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Review

Noble Metal Complexes in Cancer Therapy: Unlocking Redox Potential for Next-Gen Treatments

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Abstract: (1) Context: Cancer is still a major problem worldwide, and traditional therapies like radiation and chemotherapy often fail to alleviate symptoms because of side effects, systemic toxicity, and mechanisms of resistance. Beneficial anticancer effects that spare healthy tissues are made possible by the distinctive redox characteristics of noble metal complexes, especially those containing palladium, gold, silver, and platinum. **(2) Methods**: The redox processes, molecular targets, and therapeutic uses of noble metal complexes in cancer have been the subject of much study over the last 20 years; novel approaches to ligand design, functionalization of nanoparticles, and tumor-specific drug delivery systems are highlighted. **(3) Results**: Recent developments include Pt(IV) prodrugs and terpyridine-modified Pt complexes for enhanced selectivity and decreased toxicity; platinum complexes, like cisplatin, trigger reactive oxygen species (ROS) production and DNA damage. Functionalized gold nanoparticles (AuNPs) improve targeted delivery and theranostic capabilities, while gold complexes, particularly Au(I) and Au(III), inhibit redox-sensitive processes such as thioredoxin reductase (TrxR). **(4) Conclusions**: Ag(I)-based compounds and nanoparticles (AgNPs) induce DNA damage and mitochondrial dysfunction by taking advantage of oxidative stress. As redox-based anticancer medicines, noble metal complexes have the ability to transform by taking advantage of certain biochemical features to treat cancer more effectively and selectively.

Keywords: cancer; noble metals; redox; theranostics; nanoparticles

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1. Introduction

Cancer remains a major global health challenge, with approximately 19.3 million new cases and 10 million deaths reported around the globe in 2020 alone. Even with improvements in early detection and treatment, the complexity and adaptability of cancer cells often renders traditional therapies, like chemotherapy and radiation, insufficient and in vain. Resistance mechanisms also present a current threat; besides off-target effects and systemic toxicity, these dangers require the development of novel therapeutic strategies that can specifically target cancer cells while sparing healthy tissues [1–4].

Metal-containing compounds have been crucial in the development of cancer therapies over time. The identification of cisplatin during the 1960s highlighted a change in a fresh period of treatment methods that capitalized on the distinct characteristics of metal compounds. Cisplatin's effectiveness prompted investigations into metal-based medications,

focusing notably on noble metals such as platinum, gold, silver, and palladium. These metals have chemical and physical traits, such as electron density and different oxidation states, that allow them to bind with different ligands effectively. These qualities make them well-suited for interacting with biomolecules and influencing the environments within cells [5–8].

The significance of metal complexes redox activity is notably important (Figure 1) in the field of oncology because cancer cells often experience increased stress compared to healthy cells as a result of their rapid growth and metabolic irregularities. This susceptibility can be taken advantage of by metal complexes that can either enhance stress levels or interfere with redox sensitive pathways to trigger cell death. For instance, platinum complexes create ROS that harm DNA and proteins, while gold complexes impede TrxR, an enzyme that maintains redox balance, in cancer cells [9–11].

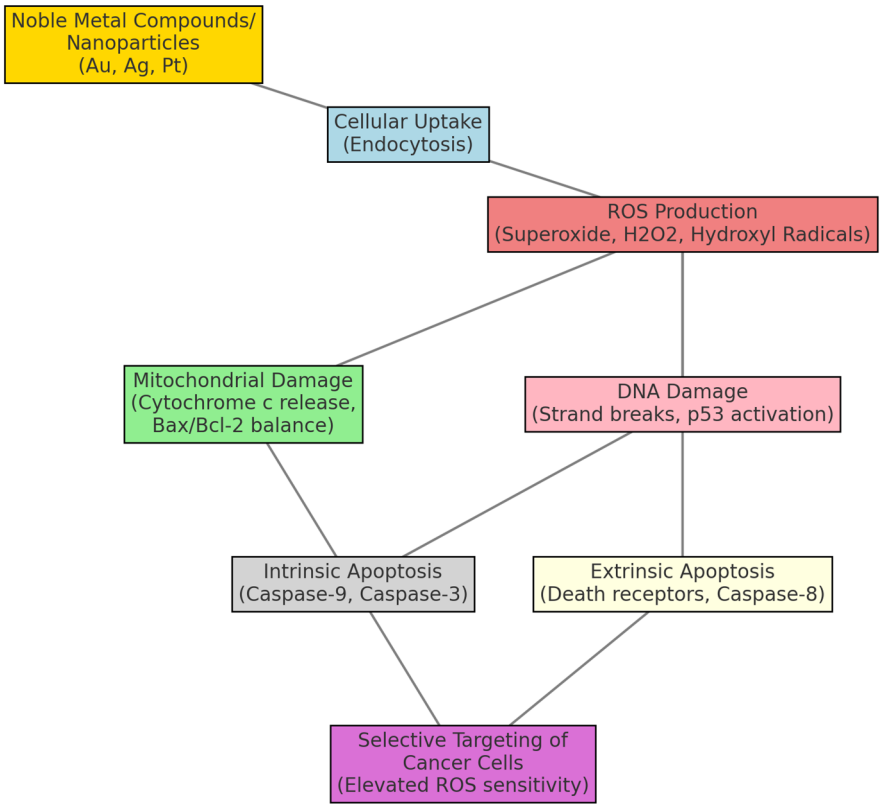

Figure 1. The pathways noble metal compounds follow to induce apoptosis in cancer cells.

This review explores the multifaceted roles of noble metal complexes in cancer therapy, focusing on their redox mechanisms, molecular targets, and clinical implications. By synthesizing insights from recent studies, we aim to provide a comprehensive understanding of their therapeutic potential and inspire further innovations in this promising field.

2. Results and Discussions

2.1. Platinum Complexes

Medications containing platinum, like cisplatin, have reinvented cancer therapy by utilizing their ability to bind to DNA and induce cellular apoptosis. This mechanism involves forming covalent bonds with the purine bases, resulting in intra-strand and inter-strand cross-links that disrupt DNA replication and transcription, leading to cell death (Figure 2). These interactions aid multiple apoptotic mechanisms, such as p53-mediated cell death and deactivation of mitochondrial activity. Besides DNA binding, Pt complexes

are powerful redox agents, amplifying oxidative stress by generating ROS, which further damage cellular macromolecules and enhance cytotoxicity [12–14].

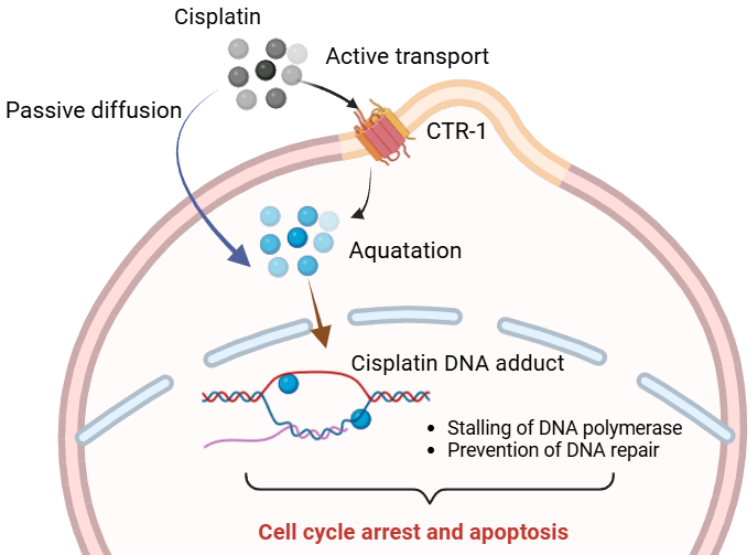

Figure 2. The steps of cisplatin-induced apoptosis in cancer cells explained by intracellular transport, aquatation in the cytoplasm, and further formation of adducts with DNA, inducing apoptosis.

Cummings et al. (2009) showed that cisplatin therapy increased ROS levels in ovarian cancer cells, which in turn led to mitochondrial membrane depolarization and activation of caspase. Similarly, other studies on oxaliplatin have highlighted its ability to produce oxidative DNA damage in colorectal cancer cells, while carboplatin exhibited a more minimized redox potency due to its slower reactivity [15]. Recent research has been focusing on designing new Pt complexes (Table 1) that exploit cancer-specific oxidative weaknesses. For instance, Pt(IV) prodrugs are reduced intracellularly to their active Pt(II) form, achieving targeted ROS generation in the hypoxic tumor environment [16–19].

Table 1. Pt-based anticancer medication currently for therapy.

Platinum Complex	Primary Target	Redox Mechanism	References
Cisplatin	DNA (guanine residues)	ROS generation, DNA damage	[12,20–22]
Oxaliplatin	DNA, ROS pathways	Oxidative stress, apoptosis	[23–27]
Pt(IV) prodrugs	Tumor-specific reduction	Redox-sensitive reduction, ROS activation	[28,29]

Pt complexes, depicted in Figure 3, are evolving at a fast pace to address the constant challenges of resistance and toxicity, which subdue their clinical efficiency, even though they are widely used. The design of these complexes is constantly updated with a focus on modifying ligands to improve pharmacokinetics, selectivity, and therapeutic effectiveness. For example, incorporating sizeable terpyridine groups has been shown to enhance the stability and cellular uptake of Pt complexes, while hydrophilic pairings improve their solubility, facilitating better in vivo biodistribution [30,31].

A study by Zhang et al. (2017) demonstrated that non-traditional ligands, like N-heterocyclic carbene (NHC) or terpyridine derivatives, offered improved redox activity and cytotoxic effects against cancer cell lines that showed resistance to cisplatin. These ligands stabilized the metallic center and improved interactions with specific biomolecules (DNA and proteins), thereby enhancing the therapeutic potential of Pt complexes. Complexes having these ligands exhibited selective toxicity, sparing normal cells and reducing side effects [32].

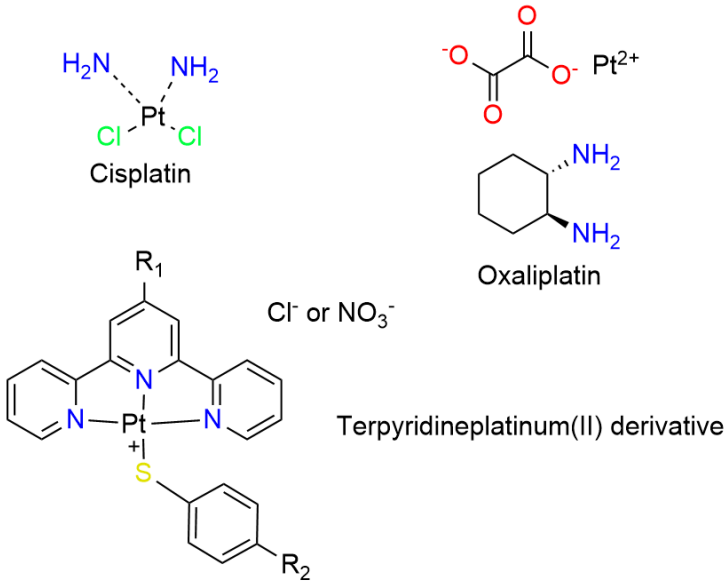

Figure 3. Pt(II) and (IV) complexes with potent redox effects on cancer cells.

Pt(II) complexes having terpyridine ligands showed particular and special cytotoxic activity thanks to their ability to intercalate DNA and inhibit enzymes like topoisomerase, which are crucial for DNA replication and repair. Lo et al. (2009) showed that complexes like these are effective at inhibiting mammalian topoisomerase II and TrxR, both of which play key roles in cancer cell proliferation and redox homeostasis. By targeting these enzymes, these Pt complexes disrupted redox balance in cancerous cells leading to apoptosis [33].

Other new and improved approaches to overcoming resistance and enhancing drug delivery are the development of Pt nanocarriers functionalized with targeting ligands. These nanocarriers increase the enhanced permeability and retention effect to accumulate selectively within tumor tissue. Modified with targeting groups such as peptides, antibodies, or small molecules, these structures ensure precise delivery of redox-active Pt medicine to cancerous cells while saving healthy tissues [34,35].

Recent research explored the potential use of Pt-terpyridine nanocarriers combined with NHC ligands, showcasing better and improved antiproliferative activity in vivo subjects with reduced systemic toxicity. This dual-ligand approach enhanced both the stability and specificity of the drug towards cancer cells. Additionally, the inclusion of nanocarriers allowed for a better and controlled drug release, ensuring that the active compound was delivered at optimal concentrations within the tumor's environment [36].

2.2. Gold Complexes: Targeting Redox Enzymes and Pathways

Gold (Au) complexes (Figure 4), in particular in the +1 and +3 oxidation states, have attracted focus thanks to their ability to disrupt TrxR, an important enzyme in maintaining redox balance. Cancerous cells secrete excess TrxR to neutralize ROS and sustain their rapid growth. Au(I) complexes, such as auranofin, selectively bind to the selenocysteine part in TrxR, permanently inhibiting its activity and inducing apoptosis (Figure 5) [37,38].

Lu et al. (2022) highlighted the enhanced efficiency of Au complexes in targeting redox-sensitive signaling pathways, leading to synergistic effects with traditional chemotherapies. The researchers demonstrated that Au(I) complexes attached to AuNPs via redox-sensitive linkers significantly improved the targeting of cancer cells. The ROS-rich environment in tumor tissues facilitated the release of the Au(I) complexes, leading to enhanced cytotoxicity and apoptosis induction. The multipotential nature of AuNPs further enhances their therapeutic efficacy. Beyond drug delivery, AuNPs can be synthesized to include imaging agents, allowing for simultaneous diagnostics and treatment, also known as theranostics.

For instance, AuNPs functionalized with fluorescent markers or radiolabels enable real-time monitoring of drug delivery and tumor progression. Such integration of therapy and diagnostics provides a powerful tool for personalized cancer treatment [39].

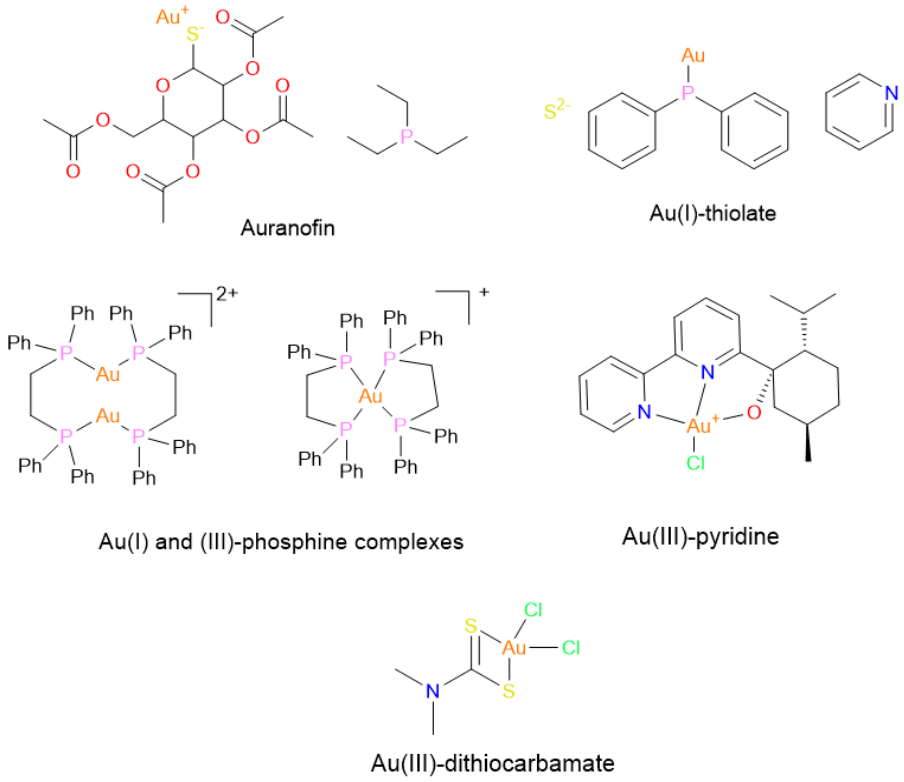

Figure 4. Au(I) and (III) complexes reported in the literature for their effects as possible anticancer drugs.

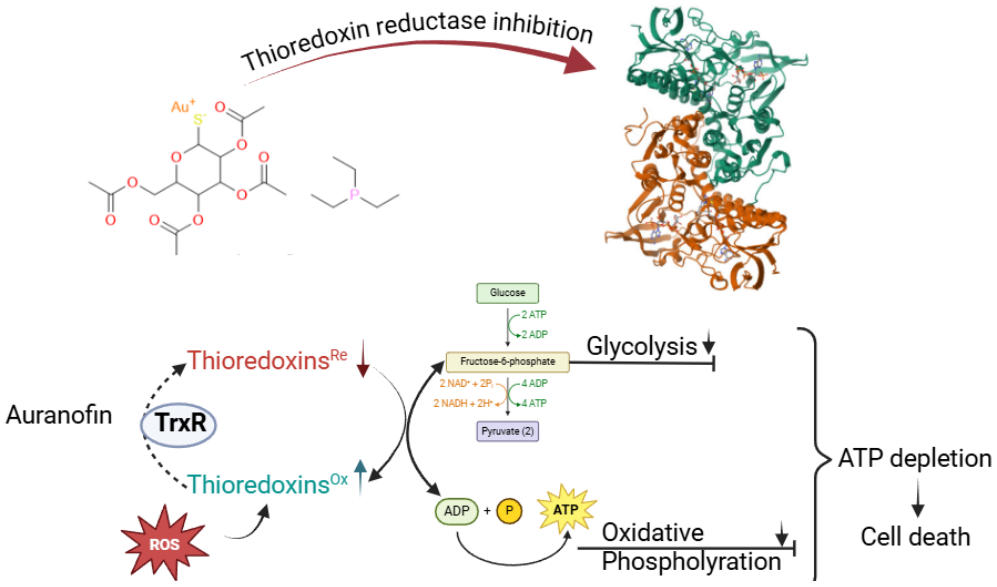

Figure 5. Mechanism of action of auranofin and gold complexes by interfering with TrxR and destabilizing ATP levels, causing cell death.

Au(III) complexes (Table 2) show additional redox properties due to their higher oxidation state, enabling them to interact with biomolecules like DNA, proteins, and ROS-generating enzymes. Thota et al. (2018) demonstrated that Au(III) complexes functionalized with phosphine ligands exhibit strong cytotoxicity in breast and prostate cancer models, primarily through oxidative mitochondrial damage [40].

Table 2. Au-based drugs with high redox potential.

Gold Complex	Mechanism	Key Findings	References
Auranofin	TrxR inhibition	ROS generation, selective redox disruption, apoptosis	[41,42]
Au (III)-phosphine	ROS generation, DNA binding	Mitochondrial dysfunction, DNA binding, apoptosis	[43]
Au(I)-thiolates	ROS generation, mitochondrial damage	ROS-induced mitochondrial damage, apoptosis	[44,45]
Au(I)-NHC complexes	Redox cycling, DNA intercalation	ROS generation, selective cytotoxicity, apoptosis	[46]
Au(III)-pyridine	DNA interaction, oxidative stress	DNA intercalation, ROS-induced apoptosis	[47,48]
Au(III)-dithiocarbamates	Metal ion exchange, ROS generation	ROS-induced DNA damage, apoptosis	[49–51]

Mechanisms targeting cancer cell redox vulnerabilities show that gold complexes have great anticancer potential. The ROS levels are dramatically increased by Au(III) complexes, reaching a maximum of 200% over baseline in sensitive cancer lines after six hours of treatment. Proteins and mitochondrial membranes are immediately damaged by this ROS influx, which leads to depolarization and functional loss in cells. Further disturbance of the redox balance may occur via the suppression of TrxR. At nanomolar doses (IC_{50}: 1–10 nM), the enzyme's activity is reduced by 85–95% when Au(III) complexes bind to selenocysteine and cysteine residues inside its active site. Apoptosis and mitochondrial cytochrome c release are both aided by the quick reduction in decreased thioredoxin brought about by this inhibition [52].

Even in cisplatin-resistant mice, structural investigations reveal that Au(I) complexes, especially those with phosphine or N-heterocyclic carbene ligands, exert strong TrxR inhibition with IC_{50} values in the 100–300 nM range. Their one-of-a-kind ligand architectures make them more selective against cancer cells while reducing collateral damage to healthy organs [53]. According to Tolbatov et al. (2024), these complexes cause a dose-dependent increase in ROS, leading to a two- to threefold rise in colon and breast cancer cells after one day of exposure. In response to this elevated oxidative stress, stress-activated MAPKs, including JNK and p38, phosphorylate and activate factors that promote cell death. The subsequent activation of caspase-3 causes cancer cells to undergo cell death [54]. The effectiveness of gold complexes is generally related to their electrical characteristics, as highlighted in a study by De Franco et al. (2022). This is because nucleophilic amino acids bind well to electron-deficient gold centers, which enhances the mechanistic precision of the complexes [55].

AuNPs have revolutionized the therapeutic opportunities of Au-based anticancer medicine, offering a platform for precise and targeted drug delivery systems. Their nanoscale size, high biocompatibility, and ability to be functionalized with a variety of ligands and biomolecules make them uniquely suited for cancer therapy. Functionalization with redox-sensitive outer layers exploits the oxidative stress and acidic environment commonly found in tumors, ensuring the controlled release of the therapeutic dose directly at the tumor site. One of the key innovations in AuNP-based systems is their ability to respond to the unique redox conditions of cancer cells. The tumor microenvironment typically exhibits elevated levels of ROS compared to normal tissues. Redox-sensitive coatings, such as disulfide linkages or thiol-based ligands, undergo cleavage in this oxidative

environment, triggering the release of conjugated anticancer agents. This selective release reduces off-target effects and enhances the therapeutic index [56–58].

Additionally, AuNPs themselves exhibit intrinsic therapeutic properties; they have been shown to disrupt cellular redox homeostasis by interacting with thiol-containing proteins and enzymes, further enhancing oxidative stress within cancerous cells. This dual-action mechanism, combining the therapeutic effects of both the nanoparticle and the conjugated drug, maximizes the anticancer potential [59,60].

2.3. Silver Complexes: Exploiting Oxidative Stress

Silver complexes (Figure 6) containing Ag(I) exhibit unique redox properties that contribute to their anticancer potential; these complexes can interact with biomolecules such as DNA, proteins, and lipids, leading to cellular dysfunction and later apoptosis. The ability of silver to generate ROS is especially crucial in cancer therapy, where high oxidative stress is a hallmark of the disease. By further enhancing this stress, silver compounds selectively induce cell death in cancer cells while sparing normal, healthy cells [61–63].

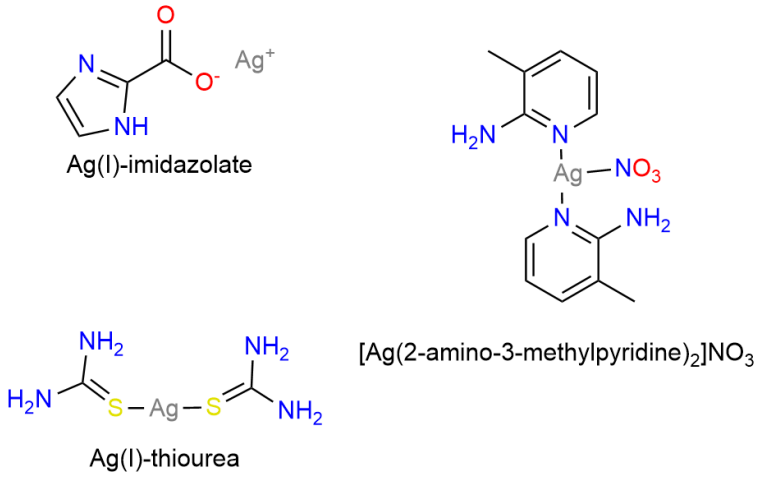

Figure 6. Ag(I) complexes used to induce oxidative stress in tumor cells.

One important mechanism (1) by which silver complexes exert their anticancer activity is the generation of ROS. Silver ions, especially in the +1-oxidation state, have high reactivity and can interact with cellular components to produce ROS, including hydrogen peroxide (H_2O_2), superoxide anions (O_2^-), and hydroxyl radicals (OH•). These ROS initiate oxidative damage to critical cellular structures, including DNA, proteins, and lipids, disrupting cellular functions and metabolism and contributing to apoptosis [64–66].

$$\begin{gathered} Ag^+ \text{ (outside)} \rightarrow Ag^+ \text{ (inside)} \\ Ag^+ + \text{R-SH} \rightarrow \text{R-S-Ag} + H^+ \\ O_2 + e^- \rightarrow O_2\bullet^- \\ 2\,O_2\bullet^- + 2\,H^+ \rightarrow H_2O_2 + O_2 \\ H_2O_2 + Fe^{2+} \rightarrow \bullet OH + OH^- + Fe^{3+} \\ \text{(Due to ROS)} \rightarrow \text{Cytochrome c} \rightarrow \text{Caspase activation} \\ \text{Caspase-9} \rightarrow \text{Caspase-3} \rightarrow \text{Apoptosis} \end{gathered} \quad (1)$$

Silver complexes, like Ag(I)-imidazolate, have been shown to induce significant cytotoxic effects in vitro by promoting oxidative DNA damage. Ag(I) ions can bind to the phosphate backbone of DNA (DNA-P), causing single- and double-strand breaks. Silver ions can also interact with sulfur-containing amino acids in proteins, disrupting cellular

functions, reactions represented in (2). This accumulation of oxidative stress ultimately leads to apoptosis, which is particularly beneficial for targeting cancer cells [67–70].

$$\begin{gathered} Ag^{+} + \text{DNA-P} \rightarrow \text{DNA-P-Ag} \\ \text{DNA-P-Ag} \rightarrow \text{DNA-P}' + Ag^{+} + \text{free radicals (single-strand break in DNA)} \\ \text{DNA-P}' + \text{DNA-P} \rightarrow \text{DNA-P-P}' + Ag^{+} \text{ (double-strand break in DNA)} \\ Ag^{+} + \text{R-SH} \rightarrow \text{R-S-Ag} + H^{+} \\ \text{Oxidative Stress} \rightarrow \text{Cellular Damage} \\ \text{Oxidative Damage} \rightarrow \text{Caspase Activation} \rightarrow \text{Apoptosis} \end{gathered} \quad (2)$$

Through pathways including oxidative stress and disturbance of protein homeostasis, silver complexes have strong anticancer action. Research emphasizes that compounds containing Ag(I) suppress the growth of cancer cells with IC_{50} values ranging from 1 to 10 μM. These complexes trigger cell death by interfering with mitochondrial activity and increasing ROS production. The effect of Ag(I) complexes on cellular energy consumption was confirmed when, after 24 h of exposure to dosages as low as 5 μM, mitochondrial membrane potential dropped by 40–50%. Additionally, by taking advantage of the heightened susceptibility of cancers to ROS, silver complexes preferentially harm cancer cells while avoiding healthy ones [71].

Research by Fabbrini et al. (2019) showed that anticancer effectiveness is enhanced by proteasome inhibition in Ag(I) complexes including N-heterocyclic ligands. Ovarian cancer cells showed IC_{50} values ranging from 1 to 4 μM in Ag(I)-NHC complexes, according to in vitro investigations. At these dosages, proton pump inhibitor-like activity in the proteasome was reduced by 70–80% after 12 h of therapy. Further reducing cancer cell viability, these complexes induce endoplasmic reticulum stress and polyubiquitinated protein accumulation. The results from these investigations show that silver complexes work at low micromolar concentrations by increasing oxidative damage and compromising proteostasis [72].

After 6 h of treatment with silver NPs (AgNPs), human glioblastoma cells showed a threefold increase in ROS creation at 20 μg/mL, indicating that the ROS-generating effect is concentration dependent. This triggers caspase-dependent cell death, which in turn causes DNA damage and lipid peroxidation, which in turn activates the ATM/ATR pathway (Figure 7). Additionally, the research demonstrated that AgNPs promote apoptosis by increasing the Bax/Bcl-2 ratio by 50%. The release of mitochondrial cytochrome c enhances the activation of caspase-3. The impact of Ag(I) complexes on cancer cells is supported by the fact that they attach to thiol groups in enzymes, which in turn disturbs cellular signaling pathways and redox equilibrium [73,74].

Birtekocak et al. (2021) further elucidated the role of AgNPs in cancer therapy, particularly in human colon cancer cells. Their study showed that AgNPs, like silver complexes, amplify ROS production, significantly increasing the oxidative stress within the cancerous cells. This ROS overload activates various biochemical pathways that culminate in apoptosis, effectively killing the cancerous cells. The study found that AgNPs were capable of generating ROS at levels sufficient to induce mitochondrial dysfunction, a key event in initiating cell death. One of the special features of silver complexes is their ability to directly interact with DNA, leading to strand breaks and disrupting the integrity of the genetic material. The DNA damage induced by silver ions is thought to be a key driver of their anticancer activity [75].

Another study by Abu-Youssef et al. (2010) showed that silver complexes with 2-amino-3-methylpyridine ligands exhibited strong binding affinity to DNA. This interaction resulted in the formation of silver-DNA complexes, which hindered DNA replication and transcription, contributing to the cytotoxic effects. These DNA-intercalating properties

of silver complexes further highlight their potential as anticancer agents, as the prevention of DNA replication and repair can effectively halt the proliferation of cancerous cells [76].

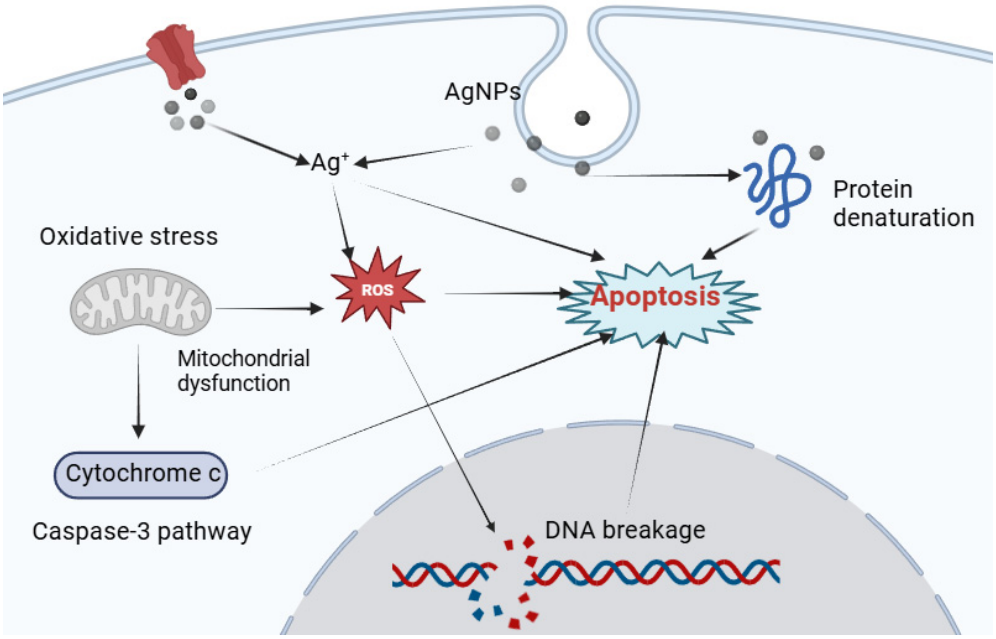

Figure 7. The general mechanism of silver ions in activating the caspase-3 pathway in inducing apoptosis.

Moreover, Ag(I)-based complexes (Table 3) can induce DNA damage through the generation of ROS, which in turn leads to the oxidation of the DNA bases, especially guanine, resulting in mutagenic lesions. This oxidative DNA damage has been implicated in the activation of DNA repair mechanisms, such as base excision repair and nucleotide excision repair, which can overwhelm the cancerous cells' ability to maintain genomic integrity, leading to apoptosis [77,78].

Table 3. Ag-based complexes used as chemotherapy drugs for different types of cancer.

Silver Complex	Primary Mechanism	Applications	References
Ag(I)-thiourea	ROS-mediated DNA damage	Lung, breast	[79–81]
Ag(I)-imidazolate	Oxidative stress, apoptosis	Prostate, colon	[82,83]
AgNPs	Amplified ROS, mitochondrial dysfunction	Colon, cervical, breast	[84,85]
Ag(I)-peptide/antibody conjugates	ROS generation, selective targeting	Various cancers (lung, breast)	[86–88]

Silver complexes present flexibility and adaptability, which allows for the fine-tuning of their redox properties, making them highly compatible for use in cancer treatment. By modifying the ligands attached to silver, researchers can influence the complex's ability to generate ROS, interact with cellular molecules, and overcome resistance mechanisms commonly found in tumor cells.

For example, El-Naggar et al. (2022) synthesized Ag(I) complexes with quinoxaline derivatives; these complexes exhibited increased DNA-binding affinity and redox activity, enabling them to efficiently disrupt DNA and induce cytotoxic effects in cancer cells. Such structural modifications have proven effective in expanding the applicability of silver complexes, particularly in targeting multi-drug-resistant cancer cell lines. This is significant given the growing problem of resistance to conventional chemotherapy agents, which often limits the efficacy of cancer treatment [89].

Silver complexes, with their ability to generate high levels of ROS and selectively interact with biomolecules, represent a promising alternative for overcoming this challenge.

2.4. Palladium Complexes: Catalysts for Redox Disruption

Despite not having been studied as thoroughly as compounds based on platinum, palladium (Pd) complexes have gained more and more interest due to their special qualities in redox-based cancer treatments. A key mechanism for causing cancer cell death is the catalytic activity of Pd(II) in boosting redox reactions, particularly the formation of ROS. Apoptosis, necrosis, and cellular malfunction may result from ROS, which are very reactive chemicals that can oxidatively damage proteins, lipids, and DNA. Rapidly proliferating cancer cells are the ones this process zeroes in on because they are more susceptible to oxidative stress than normal cells (Figure 8) [90,91].

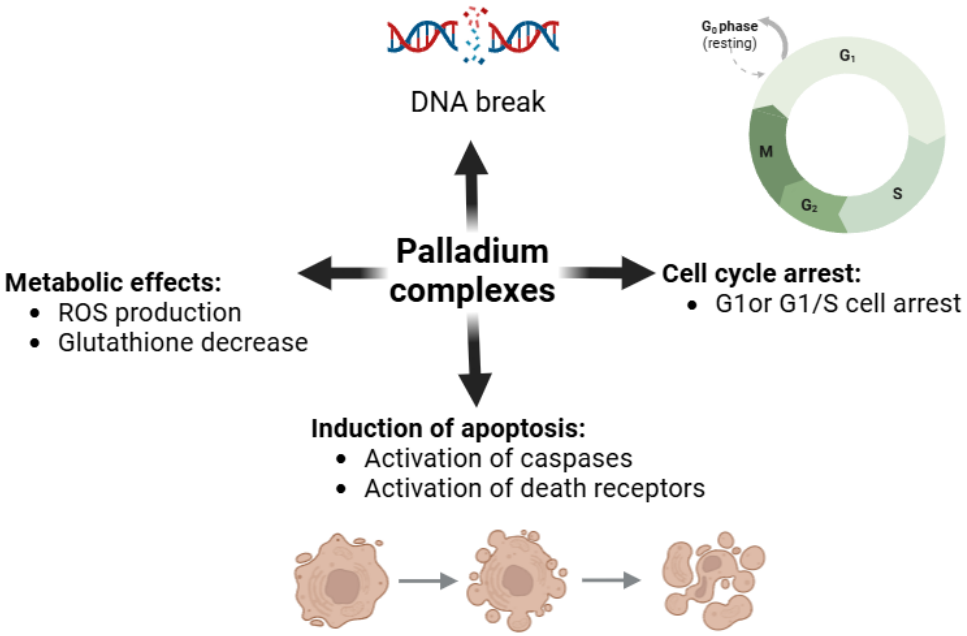

Figure 8. The multitude of mechanisms in which palladium complexes induce apoptosis in cancer cells.

Due to their capacity to promote ROS generation, Pd(II) complexes with ligands like terpyridine have become attractive prospects for the creation of anticancer drugs. The cytotoxic effects of palladium complexes on several cancer cell types provide evidence of their medicinal potential. One important step in the start of apoptosis is mitochondrial malfunction, which Pd(II)-terpyridine complexes have been shown to cause. When Pd(II) and mitochondrial components interact, cytochrome c is released, which starts the caspase cascade and eventually results in programmed cell death. The remarkable selectivity of Pd(II)-terpyridine complexes for cancer cells, which permits less damage to healthy tissues, is one of its main benefits. Pd(II)-terpyridine complexes were shown to preferentially accumulate in breast cancer cells while sparing normal cells in research by Savić et al. (2019) [92]. The complexes' distinctive physicochemical properties, such as their lipophilicity and membrane-crossing capabilities, improve their targeting capabilities and allow for selective absorption. Furthermore, terpyridine ligands' highly flexible structure permits the fine-tuning of their redox characteristics and interactions with biological targets. It is feasible to maximize the therapeutic efficiency of these complexes and customize them to treat various cancer types by altering the palladium coordination environment [93–95].

The creation of Pd(II) complexes (Table 4) that combine targeted delivery methods with increased ROS production is the subject of further investigation. For instance, Pd(II)-terpyridine complexes may be functionalized with biomolecules that bind to cancer cell receptors or conjugated with nanoparticles to enhance their accumulation at tumor locations and lessen systemic toxicity. Because palladium complexes may interact with important

biological components, including proteins, lipids, and DNA, while still exhibiting selective cytotoxicity, they hold promise as a platform for next-generation cancer treatments.

Table 4. Pd-based drugs with high redox potential against cancer cells.

Palladium Complex	Mechanism of Action	Target Cells/Cancer Types	Key References
Pd(II)-terpyridine complexes	ROS-induced mitochondrial dysfunction and apoptosis	Breast cancer, colorectal cancer	[92]
Pd(II)-terpyridine complexes	DNA binding, oxidative stress-induced apoptosis	Ovarian cancer, lung cancer	[96]
Pd(II) complexes with phosphine ligands	DNA intercalation, ROS generation	Melanoma, liver cancer	[97]
Pd(II) complexes with heterocyclic ligands	Redox cycling, ROS production	Pancreatic cancer, breast cancer	[98,99]

The promise of palladium-based complexes (Figure 9) as future anticancer medicines is highlighted by their flexibility, especially when terpyridine and other redox-active ligands are included. A number of questions remain, including how well Pd(II)-terpyridine complexes work in vivo, what dosages work best, and whether or not they may be used in combination with other anticancer medications.

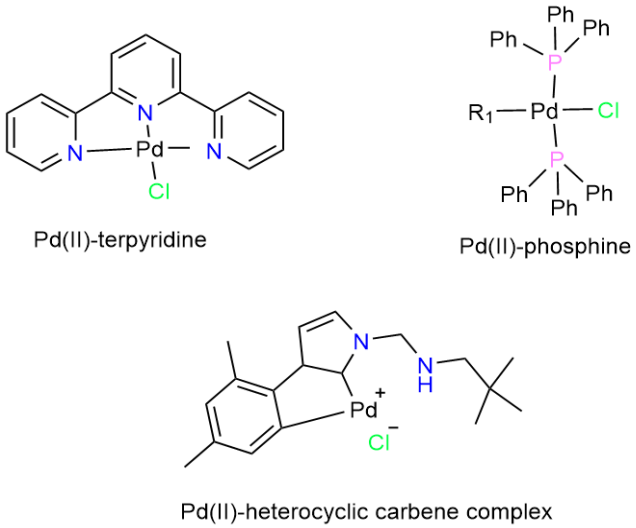

Figure 9. Pd(II) complexes that induce apoptosis in tumor cells.

Romashev et al. (2022) discovered that heteroleptic Pd(II) complexes with redox-active quinonoid ligands attacked cancer cells in a number of different ways. Cytotoxicity was produced by the complexes at IC_{50} values between 1.5 and 3.2 μM, and they showed a significant selectivity for cancer cells. Following 12 h of exposure to 2 μM of Pd(II) complex, detailed ROS quantification experiments revealed a 150% rise in ROS levels compared to the unexposed control group. Increased ROS cause oxidative stress on lipids and proteins, which compromises the integrity of the mitochondrial membrane. Additional evidence of DNA intercalation by these Pd(II) complexes comes from the substantial hypochromic effects and bathochromic shifts seen in UV-visible spectra. Approximately 2.3 times 10^5 M^{-1} was determined for the binding affinity constants, indicating a strong interaction with DNA that impedes the processes of replication and transcription [100].

Conducting further research into arylamide-liganded cyclometallated Pd(II) complexes, Dolengovski et al. (2024) built upon this earlier investigation. Reversible redox peaks indicated electron transfer capacity conducive to oxidative stress, which was vali-

dated using cyclic voltammetry, indicating that these complexes displayed redox cycling behavior. There was a clear relationship between redox potential and cytotoxicity, as shown by their IC_{50} values ranging from 2.8 to 6.5 μM in lung and colon cancer models. A maximal 2.5-fold increase at 4 μM after 24 h was achieved in ROS generation, which was dependent on both time and dosage. There was a 60% drop in mitochondrial membrane potential and cellular viability tests connected this oxidative damage to apoptosis in the mitochondrial pathway. Furthermore, apoptosis via the intrinsic route was confirmed by Western blotting, which showed an increase in Bax and cleaved caspase-3 [91].

Other studies focused on Pd(II) complexes with Schiff base ligands and their DNA-binding and enzyme-inhibiting capabilities. Results from fluorescence quenching tests showed that there was substantial intercalation and disturbance of DNA stability, with binding constants reaching up to 3.1×10^6 M^{-1}. The resolution of DNA supercoiling was impaired, as topoisomerase inhibition experiments demonstrated an enzymatic suppression of over 85% at 5 μM [101]. Lastly, in cell-specific lines, Vojtek et al. (2019) showed that Pd(II) complexes were effective against triple-negative breast cancer, with IC_{50} values < 1 μM. Highlighting the multi-faceted anticancer tactics of Pd complexes, cell cycle arrest in the G2/M phase was the result of the synergy between ROS production and DNA-binding capacities [102].

The creation of prodrugs based on Pd(II) that are activated in the tumor microenvironment might also lead to improved outcomes during treatment, fewer side effects, and more precise targeting of cancer cells. By extending the therapeutic window of palladium-based medicines, these initiatives have the potential to solidify their position as an essential class of metallodrugs in cancer treatment.

There are still issues with palladium complexes' stability and bioavailability, despite the fact that they show encouraging redox activity.

Researchers are exploring ligand designs that enhance their pharmacokinetic properties, such as incorporating bulky, electron-donating groups to improve solubility and tumor specificity.

3. Preparation Process—Literature Review

This literature review on noble metal complexes in cancer treatment includes papers that were handpicked after a long and methodical selection process to guarantee high quality, reliability, and coverage of the topic. To begin, we combed through a large number of scientific publications' worth of research papers utilizing databases like PubMed, Scopus, and Google Scholar. To narrow the search, we used keywords like "cancer therapy", "noble metal complexes", "platinum-based drugs", "gold complexes", and "redox mechanisms" to find the best research. With an emphasis on more recent developments in the subject, only publications published in the previous 20 years were taken into account.

Included articles contributed directly to our knowledge of noble metal complexes' function in cancer treatment; in particular, studies that investigated these compounds' biological processes, molecular interactions, and therapeutic promise were given preference. Research on complexes based on palladium, gold, silver, and platinum that shed light on their synthesis, redox behavior, and cytotoxic effects was given precedence. Both experimental investigations, including in vitro and in vivo models, and clinical trial data were included to make sure the review addressed a variety of viewpoints. The trustworthiness of the source was also considered as an additional factor for inclusion. For this evaluation, we strictly regarded peer-reviewed publications in medicinal chemistry, oncology, and biochemistry journals with a high impact factor. This made sure that the data were solid and backed by solid science. Additionally, articles detailing new complicated designs,

innovative methodology, and developing treatment approaches (such as targeted drug delivery systems and ways to combat drug resistance) were given preference.

To guarantee a comprehensive overview, articles were selected to reflect both historical perspectives on established treatments, like cisplatin, and newer advancements in the field, including the exploration of AuNPs and novel palladium complexes. Special attention was given to studies that focused on understanding the molecular targets of these metal-based compounds, such as DNA, proteins, and redox-sensitive enzymes, as well as their ability to induce oxidative stress, a key mechanism in cancer cell destruction. Only studies that were relevant to the review's aim—providing a detailed understanding of the potential and challenges of noble metal complexes in cancer therapy—were ultimately selected.

By employing this rigorous selection process, a well-rounded and current body of literature was identified, offering valuable insights into the therapeutic applications and limitations of noble metal complexes in the treatment of cancer.

4. Conclusions

In summary, the distinct redox properties of noble metal complexes (e.g., palladium, platinum, gold, and silver) make them very promising cancer treatments. The literature review concludes that the ability of platinum-based medicines to inhibit DNA replication and generate ROS makes them an important component of cancer chemotherapy. These treatments include cisplatin, oxaliplatin, and the more modern Pt(IV) prodrugs. New platinum complexes with improved pharmacokinetics, selectivity, and reduced side effects have been developed in response to the persistent problems of resistance and toxicity. The therapeutic potential of these platinum-based medicines has been enhanced by innovations such as tailored drug delivery systems, better ligands, and nanocarriers.

Research has shown that gold complexes, particularly those containing the +1 and +3 oxidation states, have a considerable inhibitory effect on TrxR. For cancer cells, this means a redox imbalance and cell death by selective killing. Their anticancer effectiveness is further enhanced when used in conjunction with AuNPs, which decrease systemic toxicity and allow for targeted medication delivery. The dual-action mechanism of AuNPs, which combines therapy and diagnostics, highlights their potential in customized medicine.

The ability of silver complexes to generate ROS and enhance oxidative stress has made them famous for their anticancer effects, and this is especially true in cancer cells that have developed resistance to many medicines. They can interact with proteins and DNA, and they can increase oxidative damage; therefore, they have potential as cancer treatment agents. AgNPs enhance therapeutic efficacy and provide additional advantages by facilitating targeted drug distribution and boosting ROS production.

Palladium complexes' ability to generate ROS and speed up redox reactions gives them great potential, despite the fact that they have received less attention from researchers than platinum-based medicines. In particular, complexes functionalized with redox-active ligands, such as terpyridine, have a specific cytotoxic effect on cancer cells. This is particularly true in colorectal and breast cancer models. Future studies on palladium-based prodrugs and customized delivery methods have the potential to enhance their effectiveness while reducing adverse effects, transforming them into valuable resources for cancer therapy.

Although noble metal complexes have shown encouraging results, they will not be able to fulfill their therapeutic promise unless advances in drug transport, molecular design, and the elimination of issues related to stability, toxicity, and resistance are addressed. Combining these metal-based medications with modern technologies, such as combination therapy and nanomedicine, is the key to improving clinical outcomes in cancer treatment. Future research should focus on optimizing these complexes for specific cancer types, en-

hancing their bioavailability, and decreasing systemic toxicity to make them more effective in cancer treatment plans as a whole.

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