Voyager: Vol. XVI, 2025 ISSN: (P) 0976-7436 (e) 2455-054X Impact Factor 8.419 (SJIF)
https://doi.org/10.31995/voyager.2025.v16.007

Evaluation of Platinum (II) and Gold (III) Complxes as Anticancer Agents

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Reference to this paper should be made as follows:
Received: 10-12-25
Approved: 20-12-25

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Voyager: Vol. XVI, 2025
Article No. 07
Pg. 057-070
Similarity Check: 13%

Online available at:
https://anubooks.com/journal-volume/voyager-vol-xvi-2025

DOI: *https://doi.org/10.31995/voyager.2025.v16.007*

Abstract

Cancer continues to be responsible for the deaths of nearly 10 million people worldwide in 2020 according to the WHO (World Health Organization). Current treatment options are diverse, but low success rates, particularly for those with late-stage cancers, continue to be a problem for clinicians and their patients. The effort by researchers globally to find alternative treatment options is ongoing. The prevalence of cancer and all associated costs, both in human and financial terms, drives the search for therapeutic drugs and treatments. Coordination compounds are emerging as a new class of cancer therapeutics. The diverse anticancer utility of cisplatin a platinum-based complex has stimulated significant interest in the development of additional transition-metal-based complexes, resulting in several analogues receiving clinical approval worldwide. The metals focused on in this paper include Pt and Au complexes; these complexes are capable of DNA intercalation and are highly biologically active. Platinum and gold complexes dominate the current metallodrug landscape. This paper reviews platinum-based chemotherapeutics and gold compounds with anticancer potential.

Keywords

cancer; intercalate; DNA; platinum; gold; cytotoxity; chemotherapeutics

Introduction

There has been fascination with the investigation of metal complexes for medicinal uses, including anticancer therapies, since the successful clinical trials and approval of cisplatin in the 1970s, the first platinum (II)-based medicinal complex [1]. Platinum (II)-based chemotherapies continue to be important in worldwide clinical cancer treatment; they are prescribed in more than 50% of all current chemotherapy regimens [2] The discovery of cisplatin is serendipitous; it is a simple platinum coordination complex which bring revolution in chemotherapy [2-3]. In the late 1960s cisplatin was found to have potent cytotoxicity, and it was approved for testicular cancer in 1978[3]. Cisplatin has theability to cure more than 90% of metastatictesticular tumors [4] demonstrated the potential of metal complexes as drugs. This success inspired the development of related platinum (II) drugs in which the first generation is: - cisplatin (Fig 1); the second generation is: - carboplatin and nedaplatin (Fig 1); and the third generation is: - oxaliplatin [5-6] Figure (1) and exploration of other transition metals as anticancer agents. Unlike purely organic agents, metal complexes offer tunable oxidation states and coordination geometries [6]. For example, Pt (II) is square-planar (d^8) while Au (III) is also(d^8) and square-planar, suggesting similar DNA-binding geometries [7]. Moreover, many metal-drugs act as prodrugs that undergo ligand exchange or redox activation in vivo (e.g., Pt (IV) '! Pt (II), Au (III)'! Au(I) [7]. Platinum and gold exhibit significant chemical and biological similarities. While platinum-based complexes are already well established in clinical oncology, these shared properties position gold as a highly promising and strategically focused element for the development of novel anticancer agents. Firstly we will discuss platinum and then we move to gold.

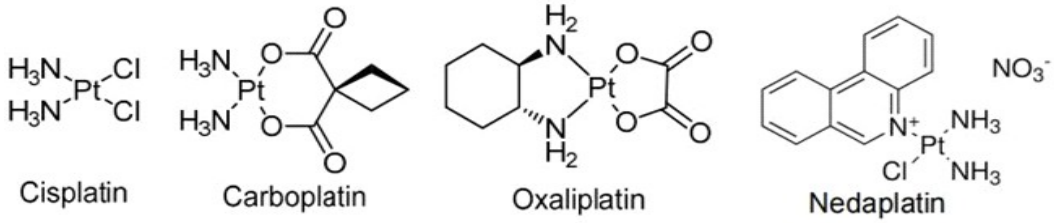

Figure 1. Chemical structures of cisplatin, carboplatin, oxaliplatin [2] and nedaplatin. (Added manually)

Interaction of platinum Complexes with DNA

Transition metal complexes can bind to DNA through either covalent bond formation or reversible intermolecular associations. The topologies of the major and minor grooves vary significantly in size, hydration, electrostatic potential and position of hydrogen-bonding sites providing many binding opportunities [8]. Reversible binding can occur by

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direct interactions in either the major or minor groove of DNA [8-9]. Positively-charged small molecules can bind to negatively charged DNA by different modes which include electrostatic attraction, covalent or coordinate binding, groove binding and intercalation (Fig. (**2**)) as well as combinations of these modes [9].

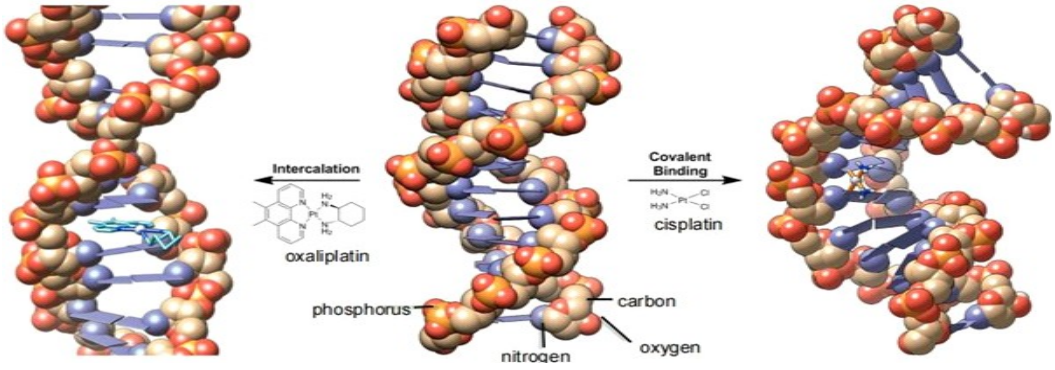

Figure 2. Schematic representation of a metal complex interacting with DNA, resulting in elongation of the double-helix [2]. Oxygen is red, **right**, sourced phosphorous is yellow, carbon is cream/white and nitrogen is blue/purple. The base pairs are also blue in color (All the namings are inserted manually)

Mechanistic studies showed that cisplatin acts as a prodrug, as it undergoes hydrolysis in aqueous media to form aqua platinum (II) complexes, which in turn covalently binds to DNA [12]. The square planar transition metal complexes $[PtCl_4]2-$ [13, 14], cisplatin [15-17], Fig. (**1**), and oxaliplatin,) bind to DNA through coordination. The anticancer activity of cisplatin primarily arises from its ability to interact coordinatively with DNA. After entering the cell, the chloride ligands of cisplatin are displaced by water molecules, producing highly reactive aqua platinum (II) species that behave as strong electrophiles and readily react with nucleophilic sites on nucleic acids [16]. In this way, cisplatin functions as a prodrug, becoming activated through hydrolysis in the intracellular aqueous environment before binding covalently to DNA [18]. The platinum centre predominantly coordinates to the N7 position of guanine bases, leading mainly to the formation of 1,2-intrastrand cross-links between adjacent guanine residues, which represent the most abundant and biologically significant DNA adducts in both cisplatin and carboplatin treatment [18–21]. In addition, less frequent adducts such as 1,3- intrastrain cross-links between non-adjacent bases and monofunctional platinum– DNA adducts have also been observed [18, 19, 22, 23]. These covalent cross-links induce substantial local distortions in the DNA double helix, including bending and unwinding of the strand [20]. Such structural changes interfere with essential cellular processes, particularly DNA replication and

transcription, thereby inhibiting cell proliferation and ultimately triggering programmed cell death (apoptosis) in cancer cells [21, 24].

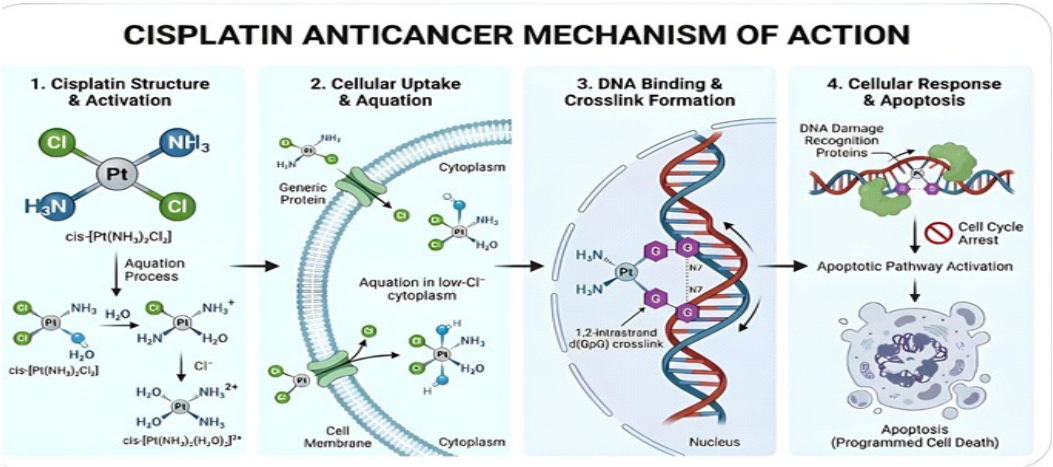

Figure (3). It described the cisplatin mechanism of linkage with DNA (created using SciSpace)

This is how the complete cycle of platinum complexes takes place inside the DNA of an organism. It is widely used for the treatment of various cancers including ovarian, testicular, lung and breast cancer [25]. This activity, however, is moderated by dose-limiting side-effects (nephrotoxicity-, neuro- and ototoxicity) [26]. So, its analogues such as carboplatin and oxaliplatin are used to overcome its side effects. **Platinum Intercalators** Transition metal intercalators have been in development for decades; the original platinum complex [Pt(terpy)(2-ME)] + (where 2-ME = 2-mercaptoethanol) was shown to bind strongly to DNA via intercalation [27-28]. Intercalation is the insertion of a complex within two adjacent base pairs of DNAS [29]. In contrast intercalators have received less attention; however, there are several recent examples of platinum intercalators that exhibit exceptionally high anticancer activity. A prominent series of complexes are composed of a general scaffold of $[Pt\ (H_L)(A_L)]^{2+}$, where H_L is a heterocyclic intercalating ligand and A_L is a bidentate ancillary ligand [28,29] Examples of intercalating molecules include $[Pt(terpy)Cl]^+$, [Pt(dpq)(en)]2+ [30, 32-34]. In 1974 the intercalative binding of the platinum (II) complexes [Pt(bpy)(en)]2+ and [Pt(phen)(en)] + was investigated using X-ray diffraction and electrophoresis. These complexes were observed to intercalate and unwind DNA due to the planarity of their intercalating ligands [33-35]. The inclusion of a metal centre into the design of intercalating compounds gives rise to a greater range of geometric diversity and structural flexibility than any purely organic molecules can achieve (Fig. (**4**)) [36].

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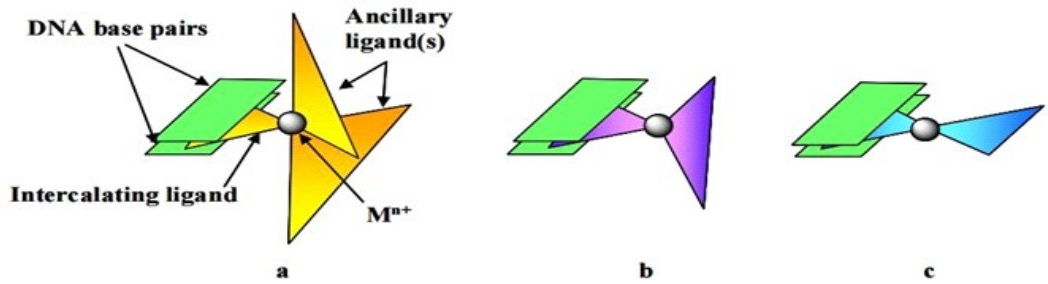

Fig. (4). Schematic representations of metallointercalators with **(a)** octahedral, **(b)** tetrahedral and **(c)** square planar geometry [35]

Cisplatin Analogues

Now we know that cisplatin is the first discovered platinum-based complex used as anticancer agents but it has some disadvantages so to overcome them other platinum-based analogues of cisplatin have been developed to overcome some of the disadvantages associated with its use. Carboplatin, Fig. (**1**) [36, 41] and nedaplatin, Fig. (**1**) are two second-generation complexes that are currently in clinical use [35,38]. Carboplatin is used for the treatment of ovarian cancer [38, 39], as it is less toxic than cisplatin and it does not induce nephrotoxicity [42, 43]. Nedaplatin is used to treat a variety of cancer types, including testicular and cervical cancer [28, 33, 39], but has only received approval in Japan. The mechanism of action of carboplatin and nedaplatin is very similar to that of cisplatin [38], the latter two of which have proven to be effective in the treatment of cancers with limited or no response to cisplatin. Oxaliplatin, Fig. (**1**) is a third- generation platinum complex that displays no cross-resistance with cisplatin [41, 42]. It has been widely utilized in the treatment of colorectal and ovarian cancers where cisplatin or carboplatin were unsuccessful [38, 39]. Oxaliplatin is more water-soluble, lacks the nephrotoxicity, and has less hematological toxicity than cisplatin or carboplatin at therapeutic doses [33,35,42].

Metal	Name	Status†
Platinum	Cisplatin	Approved in 1978. Worldwide use
	Carboplatin	Approved in 1989. Worldwide use
	Oxaliplatin	Approved in 1996. Worldwide use
	Heptaplatin	Approved in South Korea
	Lobaplatin	Approved in China
	Nedaplatin	Approved in Japan

Table 1: - platinum derivatives and its stutus about clinical use [referenced from clinicaltrials.gov website]

Gold [III] Complexes

Gold (III) compounds constitute an emerging class of biologically active substances, of special interest as potential anticancer agents. During the past decade a number of structurally diverse gold(III) complexes were reported to be acceptably stable under physiological-like conditions and to manifest very promising cytotoxic effects against selected human tumour cell lines, making them a good candidates as anti-cancer drugs[45].We know that [d^8]Au(III) complexes are isoelectronic and isostructural with Pt(II) complexes, having geometry [square planar][45] so gold(III) compounds soon appeared to be excellent candidates for anticancer evaluation[45]. However, at variance with platinum (II) compounds, gold (III) analogues were found to manifest [45], on the whole, a rather poor stability profile being kinetically more labile than the corresponding platinum (II)compounds, light-sensitive and easily reducible to metallic gold [46]. To increase the stability of gold (III) complexes, we looked for those ligand systems that have the following characteristics: **1**- strong -donor which can stabilize the electrophilic and oxidizing gold (III) ion, **2**- strong chelating effect to avoid demetallation, and **3**- rigid ligand scaffold to stabilize the four-coordinate gold (III) by raising the kinetic barrier (inner-sphere re- organization energy) for reduction to two coordinate gold(I) [48-49]. In this regard, we have examined the gold (III) complexes containing porphyrin and chelating cyclopentolate ligands. During the 1990s, renewed interest for anticancer gold (III)- based compounds emerged place, especially when a few novel gold (III) complexes, exhibiting improved stability, lower toxicity and favorable in vitro pharmacological properties, were made available for pharmacological testing [48]. A few compounds, namely [Au(en)$_2$] Cl_3, [Au(dien)Cl] Cl_2, [Au(cyclam)]$(ClO_4)_2Cl$, [Au(terpy)Cl]Cl_2 , and [Au(phen)Cl_2]Cl[49] , (Fig. 1), were characterized both in the solid state and in solution [48-51].It is worth noting that very recent results suggest that these gold(III) dithiocarbamate compounds most likely act through inhibition of the cancer cell proteasome [50], a quite novel and unexpected mechanism for anticancer metallodrugs.

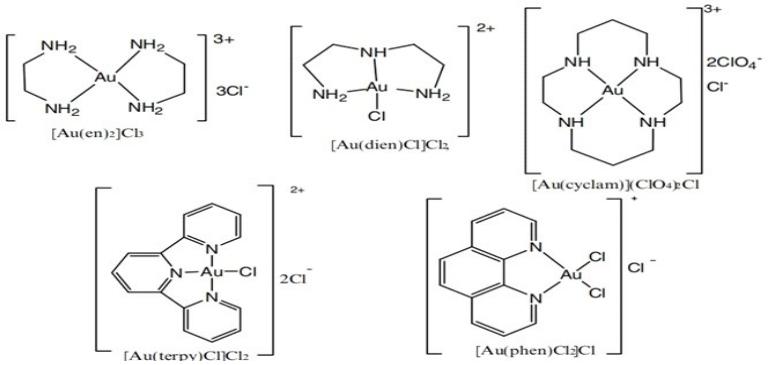

Figure 5. describing gold complexes [44] (namings are added manually)

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All the mentioned gold (III) porphyrins displayed excellent in vitro antiproliferative effects, with IC50 values of 0.1–1.5 lM[44-45]. The lack of cross-resistance with classical platinum (II) compounds again suggests that gold (III) porphyrins and cisplatin induce cytotoxicity through quite distinct mechanisms [44].

After a lot of research, we found that TPP exhibits a lot of potential in anticancer activities with transition metals Here we will now focus Au complex with TPP [35,51].

We have found that the [Au(TPP)]Cl (H_2TPP = tetraphenyl porphyrin) complex exhibited potent in vitro anticancer activities toward a panel of cancer cell lines, including cisplatin and multi-drug resistant cell lines, with sub-micromolar IC50 values[51].Notably, [AuIII(TPP)]Cl (**1a**, Fig. 6) exhibits the highest cytotoxicity toward nasopharyngeal carcinoma (NPC) cells such as SUNE1 (IC50 = 0.11 lM, 48h)Complex **1a** exhibits <“10-fold higher toxicity to the cancer cells than the normal cells, and thus renders a safe therapeutic window for anti-NPC[51].

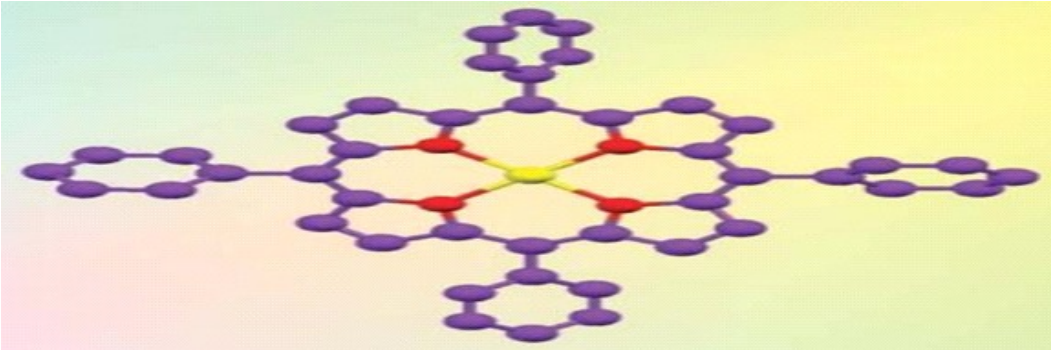

Fig. 6. X-Ray crystal structure of [AuIII (TPP)] + (**1a**).[53]

Complex **1a** induced cytotoxicity in NPC cells *via* an apoptotic pathway. Functional proteomic studies revealed several alterations of cytoplasmic protein [52] expression including those enzymes participating in energy production and proteins involved in cellular redox balance, suggestive of mitochondria being centrally involved in the induced-apoptosis [55]. Till now **1a** functions and their effects are not fully discovered so we understand the logistic change in the nasopharyngeal carcinoma (SUNE1) [53] and normal peripheral blood mononuclear cells (PBMCs). Figure (6) it clearly shows the variation between these two cells when induced by **1a.** Its main target is mitochondria not DNA so these distinct properties made it an attractive candidate for the anti-cancer research [53]. Among the literature-reported anti-cancer gold (III) complexes, the [Au(acetato)2(damp)] and [Au(malonato)(damp)] (where damp= 2- [(dimethylamino)methyl] phenyl) reported by Buckley and co-workers gave <“40% tumor reduction under in vivo conditions [52].

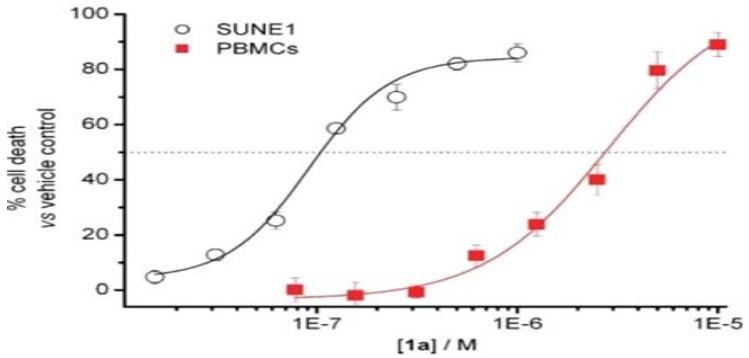

Figure. 7 Cytotoxic profiles of **1a** toward nasopharyngeal carcinoma (SUNE1) and normal peripheral blood mononuclear cells (PBMCs).

Graphs show the percentage cell death compared to the vehicle control upon incubation with increasing amounts of **1a**. [53]

With the approval from the Committee on the Use of Live Animals for Teaching and Research (The University of Hong Kong), in vivo study showed that intra- peritoneal injection of **1a** would induce tumor apoptosis [53] and inhibit (over 80%) of both cisplatin-sensitive and cisplatin-resistant NPC cells without noticeable systemic side effects (Fig. 8, unpublished work).[53]

As demonstrated by a DNA microarray study, **1a** up-regulated genes that increase apoptosis, stabilize *p53*, and decrease proliferation and down-regulated genes playing roles in angiogenesis, invasion, and metabolism.[55**]**

Although gold in the oxidation state +III in a physiological medium is often easily reduced to gold(I) or gold nanoparticles, the development of chelating ligands with nitrogen donors, cyclometalated structures and dithiocarbamates has opened the way to enable Au (III) complexes to be used for chemotherapeutic purposes. nitrogen donors, cyclometalated structures and dithiocarbamates has opened the way to enable Au (III) complexes to be used for chemotherapeutic purposes [56].

Figure. 8 Tumor reduction of NPC-bearing mice after the **1a** treatment [53].

In vivo studies showed that **1a** at the 0.5 mg kg”1 level significantly prolonged the survival of HCC-bearing rats without causing a significant drop in body weight of the rats and affecting the plasma aspartate aminotransferase level.[55**]**

The mechanisms by which these compounds are able to exert antiproliferative effects are slowly beginning to emerge [56]. Different trends have been highlighted, although details remain very sketchy [56]. Improving the selectivity of the compounds for cancer cells over healthy tissue in order to limit the side effects remains a major challenge, although some promising results have been obtained. More sophisticated synthetic approaches are required to fully utilise the potential of Au (III) complexes for the development of new generations of anticancer drugs.

Conclusion

Platinum (II) and gold (III) complexes represent two key classes of transition-metal anticancer agents. Platinum-based drugs like cisplatin, carboplatin, and oxaliplatin are well-established therapeutics, and their mechanisms of DNA binding and cytotoxicity are well understood. These Pt (II) complexes form stable DNA cross- links that disrupt replication, and they benefit from decades of clinical experience. Their advantages include proven efficacy against various solid tumors and the ability to modify their ligand sphere to adjust potency and toxicity. However, platinum drugs also have significant limitations, including dose-limiting side effects (nephrotoxicity, neurotoxicity, ototoxicity) and development of drug resistance.

Gold (III) complexes offer a complementary approach. Owing to their structural analogy to Pt (II), many Au (III) compounds can engage biological targets in similar ways, yet they also exhibit distinct chemistry. Some Au (III) complexes have shown potent activity against cancer cells, including strains resistant to cisplatin. The advantages of Au (III) complexes include their unique reactivity toward biomolecules and their modularity through ligand design. In particular, Au (III) compounds can exploit diverse mechanisms beyond DNA cross-linking, potentially bypassing platinum resistance pathways. The main challenge with Au [III] complexes is their instability under physiological conditions. Rapid reduction of Au[III] often leads to inactive species or gold nanoparticle formation.

Stability must be engineered through ligand frameworks: strong ó-donating, multidentate ligands and rigid scaffolds are needed to protect Au (III) from reduction. Selectivity is another concern: gold compounds must selectively kill cancer cells while sparing healthy cells to be therapeutically useful. Future research should therefore focus on two fronts. First, the design of ligands and coordination environments that further stabilize Au (III) in vivo is critical. Second, improving the delivery and selectivity of gold complexes is essential. This may involve linking Au (III) complexes to tumor-targeting

molecules or developing prodrug strategies that activate specifically in the tumor microenvironment.

Acknowledgment: - The authors would like to express their sincere gratitude to the **Head of the Department of Chemistry**, Meerut College, Meerut, and the **Principal of Meerut College,** Meerut, for providing the necessary laboratory facilities and a supportive academic environment, which greatly contributed to the successful completion of this research work.

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