Review Article

Cisplatin and Nano-Particle Formulations of Cisplatin For Cancer Therapy: A Review

ABSTRACT

Cisplatin (cis-(diammine)dichloridoplatinum(II)) is the first platinum-based compound approved by the United States Food and Drug Administration (FDA) (U.S.). This is a first-line chemotherapeutic treatment used alone or combined with other anticancer drugs to treat a broad spectrum of malignancies, with cisplatin-based nano-formulations currently in clinical studies. Cisplatin has several drawbacks, including low aqueous solubility, drug resistance, and toxicity, all of which can be addressed by encapsulating the drug in Nemours nanocarriers. The various nano-delivery technologies developed for Cisplatin are covered in vast literature from different electronic databases. This review focuses on comparative findings over the recent advancements, developments, innovations, and updated literature for various CDDP nano-carrier systems.

Keywords- Cancer, Cisplatin, Nano-technology, Nano-formulation, Food, and Drug Administration.

INTRODUCTION

Cervical cancer is the second-highest prevalent cancerous cancer in women worldwide, and it poses a significant health risk to women. Cervical cancer is thought to be caused by a persistent infection with the high-risk human papillomavirus (HPV) (1,2). The established etiology has aided in developing and implementing a comprehensive cervical cancer prevention and control system.

In 1846, cervix cancer was the most often observed malignant in western Europe (3), and it was first linked to smegma in the 1940s and 1950s (3). Almost 1/3 of all deaths were reported in Paris. In most cases, the cervix was considered the primary source. Several etiological ideas in popularity now were addressed then. Many authors have reported the relative infrequency of cervical cancer among Jewish women. According to these historical observations, it could be induced by a sexually transmitted agent (4-5).

The possible involvement of husband circumcision was not taken seriously until 1935. More recent studies of this kind were inconclusive. A definite reduction in the death rate from cervical cancer has been evident since 1950. The concurrent rise in incidence is accounted for by the more numerous in situ cases found through cytologic screening. Non-white women in America above age 60 and the elderly in England and Wales have not shown equally improved rates(5). The hypothesis that the genital strain of the herpes simplex virus (HSV-2), a venereal transmitted virus, is associated with cervical cancer has been advanced, and much new evidence has recently been reported (3-6).

Traditional "Pap smears, visual inspection with acetic acid and Lugol's iodine (VIA/VILI), liquid-based cytology (LBC), and HPV testing are the most prevalent cervical cancer screening treatments' (7). Pap smear has drastically reduced the disease burden of cervical cancer in industrialized countries, particularly in the United States, since the 1950s (7-8). Traditional Pap smear accuracy is affected by the degree of the cytological room, competent technicians, sample procedure, slide quality, dyeing capabilities, and cytological personnel experience (7-9). In wealthy countries with high-quality experimental circumstances and technical capabilities, cytology can have a sensitivity of up to 80%. In places when resources are few, it can be as low as 30%. (7).

However, various studies have described that treatment for cervical cancer is determined by several parameters, including the patient's age, illness stage, histological type of tumor, regional and distant metastases, degree of tumor differentiation (grade-G), primary lesion size, primary tumor development

pattern, and overall health. Surgery, radiation, and hormone chemotherapy are the three treatment techniques used today (10).

Nonetheless, the first two modes, alone or in combination, dominate. In pre-invasive (Ca In-situ) and microinvasive stage (stage Ia) cervical cancer, Surgery is employed as the sole treatment option. In the Ib and IIa stages, Surgery and radiation are combined, but only radiation is used in the IIb, IIIa, IIIb, and IVa stages. In stage IVb, (cervical cancer with distant metastases) are utilized Chemotherapy and locoregional radiotherapy (10). On the other hand, for cancerous patients with early-stage cervical cancer and locally advanced cervical cancer who have access to conventional treatments, including Surgery, Chemotherapy, or radiotherapy (R.T.), there is no standard treatment for patients with metastatic cervical cancer because of its heterogeneous manifestations (10).

The HPV vaccine was developed parallel by researchers at Georgetown University Medical Center, the University of Rochester, the University of Queensland in Australia, and the United States, beginning in the mid-1980s. In 2006, the National Cancer Institute (NCI) reported that the U.S. The first preventive HPV vaccine, marketed by Merck & Co. as Gardasil, was approved by the Food and Drug Administration (FDA) (7). With the support of the World Health Assembly, the World Health Organization announced a strategy to eliminate cervical cancer by 2050 in November 2020. The plan calls for 90 percent of girls to be vaccinated by the age of 15, 70 percent of women to be screened by the age of 35 and again by the age of 45, and 90 percent of women with cervical illness to be treated (11).

Chemotherapy is the intravenous delivery of anticancer agents circulating throughout the body and eliminating tumor cells (12-13). Chemotherapy is still the first-line therapeutic option for advanced NSCLC (IIIb and IV). According to a 2016 study, nearly 53% of patients with Stage IIIb or IV NSCLC received Chemotherapy with or without radiation therapy. However, the relatively protracted premalignant phase of cervical carcinogenesis (five to ten years) provides significant potential for conservative intervention and a big window for chemoprevention or immunization to affect disease progression (12-15). Not only is the cervix an appropriate, accessible organ for chemoprevention studies, but it is also an ideal organ for studying squamous carcinogenesis. Cervical lesions are easily accessible and can be monitored safely with Pap smears and colposcopy, complemented with relevant biomarkers. Cervical biomarkers under investigation include proliferation markers (PCNA), regulatory

markers (ras, myc, p53, retinoic acid receptors, spermidine/spermine ratios), differentiation markers (involucrin, cornified, keratins), and signs of genetic instability (chromosome polysomy)((16).

Numerous single and combined medication regimens have also been clinically evaluated to achieve the best therapeutic efficacy possible. Platinum medicines such as Cisplatin and carboplatin, as well as platinum doublets such as cisplatin/gemcitabine, cisplatin/pemetrexed, pemetrexed/carboplatin, and emcitabine/carboplatin, are frequently suggested chemotherapeutic regimens (Table-1) (17). Pemetrexed, an antifolate, is only licensed to treat non-squamous carcinomas.

Additionally, molecular targets such as bevacizumab, which inhibited VEGF to paclitaxel/carboplatin, improved overall patient survival and was thus authorized to treat non-squamous carcinomas. Other clinical trials combining bevacizumab with other platinum doublets, on the other hand, have seen evidence of increased toxicity. Cetuximab, another monoclonal antibody directed against the epidermal growth factor receptor (EGFR), did not enhance patient outcomes and, as a result, has been a limited effect on cervical cancer (12-17). Chemotherapy has several drawbacks, most notably damage to healthy tissues. For example, platinum-based medicines containing Cisplatin have severe dose-limiting adverse effects such as nephrotoxicity, cardiotoxicity, peripheral neuropathy, and anemia. Apart from these disadvantages, Chemotherapy can induce exhaustion, hair loss, and nausea. These constraints significantly restrict the dose delivered to the patient, reducing the medications' therapeutic efficacy (11-18).

Another significant disadvantage of Chemotherapy is the hydrophobic nature of chemotherapeutic agents, which restricts their administration to low concentrations and reduces absorption (15). Additionally, chemo-resistance in cancer cells contributes to the drug's lack of efficacy (16). As a result, there is a critical need to optimize the administration of chemotherapeutic medications and increase their therapeutic effectiveness while reducing off-target pharmacological side effects (11-14).

As a result, the current research focuses on comparing Cisplatin (an anticancer drug) and nano-formulations-cisplatin load nano-anticancer drug, improving therapeutic response, and numerous different cancer resistance tactics. Novel approaches to aggressive cervical cancer treatment are expected to reduce side effects, toxicity, and the frequency with which current medications are administered in the future and conquer MDR and increase survival rates.

Table-1 shows the different treatment-based regimens of cervical cancer according to WHO guidelines.

First-line novel agent	Second-line novel agent	
Platinum-based	Bevacizumab	Imatinib
Cisplatin-based	Lapatinib	Temsirolimus
Carboplatin + paclitaxel	Pazopanib	Cetuximab
Carboplatin + bevacizumab + paclitaxel	Cisplatin – cetuximab	Topotecan
Carboplatin based	Erlotinib	Gemcitabine
Docetaxel based	Gefitinib	Ifosfamide

CISPLATIN

Cis-diamminedichloro platinum (CDDP, henceforth Cisplatin) is an intravenous chemotherapy medication used to treat "Testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancer, esophageal cancer, lung cancer, mesothelioma, brain cancer, and neuroblastoma" (18). Moreover, Cisplatin is a highly effective treatment for testicular cancer, with cure rates rising from 10% to 85% since its introduction (19). Cisplatin is also used in Auger treatment (20). Several studies reported that platinum-based antineoplastic therapy is attached to DNA and prevents replication (21). While these drugs are associated with severe side effects like numbness, difficulty walking, allergic reactions, electrolyte difficulties, heart disease, bone marrow suppression, hearing problems, kidney damage, and vomiting (22). If used during gestation, one significant hazardous effect can also harm the fetus (22).

Miessler and Tarr had defined the molecular structure of Cisplatin. The square planar coordination complex cis-[Pt $(NH_3)_2Cl_2$] as cisplatin (23)[:286–8](24)[:689] The cis isomer has two identical ligands in neighboring locations, as indicated by the prefix cis.:550 This molecule's systematic chemical name is cis–diamminedichloroplatinum, (23):286 where ammine with two m's denotes an ammonia (NH_3) ligand rather than an organic amine with one m. (23)[:284]

In 1965, Barnett Rosenberg (Biophysics researcher at Michigan State University (MSU) discovered Cisplatin during his experiment. During his research, he found that microscopic images of dividing cells resembled the pattern of iron shavings exposed to a magnetic field and implied that an electrical area might also influence cell division. However, the studies reports had declared that platinum has no biological records, so they used platinum electrodes in a solution containing the standard laboratory bacteria "*E. coil" i*n their experiment (25). Further, the bacterial cells were immobile and did not divide as soon as the current was turned on, yet they continued to grow to 300 times their average length and began to separate again after the power was turned off. The electrical field appeared to be in charge of "cell division." "Dr. Rosenberg and his colleagues were unaware of what they had uncovered, and then they could have found a way to control cell proliferation with electrical currents" (26-29). In addition, they had spent two years finding the reason for the dramatic effect. However, finally, they recognized it had nothing to do with electricity. The platinum compound emitted by the electrodes, not the electric field, prevented cell division. He will be back in two years with "**CISPLATINE"** (30-32).

Even though "Dr. Rosenberg" has stated that Cisplatin would similarly impede cell division in malignancies after multiple experimental studies, it was declared highly toxic of Cisplatin. Its large quantity was causing kidney damage so through experiment, they concluded that animal models could tolerate low dosages. After the investigation, it was clear that Cisplatin can decline the number of malignant cells (29-32).

'In 1978, the United States approved cisplatin for cancer treatment after long-term research and subsequent research projects funded for developing different anticancer effects of cisplatin analogs such as carboplatin, oxaliplatin, and satraplatin'. Still, the investigation continues to resolve or reduce the toxicity of the substance. Generally, Cisplatin affects the DNA repair process (figure-1) because cancer cells typically have defects in their DNA repair mechanism (33-35).

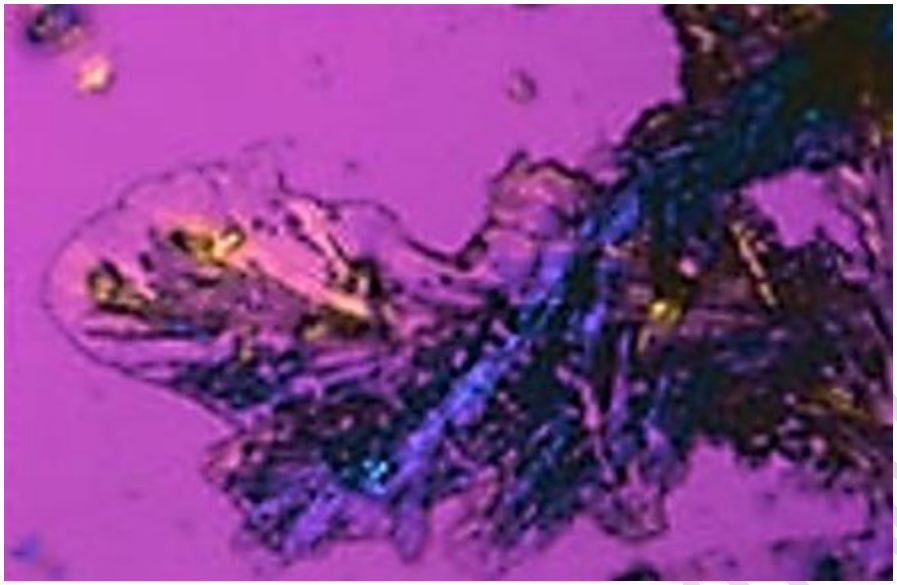

Figure- 1 Microscopic representation -effect of cisplatin-based Chemotherapy on solid tumors(33-35).

Although Cisplatin is synthesized from **"Potassium Tetrachloroplatinate"** through several procedures, one stumbling block is the ease with which Magnus' green salt (MGS); that has the same empirical formula as "Cisplatin." Dhara has explained that the classic method of avoiding MGS entails converting '**K_2PtCl_4 to K_2PtI_4'** (36-37) PtI_2 $(NH_3)_2$, (isolated after the reaction with ammonia) formed **(36-37).**

The mode of action of cisplatin resistance (CPR) is very complex and consist of different steps of "molecular mechanism," and is often associated with the following phases-(37)

1) 'Decline concentration of **'Platinum-based compound'** accumulation inside cells

2) Intensification in '**DNA damage repair mechanism**.'

3) Deactivation of the **'Apoptosis'**- "Programmed cell death process."

4) Activation of the **'Epithelial-mesenchymal transition' (EMT)**

5) Modification in **"DNA methylation, microRNA profile, and cancer stem cell distinguishes and expresses stress response chaperones"** (Figure 2).

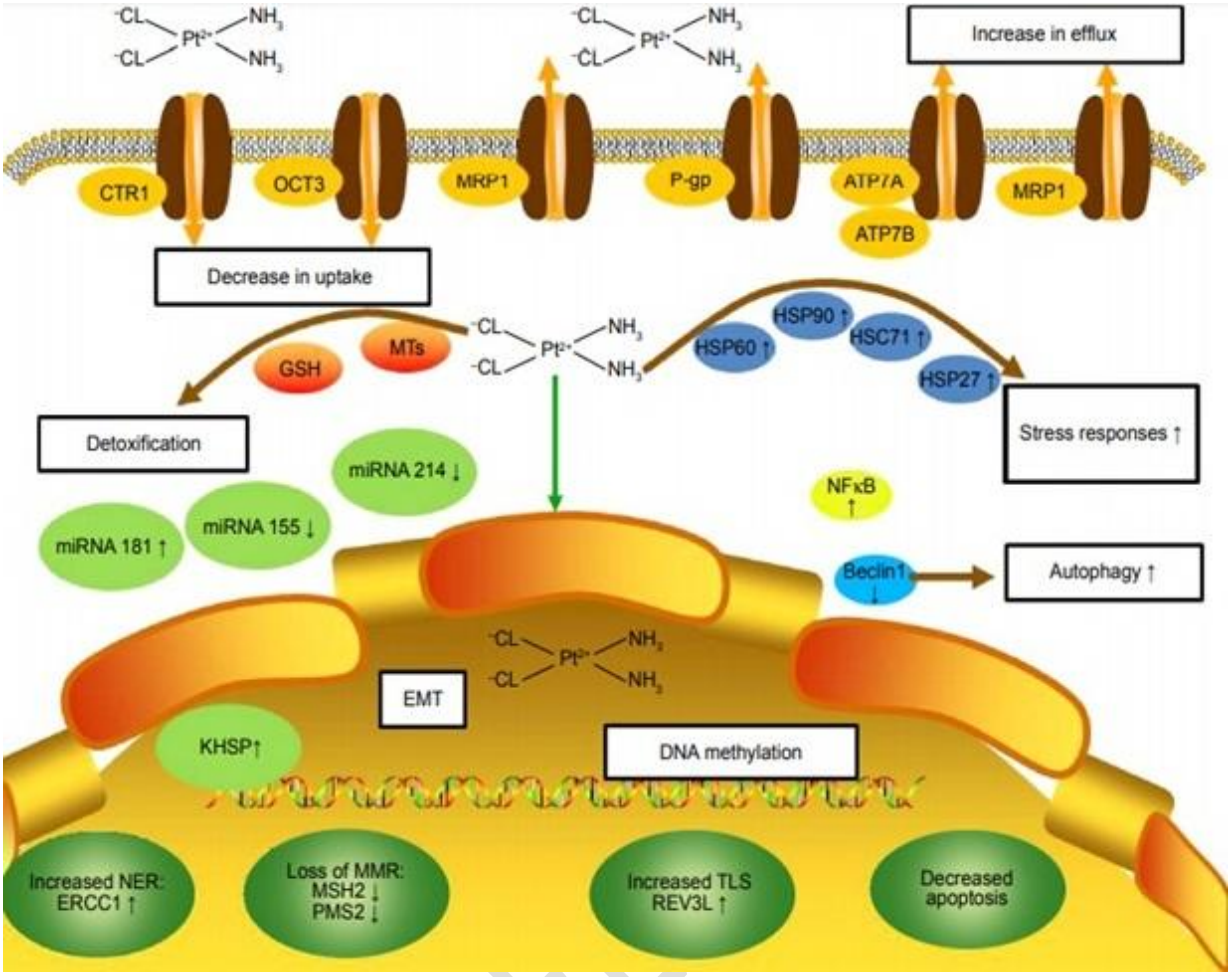

Figure 2-CPR Molecular Mechanisms in Cervical Cancer (37)

However, CPR could be caused by decreased cisplatin intracellular accumulation and reduced intracellular cisplatin accumulation through different procedures like -**Reduced uptake, Increased efflux**, and **Inactivation by thiol-containing proteins** (all involved in reduced formation '**Cisplatin–DNA Adduct" complex**) known as **"Cisplatin Resistance"**(38).

Cancer cells are treated with acquired CPR to reduce cisplatin absorption in the cervix. When compared to the original cell lines, the cisplatin-resistant "HeLa-CPR cells" (HeLa-CPR) and A431 (A431/Pt) cells have a 50% and 77% reduction in cisplatin absorption, respectively (38-39). The number of Cisplatin–DNA adducts is two to three times lower in "HeLa-CPR cells," while the "HeLa-CPR cells" have a similar rate of Cisplatin–DNA adduct removal as the parental HeLa cells. However, the "HeLa-CPR cells" remove Cisplatin–DNA adducts identical to the parental "HeLa-CPR cells."After short-term drug exposure, "Platinum Accumulation," "DNA bound platinum," and interstrand cross-link frequency are likewise reduced in A431/Pt cells (CPR cervix squamous carcinoma cells). Thus, poor absorption

may contribute to CPR in cervical cancer cells to an increased “Cisplatin–DNA Adduct” complex (40-41).

Generally, Cisplatin has a passive transport mechanism to pass through the cell membrane. 'Copper transporter 1 (CTR1)' has been discovered "lipophilicity," a transmembrane protein essential for maintaining copper homeostasis, and the influx of Cisplatin and its analogs into cells must be controlled (37)."CTR1" is involved in different activities like to be recognized to regulate the inflow of Cisplatin and its analogs into the cells and downregulated in various CPR1 cell lines, including “HeLa-CPR cells” (37).

Several findings defined that in comparison to mock-transfected cells, "HeLa-CPR cells" overexpressing CTR1 accumulate two points two times extra Cisplatin. (42-43). In a rat model of cervix cancer, the C-terminus of CTR1 protein was required for cisplatin uptake in "HeLa cells," In contrast, the quantity of "DNA–cisplatin adducts" was related to 'CTR1' mRNA levels in various organs. Overexpression of 'CTR1' in the parental cells A431 and the CPR cells A431/Pt, on the other hand, does not affect cisplatin absorption or sensitivity, suggesting that 'CTR1's role in cisplatin transmembrane transport may vary in different types of cervical cancer cells (42-43).

“Multidrug resistance proteins (MRPs), MRP1, MRP2, MRP3, and MRP5”, as well as ATP-binding cassette (ABC) transporters, might be involved to promote CPR via enhancing cisplatin export (37). Overexpression of “MRP1” has been linked to CPR in a few cervix cancer cell (CCC) lines. “MRP2” contributes to enhanced cisplatin efflux in CPR human liver cancer cells and embryonic kidney cells.MRP2 expression is significantly reduced in CPR (37). cervical cancer KB-CP20 cells improved considerably in cisplatin-sensitive KB-8-5-11 cells, demonstrating that "MRP2" is inversely related to CPR in cervical cancer cells (44). “MRPs, P-glycoprotein (P-gp, ABCB1) (an ABC transporter)” also mediates cisplatin efflux and enhances CPR. In the CPR cervical cancer cell line SiHaR, P-gp is overexpressed. When "HeLa-CPR cells" are exposed to Cisplatin, P-gp expression increases rapidly, and overexpression of P-gp reduces cisplatin-induced apoptosis in “HeLa-CPR cells” (45). ***‘P-gp activity and expression were reduced in CPR “HeLa-CPR cells,” and neither the non-P-gp-specific inhibitor probenecid (which inhibits numerous ABCs) nor the P-gp-specific inhibitor verapamil affected cisplatin sensitivity***. These findings show that “P-gp” may not play a significant role in CPR in “HeLa cells” (37).

Some previous findings suggested that DNA damage has been caused by "cisplatin–DNA adducts."This complexity leads to cytotoxicity, and few cisplatin molecules attach to DNA, which is sufficient to start the DNA damage-induced death cascade. In contrast, others can actively bind to cytoplasmic nucleophilic substances like "Glutathione (GSH), methionine, metallothioneins (M.T.s), and thiol-containing proteins" after entering the cells (37). However, 'Glutathione (GSH), methionine, metallothioneins (M.T.s), and thiol-containing proteins' can attach to cytoplasmic nucleophilic molecules with potency, and the cisplatin binding to thiol-containing nucleophilic species/thiol-containing proteins depletes intracellular antioxidant reserves, promoting oxidative stress, while also reducing the availability of "Reactive cisplatin" (46).

According to Chao et al. in "CPR HeLa cells," neither the intracellular GSH level nor the GST activity was raised (47). At the same time, Roy and Mukherjee discovered that the GSH level in the CPR clone "SiHaR," generated from SiHa, remained unchanged. Still, its significance in 'CPR' cervical cancer is unidentified (48). Other studies have defined that metal homeostasis and detoxification are regulated by "M.T.s" (low-molecular-weight thiol-containing proteins), and they can bind to cisplatin resulting in the establishment of the 'CPR' phenotype. Mellish et al. looked at the role of M.T.s in CPR in five different human cervical squamous carcinoma cell lines and discovered a link between "M.T." expression and 'CPR' (49-50).

Further studies looked that inter-and intra-strand DNA adducts frequently fail to initiate the apoptotic cascade in 'CPR' cancer cells. Compared to their parental 'cisplatin-sensitive counterparts,' tumor cells with acquired CPR have a more extraordinary ability to repair "cisplatin-induced DNA lacerations" or tolerate a high amount of unrepaired DNA lesions. Multiple DNA repair pathways can detect 'cisplatin-induced DNA lacerations,' which frequently cause DNA distortion. The most common DNA repair mechanisms are nucleotide excision repair (NER) and mismatch repair (MMR) (50).

"NER" is a highly conserved DNA repair process and a primary pathway for repairing 'DNA–cisplatin adducts,' typically targets "DNA damages" that alter DNA helical structure and interfere with DNA replication and transcription. Excision repair cross complementation group 1 is one of the more than "20 proteins" involved in "NER" (ERCC1). "ERCC1" is a single-strand DNA endonuclease that works in tandem with ERCC4 to incise DNA on the 5′ side of bulky lesions such DNA–cisplatin adducts. Its

expression is elevated in 'CPR' CCC- HCA-1R and locally progressed cervical squamous cell carcinoma patients. The expression of "ERCC1" has a negative relationship with cisplatin sensitivity. Furthermore, in patients receiving adjuvant cisplatin chemotherapy or chemoradiotherapy with Cisplatin, reduced "ERCC1" expression is an independent prognostic factor linked to a survival benefit (37-44).

“DNA MMR” is an evolutionarily conserved process that corrects mismatches during DNA replication but is not caught by DNA proofreading. To detect cisplatin-induced DNA damages, a healthy functioning MMR system is essential. As a result of “MMR” deficiency, DNA damage tolerance and CPR may emerge. ‘MutS homolog 2 (MSH2)’ protein has been revealed to be one of the MMR proteins. ‘MSH2’ protein expression was considerably lower in CPR A431 cells than in parental cells. PMS2 (post-meiotic segregation 2) is another critical component of the MMR system (47). ‘REV3L imparted cisplatin resistance in cervical cancer cells via regulating apoptosis and the expression of anti-apoptotic proteins such B-cell lymphoma 2 (Bcl-2), myeloid cell leukemia sequence 1 (Mcl-1), Bcl-extra significant (Bcl-xL), and pro-apoptotic Bcl-2-associated x protein’, according to Yang et al. (Bax)(51-52).

"Cisplatin-induced Apoptosis" is essential for the antitumor activity of Cisplatin or anticancer activity of Cisplatin. It induced apoptosis by activating either the intrinsic mitochondrial route or the extrinsic death receptor system (50). Several proteins, like the Bcl-2 family of proteins and p53, and several signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway and nuclear factor-κB (NF-κB) pathway, contribute to the extrinsic and intrinsic apoptosis pathways. 'CPR' may develop due to specific proteins and signaling pathways (53).

During apoptosis, several other factors like “Caspases, anti-apoptotic proteins, Bcl-2, Bcl-xL, Mcl-1, Bcl-w, Bag-1, and A1” (Regulate the mitochondrial permeability) outer membrane and the release of cytochrome c and other pro-apoptotic proteins to control the apoptotic process tightly. The activation of caspases and the overexpression of anti-apoptotic proteins, as well as the inhibition of pro-apoptotic effector proteins, all contribute to the development of CPR.) and 'MAPK pathway is coordinated with each other and play an essential role in apoptosis and significant activity of caspase-3, caspase-8, and caspase-9 is decreased in CPR cells'. The functions in the intricate intracellular signaling network that controls gene expression respond to various external inputs by the “MAPK pathway” (53). Brozovic et

al. discovered that HeLa cells with acquired CPR had lower cisplatin-induced apoptosis and Bcl-2 and p-Bad than parental cells (54-55).

From some other research, “SiHa cells" are more resistant to Cisplatin than "HeLa cells," have 'lower caspase-3, caspase-8, and caspase activity, as well as cisplatin-induced cleavage of poly(adenosine diphosphate [ADP]-ribose) polymerase’ (56). 'Cisplatin-sensitive "HeLa cells," Cisplatin activates stress-activated protein kinase/c-Jun-N-terminal kinase-SAPK/JNK (one of the mammalian type MAPKs), p38 kinase, and ERK dose-dependently, but cisplatin-mediated activation of SAPK/JNK is significantly inhibited in the CPR subline’ (57). Consequently, it appears that adequate “MAPK” activation is required for cisplatin-induced apoptosis (56).

Another factor contributing to the apoptosis process- 'p53' wild-type p53 stabilization and activation are essential for cisplatin-induced apoptosis. As a result, p53 deficiency can impede apoptosis and lead to 'DNA damage tolerance, boosting treatment resistance' (41-45).

In addition, “NF-B" is widely expressed and regulated, usually as a heterodimer or homodimer generated by members of the "NF-B family ."Immunoregulation, inflammation, growth regulation, apoptosis, and carcinogenesis are all controlled by 500 genes. Constitutive activation of "NF-B" suppresses chemotherapy-induced apoptosis in various forms of cancer, including cervix cancer, according to numerous *in vitro* and *in vivo* investigations(37).

The importance of "EMTs" in acquired "CPR" has been more recognized in recent years. In a recent investigation, we discovered that seven days of low-concentration Cisplatin (1 M) treatment caused EMT in cervical cancer cell lines "HeLa and C4-1" via activating the transforming growth factor pathway (37). The importance of EMTs in acquired CPR has been more recognized in recent years. TWIST1, a conserved transcription factor belonging to the essential helix-loop-helix protein family involved in "EMT" and expression, appears to favor the ‘MDR1/P-gp' term in cervical cancer. RNAi silences its expression in cancerous cell lines-"HeLa cells," which decreases cell proliferation, inhibits rhodamine 123 efflux, and sensitizes the cells to Cisplatin (37,55).

Moreover, another essential factor - human fetal “Astrocytes were the first to detect Astrocyte elevated gene-1 (AEG-1)", activated by human immunodeficiency virus-1 (HIV-1). Knocking down

"AEG-1" prevents "EMT" and lowers 'CPR' in CC cells. These data suggest that 'EMT' may play cervical carcinoma CPR development (55).

Multiple pathways involved in the cellular response to Cisplatin have been identified to be regulated by microRNAs. Its' influence on the development of 'CPR' in cervix cancer has been studied. Upregulation of "miR-181" appeared to correlate with 'CPR' considerably in cervical squamous cell carcinoma, and "miR-181" prevented apoptosis and promoted 'CPR' by targeting protein kinase C- (PRKCD)(45).

Although, "MiR-214" improved the susceptibility of "HeLa cells" to Cisplatin by directly reducing 'Bcl2l2 expression and raising Bax, caspase-9, caspase-8, and caspase-3' expression, according to Wang et al. Furthermore, in the nucleus of "HeLa cells" exposed to Cisplatin, KH-type splicing regulatory protein, which interacts with Drosha and enhances the binding and subsequent processing of particular pri-microRNAs such as ‘pri-let7a-1 and pri-miR-21’, is increased. These findings suggest that the levels of specific microRNAs may be used to predict cisplatin responsiveness in patients (57).

In several cell culture models, “DNA methylation” is essential for the formation of 'CPR.' Aberrant "DNA methylation" may impact the sensitivity of cancer cells to Cisplatin by altering the expression of genes that are important for treatment response. Epigenetic medicines like 5-azacytidine have been demonstrated to reverse 'CPR' by blocking abnormal "DNA methylation"(58-59). Combining Cisplatin and 5-aza-2′-deoxycytidine, a demethylating agent, considerably improves cisplatin sensitivity in ME180 parent cells and CPR subclones, and removing 5-aza-2′-deoxycytidine quickly restores CPR (58).
Molecular chaperones involved in general stress responses, like "Autophagy and HSPs," can enhance 'CPR' through various methods, the majority of which are indirect. In HeLa cells, Cisplatin stimulates autophagy, and inhibiting autophagy causes endoplasmic reticulum (E.R.) stress, which increases "cisplatin cytotoxicity." Pretreatment of cervical adenocarcinoma “HeLa cells” and “Squamous cell carcinoma CaSki cells” with the autophagy inhibitor bafilomycin efficiently sensitizes both cells to cisplatin (59).

In addition, ‘CPR' has been studied using a system biology approach. "S100A8 and S100A9 protein" levels were elevated. In contrast, the annexin A2 level was lowered in patients with cervical cancer who failed to respond to cisplatin-based neoadjuvant chemotherapy treatment in earlier research on proteomics profiling. According to quantitative proteomics and protein interaction network analysis, three hundred seventy-four proteins were differently elevated in ‘CPR’ versus cisplatin-

sensitive “HeLa cells.” “DNA binding, DNA damage repair, energy-producing metabolic pathways, and stress response “are all involved in the differentially expressed proteins (60). However, they are not clinically feasible due to their low solubility in aqueous solutions, short serum half-life, and in vivo toxicity due to their non-selective character. Along with small-molecule DNA-PK inhibitors, nucleotides (for example, GRN163L) and antibodies (for example, ScFv 18-2) for radiosensitization have piqued the interest of various researchers, owing to their biological characteristics, which overcomes difficulties such as low solubility and short half-life (61).

In short, medication resistance in cancer appears to rise in terms of therapeutic efficiency. Resistance mutations in cancer during therapy may be blamed for the 25% rise in disease burden. Normal cells are harmed when exposed to excessive concentrations of chemotherapeutic drugs. Chemotherapy that is used for a long time creates acquired resistance. Traditional therapies could not specifically target cancer cells, necessitating nanocarriers or bioengineering for polychemotherapy, and components can be used as an alternative treatment method to reduce resistance(41-47).

A few studies focus on nanotherapeutic techniques as an alternative to traditional Chemotherapy (44). These components extractives work in numerous ways to combat cancer resistance and deliver the best results. In combination therapy, poor solubility and bioavailability are significant limitations. However, the nanotechnological technique improves bioavailability and the functional characteristics of transport across cell membranes.

Role of nontechnology

Nanotechnology (N.T.) is a process of making nanomaterials at the atomic and molecular level, with nanomaterials ranging in size from 1 to 100 nm in at least one dimension. N.T. has been widely applied in clinical medicine targeting and used to improve cancer management in various ways, and it has emerged as a viable tool for cancer treatment. Ferrari, 2005 observed that nanoparticles of specific sizes could aggregate at the site of tumors, reducing adverse therapeutic effects and increasing treatment efficacy through a passive targeting method. Precise active tumor targeting delivery has also been investigated to boost anticancer medication accumulation at tumor sites (63).

N.T. is being studied more and more to increase early detection and vaccine and treatment efficacy in cervical cancer; N.T. may help overcome drug delivery barriers and improve the effectiveness of cervical cancer treatment (60). Thus, NT has significantly improved drug delivery by providing several benefits, including improved delivery of poorly water-soluble drugs, longer drug circulation lifetime in the

body, targeted drug delivery to cells or tissues, transcytosis of drugs across tight epithelial and endothelial barriers, co-delivery of two or more medications for combined treatment, and visual-based drug delivery (61-62), while it has some disadvantage like the targeting aspects, is demerits; Excessive use of detergent-polyvinyl alcohol resulted in toxicity. It is not possible to stop using this medication. Polymeric nanoparticles have the potential to disrupt autonomic homeostasis. It will directly impact the heart and vascular system(61).

Because of their unique features, nanoparticles have sparked a lot of attention in recent years for various medicinal applications. One of the most significant advancements in the relative application of nanoparticles is the recognition of steric stabilization, which can increase particle stability in the biological environment and provide opportunities for nanoparticles to be used in the development of drug delivery systems (DDSs) for drug targeting and controlled drug release(64). The right design of surface ligands on these nanoparticles is required to permit their use in such applications. In light of this, surface-modified functionalized nanoparticles can be used to specifically interact with target molecules on the cell membrane or within the cell (64-69).

The first technique involves conjugating the proper ligands or adding targeting moieties to the DDS to increase drug placement. The second technique employs trigger-controlled drug release, limiting drug release at the targeted site using externally controlled mechanisms to destroy cancer cells. Light has sparked a lot of attention among external stimuli because it allows for spatiotemporal control of payload release (70).

Efficient polycation with multifunction through folate, Boro,Casein N.P.s,Fucoidan N.P.s,

The issue is the creation of polymer is building a carrier system that is highly accurate, efficient and reproducible, and versatile at the same time. When Hartmann et al. created definitive polycationic structures, libraries of polycations and explicit relation between structure and activity were developed (70); this was a big step forward inaccurate vector synthesis. By Dohmen et al.'s work on adding numerous substructures to the polycationic backbone or to the Cisplatin itself, the functionality of these polymers was improved. The synthesis was based on a linear backbone of polyaminoamides that uses Stp as a construction block (16-amino-4-oxo-5,8,11,14-tetraza-hexadecanoic acid) (70-72). The importance of cellular uptake of nanoparticles is vital to understand through N.P. Scan aids in drug delivery into cells. The characteristics of the material, electric charge, shape, size, and surface qualities

can be used to define the cellular absorption of polymeric nanoparticles. It is challenging to analyze the kinetics of nanoparticle cellular absorption in the body due to their degradability. Due to contact-mediated cellular absorption of putrescent, a dye released by nanoparticles, cellular uptake would be significant, according to a Spring 2013 thesis. (73).

Although, two cell lines from an experiment were used in a recent study. During the investigation, it was discovered that when both cell lines' surface characteristics and particle size were changed, the reactions of both cell lines differed. A cell absorbs free dye during the experiment, as illustrated in the images on paper (73-74). Surfactants Poloxamer 188 and Polysorbate 80 were employed to improve cellular absorption of polymeric nanoparticles, and due to their small size, molecules have an easy time penetrating the cell membrane compartment (74).

The plasma-containing membrane contains a variety of mechanisms for nutrition acquisition between or among cellular regions. CO2 and O2 are nonpolar molecules that diffuse into the membrane. The active transport mechanism of ion channels and protein pumps transports ions and certain amino acids (75). Endocytosis is used to transport hydrophilic biomacromolecules. Endocytosis is a transport mechanism for vesicles across the plasma membrane. The surface features, physical and chemical properties of polymeric nanoparticles influence their biodistribution and cellular uptake. In nano-immune interactions, the recognition of particles and the engulfing process through immune cells should be considered. Primary cells are frequently employed to assess nanoparticle biocompatibility. Compared to tr-cell lines, primary cells are closer to in vivo settings (76).

Nanoparticles have been utilized exclusively to improve the efficacy of medications with low bioavailability and therapeutic windows (nucleic acid drugs and antitumor therapies), according to reports (79). Their biodistribution and pharmacokinetic characteristics determine drugs' therapeutic value and side effects. Surface-charge chemistry takes into account physical and chemical parameters. The biodistribution extent and pharmacokinetics were calculated using these considerations (80). Nanoparticles' intracellular destiny has a significant impact on bioavailability after being internalized by cells. For better drug delivery systems, hurdles in intracellular delivery and releasing patterns of the drug have been overcome (Huang and Li,2007). Neovascularization occurs when malignant cells proliferate and require blood arteries to deliver nutrition and oxygen (61-69).

This causes aberrant structures to grow around the malignant cells, such as fenestrated endothelium. The ideal size of nanoparticles avoids renal elimination and MPS, allowing them to enter

through the EPR. Furthermore, nanoparticle size and pore range may differ by species and tumor type. Nanoparticles are more extensive and easily trapped in the region of the extracellular space (81). During extravasation, it is unable to penetrate leaky vessels. On the other hand, nanoparticles smaller than 20 nm have deep penetrability into the perivascular area of tumor cells when subjected to hydraulic pressure (82).

As functionalized nanoparticles (F.N.), the cationic coating was used, and F.N. was delivered into living cells without any endocytic internalization modification. Internalization is considered non-selective since it is dependent on particle adsorption on the cell surface(83). Folates have been used with cytotoxic medicines for decades, and hundreds of thousands of patients receive them each year. Folate metabolism is a complicated process. The administration of folates in the treatment of cancer with 5-fluorouracil causes the formation of [6R]-5,10-methylenetetrahydrofolate, and the increased concentration of this molecule causes the ternary complex containing thymidylate synthase, 2′-deoxy-uridine-5′-monophosphate, and [6R]-5,10-methylenetetrahydrofolate to stabilize. The latter is the only natural folate that can attach to the ternary complex without the need for metabolic activation, whereas other folates require metabolic activation. In the study of folate/cytotoxic combos, modulation of thymidylate synthase activity became central, and despite widespread use, research into the folate component was neglected, leaving significant concerns unsolved.

The presence of coumarin and nanoparticles [d=2.6] and their conjugates with folic acid are required for cell recognition. It is identified by folate receptors, which are present on the cell's surface. After incubation of K.B. cells, referred to as Pharyngeal cells from the human body, coumarin and folic acid are present by Fourier transform infrared spectroscopy. Cellular recognition of polymeric nanoparticles has been discovered, resulting in a more efficient cell delivery mechanism (84).

To boost polyplex stability through the production of disulfides, cysteines were introduced. Polyethylene glycol (PEG) was connected by branching lysine to protect and avoid undesired interactions among polyplexes in the body. Folic acid was included as a target ligand to target the manufactured vectors for folate overexpressingtumorcells (79, 83). The endosmotic domain Inf7 was covalently linked to Cisplatin itself and is strongly lytic at endosomal P.H. to enable an endosomal escape of the polyplexes. Similarly, the most often used boron nitride nanotube optimal delivery

capsule to reduce the volume. The material needed for encapsulation is, therefore, the least possibletoxicity (80-84).

This approach was used to encapsulate Cisplatin, boron nitride, carbide, and boron nanotubes in silicone can be extended to any number of drugs. Alternative nanotube materials or compounds. It is suitable for providing general guidance for future experiments and Studies of molecular dynamics (85).

In addition, boron Nitride Nanotubes (BNNTs) are structural counterparts of carbon nanotubes (CNTs) and exhibit many of the same features as CNTs due to their similar structure. BNNTs, on the other hand, outperform carbon nanotubes in terms of chemical stability and resistance to oxidation at high temperatures. The nature of BNNTs' partial ionic bond is related to their exclusive nature. For example, polar B–N bonds create a more significant interaction between hydrogen and the nanotube, making BNNTs preferred to CNTs for hydrogen storage applications. Compared to CNTs of identical diameter and length, BNNTs have shown superior water penetration capabilities. because of their chemical inertness and structural stability, BNNTs are less harmful to humans and the environment, making them more suitable for medicinal applications like drug delivery. Biomedical uses of BNNTs, on the other hand, are yet largely unexplored. The first biocompatibility tests on BNNTs have begun in some studies. When BNNTs were injected into rabbits, there were no significant adverse effects for in vivo studies, indicating that BNNTs have the best biocompatibility. BNNTs were tested on human cells and found noncytotoxic, suggesting that they are biocompatible materials for biomedical purposes.

These experiments showed that BNNT is harmless and might be used in biological systems where CNT toxicity is an issue. As a result, BNNTs can be used in nanomedicine. When BNNT was compared to CNT in terms of electrical and structural properties, it was determined that BNNT might be used as a drug delivery vehicle for platinum-anticancer medicines (80). Using Density Functional Theory has predicted the encapsulation of platinum-anticancer medicines into single-walled boron nitride and carbon nanotubes (DFT). They discovered that encapsulating pharmaceuticals inside nanotubes is preferable to drug adsorption outside of nanotubes (81-84). Nanotubes are therefore critical in novel medication delivery since they can transport encapsulated drugs into the inner volume. Cisplatin was chosen as an anticancer agent, and the behavior of this medication in aqueous solutions enclosed in zigzag CNT and BNNT was studied. The solvation and binding free energies of the related structures in aqueous solution were estimated using Monte Carlo simulation after CNT, BNNT, Cisplatin, and their complexes were first modeled using quantum mechanical calculations. BNNT has higher solvation in

water than CNT due to a more considerable electrostatic contribution to the total solvation free energy (81-83).

Casein is a naturally occurring protein that comes from milk. It was widely employed in the medication delivery system due to its non-toxic, low-cost, and biodegradable qualities. Zhen et al. created cisplatin-loaded casein nanoparticles in a spherical shape with a diameter of 257 nm. A hepatic H22 mouse model was used to test the antineoplastic activity of nanoparticles loaded with Cisplatin. These nanoparticles greatly enhanced cell penetration, tumor targeting, and tumor progression inhibition (84).

Fucoidan N.P.s are emerging nanocarriers because of their multifunctional capabilities, including anti-inflammatory, anticoagulant, and anticancer properties. Cisplatin and fucoidan nanoparticles were created in this study to help with immunotherapy and Chemotherapy. Compared to HCT-8 cells treated with Cisplatin alone, nanoparticles displayed more significant cytotoxicity in an antitumor assay (85).

CONCLUSION AND FUTURE RECOMMENDATIONS

Cisplatin has been shown to have antitumor activity in a variety of malignancies. The current analysis focuses on the comparative findings of Cisplatin and cisplatin-loaded nano-based formulations containing folate, boron, etc. These have yet to be marketed to treat various malignancies. Nano-drug delivery-based formulations can improve the physicochemical properties of anticancer medications and make them more effective in their targeting. We believe that a target nano-drug carrier for the successful delivery of Cisplatin cis-(diammine)dichloridoplatinum(II) (CDDP) can be created. The most important findings of this review study are the toxicities and drug resistance that can be decreased by combining Cisplatin with other chemotherapeutic drugs with nanotechnology and increased drug effectiveness.Furthermore, combining Cisplatin with other anticancer drugs improved the therapeutic profile, tolerability, and efficacy. Future nanomedicine-based drug delivery systems appear to be promising, potentially improving cancer therapy outcomes. Furthermore, more new efforts must be made to target moiety to reduce toxicities, a big issue with cancer medications.

DISCLAIMER:

The products used for this research are commonly and predominantly used products in our area of research and country. There is no conflict of interest between the authors and producers of the

products because we do not intend to use these products as an avenue for any litigation but the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

COMPETING INTERESTS:

Authors have declared that no competing interests exist.

References:-

1. AdelusiB. Carcinoma of the cervix: can a viral etiology be confirmed? IARC Sci Publ. 1984;63:433-50.
2. Adler DH, Wallace M, Bennie T, et al . Cervical dysplasia and high-risk human papillomavirus infections among HIV-infected and HIV-uninfected adolescent females in South Africa. Infect Dis Obstet Gynecol. 2014;498048.
3. Alberts DS, Blessing JA, Landrum LM, et al. Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: a gynecologic oncology group study. Gynecologic Oncology. 2012; 127: 451–455.
4. Alivisatos AP, Johnsson KP, Peng XG, WilsonTE, Loweth CJ, et al. Nanotechnology and nucleotide. Nature. 1996; 382: 609-611.
5. Albanese A, Tang PS, Chan WCW. Heej ect of nanoparticle size, shape, and surface chemistry on biological systems. Ann Rev Biomed Eng. 2012; 14: 1-16.
6. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer, 2017;715-725.
7. Arbyn M, Walker A, Meijer CJ. HPV-based cervical-cancer screening in China. Lancet Oncol.2010;11:1112–3.
8. Alderden RA, Hall MD, Hambley TW. The Discovery and Development of Cisplatin". J. Chem. Educ. 2006: 83 (5): 728..
9. Arbyn M, Verdoodt F, Snijders PJ, et al.Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol. 2014;15:172–83.

10. ArnheimDahlström L., Andersson K., Luostarinen T., Thoresen S., Ögmundsdottír H., Tryggvadottír L., et al. . Prospective seroepidemiologic study of human Papillomavirus and other risk factors in cervical cancer. Cancer Epidemiol. Biomark. Prev.2011; 20: 2541–2550.

11. AronowitzJN. Afterloading: The Technique That Rescued Brachytherapy. Int J Radiat Oncol Biol Phys.2015; 92(3):479-87.

12. Aronov O., A. T. Horowitz, A. Gabizon, and D. Gibson.Folate-targeted PEG as a potential carrier for carboplatin analogs. Synthesis and in vitro studies," Bioconjugate Chemistry.2003;14(3) 563–574.

13. Arulogun OS, Maxwell OO. Perception and utilization of cervical cancer screening services among female nurses in University College Hospital, Ibadan, Nigeria. Pan Afr Med J.2012;11:69

14. Asthana S, Busa V, LabaniS Oral contraceptives use and risk of cervical cancer-A systematic review & meta-analysis. Eur J ObstetGynecolReprod Biol. 2020;247:163–75.

15. Avan A, Postma TJ, Ceresa C, Avan A, Cavaletti G, Giovannetti E, Peters GJ.(2015) Platinum-induced neurotoxicity and preventive strategies: past, present, and future". The Oncologist. 20 (4): 411–32.

16. Bajaj A, Rana S, Miranda OR, Yawe JC, Jerry DJ, et al. (2010) Cell surfacebased di;erentiation of cell types and cancer states using a gold nanoparticle-GFP based sensing array. Chem Sc.2015;i 1: 134-138.

17. Bao H, Sun X, Zhang Y, et al .The artificial intelligence-assisted cytology diagnostic system in large-scale cervical cancer screening: A population-based cohort study of 0.7 million women. Cancer Med.2020;9:6896–906.

18. Bao H, Bi H, Zhang X, et al .Artificial intelligence-assisted cytology for detection of cervical intraepithelial neoplasia or invasive cancer: A multicenter, clinical-based, observational study. Gynecol Oncol.2020;159:171–8 .

19. Basotra M, Singh SK, Gulati M. Development and validation of a simple and sensitive spectrometric method for estimation of cisplatin hydrochloride in tablet dosage forms: Application to dissolution studies. ISRN Anal Chem.2013:8.

20. Belinson J, Qiao Y, Pretorius R, et al. Shanxi Province cervical cancer screening study II: self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. Int J Gynecol Cancer.2003; 13:819–26.

21. Benedet JL, Bender H, Jones H 3rd, Ngan HY, PecorelliS. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology Int J Gynaecol Obstet.2000; 70(2):209-62.

22. Bhatnagar I, Venkatesan J, Kim S-K. Polymer functionalized single walled carbon nanotubes mediated drug delivery of gliotoxin in cancer cells. Journal of Biomedical Nanotechnology.2014;10: 120–130.

23. Bi S, Zhou H, Zhang S. Multilayers enzyme-coated carbon nanotubes as biolabel for ultrasensitive chemiluminescence immunoassay of cancer biomarker. Biosensors and Bioelectronics.2009;24: 2961–2966.

24. Blanco, E., Shen, H., & Ferrari, M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature biotechnology*,2015; *33*(9), 941–951.

25. BortotB, Mongiat M, Valencic E, et al. Nanotechnology-Based Cisplatin Intracellular Delivery to Enhance Chemo-Sensitivity of Ovarian Cancer. Int J Nanomedicine.2020; 15:4793-4810.

26. Bobdey S, Sathwara J, Jain A, Balasubramaniam G. Burden of cervical cancer and role of screening in India. Indian J Med Paediatr Oncol.2016; 37(4):278-285.

27. Boontheekul. T, H. J. Kong, and D. J. Mooney, “Controlling alginate gel degradation utilizing partial oxidation and bimodal molecular weight distribution,” Biomaterials(26)15; 2005;2455–2465.

28. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;(68)394–424.

29. Beretta GL, Gatti L, Tinelli S, et al. Cellular pharmacology of cisplatin in relation to the expression of human copper transporter CTR1 in different pairs of cisplatin-sensitive and -resistant cells. BiochemPharmacol.2004;68(2):283–291.

30. Brigger I, Dubernet C, CouvreurP. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev.2012;64:24-36.

31. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev.2002; 54: 631-651.

32. Bruni L, Diaz M, Castellsagué X, et al.Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 22010;02:1789–99.

33. Cao Z-T, Chen Z-Y, Sun C-Y, Li H-J, Wang H-X, Cheng Q-Q, et al. Overcoming tumor resistance to cisplatin by cationic lipid-assisted prodrug nanoparticles. Biomaterials.2016;94:9-19.

34. Calixto G, Bernegossi J, Fonseca-Santos B, ChorilliM. Nanotechnology-based drug delivery systems for treatment of oral cancer: a review. Int J Nanomedicine.2014; 9:3719-3735.

35. Carpenter DP. Reputation and power: organizational image and pharmaceutical regulation at the FDA. Princeton, NJ: Princeton University Press.2010; ISBN 978-0-691-14180-0.

36. Casagrande N, De Paoli M, Celegato M, et al. Preclinical evaluation of a new liposomal formulation of cisplatin, lipoplatin, to treat cisplatinresistant cervical cancer. Gynecol Oncol.2013;131(3):744–752.

37. Castle PE, Porras C, Quint WG, et al. Comparison of two PCR-based human papillomavirus genotyping methods. J Clin Microbiol.2008; 46:3437–45.

38. Chabner B. Barnett Rosenberg.In memoriam (1924-2009). Cancer ResExit Disclaimer. 2010;70;428-429.

39. Chenthamara, D., Subramaniam, S., Ramakrishnan, S.G. et al . Therapeutic efficacy of nanoparticles and routes of administration. Biomater Res 2019;**23,** 20.

40. Choi,H. S. R. Choi, R. Zhou, H. F. Kung, and I. W. Chen.Iron oxide nanoparticles as magnetic resonance contrast agent for tumor imaging via folate receptor-targeted delivery," Academic Radiology.2004;11(9) 996–1004.

41. Chidambaram M., R. Manavalan, and K. Kathiresan(2011).Nanotherapeutics to overcome conventional cancer chemotherapy limitations," Journal of Pharmacy and Pharmaceutical Sciences.(14)1;67–77, 2011

42. Chavez JD, Hoopmann MR, Weisbrod CR, Takara K, Bruce JE. Quantitative proteomic and interaction network analysis of cisplatin resistance in HeLa cells. PLoS One. 2011;6(5):e19892.

43. Chen W, Zhang X, Molijn A, et al. Human papillomavirus type-distribution in cervical cancer in China: the importance of HPV 16 and 18. Cancer Causes Control.2009;20:1705–13.

44. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin.2016;66:115–32.

45. Chai Z, Hu X, Lu W. Cell membrane-coated nanoparticles for tumor-targeted drug delivery. Sci China Mater.2017;60:504-10.

46. Chao CC. Enhanced excision repair of DNA damage due to cisdiamminedichloroplatinum(II) in resistant cervix carcinoma HeLa cells. Eur J Pharmacol. 1994;268(3):347–355.

47. Chen Y, KeG, Han D, Liang S, Yang G, Wu X. MicroRNA-181a enhances the chemoresistance of human cervical squamous cell carcinoma to cisplatin by targeting PRKCD. Exp Cell Res.2014; 320(1):12–20.

48. Mellish KJ, Kelland LR, HarrapKR. In vitro platinum drug chemosensitivity of human cervical squamous cell carcinoma cell lines with intrinsic and acquired resistance to cisplatin. Br J Cancer.1993;68(2):240–250.

49. Chhabra S, Bhavani M, Mahajan N, et al. Cervical cancer in Indian rural women: trends over two decades. J ObstetGynaecol. 2010;30(7):725–728.

50. Yang L, Shi T, Liu F, et al. REV3L, a promising target in regulating the chemosensitivity of cervical cancer cells. PLoS One.2015); 10(3): e0120334.

51. Yang C., A. Rait, K. F. Pirollo, J. A. Dagata, N. Farkas, and E. H. Chang. “Nanoimmunoliposome delivery of superparamagnetic iron oxide markedly enhances targeting and uptake ihuman cancer cells in vitro and in vivo,” Nanomedicine, 2008;4:318–329.

52. Cho K, Wang X, Nie S, Chen Z, Shin DM.Herapeutic nanoparticles for drug delivery in cancer. 2008;14: 1310-1316.

53. BrozovicA, Fritz G, Christmann M, et al. Long-term activation of SAPK/JNK, p38 kinase and fas-L expression by cisplatin is attenuated in human carcinoma cells that acquired drug resistance. Int J Cancer.2004;112(6):974–985

54. Ross JS, Schenkein DP, Pietrusko R, et al. Targeted therapies for cancer 2004. Am J Clin Pathol2004;122:598–609.Christie DA, Tansey EM, Thomson AJ, eds. The Discovery, Use and Impact of Platinum Salts as Chemotherapy Agent for Cancer. Wellcome Trust Witnesses to Twentieth Century Medicine.2007; 30;6–15.

55. Chumduri, C., Gurumurthy, R.K., Berger, H. et al . Opposing Wnt signals regulate cervical squamocolumnar homeostasis and emergence of metaplasia. Nat Cell Biol2021;23, 184–197 .

56. Wang X, Zhang M, Zhang L, Li L, Li S, Wang C, et al.. Designed synthesis of lipid-coated polyacrylic acid/calcium phosphate nanoparticles as dual pH-responsive drug-delivery vehicles for cancer chemotherapy. 2017;23:6586-95.

57. Clements AE, Raker CA, Cooper AS, et al .Prevalence and patient characteristics associated with CIN 3 in adolescents. Am J Obstet Gynecol.2011; 204:128.e1–7.

58. Cisplatin. The American Society of Health-System Pharmacists. Archived.2016.

59. Cisplatin .Use During Pregnancy". Drugs.com2020.

60. Cohen PA, Jhingran A, Oaknin A, et al .Cervical cancer. Lancet. 2019;393:169–82.

61. Cooper D, Hoffman M, Carrara H, et al. Determinants of sexual activity and its relation to cervical cancer risk among South African women. BMC Public Health.2007;7:341.

62. Crosbie EJ, Einstein MH, Franceschi S, et al. Human papillomavirus and cervical cancer. Lancet.2013; 382:889–99.

63. Dasari S, TchounwouPB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J pharmacol.2014;0:364-78

64. DharaSC . Cisplatin. Indian J. Chem970;. 8: 123–134

65. Dhar S, Daniel WL, Giljohann DA, Mirkin CA, Lippard SJ (2009). Polyvalent oligonucleotide gold nanoparticle conjugates as delivery vehicles for platinum(IV) warheads". Journal of the American Chemical Society. 131 (41): 14652–3.

66. Dhillon PK, Yeole BB, Dikshit R, et al(2011). Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976–2005: an age-period-cohort analysis. Br J Cancer. 2011;105(5):723–730.

67. Doherty B, Lawlor D, Gillet JP, Gottesman M, O'Leary JJ, StordalB. Collateral sensitivity to cisplatin in KB-8-5-11 drug-resistant cancer cells. Anticancer Res.2014;34(1):503–507.

68. De RodaHusman AM, Walboomers JM, van den Brule AJ, et al. The use of general primers GP5 and GP6 elongated at their 3' ends with adjacent highly conserved sequences improves human papillomavirus detection by PCR. J Gen Virol.1995;76:1057–62.

69. Hartmann, L., Hafele, S., Peschka-Suss, R., Antonietti, M., and Borner, H. G. Tailor-Made Poly(amidoamine)s for Controlled Complexation and Condensation of DNA. Chemistry.2008; 14, 2025-2033.

70. Dohmen, C., Edinger, D., Frohlich, T., Schreiner, L., Lachelt, U., Troiber, C., Radler, J., Hadwiger, P., Vornlocher, H. P., and Wagner, E. Nanosized Multifunctional Polyplexes for Receptor-Mediated SiRNA Delivery. ACS Nano 2012;6, 5198-208.

71. Dobrovolskaia MA, McneilSE . Immunological properties of engineered nanomaterials. Nat Nanotechnol.2007; 2: 469-478.

72. Du J, Lane LA, NieS. Stimuli-responsive nanoparticles for targeting the tumor microenvironment. J Control Release. 2015;219:205-14.

73. Du X, Wang X, Li H, Sun H.. Comparison between copper and cisplatin transport mediated by human copper transporter 1 (hCTR1). Metallomics. 2012;4(7):679

74. Einhorn LH . Treatment of testicular cancer: a new and improved model". J. Clin. Oncol. 1990;8 (11): 1777–81.

75. Fahey MT, Irwig L, Macaskill P. Metaanalysis of Pap test accuracy. American Journal of Epidemiology.1995;141: 680–689.

76. Ferlay J, Shin HR, Bray F, et al.Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer.2010;127:2893–917.

77. Ferlay J, Colombet M, SoerjomataramI. Global and Regional Estimates of the Incidence and Mortality for 38 Cancers: GLOBOCAN. Lyon: International Agency for Research on Cancer/World Health Organization.2018.

78. Franken NA, Rodermond HM, Stap J, Haveman J, van Bree C. Clonogenic assay of cells in vitro. Nat Protoc.2006; 1:2315-9.

79. FrrariM. Cancer nanotechnology: opportunities and challenges. Nature Reviews Cancer.20055: 161–171.

80. Langer T, Hoffman RD. Pharmacophores and Pharmacophore Searches. Mannhold R, Kubinyi H, Folkers G, editors. Hoboken: John Wiley & Sons; 2006:395.Ferlay J, Colombet M, SoerjomataramI. Global and Regional Estimates of the Incidence and Mortality for 38 Cancers: GLOBOCAN. Lyon: International Agency for Research on Cancer/World Health Organization.2018.

81. Galluzzi L, Vitale I, Michels J, Brenner C, Szabadkai G, Harel-Bellan A, et al. Systems biology of cisplatin resistance: past, present and future. Cell Death Dis.2014;5:e1257.

82. GalluzziL, Senovilla L, Vitale I, et al. Molecular mechanisms of cisplatin resistance. Oncogene.2012;31(15):1869–1883.

83. Zhen X, Wang X, Xie C, et al. Cellular uptake, antitumor response and tumor penetration of cisplatin-loaded milk protein nanoparticles. Biomaterials. 2013;34:1372–1382.

84. Hwang PA, Lin XZ, Kuo KL, et al. Fabrication and cytotoxicity of fucoidan-cisplatin nanoparticles for macrophage and tumor cells. Materials. 2017;10:291.