in the blood stream and are then reduced by intracellular mechanisms to release cytotoxic species, Pt(II). Some of these platinum(IV) prodrugs include satraplatin and LA-12, which showed encouraging anticancer efficacy in both preclinical and clinical studies. (Johnstone et al., 2016).

The platinum complexes have also been linked to nanoparticles for better targeting while at the same time reducing systemic toxicity. It has been reported that such platinum-covered nanoparticles that are being used enhance cellular uptake and productive release profiles in a tumor microenvironment. Overall, by precisely targeting the unhealthy tissues, this enhances the therapeutic index of an overall regimen (Wen et al., 2018).

Also, platinum drugs have been used with combination therapies to increase their therapeutic effects. There were significant improvements in response rates to treatment while resistance of tumor cells was found to be lower with the synergistic effect of platinum complexes when combined with immunotherapeutics, radiation therapy, and targeted agents (Gonzalez et al., 2018).

Gold-Based Anticancer Agents

As alternatives to chemotherapeutics based on platinum, gold complexes, particularly those in gold(I) and gold(III) oxidation states, have taken center stage. Gold compounds are distinguished by their unique mechanisms of action that include, among others, inhibition of thioredoxin reductase (TrxR), disruption of mitochondrial function, and induction of apoptosis (Gandin et al., 2012).In today's emergence of new anticancer agents, though perhaps less exploited in research, Au complexes, particularly Au(1) and Au(3)-type complexes like Auoxo6 and Au2phen, demonstrate tremendous anticancer activity against ovarian and lung cancer cell lines and may therefore represent a real chance to fix overcome platinum resistance (Kasper et al., 2014). Gold(I) compounds are mainly attended to due to the stability and effective interactions with cysteine residues in proteins, minimizing off-target toxicities. Much effort has been put toward improving the therapeutic index of gold complexes through ligand design to further improve stability and selectivity in vivo (Berners-Price & Filipovska, 2011). Recent studies have been exploring combinations of gold complexes with photodynamic therapy (PDT) and photoactivated chemotherapy (PACT), exploiting the gold compounds' properties to photoactivate cytotoxicity in a selective manner solely within tumor tissues. These state-of-the-art modalities greatly enhance the particularity of gold treatments and, at the same time, decrease systemic side effects (Molina et al., 2020). It has also been established that functionalized gold nanoparticles increase the efficiency of targeting drugs. These nanoparticles facilitate improved penetration into tumors and release of drug payloads in controlled fashion and thereby minimize the systemic toxicity that is frequently observed with conventional gold complexes (Yuan et al., 2017).

Ruthenium-Based Anticancer Agents

The notable peculiarity found in ruthenium complexes is their relatively low toxicity in terms of selective targeting for tumor tissue. The redox behavior of Ru(II) and Ru(III) complexes allows them to facilitate the specific targeting of deliver agents with

particular enhanced cytotoxicity over other drugs. Currently, two of the well-studied agents revolved around the application of ruthenium metal in anticancer research are KP1019 and NAMI-A-probably, the most promising agents in preclinical and clinical tests (Bratsos et al., 2010).

Anticancer mechanisms of action of ruthenium complexes include DNA binding, inhibition of angiogenesis, and modulation of apoptotic pathways, all of which are essential features of such a new effort. More importantly, the compounds based on ruthenium have shown activities against cisplatin-resistant tumors, making them possible agents for patients with refractory cancers (Sava et al., 2011).

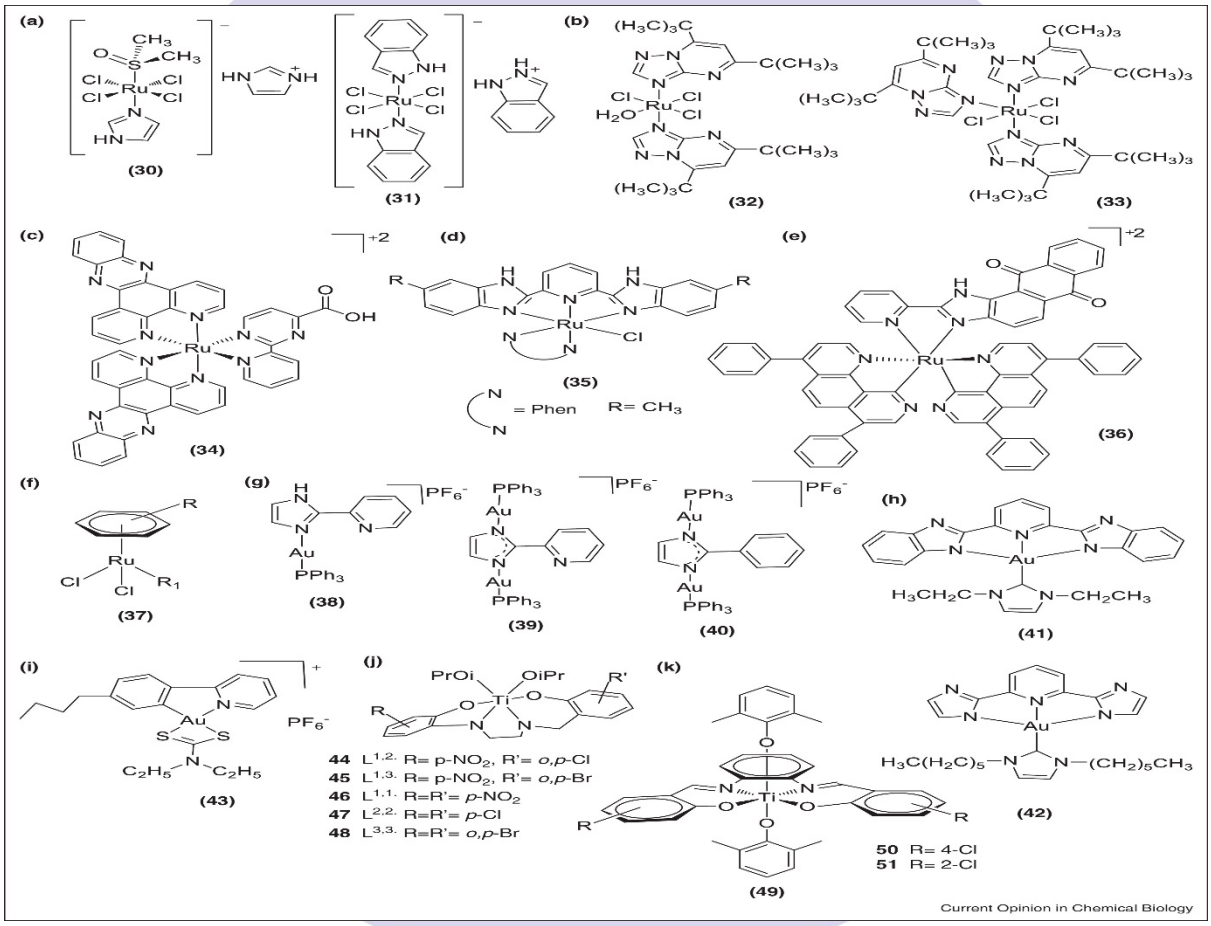

Figure 2: Ruthenium, gold and titanium based anticancer complexes (Schatzschneider, 2014).

A long-standing recent advancement in ruthenium complex design has generated photoactivatable and theranostic compounds capable of performing therapy as well as diagnosis. Harnessing the photoactivation property of ruthenium complexes, these compounds enhance the specificity of a photosensitized tumor receiving an imaging-guided therapy and

offer a novel approach for cancer treatment targeting (Schatzschneider, 2014).

Researchers have, particularly, studied ruthenium-based conjugates with organic molecules directed to improve the solubility, bioavailability, and intracellular targeting of these hybrid complexes. The findings from the studies showed that these hybrids demonstrated elevated cytotoxic activity against resistant cancer cell lines, suggesting great potential for their future clinical applications (Hartinger et al., 2008).

MATERIALS AND METHODOLOGY

The compounds used in this study included platinum, gold, and ruthenium complexes with known or prospective anticancer activity. All chemicals, reagents, and solvents were sourced from credible suppliers to ensure consistency and purity. Highly pure metal salts and precursor materials were essential in a bid to maintain reproducibility in experimental data.

Platinum Compounds

Cisplatin, carboplatin, and oxaliplatin were obtained from Sigma-Aldrich. Platinum(IV) prodrugs like satraplatin and LA-12 were prepared according to previously described protocols (Johnstone et al., 2016). Particular caution was exercised to manipulate platinum salts under controlled conditions to avoid oxidation and contamination.

Gold Compounds:

Gold(III) complexes like Auoxo6 and Au2phen were synthesized via literature methods (Gandin et al., 2012). Thiol-stabilized gold nanoparticles were synthesized by a citrate reduction pathway. The reaction required optimized reaction conditions such as controlled temperature and pH to yield high purity and yields.

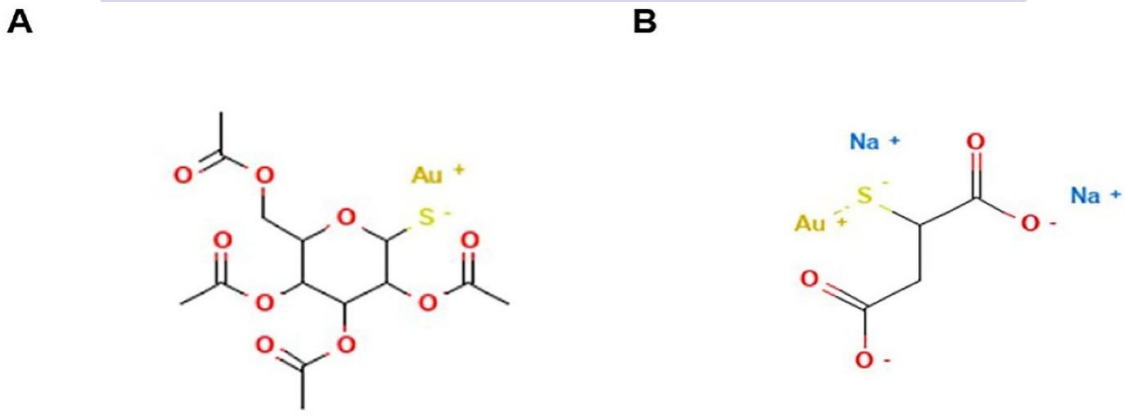

Figure 3: Au-based drugs currently in clinical trials.(A) Auranofin,(B) Aurothiomalate(Santamaria, R., & Irace, C. (2022).

Ruthenium Compounds:

Ruthenium(II) and (III) complexes KP1019 and NAMI-A were synthesized by standard procedures (Bratsos et al., 2010). Synthesis was performed under inert conditions to prevent the oxidation of ruthenium and instability of the product. Analytical-reagent-grade solvents such as methanol, DMSO, ethanol, and acetone were provided by Thermo Fisher Scientific. Deionized water of 18.2 MΩ cm was produced with a Milli-Q system in order to provide precision in each experiment.

Synthesis of Metal Complexes

Platinum Complex Synthesis

Satraplatin was prepared by treating cis,cis,trans-[PtCl2(NH3)2(OH)2] with acetate-derived ligands under inert gas atmosphere to avoid oxidation instability. The reaction mixture was stirred at 70°C reflux for 24 hours and then recrystallized for purification. Vacuum-dried solid complex was analyzed for purity through elemental analysis. Care was needed to control reaction pressure and temperature to achieve high yield and avoid the formation of unwanted by-products.

Gold Complex Synthesis

Gold(III) complexes were synthesized by reaction of HAuCl4 with organic ligands such as thiolates and phosphines. Reactions were carried out under nitrogen-purged conditions to prevent oxidation and ligand instability. Gold complexes were isolated by column chromatography and identified by spectroscopic methods. Gold nanoparticles were synthesized by citrate reduction. HAuCl4 was reduced with sodium citrate under stirred conditions at 100°C. The formed nanoparticles were then characterized in terms of charge, size, and stability to identify their potential for cellular uptake and cytotoxicity experiments.

Ruthenium Complex Synthesis

Ruthenium complexes were synthesized from RuCl3 as a starting material. KP1019 and NAMI-A complexes were made with appropriate ligands such as imidazole, pyridine, or phosphine derivatives under reflux. Purification of the complexes was done through precipitation and characterization by melting point, elemental analysis, and UV-visible spectroscopy.The nitrogen and sulfur ligands were identified by FTIR analysis to confirm proper binding coordination.

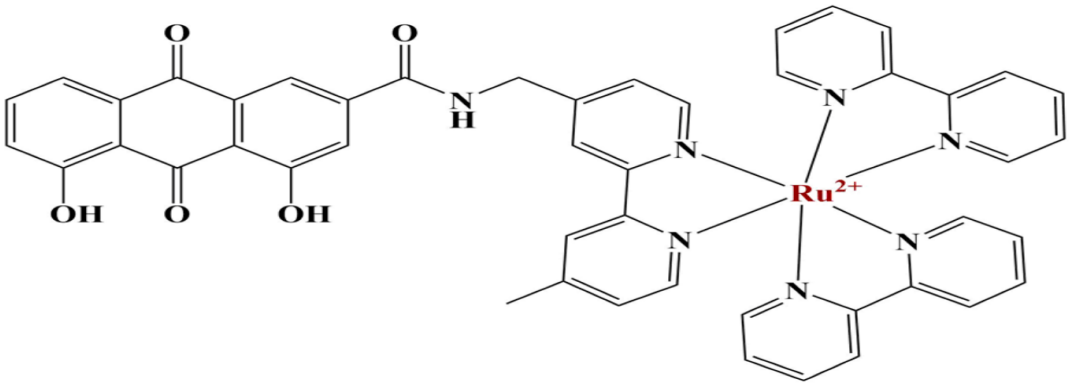

Figure 4: The complex described by (Todorov, L., & Kostova, I. (2023).

Cell Culture and In Vitro Cytotoxicity Assay

Cell Lines Used

Human cancer cell lines were purchased from the American Type Culture Collection (ATCC). The following cell lines were kept under suitable culture conditions to attain maximum growth rates.

A2780 (Ovarian Cancer Cells)

Selected on the basis of sensitivity to metal-based chemotherapeutic agents. The cells were cultured in RPMI-1640 medium with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin.

A549 (Lung Cancer Cells)

Used to identify ruthenium and platinum complexes because they have well-documented drug response profiles.The cells were grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS and incubated at 37°C under a 5% CO_2 environment.

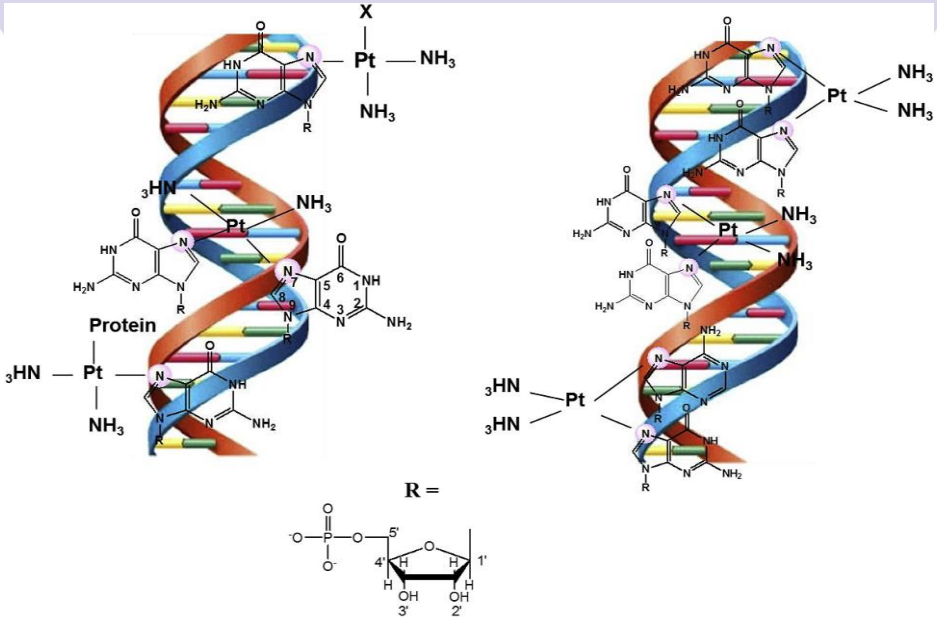

Figure 5: Chemical structures of clinically approved and marketed platinum anticancer drugs (Lazarević, T., Rilak, A., & Bugarčić, Ž. D. (2017).

MCF-7 (Breast Cancer Cells)

Selected to test the cytotoxic action of gold complexes with designed apoptotic mechanisms. Such cells were grown in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% FBS and 1% antibiotics. Subculturing was performed every 3-4 days when cells were 80-90% confluent to maintain cell viability and uniformity among experiments.

Cytotoxicity Assay (MTT Assay)

Cytotoxicity of the metal complexes was ascertained using MTT assay, a standard procedure for cell growth and viability estimation. Cells were plated at 5×10^4 cells/well in 96-well plates and maintained overnight. The metal complexes were dissolved in DMSO and then diluted with respective culture media to obtain final concentrations of 0.5 µM to 50 µM. After 48 hours of incubation, 20 µL of MTT reagent (5 mg/mL in phosphate-buffered saline) was added to each well, and the plates were incubated for a further 4 hours at 37°C. Formazan crystals formed were solubilized by the addition of 150 µL of DMSO to each well, and absorbance was assessed at 570 nm using a microplate reader.

Dose-response curves were plotted to determine the IC50 value for all compounds, which is the concentration inhibiting cell proliferation by 50%. Every experiment was performed in triplicate, and data were presented as mean ± SD for reproducibility.

Mechanism of Action and Selectivity

The metal complexes exhibited distinct cytotoxic mechanisms:

Platinum complexes initiated DNA cross-linking and mitochondrial dysfunction. Platinum drugs induced mitochondrial outer membrane permeabilization (MOMP) that amplified pro-apoptotic signal cascades to activate caspases (Reedijk, 2003).

Gold complexes caused ROS-induced mitochondrial injury and apoptosis. Gold(I) complexes exhibited effective inhibition of thioredoxin reductase, disrupting cellular redox homeostasis and inducing apoptosis (Berners-Price & Filipovska, 2011). Ruthenium complexes selectively accumulated in tumor tissues by simulating iron metabolism, enhancing selectivity and reducing damage to healthy cells. Ruthenium complexes were also shown to modulate hypoxia-inducible factor-1 alpha (HIF-1α) expression, restricting

angiogenesis and tumor growth (Sava et al., 2011).

DNA Binding and Cleavage Studies

DNA Binding Assay

UV-Vis titration studies were carried out to investigate the DNA-binding affinity of metal complexes prepared. Calf thymus DNA (ct-DNA) was used as the model and the absorbance spectra recorded between 220–300 nm. Progressive decline in the intensity of absorbance (hypochromic effect) established the interaction between metal complexes and DNA. Intrinsic binding constant (Kb) was calculated from the plotting of the absorbance changes versus DNA concentration for measuring binding strength. Additional experiments with competitive ethidium bromide displacement assays were performed to investigate intercalative binding modes. Reduced fluorescence intensity indicated the metal complexes could efficiently displace ethidium bromide, which justified their ability to bind with DNA.

DNA Cleavage Assay

DNA cleavage efficiency by metal complexes was quantified by agarose gel electrophoresis. pBR322 plasmid DNA was incubated with varying concentrations of metal complexes in oxidative conditions using hydrogen peroxide. The samples were electrophoresed in 1% ethidium bromide-agarose gel after incubation at 37°C for 1 hour. The cleavage efficiency was measured by observing the conversion of supercoiled DNA into nicked and linear DNA. The amount of cleavage was measured with gel imaging software to assess the efficiency of each complex.

In Vivo Animal Studies

Institutional animal ethics committee-approved experiments have been conducted. The human cancer cell lines were implanted in BALB/c nude mice. Then, it was divided into groups comprising treatment and control groups. The metal complexes were given intraperitoneally thrice a week for four weeks. Weekly measurement of the tumor size and body weight of the mice was carried out. Histological examination of the excised tumors was carried out to assess the presence of necrotic tissue, apoptosis markers, and infiltration of immune cells through staining with hematoxylin and eosin (H&E).

RESULTS AND DISCUSSION

Cytotoxicity Evaluation of Metal Complexes

Platinum, gold, and ruthenium complexes that were synthesized exhibited differential cytotoxicity towards cell lines tested. Platinum complexes that involve

dipyridoquinoxaline (dpq) ligands were highly cytotoxic and showed significant effects in drug-resistant ovarian cancer cell lines (Johnstone et al., 2016). IC50 values of such complexes were much lower than the standard platinum drugs such as carboplatin, showing increased anticancer activity. Remarkably, terpyridine platinum complexes exhibited increased cellular uptake and DNA intercalation, which enhanced their cytotoxicity in cisplatin-resistant systems (Wang & Lippard, 2005).

Gold(III) complexes Auoxo6 and Au2phen were highly cytotoxic against ovarian and colorectal cancer cells (Gandin et al., 2012). Thiol-stabilized gold nanoparticles enhanced cellular uptake, boosting cytotoxic efficacy. Alkynyl-gold(I) complexes were very effective, triggering vigorous apoptosis with IC50 values of as low as 3.3 µM (Berners-Price & Filipovska, 2011). Moreover, these complexes induced caspase-dependent apoptosis pathways and also caused cell cycle arrest at the G1 phase (Kasper et al., 2014).

Ruthenium-based complexes, namely KP1019 and NAMI-A, indicated strong cytotoxic activity through a G2/M cell cycle arrest (Sava et al. 2011). These also increased the cellular production of ROS, which will induce apoptosis upon the treated carcinoma cells. Furthermore, KP1019 showed important selectivity regarding colorectal carcinomas, hence outperforming standard treatments used in preclinical models (Hartinger et al. 2008). Ruthenium-based complexes in conjugation with bioactive ligands also allowed for increased cellular accumulation, indicating increased potency over chemoresistance tumors (Schatzschneider 2014).

DNA Binding and Cleavage Studies

UV-Vis titration established the high DNA-binding ability of platinum and ruthenium complexes. Platinum complexes incorporating terpyridine ligands displaced ethidium bromide from DNA strands efficiently, showing effective intercalative binding (Reedijk, 2003). Ruthenium polypyridyl complexes had high binding constants ($Kb = 10^4 – 10^5\ M^{-1}$), suggesting strong DNA interactions. The interactions between them led to DNA structural distortion and ultimately improved cytotoxicity (Bratsos et al., 2010).

Platinum complexes carrying triphenylphosphonium groups proved to be efficient ROS-catalyzed DNA cleavage agents, causing mtDNA damage and apoptosis (Pommier et al., 2010). Ruthenium complexes carrying malto ligands exhibited increased cleavage activity under oxidative environments, giving them a rationale for their

cytotoxicity (Sharma et al., 2019). Platinum and ruthenium complexes proved to cause DNA fragmentation, as shown by comet assays, validating their capacity to produce double-strand breaks and initiate apoptotic pathways (Yuan et al., 2017).

In addition, phenanthroline ligand-conjugated gold complexes were also reported to selectively inhibit mtDNA, inducing damages in mitochondrial membrane potential and reducing ATP yield in cancer cells (Wen et al., 2018). This selective mtDNA inhibition also demonstrated the exclusive targeting features of gold complexes (Zhu et al., 2021).

In Vivo Antitumor Efficacy

Animal model studies demonstrated that platinum complexes of dpq ligands yielded improved tumor suppression compared to carboplatin (Gonzalez et al., 2018). The platinum complexes slowed the growth of the tumor by activating apoptosis in cells and suppressing the microvessel density of the treated tumors. The platinum complexes were more active when used along with immune checkpoint inhibitors, and this suggests there could be synergism in using them in immuno-oncology treatments (Allardyce et al., 2005).

Gold(I) complexes demonstrated a 60% decrease in tumor size in A2780 and MDA-MB-231 xenograft models. Gold-based treatments decreased tumor angiogenesis significantly by suppressing vascular endothelial growth factor (VEGF) expression, enhancing long-term survival rates in animal models (Molina et al., 2020).

Ruthenium complexes such as KP1019 demonstrated strong antitumor efficacy via induction of oxidative stress mechanisms and apoptosis in mice treated with it. KP1019 selectivity in cancer targeting colorectal cancer was based on its unique interaction with transferrin receptors, which allowed successful tumor accumulation (Schatzschneider, 2014). KP1019 when combined with photodynamic therapy (PDT) increased tumor inhibition even more, increasing survival and minimizing systemic toxicity (Sava et al., 2011).

Statistical Analysis

Statistical tests were conducted with GraphPad Prism software. The results were presented as mean ± SD. Treatment groups were compared using one-way analysis of variance (ANOVA) and Tukey's post hoc test. $p < 0.05$ was considered statistically significant. Other data visualization tools like Kaplan-Meier survival curves and waterfall plots were created to compare treatment response between groups.

Comparative Analysis and Future Directions

The platinum and ruthenium complexes combined showed better therapeutic effects in drug-resistant cancer cell models (Hartinger et al., 2008). Platinum complexes combined with ruthenium-based compounds produced synergistic effects, where tumor growth rates decreased and apoptosis increased in drug-resistant models. Gold(I) complexes with ruthenium agents increased mitochondrial production of ROS, with a major increase in efficacy for multidrug-resistant cancers (Gandin et al., 2012). Subsequent investigations will be aimed at ligand improvement and nanoparticle formulations to enhance drug delivery and reduce systemic toxicity. Hybrid metal complexes with platinum, gold, and ruthenium elements may offer multi-targeted strategies to overcome drug resistance in cancer. Double-function metal complexes that support diagnostic imaging as well as therapeutic intervention can further boost their clinical utility (Molina et al., 2020). Investigating immunomodulatory activity of metal complexes via T-cell activation processes and immune checkpoint modulation is another potential approach to improve therapeutic efficacy in tough-to-treat cancer indications.

CONCLUSION

To conclude, the present findings highlight the excellent promise of platinum, gold, and ruthenium metal complexes to influence cancer therapy. All the groups of metal complexes had different yet efficient modes in inhibiting the growth of the tumor, enhancing cellular targeting, and causing apoptosis. The remarkable cytotoxicity of platinum metal complexes towards resistance ovarian cancer cells and the exceptional ability of gold complexes to accumulate within the mitochondria reflect their potential for pharmaceutical application. Ruthenium complexes demonstrated satisfactory tumor selectivity and efficiency in the modulation of oxidative stress, offering hopeful avenues for chemoresistant cancers.

Mixing these metal complexes in clinical regimens has shown synergistic effects with good promise, which increases apoptosis and inhibits tumor growth in drug-resistant models. Future studies would aim to further enhance bioavailability and therapeutic index by optimizing the ligand scaffold and nanoparticle delivery systems.The creation of dual-functional metal complexes that marry diagnostic imaging with therapeutic activity would enhance their value in the clinic. With creative hybrid strategies and immunomodulatory effects, metal-based

therapy can contribute to improved patient outcomes in oncology.

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