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CURRENT METALLODRUGS SUCCESS IN BREAST CANCER TREATMENT

BY

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Abstract

Breast cancer has surpassed lung cancer as the most commonly diagnosed cancer worldwide, posing a serious concern. Given the potential fatality of this disease, effective therapy is crucial. Current treatment options for breast cancer include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Metallodrugs are designed by employing ligand substitution to modify the existing chemical structure or by developing a completely new component with improved safety and cytotoxic profile. Metals have shown promise in combating cancer due to their attractive therapeutic properties and their ability to generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative damage and cellular death. The subsequent paragraphs provide a comprehensive list of recently discovered metal complexes (in vivo/vitro), their mechanism of action against tumors, and the mechanistic details obtained by various researchers. This study focuses on the research conducted by numerous specialists over the past 22 years and provides detailed information on the use of metals as a therapeutic agent in breast cancer treatment. The following review highlights several promising metal-based therapies for the future, as well as the origins, drug development, and ongoing research being conducted and considered for market entry. In summary, this research provides a few important references to new metal-based therapies for cancer treatment, and despite the relatively recent emergence of this treatment approach in the cancer sector, these developing drugs are expected to have several success stories.

Keywords: *breast cancer, metallodrugs, metal complexes, chemotherapy, ruthenium complexes.*

Background

Breast cancer is increasingly being attributed to improper medication therapy. Metallodrugs have a significant function to play in a number of diseases, but primarily in cancer. The aim of the article is to run through the current and past of the development of an metallodrug for the breast cancer treatment with keeping in mind its brighter future. The collection of literature was done from few recognized publishing houses like Springer, Science Direct, Bentham Science, Wiley, Taylor & Francis.

Main Text

1. Introduction

1.1 Breast Cancer

Breast cancer has surpassed lung cancer as the most common malignancy diagnosed worldwide, approximately 2.3 million of new-fangled cases (11.7 percent of all malignancies worldwide) (1). Five to ten percent of those with breast cancer are first identified with advanced or metastatic disease; up to one-third of those with early breast cancer may go on to develop advanced or metastatic sickness (2–4). The 5-year relative survival rate for denovo metastatic breast cancer increased from 18% to 36% between 1992 and 2012, while people with advanced breast cancer are surviving longer on average as a result of better treatment choices (4).

Three types of additional breast cancer subtypes are identified (5):

i) Histological subtypes:

a) Preinvasive
Ductal carcinoma in situ (DCIS), Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral.

b) Invasive
Ductal carcinoma no special type (NST), Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood.

ii) Intrinsic subtypes (PAM50):

a) Basal

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BRCA mutations; TP53 mutations; genetic instability; medullary-like histology poorly differentiated.

b) Claudin low
Largely triple negative; metaplastic.

c) HER2-enriched
HER2-enriched HER2 amplification; GRB7 amplification; PIK3CA mutations; TOP2 and/or MYC amplification; NST, micropapillary histology and pleiomorphic lobular.

d) Luminal B
ESR1 mutations (30–40%) a; Luminal B PI3KCA mutations (40%); ERBB3 and ERBB2 mutations; NST, atypical and micropapillary lobular histology.

e) Luminal A Activation of FOXA1, GATA3, ERS1, XBP1; NST, classic lobular histology and tubular cribriform.

iii) Surrogate intrinsic subtypes:

a) Triple-negative
PR–, HER2–, ER–; high grade; high NST histology; Ki67 index; special type histology (adenoid cystic, secretory, metaplastic and medullary-like); save for a few unique varieties, dismal prognosis.

b) HER2-enriched (non-luminal)
HER2+, PR–, ER–; high grade; NST histology; high Ki67 index; intermediate prognosis; aggressive illness that is responsive to specific treatments.

c) Luminal B-like HER2+
ER+ but less pronounced ER and PR than luminal A-like; HER2+; high Ki67 index; higher grade; pleiomorphic and NST; responds to targeted therapies; intermediate prognosis.

d) Luminal B-like HER2–
ER+ nevertheless PR and ER expression inferior than in luminal A-like; HER2–;high Ki67 index; high-risk GES; higher grade; NST, lobular and micropapillary pleiomorphic histology; transitional prognosis.

e) Luminal A-like
Luminal A-like Sturdily PR+ and ER+; HER2–; low-slung proliferation rates; typically, low grade; low Ki67 index; low-risk GES; NST, classic lobular histology and tubular cribriform; upright prognosis.

All breast cancers arise from the terminal duct lobular units of the collecting duct, which is the functional unit of the breast. Various molecular and histological characteristics have been utilized to develop different classifications, as they have significant therapeutic implications. The most prevalent subtypes of breast cancer are classified by their histological subtypes. Ductal carcinoma, also referred to as "no special type" (NST), and lobular carcinoma are the invasive forms, whereas lobular carcinoma in situ and ductal carcinoma in situ, also known as lobular neoplasia, are the non-invasive precursors of these lesions. The essential subtypes of Sorlie and Perou (6) rely on the PAM50, a list of 50 genes that express themselves, as their foundation (7). The main proteins that are expressed in histology and immunohistochemistry to ascertain the surrogate essential subtypes, which are frequently used in clinical settings, include the progesterone receptor (PR), oestrogen receptor (ER), the proliferation marker Ki67, and human epidermal growth factor receptor 2 (HER2). Tumors that are triple-negative lack the countenance of PR, HER2, and ER. Tumors articulating PR and/or ER are referred to as hormone receptor-positive tumours. The qualities (such proliferation and grade) in green are correlated with the relative location of the boxes. Negative -; positive +. GES stands for gene expression signature. ESR1 mutations are brought on by targeted therapy with aromatase inhibitors. The countenance of normal breast components is an artefact because of the restricted tumour cellularity (5).

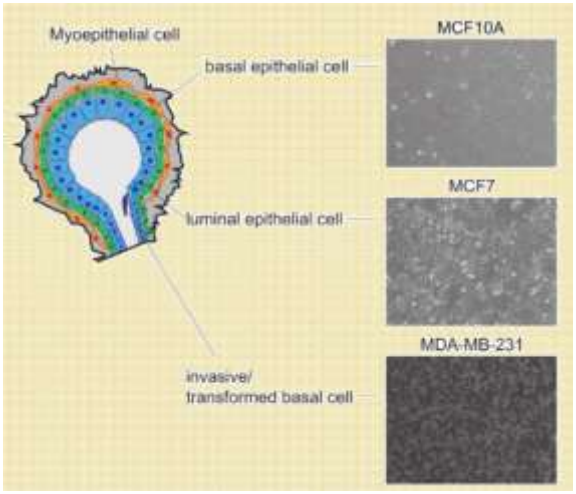

Figure 1 Different types of breast cell line (8)

1.2. Physiology of the Breast

Physically, the breast is an organ with a focus on producing milk (lactation), including secretion, ejection and synthesis of milk (9–11). The lactiferous ducts and tiny saccules known as alveoli make up the breasts' secretory organs. These secretory organs are managed by a complex system of growth factors and hormones that control milk production. The fluctuation of these hormones results in significant histologic changes in the breast throughout pregnancy and the menstrual cycle (11,12).

There are no obvious functional or anatomical distinctions between the male and female breasts before puberty. According to histology, the prepubertal breast in both boys and females is made up of several rudimentary ducts that are circumferentially oriented and converge towards the nipple. Each primitive duct has underdeveloped but possibly secretory acini at the blind end (10).

The female breast undergoes significant change throughout puberty, culminating in a discernible sexual dimorphism. These changes are the result of the breast's unique response to certain common hormonal stimuli. The breast physiology explanation that follows only relates to female breasts (10).

Lactation, which refers to the creation, secretion, and evacuation of milk, is the primary function of the female breast. The female breast is another obvious secondary sexual trait. Oestrogen (oestradiol), which causes the duct system to multiply and branch out as well as the nipples to mature and become more noticeable, is crucial for the development of the

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female breast throughout puberty. But at the ab-areolar extremities of the ducts, oestrogen and progesterone function together and synergistically to promote the formation and proliferation of acini (alveoli). In the breast tissue, a range of paracrine factors, some of them which are stimulatory and others of which are inhibitory, regulate cell division and differentiation. These paracrine regulators include the growth factors insulin-like growth factor B, epidermal growth factors, and transforming growth factors (10).

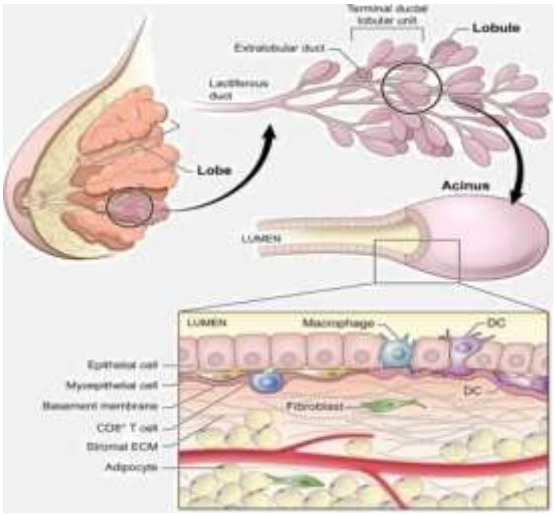

Figure 2: Breast Physiology (13)

2. Breast cancer-related metal complexes with clinical evidence

2.1. Platinum (Pt)

Spanish scientist Antonio de Ulloa received credit for discovering platinum in 1748 (14). With an atomic mass of 195.084, an atomic number of 78, and the symbol Pt, platinum is classified as a transition metal. The term "platina," which means "little silver" in Spanish, is the origin of the name platinum. Inorganic chemistry experts often refer to the compound cis-[PtCl2(NH3)2], also known as cisplatin, as an example of how some inorganic compounds' beneficial health effects were discovered by chance throughout history. In 1960, it was observed that the replication of Escherichia coli was halted in the presence of platinum electrodes (15), and Barnett Rosenberg et al. mistakenly hypothesised that one of the compounds produced from the experimental materials and conditions, [(NH4)2][PtCl6], was the cause of the observed inhibition (16,17). The observation of Escherichia coli replication being affected by platinum electrodes was originally made with the aim of studying the impact of electric fields on mitosis in these bacteria. However, this chance discovery led to the development of cisplatin, which is now a chemotherapeutic drug used to treat cancer in situ. In addition, cisplatin is successfully used in combination treatments to treat metastatic cancer. For example, Franciosi et al. (2011) investigated the effectiveness of cisplatin/etoposide treatment in patients who had undergone radiation therapy for brain metastases from breast cancer, non-small-cell lung carcinoma, and melanoma. The study found that individuals with brain metastases from breast cancer and non-small-cell lung cancer respond well to the cisplatin/etoposide combination treatment (18).

The authors report a small preclinical study in which they investigated the effects of tocilizumab on the effectiveness of cisplatin in a model of triple-negative breast cancer. They found that tocilizumab reduced the process of epithelial-mesenchymal transition (EMT) and increased programmed cell death, or apoptosis, which enhanced the lethal effects of cisplatin both in vitro and in vivo. The study suggests that the combination treatment of tocilizumab and cisplatin may decrease the proliferation of highly aggressive breast cancer cells (19).

Originally known as JM8, carboplatin is a second-generation anticancer medication that is mostly used to treat ovarian cancers but has also shown promise in treating head and neck, cervical, breast, lung, and bladder cancers (20). The low toxicity of carboplatin, which may be caused by the presence of a chelating 1,2-cyclobutanedicarboxylate ring (leaving group) and a particular shape of the ligand, is largely responsible for its efficacious intervention (21).

The statement suggests that the reduction and intracellular changes of both Pt (II) and Pt (IV) complexes can be utilized as opportunities to modify the bioactive ligands and develop them as molecules that can target tumors. In other words, altering these complexes can help in designing ligands that can specifically target cancer cells, making them potential candidates for cancer treatment (22). Barnes et al. developed a Pt(IV)-estrogen combination to sensitise ER(+)-breast cancer cells and overcome cisplatin resistance based on the discovery that estrogen-treated ER(+) breast cancer cells are sensitised to cisplatin (23). The substance's intracellular decrease leads to the release of one equivalent of cisplatin and two equivalents of estrodiol. In addition, the upregulation of the high mobility group protein (HMGB1) occurs as part of its mechanism, which is critical for inhibiting platinum-DNA adduct repair (22,24). Additionally, they have several negative effects.

2.1.1. Pt (II)

Breast cancer therapy study with Pt (II) has several evaluations and investigations, and the review will evaluate some of them.

According to Carmichael research, the vitality of MCF-7 and MDA-MB-231 breast cancer cells was assessed using the Carmichael technique, which used 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (25). MCF-7 and MDA-MB-231 cells were treated for 24 hours with varied doses of the chemicals Pt10 Pt2(3-ethylpyridine)4(berenil)2, Pt11 Pt2(3-butylpyridine)4(berenil)2, and cisplatin. Although cytotoxicity was concentration-dependent in both cell lines, it was more evident in MDA-MB-231 at shorter durations than in MCF-7. They discovered that the chemicals Pt10 and Pt11 reduced the number of viable cells in both oestrogen receptor-positive (MCF-7) and oestrogen receptor-negative (MDA-MB-231) breast cancer cells more than cisplatin. According to the findings of this investigation, the examined Pt10 and Pt11

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have strong impacts that reduce breast cancer cell's capacity to survive, with IC_{50} value after 24h of incubation in MCF-7 and MDA-MB231 breast cancer cells 45 ± 2M and 30 ± 2M for Pt10 and 20 ± M and 11 ± 2M for Pt11, respectively. After 24h of incubation IC_{50} values for the cisplatin alone in MDA-MB-231 and MCF-7 cells were 93 ± 2 and 82 ± 2M, respectively (26).

The anti-growth impact of the platinum (II) complex was further studied using the RTCA system (xCELLigence) for additional investigations in another research. This technique allows for the determination of the individual dosages of the complex that cause cytotoxic, cytostatic, or anti-proliferative effects. The combination was applied 24 hours after the cells were seeded. Both cell lines were cytotoxic at significantly greater dosages of 25 and 50 M. 12.5µM was likewise cytotoxic to MDA-MB-231 cells, however it seems to be cytostatic to MCF-7 cells. The combination had an antiproliferative impact on both cell lines at 6.25µM and lower dosages. The findings showed that MDA-MB-231 cells were somewhat more sensitive than MCF-7 cells, which was consistent with the MTT and ATP viability test results (27). Platinum (II) complexes may have anticancer properties in many cancer types (28–30). Indeed, they discovered that the platinum (II) complex inhibited the proliferation of MCF-7 and MDA-MB-231 human breast cancer cell lines in a dose-dependent way (27).

2.1.2. Pt (IV)

In TNBC cell lines, platinum (IV) coordination compounds with cisplatin and bioactive ligands in axial positions—such as COX- and PD-L1 inhibitors, RAD51-targing moieties, vitamins, DNA-alkylating agents, tumour vascular disrupting agents, and other drugs—have proven to be effective. These compounds can also combine effects on various cellular compartments (31–35).

NSAIDs (indomethacin and ibuprofen) and other cyclooxygenase inhibitor-containing cisplatin conjugates, such as Pt-IBu, have been described by Hey-Hawkins and colleagues (31), on the TNBC MDA-MB-231 cell line, were discovered to be cytotoxic (with complex displaying IC_{50} value in the nanomolar range 0.05 nM, 72 h). However, it was shown that the potency was not primarily caused by COX-2 suppression (31). The biotinylated Pt(IV) conjugates disclosed by Guo, Wang, and colleagues include Pt-Bio-1 (32), exhibited more cytotoxicity than cisplatin (18 ± 2.7 µM, 48 h) on the MDA-MB-231 cell line, but was more selective when tested on healthy MCF a breast cell lines. The authors discussed how platination of the cell and better interactions with DNA upon reduction to Pt (II) species were both enhanced by having one unsubstituted axial ligand (32). Additionally, these authors discussed cisplatin conjugates containing RAD51-targeting moieties, which mediate how sensitive cancer cells are to DNA-damaging substances through homologous recombination. Examples of these compounds include artesunate (PtArt2) (33).

Recently, Guo, Wang, and colleagues reported the discovery of a Pt (IV) combination with a tumour vascular disrupting drug (DMA=5,6-dimethylxantthenone-4-acetic acid) and cisplatin (10, PDMA) (34). MDA-MB-231 TNBC cell lines were shown to be more cytotoxic to a substance than cisplatin (3.3 ± 0.4 µM, 72 h). Compounds with axial ligands have higher lipophilicity and cellular uptake. The substance was discovered to have antimigratory and antiangiogenic characteristics as well as to damage DNA (by increasing expression of the H2AX DNA damage marker). A Tg zebra fish model was used to illustrate the compound's antiangiogenic effects, and it also showed that it was less hazardous than cisplatin in this model (34).

2.2. Palladium (Pd)

In 1802, William Hyde Wollaston discovered palladium, but due to a controversy which arose, the credit of discovery was given to Richard Chenevix (14). The origin of the name came from Pallas (Greek goddess of wisdom), a name given to an asteroid. It is mined from ores of copper, mercury, nickel, and platinum. It is a transition metal, as well as a PGM, with a symbol of Pd, atomic number of 46, and atomic mass of (36). Palladium has medical application in the timely treatment of tuberculosis, but other options were sought due to deleterious drawbacks. further uses for palladium in medicine are their activities as antimicrobial and anticancer agents (14,37). Ahmad et al. synthesized Pd(II) complex, [Pd(PPh3)2(Imt)2Cl2.3.5H2O], where Imt is imidazolidine-2-thione, and screened it against two Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) and two yeasts (Candida albicans and Saccharomyces cerevisiae) (14,37). They came to the conclusion that the yeast test produced substantial activity whereas the antibacterial test only produced modest activity. In order to create four Pt(II), Pt(IV), Pd(II), and Pd(IV) coordination compounds, Bakalova et al. used the carrier ligand 3-amino—tetralonespiro-5′-hydantoin. In vitro tests were performed on all substances using the SKW-3 human tumour cell line. Compared to Pd(II) coordination compounds, the antitumor activity of the Pt(II) coordination compound was stronger, although it was less active than cisplatin (14).

In the case of anticancer research, Elhusseiny and Hassan stated that the complexes were tested against three cell lines (breast carcinoma (MCF-7), colon carcinoma (HCT 116), and liver carcinoma (HEPG2). They also observed that three of the twelve synthesised Pd(II) complexes demonstrated the best efficiency against three cancer cell lines at 10 mg/ml concentration (HCT116, HEPG2, and MCF-7) (14).

Many new mononuclear, dinuclear and multinuclear palladium complexes with reduced cross-resistance to cisplatin, decreased toxicity and high specificity have been developed (38–41). Similar to platinum agents, DNA is also their major target in the cell. The Pd(II) ions are capable of interacting with DNA, thus enabling cross bindings and inhibiting its synthesis as well as inducing apoptosis. Palladium complexes might materialize a concept of tumour targeting which would result in drugs with other spectrum of activity and lack of cross-resistance as compared with platinum drugs (42).

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Two Pd(II)-NHC complexes were studied by Panda et al., including "A," a bis(NHC) complex, and "B," a mixed complex, both of which included pyridine as a characteristic ligand for the active trans platinum complexes (43). The palladium centre was replaced in a trans-geometric fashion in both complexes. With regard to cervical cancer (HeLa), breast cancer (MCF-7) and colon cancer (HCT 116) cell lines, "A" demonstrated more cytotoxicity (from 2- to 20-fold) than cisplatin. Additional research revealed that "A" prevented the multiplication of tumour cells by stopping the cell cycle in the G2 phase and preventing the cell from entering the mitotic phase. This findings revealed that a p53-dependent mechanism led to programmed cell death in the treated cells. These findings together made it abundantly evident that compound "A" followed the same cellular mechanism as cisplatin (42).

Li et al. developed a Pd(II)–NHC complex “C” with higher cytotoxic activities than cisplatin and the corresponding Au(I)–NHC and Ag(I)–NHC complexes against breast cancer cells (MCF-7 and MDA-MB 231) (44). The IC_{50} of “C” (4.50 mM) in MDA-MB 231 cells is 3-fold lower than that of Au(I)–NHC complex 21 (14.22 mM) and approximately 10-fold lower than that of Ag(I)–NHC complex 7 (46.58 mM) and cisplatin (48.43 mM). This finding demonstrated that the antitumor activities of the amino-NHC metal complexes were not solely dependent on molecular hydrophobicity and that activities could be altered by the choice of the metal ion. Interestingly, IC_{50} of the complex displayed similar trends in the estrogen receptor positive (ER+) cell line MCF-7 and estrogen receptor negative (ER-) cell line MDA-MB 231, indicating that the effects on cell viability might be caused by an ER-independent pathway (42).

Chemotherapeutic mechanisms of Pd(II) complexes against TNBC:

DNA damage: Palladium complexes can act as a novel class of metal-based agents that bind covalently to the nitrogen bases of DNA, resulting in DNA fragmentation by hindering an adequate DNA synthesis and RNA transcription from the affected DNA areas. DNA damage occurs through formation of crosslinks, preventing DNA strands from being separated for synthesis or transcription, and inducing mispaired nucleotides, leading to mutations (45). A number of palladium complexes, including "L," "H," "E," "M," "N," "J," and "K," have been shown to alter DNA conformation or break DNA (46).

Cell cycle arrest: It is well accepted that carcinogenesis is associated with cell cycle deregulation and/or overexpression of growth kinases (47). The effects of palladium complexes ("D," "E," and "I") on TNBC cells' cell cycle arrest in G1 or G1/S phase might be either direct or indirect. It has also been noted that cells designated "D" and "E" have the sub-G1peak, which is often associated with dying cells. In fact, DNA damage may cause a cell cycle to be stopped by activating the p53 pathway, which can either start DNA repair or cause apoptosis (46).

Levels of reactive oxygen species rising: Reactive oxygen/nitrogen species (ROS/RNS) are produced during metabolic processes and can interact with biomolecules to cause DNA mutations, oxidation of amino acyl residues in proteins, and lipid peroxidation. These reactions also result in the production of more free radicals, which raises the possibility of mutation (48). ROS production was reported for “F” and “G”. Notwithstanding ROS-induced damage, this can be restored by internal surveillance and repair systems. High ROS levels, however, overwhelm cellular detoxification mechanisms and halt cell proliferation and, after prolonged arrest, cells can die from apoptosis. The decrease in glutathione levels, indicating an increase in the intracellular redox status, was reported for “H” (46).

Table A Palladium complexes and their activity against triple negative breast carcinoma

Group	Complex no.	Complex designation	Cell line	IC_{50}	Target/mode of action	Selectivity toward TNBC	Year and Reference
Derivatives of ethyl diamine	D	3a dichlorido[O,O’-diethyl-(S,S)- ethylenediamine-N,N’-di-2-(4-methyl) pentaneate]palladium(II)	MDA-MB-453	72 h: 3a >200 **µ**M	DNA fragmentation, induction of apoptosis and sub-G1 cell cycle arrest	NA	2014 (49)
Derivatives of biogenic polyamines	L	Pd_2SpmCl_4	MDA-MB-231	72 h: 2.8 **µ**M Ref. drug: cisplatin 3.2 **µ**M	Induction of doublestranded Breaks in DNA (stronger effect than for cisplatin). Interfering with microtubules. Synergism	Tested vs normal human fibroblasts (BJ)	2011 (50)

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					with cisplatin		
	H	Pd_2BENSpm	L56Br-C1	72 h: 0.4 **µ**M	DNA damage. Reduction of GSH and polyamine levels	Tested vs normal breast epithelial cells (MCF-10A)	2013 (51)
Derivatives of benzyl amine/imine	E	[{ClPd(C_6H_4)CH=N(2,6-di-iPr-C_6H_3)}$_2$($mPh_2P(CH_2)_2PPh_2$)]	MDA-MB-231	48 h: 0.193 **µ**M	DNA damage. Intrinsic induction of apoptosis via release of cytochrome c, upregulation of PUMA, Bax and downregulation of Bcl-2. Extrinsic induction of apoptosis via activation of caspase 8. Induction of autophagy and G1 cell cycle arrest. Putative anti-cancer stem cell activity	NA	2015 (52)
Derivatives of pyridine/ pyrazole/imidazole / pyrrol/triazole and their combinations	M	Pd_2Hmtpo	BT-20	Exposure of 2.81 **µ**M for 48 h reduced	DNA fragmentation	NA	2002 (53)
	N	([PdCl(terpy)](sac).2H_2O)	Ehrlich ascites carcinoma MDA-MB-231 (in vivo)	48 h: 46.50 **µ**M In vivo: complex 70% reduction, cisplatin 47% reduction, paclitaxel 59% reduction	Increase of cleaved PARP, caspase 3 activity and pyknotic nuclei	NA	2014 (54)
	F	[Pd(sac)(terpy)](sac).4H_2O	Ehrlich ascites carcinoma MDA-MB-231 (in vivo)	72 h: 0.09 **µ**M In vivo: complex 68% reduction, cisplatin 33%	Disruption of tubules. Apoptosis via DR4 and DR5	NA	2011 [78] (55)

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				reduction, paclitaxel 69% reduction			
	K	19a ([Pd(bpma)(sac)](sac).2H_2O) 19b ([Pd(bpma)Cl](sac).2H_2O)	MDA-MB-231	72 h: 19a 9.3 **µ**M 19b 4.2 **µ**M	Induction of apoptosis via Fas death receptor. Increase of cleaved PARP and caspase 3 activity	NA	2013 [83] (56)
	I	27a [{Pd(2,2'-bipy)Cl}$_2$(**µ**-pz)](ClO]$_4$)$_2$	MDA-MB-231	48 h: 27a 17 **µ**M	Induction of apoptosis and necrosis. G1/S cell cycle arrest	Tested vs normal human fibroblast (MRC-5)	2017 [91] (57)

2.2.1. Pd (II)

A group of cationic palladium (II) compounds with saccharinate and triamine ligands, such as bis(pyridinylmethyl)amine (bmpa) or 2,2':6',2'-terpyridine (terpy), were reported by Ulukaya and colleagues. These compounds were effective against TNBC cell lines and, in some cases, mice models (selected compounds "P"–"K") (35,58,59). The compounds are apoptotic (58). DNA damage (induction of double strand breaks, DNA fragmentation, and change of secondary structure) as well as an increase in cleaved PARP, induction of caspase activity, and pyknotic nuclei are present for compound "O" (35). An in-depth biochemical and proteomic analysis of compound "K" revealed that its mechanism of action involves inducing ROS, DNA damage (primarily by formation of DSBs), and NHEJ was suggested as a potential mechanism of repair. For compound "K," apoptosis was shown to proceed via the DR4 and DR5 genes (35,59).

According to another study by the same researcher, we examined the potential apoptosis-inducing action of the complex at precisely this level, taking into mind that the dose of roughly 3.12 mM is nearly an equal dose to the IC_{50} value. MDA-MB-231 cells were treated for 48 and 72 hours, however there was no change in the levels of the apoptotic marker M30-antigen. It was greatly enhanced in MCF-7 cells with the same treatment, in contrast, demonstrating the complex's ability to cause apoptosis in MCF-7 cells but not MB-MDA-231 cells. The Using agarose gel electrophoresis to find DNA fragmentation and observation of the ladder pattern both supported the conclusion that apoptosis had occurred in the MCF-7 cells (55).

Both kinds of cells were subjected to the growth inhibitory effects of the Pd (II) complex (1,56 - 100 µM), which were dosage and time dependent. But the mammospheres (CSCs, MCF-7s) were only harmed at comparatively higher dosages (25 and 50µ M), indicating their relative tolerance to the substance in comparison to the parental cells (MCF-7 cells). According to the rises in M30 levels and the presence of pyknotic nuclei, both types of cells suffered apoptosis. The greater dosages than those employed for MCF-7 cells were necessary due to the relative resistance that was still present in cancer stem cells (MCF-7s) (60).

2.3. Gold (Au)

In the last few decades, researchers have focused on the study of coated gold nanoparticles. These nanoparticles are intriguing prospects for various biological applications, including the treatment of cancer, due to their optical characteristics, chemical stability, biocompatibility, and size [53] (61). Consequently, recently developed gold-based compounds with anti-cancer potential have been created. Some interesting Au (I) phosphane antitumor compounds have been reported, such as [Au(d2pypp)2]Cl, [Au(PPh3)]Cl, [Au2(dppe)]Cl2, and [Au3(dpmp)]Cl; in addition, a heterometallic compound [(gC5H5)2TiMe(l-mba)Au(PR3)] has been reported, with its mode of action identified as mitochondrial dysfunction or autophagy (62–65).

Bis-[4,5-dichloro-(N-methyl-N'(2-hydroxy-2-phenyl) ethyl-imidazole-2-ylidene)gold(I)][dichloro-gold] (AuL7) is a gold-based compound with potential antimetastatic activity in the breast cancer metastatic cell line MDAMB-231. This substance inhibits topoisomerase II and tubulin polymerization; Apoptosis is brought on by cellular arrest at the G2-M checkpoint, which is also exacerbated by it, as well as by an increase in oxidative stress and caspases (66).

2.3.1. Au (I)

Au(I) complexes' exact mode of action is still unknown, but several studies have suggested that they may cause apoptosis by inhibiting selenium and sulfur-containing enzymes like glutathione reductases, glutathione peroxidases, glutathione-S-transferases, cysteine proteases, thioredoxin reductase (TrxR), and poly (ADPribose) polymerase 1 (PARP-1) (67). In fact, the metal ion Au(I) is a soft metal centre with a significant attraction for soft ligands like thiols of cysteines and thioethers of methionines. It also exhibits a stronger affinity for selenols of selenocysteine residues (68,69). However, multiple X-ray crystallographic investigations

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shown that Au(I) ions may bind solvent-exposed material even when free thiols are present. Moreover, even in the absence of cysteines, methionines, and histidines, Au(I) complexes may bind the Arg and Lys side chains as well as the N-terminal of Ala. For example, the model protein thaumatin binds to Au(NHC)Cl (where NHC = 1-butyl-3-methyl-imidazole-2-ylidene) at the lysine side chains and at the N-terminal tail; the metal binds the protein after releasing the Cl ligand but keeping the NHC fragment (67,70). Due to their great selectivity for thiols, linear Au(I) complexes are potent inhibitors of the Se-free enzyme glutathione reductase (GR) (67).

Those with phosphine, thiosugar, N-heterocyclic carbenes (NHC), alkynyl, and other sulfur-based ligands, such as thiosemicarbazone, are among the most popular Au(I) compounds produced and studied as possible anticancer medicines (67,71).

One study found that, when compared to cisplatin, the two provided chemicals (a,b) exhibit better anti-tumor action on basal-like breast cancer (BLBC):

Cancer cell viability was estimated by MTT assay at 24h treatment using the human MDA-MB-231 cells and the murine A17 cells as models of BLBC (72). Among the tested drugs, only compounds “a” and “b” exhibited a remarkable in vitro anticancer efficacy against both murine and human cell lines, being able to decrease in a dose-dependent manner, cell viability with IC_{50} values at low µM concentrations. compounds “a” and “b” displayed a stronger antineoplastic activity respect to cisplatin. In particular, the response of MDA-MB231 cells to compounds “a” and “b” compared to cisplatin, but was stronger and more rapid in its effects. In fact, compounds “a” and “b” showed IC_{50} values of 19.28 µM and 14.83 µM, respectively, after 24h treatment, whereas cisplatin displayed an IC_{50} value of 50.49 µM only after a 48h treatment. In addition, in vitro screening was completed evaluating the cytotoxicity of the separate moieties of compounds “a” and “b”, corresponding to free azoles (ImH(Cl)2 and ImH(CN)2 for compounds “a” and “b”, respectively), and triphenylphosphane moieties (Ph_3PAuCl and the bare Ph3P). Of note, only Ph3PAuCl Both MDA-MB-231 and A17cells' viability might be reduced by moiety at 24h, with an IC_{50} value of 22.27 µM and 18.29 µM, respectively (73). The anticancer efficacy of compounds “a” and “b” was also confirmed on two other in vitro models of breast cancer: the human BLBC MDA-MB-468 cells and human mammary epithelial HMLE cells overexpressing FoxQ1, characterized by stemness traits and chemoresistance (73,74). HMLE/FoxQ1 line revealed to be the most responsive cells to both compound 1 and 2, displaying IC_{50} values of 7.41 µM and 9.27 µM at 24h, respectively. Of note, cisplatin was less effective than compounds “a” and “b” also in HMLE/FoxQ1 and MDA-MB-468 cells, inducing a significant decrease in cellular viability only after 48h treatment with an IC_{50} value of 34.12 µM in HMLE/FoxQ1, and after 24h treatment with an IC_{50} value of 32.50 µM in MDA-MB468 cells (73).

Table B IC50 Values of Compounds 1−2, cisplatin on MDA-MB-231 and HMLE/FOXQ1

Compound	Cell Line	Time	IC_{50} Mean ± SD[a] [µM]	Reference
Compound “a”	MDA-MB-231	24h	19.28 ± 1.06	(73)
	HMLE/ FoxQ1	24h	7.41 ± 1.06	
Compound “b”	MDA-MB-231	24h	14.83 ± 1.05	
	HMLE/ FoxQ1	24h	9.27 ± 1.06	
Cisplatin	MDA-MB-231	48h	50.49 ± 2	
	HMLE/ FoxQ1	48h	34.12 ± 2.17	
[a]SD: standard deviation.				

1.2.1. Au (III)

UBIQUITIN-PROTEASOME PATHWAY (2010 study)

The ubiquitin-proteasome pathway plays a crucial role in maintaining cellular homeostatic function by selectively degrading proteins involved in critical cellular functions. These include selective degradation of oxidatively damaged, mutated, or misfolded proteins, as well as those involved in cell proliferation, cell cycle progression, and apoptosis (75). Proteins destined for degradation are first tagged with a chain of ubiquitin molecules by a multi-enzymatic system consisting of Ub-activating (E1), Ubconjugating (E2), and Ub-ligating (E3) enzymes (76). The ubiquitin-tagged protein is then translocated to the 26S proteasome where it undergoes protein degradation, and the ubiquitin molecules are subsequently recycled. The 20S proteasome constitutes the proteolytic core of the 26S proteasome complex and mediates at least three distinct enzymatic activities, which function as a catalytic machine. These activities include the chymotrypsin-like, trypsin-like, and peptidylglutamyl peptide hydrolyzing-like (PGPH) activities (22).

The anticancer activity of gold coordination compounds has been studied in order to produce a stronger cytotoxicity profile with a wider spectrum of activity than that of platinum-based compounds (22,77). The inquiry into gold-protein interactions was prompted by studies that revealed interactions of gold(III) complexes with DNA, the preferred target of platinum, did not present a suitable binding mechanism (22). The exploration of gold compounds as possible anticancer drugs resulted from the discovery that gold(III) is isoelectronic to platinum(II) and that tetracoordinate gold(III) complexes are in square-planar geometries similar to cisplatin (77). A gold(III) dithiocarbamate derivative known as Au(DMDT)Br2 has been shown in laboratory studies to be a molecular target for the

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proteasome. For the first time, we demonstrated that the highly metastatic MDA-MB-231 breast cancer cells' chymotrypsin-like activity is inhibited by this gold(III) dithiocarbamate analogue in a purified rabbit 20S proteasome (IC50 = 7.4 mol/L) and 26S proteasome (141). Apoptosis is induced and proteasome target protein p27 accumulates when proteasomal activity is inhibited (78). Additional research on the mechanisms underlying two new gold dithiocarbamate derivatives, (AUL12) with a trivalent oxidation state and (AUL15) with a monovalent oxidation state, which differ in the metal's oxidation state. The chymotrypsin-like activity of isolated 20S and 26S proteasome was shown to be inhibited by both types of gold dithiocarbamate, although at dramatically different amounts. This led to an accumulation of ubiquitinated proteins, proteasome target proteins, and the triggering of cell death (22).

Two gold(III) complexes, square-planar [Au(DPP)Cl2]+ - Complex 1 and distorted square-pyramidal [Au(DMP)Cl3] Complex 2, have been recently (2022) studied. Apoptosis was triggered from the mitochondria in MDA-MB-231 cells using Complex 2 (where DPP=4,7-diphenyl-1,10-phenanthroline and DMP=2,9-dimethyl-1,10-phenanthroline). This was because there was an imbalance in the expression of pro- and anti-apoptotic Bcl-2 family members, and caspase 9 was activated. Comparing Complex 1 with Complex 2, Complex 1 has more activity, which is consistent with its structural properties (79).

1.3. Silver (Ag)

For many years, silver complexes were utilised as antibacterial agents, and they are presently used as antiseptics (42). Some of them also showed in vivo and in vitro anticancer activity. Some forms of cancer have been shown to be resistant to the anticancer effects of silver complexes made from coumarin, and silver carboxylate dimers have similar properties (80). Additionally, a new hydrogen-bonded bimetallic supramolecular coordination polymer [SnMe3(bpe)] and several silver complexes with phosphine ligands were able to inhibit cisplatin-resistant cell lines. [Ag(CN)2] Specific in vivo and in vitro anticancer effects of 2H2O were observed (81). The release of Ag+ ions into the environment, which then infiltrate cell membranes and interfere with their function, appears to be the common mechanism of action for all silver complexes. The major drawback of current silver medications, such as silver sulfadiazine, is that they rapidly lose their effectiveness as a result of the Ag+ ions' fast release. In order to limit the rapid release of silver ions, it is crucial for silver complexes to have ligands that tightly coordinate with the silver. Ag-NHC complexes were used as part of a really clever technique to get around these challenges (42).

1.3.1. Ag (I)

On the TNBC cells MDA-MB-157 and MDA-MB-231, considerable cytotoxicity has been reported for silver (I) compounds with N-heterocyclic carbene ligands generated from 4,5-dichloro-1H-imidazole or 4,5-diarylimidazole, respectively (42).

1.3.2. Ag N-heterocyclic carbene complexes

Youngs et al. described a series of Ag–NHC complexes derived from 4,5-dichloro-1H-imidazole (82). All complexes exhibited cytotoxic activity against ovarian (OVCAR-3) and breast (MB157) cancer cells in vitro (42).

Willans et al. created a range of monodentate, bidentate, and macrocyclic cationic Ag-bis(NHC) complexes with cytotoxicity on par with cisplatin. In MCF-7 and DLD-1 cell lines, complexes containing bidentate ligands were more active than those with monodentate and macrocyclic ligands. The pace at which silver salt is released appears to have a significant impact in the stability of the complex. Since the maximum concentration at which these compounds were tested, 100 mM for AgBr, AgPF6, and imidazolium salts utilised for comparison, the synergistic impact of both the silver centre and the NHC ligand definitely plays a role in the cytotoxicity of silver NHCs (83).

Schobert et al. coupled silver fragment with N-methyl-4,5-diarylimidazolium salts, which were modelled after the naturally occurring anticancer medication combretastatin A-4 and shown potential antitumor effects (84). These silver complexes were less cytotoxic than the comparable Au(I)-NHC complexes but nevertheless had notable antiproliferative effects in the chosen cell types. Additionally, the p-ethoxy group (complex a) replaced the p-methoxy group (complex b), which resulted in unpredictable changes to the activity of the silver complexes. Results of cytotoxicity tests on breast cancer (MCF-7 and MDA-MB 231) and colon (HT-29) carcinoma cells showed that the activity of the silver complexes was regulated by the substituents at the 4,5-standing phenyl rings. In comparison to the fluoro- and methoxy-substituted complexes, the 4-OH substituted complex was less active. The most active compound, bromo[1,3-diethyl-4,5-bis(4-fluorophenyl)imidazol-2-ylidene] silver(I), had activity levels that were equivalent to cisplatin against HT-29 cells but somewhat lower against MCF-7 cells and higher against MDA-MB 231 cells. These targets may be ruled out as being implicated in the mode of action because they were only sporadic active at the ER, COX enzymes, and DNA (42).

2.4. Copper (Cu)

Being a necessary micronutrient and a crucial cofactor for several metalloenzymes involved in mitochondrial metabolism (cytochrome c oxidase), or cellular radical detoxification against reactive oxygen species (ROS), copper plays vital roles in several cellular processes (superoxide dismutase) (85). For endothelial cells to proliferate and migrate and for angiogenesis to occur, copper is necessary (86). The development, invasion, and metastasis of tumour cells depend on the complicated process known as angiogenesis (87). It has been established that the growth of new blood vessels is necessary for tumours to grow larger than 1-2 mm^3. Studies conducted in vitro have demonstrated that copper stimulates endothelial cell growth and migration, acting as a key angiogenic effector (88). The idea of employing copper chelators in antiangiogenic therapy as a

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kind of cancer treatment has attracted a lot of interest because of research showing how important angiogenesis and copper are in the growth of tumours (86). Increased copper promotes metastasis and tumour development. It is found in a number of lung, breast, prostate, colon, and brain cancers and acts as a prognostic marker for the illness. The development of copper complexes (CuC) as anticancer medicines was sparked by the divergent reactions of normal and malignant cells to copper. Many discovered CuC exhibit great cytotoxicity and effective anticancer activity and contain various sets of S, O, or N ligands (89). The anticancer properties of copper medicines are mediated by many mechanisms. They have chelating properties, interact with endogenous copper, and sequester it, lowering the amount of copper that is available for tumour development and angiogenesis (90). Ionophores, on the other hand, cause cytotoxicity, intracellular copper buildup, and the activation of the apoptosis inhibitor factor (XIAP) (86). Other CuC are proteasome inhibitors (86). Clinical trials are currently being conducted for a number of CuC, including a number of copper/disulfiram-based drug combinations for therapy and as diagnostic tools (metastatic breast cancer and germ cell tumour), a number of casiopenas compounds and elesclomol (leukaemia), and thiosemicarbazone-based copper complexes labelled with a radioactive isotope for positron emission tomography imaging of hypoxia (in head and neck cancers) (91).

2.5. Ruthenium (Ru)

Ruthenium, symbol Ru, is a d-block transition metal, PGM, with the atomic number 44 and mass number 101.0 (92). Ruthenium is the sole element in Group 8 with two electrons in the outermost shell. It has eight oxidation states, the most frequent of which are +2, +3, and +4. In 1808, Polish scientist Jedrzej Sniadecki found ruthenium in South America and dubbed it "vestium" after the planet Vesta (92). Due to the failure to validate Jedrzej Sniadecki's finding, Gottfried W. Osann, a Russian scientist, found ruthenium in 1928. Karl Karlovich Klaus (Carl Ernst Claus), another Russian scientist, discovered ruthenium a second time in 1944, also owing to the inability to confirm Gottfried W. Osann's discovery, which could be validated. As a result, authorities referred to him as the discoverer. The name is derived from the Greek word "Ruthenia," which means "Russia" (14).

2.5.1. Arene Ru(II) complexes with N,N-chelating ligands

Aliphatic diamine, aromatic diamine, and pyridine derivatives are examples of common N,N-chelating ligands. Sadler has thoroughly investigated arene ruthenium compounds including ethylenediamine (en) chelating ligands (93). Variation in the leaving group, the N,N-chelating ligand, and the arene ring, according to Sadler's group, can have a considerable influence on chemical and biological activity (93). Montani et al. investigated 4e's in vivo anticancer efficacy and discovered that it significantly reduced the development of A17 triple negative breast cells implanted into mice (94). Because of its high hydrosolubility, 4e was swiftly removed from the liver, kidney, and circulation, and it had remarkable therapeutic effectiveness with little side effects. 4e induced a considerable decrease in the number of tumor-infiltrating regulatory T cells, according to immunohistological tests.

Chow et al. used high-throughput screening to create a more effective arene Ru(II) molecule, when compared to cisplatin. Compound had IC_{50} values in the micromolar range against A2780, A2780cisR, MCF7, HCT116, and SW480 cells. The water-soluble and stable half-sandwich arene Ru(II) Schiff-base (RAS) complexes were also found to induce non-apoptotic programmed cell death (PCD) via the ER stress pathway. Despite minor structural differences, the mechanisms of action of the two complexes were considerably different. A compound caused ROS-mediated ER stress, but other compound had no effect on ROS. When compared to therapeutic medications like oxaliplatin, these two complexes were more effective against apoptosis-resistant cells. This study lays the groundwork for targeting ER stress regulation with Ru(II) complexes to circumvent apoptosis resistance (95).

2.5.2. Ru (III)

Although this oxidation state has the potential to produce prodrugs, it is rarely researched due to the relatively inert nature of ruthenium (III) complexes. While ruthenium (III) compounds NAMI-A and KP1019/KP1339 have passed phase clinical studies in other cancer types, it is still unclear if they are effective against TNBC. When compared to the control line HBL-100, whole transcriptome analysis of NAMI-A in MDA-MB-231 cells demonstrated choosing the TNBC cell line with preference, with early response genes associated with direct or indirect roles in metastasis, cellular invasion, cytoskeleton remodelling, and cell cycle regulation being involved. In the aforementioned research by Amici and coworkers, NAMI-A demonstrated tumour decrease in vivo (approximately 28% compared to control), although showing essentially minimal cytotoxicity in the same TNBC cell line (IC_{50}= 840.21±0.03 M, 72 h). Although its salt counterpart KP1339 did not exhibit this activity, KP1019 showed significantly stronger cytotoxicity in MDA-MB-231 cells (IC_{50}= 0.847±0.22 M, 24 h), resistance to detachment after treatment, inhibition of MMP2/MMP9 activity, and antimigratory and anti-invasion capabilities. (96,97).

Following encapsulation, there was an increase in cytotoxicity (IC50 = >250 M Azi-Ru, IC_{50} = 12.1±3 HoThyRu/DOTAP, 48 h), and autophagic cell death was seen after treatment with rapamycin and verified by increased expression of autophagosome-related proteins LC3I and LC3-II. Additionally, the in vivo effectiveness of this nanosystem was examined in MCF-7 xenografted athymic nude mice dosed with 15 mg/kg once weekly throughout a 28-day trial, which revealed a substantial reduction in tumour weight and volume with HoThyRu/DOTAP therapy and no evidence of toxicity. (35).

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2.5.3. Arene Ru (II) complexes with N,O-, O,O- and C,N-ligands

Tetrahydroisoquinoline, a few amino acid ligands, and the O,O-ligands are typical b-diketonate and pyrone ligands. These ligands all act as N,O-chelating ligands. In the human cancer cell lines MCF-7, A549, and MDAMB-231, Chelopo et al. evaluated the anticancer effectiveness of several arene Ru(II) complexes containing 1,2,3,4-tetrahydroisoquinoline amino alcohol ligands. Only MCF-7 cells were somewhat responsive to these complexes, with the lowest IC_{50} value for a complex being 34 mM.

Frik et al. created a number of iminophosphorane Ru(II) complexes that are water soluble. In various human cancer cell lines, it was discovered that the majority of the complexes were more cytotoxic than cisplatin. After 28 days of therapy, the most efficient compound, 6k, led to a 56% reduction in tumour growth in mice receiving xenografted breast cancer MDA-MB-231 cells while exhibiting little systemic toxicity (14 doses of 5 mg kg-1, every other day). Pharmacokinetic investigations showed that 6k arrived quickly in plasma and was highly absorbed in breast tumour tissues as opposed to kidney and liver tissues. According to mechanistic investigations, this combination did not bind with DNA or block the protease cathepsin B; instead, it mostly caused cell death by conventional or caspase-dependent apoptosis, independent of p53. Lord et al. created Ru(II) complexes with N,O-ligands. In the HT-29 and MCF-7 cell lines, the majority of the complexes had cytotoxic effects (95,98).

2.5.4. Ru (II)–silica composites

Silica has long been employed as a nanocarrier for medication delivery in medicinal applications (95,99). Silica nanoparticles are non-toxic to cells and endocytose easily in acidic liposomes. These nanoparticles are a suitable nanocarrier for Ru(II) complexes and other medications due to their release in certain pH conditions, photon activation, redox activation, and tumour targeting. Frasconi and colleagues created ruthenium-silica nanoparticles with improved cellular uptake and photoactivation. By coordinating the monodentate ligand (3-isocyanato-propylethoxysilane with 4-(aminomethyl)-benzonitrile), the Ru(II) complex was covalently bonded to the mesoporous silica nanoparticles (MSNPs) to create MSNPs2. The MSNPs2 cellular absorption was quick, and the ruthenium complexes were promptly released and converted into a cytotoxic aqua complex that formed monoadducts with DNA following light irradiation. Furthermore, the MSNPs2 had an 82% absorption efficiency and a 35% release efficiency when loading paclitaxel. Cytotoxicity tests revealed that empty MSNPs2 exhibited no cytotoxicity against MDAMB-231 cells. Light activation, on the other hand, greatly increased the cytotoxicity of docetaxel-loaded MSNPs2 in MDAMB-468 and MDAMB-231 breast cancer cell lines but had no effect on the cytotoxicity of free paclitaxel (95).

2.5.5. RM175

Sadler pioneered the use of diamine-based Ru(II)-arenes as an organometallic anticancer agent. Coordination of an inert bidentate 1,2-ethylene diamine (en) moiety and one chlorido leaving group to the metal-arene core resulted in, for example, [(Z6 -arene)RuCl(en)]PF6, where arene is a substituted arene (100).

RM175 and its homologue HC11, [RuCl(en)(Z6 -tetrahydroanthracene)]PF6, were studied in a panel of 13 cell lines in 2006 (101). The two metallodrugs were especially active in breast cancer and non-small cell lung cancer cell lines, with HC11 showing the most activity in vitro. Both drugs significantly delayed tumour development in the A549 in vivo xenograft model following i.p. single-dose treatment (101). RM175 has also been studied in vivo for its antimetastatic activity in MCa mammary cancer xenograft models. RM175 was found to inhibit the development of both primary and secondary tumours at a daily dosage of 10 mg kg-1 for 5 days. Furthermore, MDA-MB-231 cells were prevented from detaching from the main tumour. Matrix metalloproteinase 2 inhibition (MMP-2). The reduction of matrix metalloproteinase 2 (MMP-2) production highlighted RM175's potential antimetastatic efficacy (100).

2.5.6. FITExP analysis of RAPTA-T

The effects of RAPTA-T were evaluated in a series of experiments that simulate the main steps of metastatic progression in vitro, i.e., detachment from the primary tumor; degradation of the extracellular matrix; and migration, invasion, and adherence to a new organ. The behavior of highly invasive breast cancer MDA-MB-231 cells was compared to that of MCF-7 cells (which are tumorigenic but not invasive) and nontumorigenic mammary epithelial HBL-100 cells (102). According to the findings, RAPTA-T is able to suppress each of these processes, and its effects are more obvious when trials are carried out on the highly invasive MDA-MB231 cells as opposed to the non-invasive MCF-7 cells or the non-tumorigenic HBL-100 cells. Interestingly, the results of tests to determine the interaction between tumor cells and extracellular matrix components might suggest that this ruthenium compound exerts its activity by interacting with cell surface molecules. Notably, in this context there was a report on the in vitro inhibitory effects of a series of RAPTA compounds on cathepsin B, a lysosomal cysteine protease of the papain family, which is involved in metabolic processes and has been implicated in tumor progression and metastasis (103).

As previously reported, the ruthenium(II) complex, RAPTA-T, is effective against primary and metastatic cancers at high dosages and at low levels when combined with other medications. Additionally, MCF-7 and MDA-MB-231 breast cancer cells are more significantly affected by RAPTA-actions T's than are normal HBL-100 cells generated from breast (102). Using untreated cells as well as paclitaxel and cisplatin-treated cells as controls, FITExP analysis of the proteins recovered from RAPTA-T treated MDA-MB-231 and MCF-7 cells was carried out. The protein is made up of PLD3, an enzyme belonging to the phospholipase D (PLD) family. Membrane phospholipids are hydrolyzed by this family of enzymes57. PLD3 is a poorly characterised protein

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that is not yet connected to the development of cancer. However, its transcript variations PLD1 and PLD2 have been demonstrated to be implicated in the growth of metastatic breast cancers58, and isoform-selective inhibitors of certain PLDs have been shown to alter invasiveness in metastatic breast cancer models (104,105).

2.5.7. FITExP analysis of RAPTA-EA

RAPTA-EA is made up of the same ruthenium(II) arene fragment as RAPTA-T, but with an ethacrynic acid (EA) moiety attached to the arene ring. EA is a glutathione transferase (GST) inhibitor, which is important in the elimination of foreign chemicals such as cancer chemotherapeutic agents, and the drug was developed to overcome GST-based resistance. Notably, GSTP1 is often overexpressed in solid tumours after anti-cancer medication exposure. RAPTA-EA inhibits GST more effectively in vitro than EA alone and produces substantially greater differential cytotoxicity in breast cancer cell lines than basic RAPTA-type complexes (105,106).

3. Conclusion

We discussed the numerous platinum, palladium, silver, iridium, osmium, iron, rhenium, zinc, copper, ruthenium and -gold based metal medicines' mechanisms of action in this review study. Apoptosis and cell viability impacts, cell cycle arrest, cytoskeleton changes, angiogenesis suppression, and DNA damage are a scarce of these pathways. Due to their ability to block signalling pathways involved in a variety of features of cancer development, such as tumour growth, angiogenesis, and metastasis, the available data on metallodrugs provide credence to the concept that they may act as chemotherapeutic agents. In the 1970s, cisplatin took the lead as an anticancer metallodrug. The development of several substitutes in the form of metallodrugs was necessary since cisplatin's numerous adverse effects would cause the treatment to be discontinued. Since then, several well-known medications have demonstrated their own unique mechanisms of action, such as platinum, which demonstrated the value of combining many medications for successful therapy. Multiple components of the ruthenium complexes, including RAPTA, NAMi-A, and KP1019, have the ability to bind proteins, causing Mitochondrial apoptosis and ultimately cell death. These components also block tumour cell invasion and reduce tumour metastasis by decreasing the release of MMP-2/9 from the extracellular matrix, which, in turn, prevents MDA-MB-231 breast cancer cells from migrating and invading respectively. Cancer must be completely eradicated as soon as feasible since it is a devastating lethal illness that significantly lowers the social and economic standing of its sufferers. In recent years, there has been a lot of global study on the creation of metal complexes for the treatment of cancer. Many scientists have worked in the field of inorganic medical chemistry to produce such medications using metallodrugs as well as drug combinations in order to meet the need.

Unquestionably, additional study on the existing metallodrugs or perhaps the creation of novel metal drugs is still required.

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