A Brief Review

CISPLATIN: A DRUG FOR THE TREATMENT OF CANCER

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Abstract:

Cisplatin, cisplatinum, or *cis*-diamminedichloroplatinum (II), is a well-known chemotherapeutic drug. It is one of the most widely used chemotherapeutic agents for various solid tumors in the clinic due to its high efficacy and broad spectrum. The antineoplastic activity of cisplatin is mainly due to its ability to cross-link with DNA, thus blocking transcription and replication, Subsequently inducing apoptosis in cancer cells. However, because of drug resistance and numerous undesirable side effects such as severe kidney problems, allergic reactions, decreased immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss especially in younger patients. Other common side effects include ototoxicity, neurotoxicity, gastrointestinal toxicity, hematological toxicity, cardiotoxicity, and hepatotoxicity. These side effects together reduce the life quality of patients and require lowering the dosage of the drug, even stopping administration, thus weakening the treatment effect Therefore, substantial effort has been made to explore the complicated biochemical processes involved in the toxicology of cisplatin, aiming to identify effective ways to reduce or eradicate its toxicity. This review summarizes and reviews the updated advances in the toxicological research of cisplatin.

Key Words: Cisplatin, Alkylating Agent, Chemotherapeutic agent,Toxicity, Computational study.

Introduction:

Cisplatin (CAS No. 15663-27-1, MF-$Cl_2H_6N_2Pt$; NCF-119875), cisplatinum, also called *cis*-diamminedichloroplatinum(II), is a metallic (platinum) coordination compound with a square planar geometry. It is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and *N*,*N*-dimethylformamide.

Cisplatin was first synthesized by M. Peyrone in 1844 and its chemical structure was first elucidated by Alfred Werner in 1893. However, the compound did not gain scientific investigations until the 1960's when the initial observations of Rosenberg (Rosenberg, Vancamp et al., 1965) at Michigan State University pointed out that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division in *Escherichia coli* created much interest in the possible use of these products in cancer chemotherapy. Since the identification of cis-dichlorodiammineplatinum (II) (cisplatin, *r)* as the agent responsible for this activity, much interest has been generated in the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer.

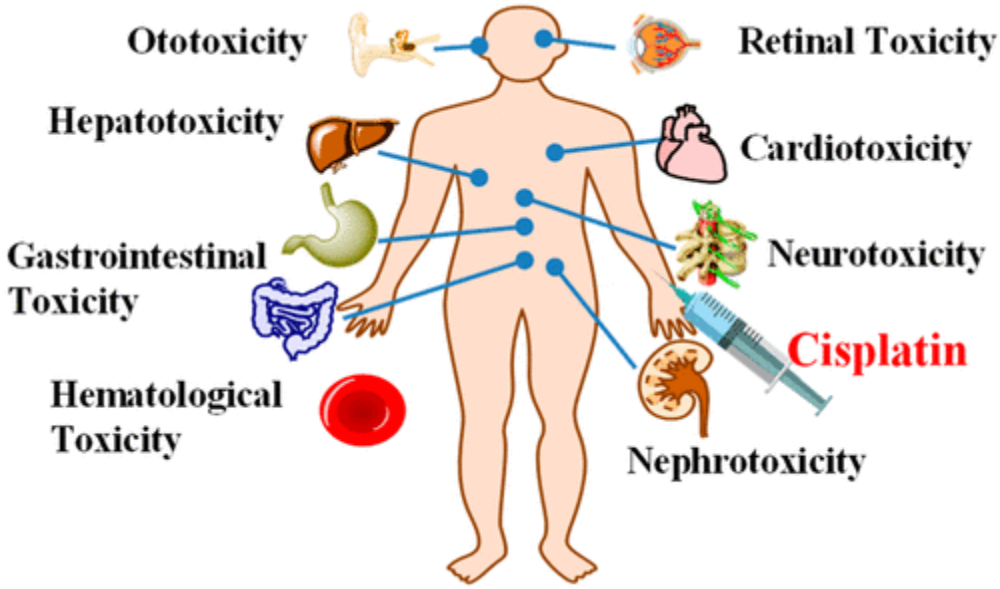

Fig.1 : Toxicity Of Cisplatin

METHOD OF WORKING:

Cisplatin is generally used in vivo by intravascular administration. 68-98% of cisplatin is bound to the protein via histidine and methionine cisplatin enters into a cell through a passive mechanism such as diffusion. Cisplatin mainly targets DNA, which exerts an anti-cancer effect by forming covalent bonds with DNA which results in damage od DNA. The two chloride and two ammonia molecules are bound to the central metal that is platinum (II) In the cis position. The bond between platinum and ammonia molecules is irreversible with substitution inert. Cisplatin is taken up into the cell from the blood, the chloride ion is displaced by water molecules. However, in the cell, the concentration of chloride ions is low

because the chloride ligand is hydrolyzed and replaced by water molecules. Hydrolyzed cisplatin serves as a potent electrophile that reacts with nucleophiles that is nitrogen atoms of nucleic acid. The SH group of the protein, which is covalently bound to the DNA. The platinum atom binds to the nitrogen atom at the 7^{th} position of the guanine and adenine bases and bridges two adjacent purine bases. The cross-link formed by these adducts is the 1,2-intrastrand cross-links [1,2-intrastrand (G a g) and 1,2intrastrand (A p G)]. These DNA adducts inhibit DNA replication and affect transcription.

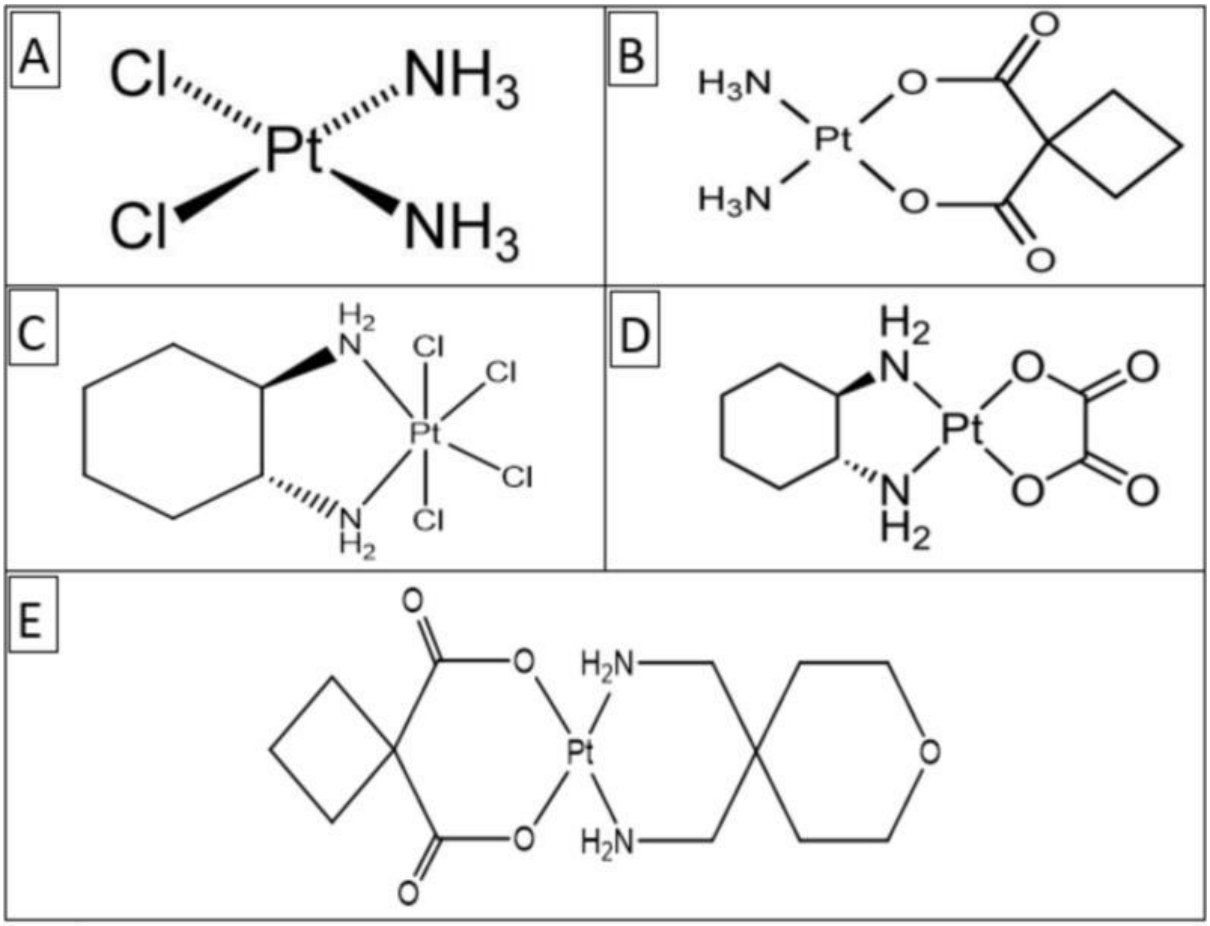

Fig.2 : Molecular Structure of Cisplatin

Alkylating agents are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells. They stop tumor growth by cross-linking guanine bases in DNA double-helix strands - directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide. In addition, these drugs add methyl or other alkyl groups onto molecules where they do not belong which in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA. Alkylating agents are cell cycle-nonspecific. Alkylating agents work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death.

Cisplatin does not undergo instantaneous and reversible binding to plasma protein that is characteristic of normal drug-protein binding. However, the platinum itself is capable of binding to plasma proteins, including albumin, transferrin, and gamma globulin. Three hours

after a bolus injection and two hours after the end of a three-hour infusion, 90% of the plasma platinum is protein bound.

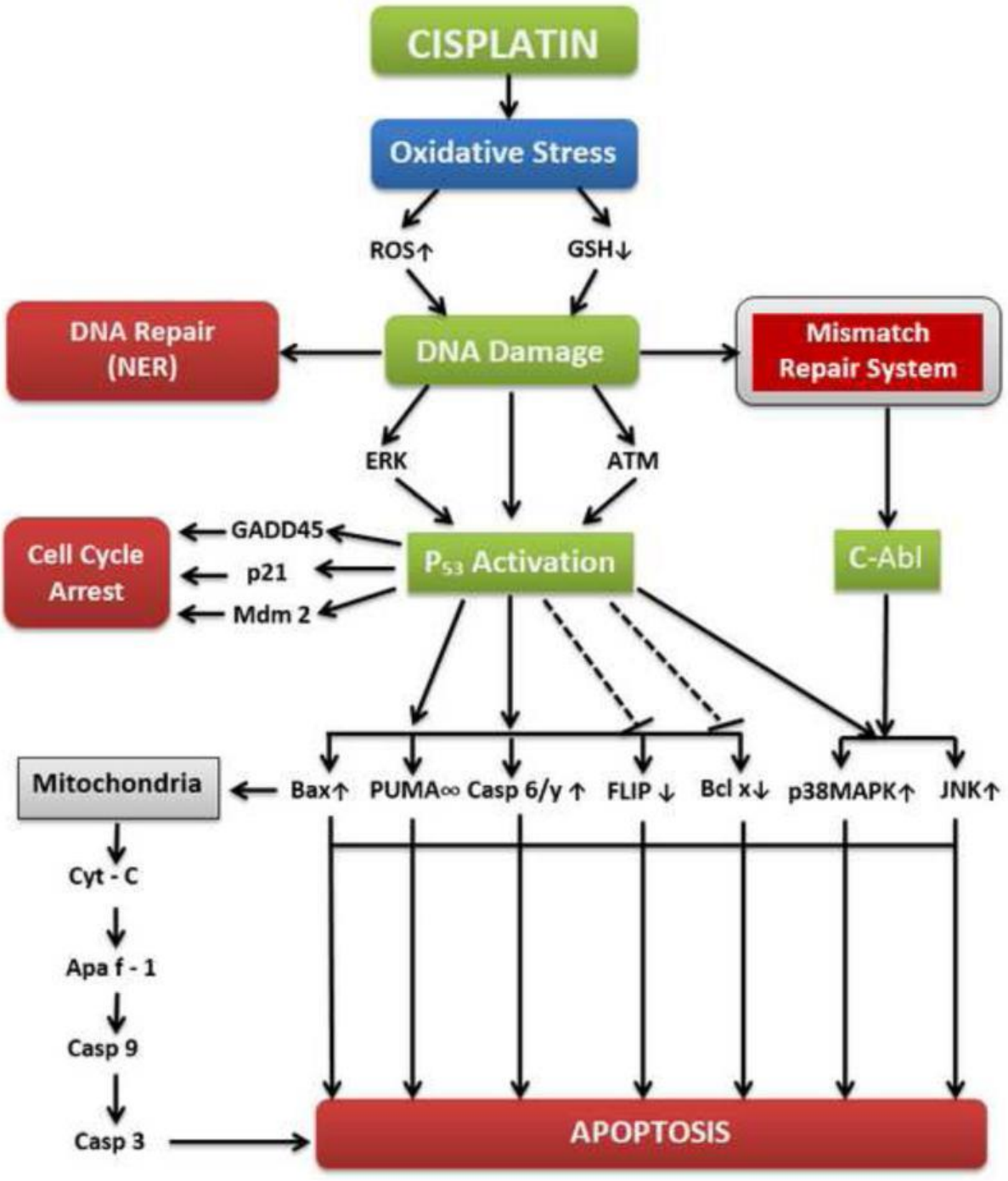

Fig.3 : Working Of Cisplatin

Computational Studies of Cisplatin

Cisplatin is one of the most effective anticancer drugs currently in use. Following the finding of its antitumor activity over three decades ago, strong research has been carried out to reveal the details of its cytotoxic activity and to design analogs with reduced side effects (Mantri and Baik, 2006). Recently, computational studies have been conducted to complement experimental works. The hydrolysis process of cisplatin which activates the drug was the goal of past research. Cisplatin–DNA interactions are the next theoretical studies, since DNA is the primary target of the drug. At present, to study the thermodynamics and kinetics of not only cisplatin–DNA complexes, but also of other complexes such as Pt(II)-based cisplatin analogs, other transition metal complexes, and DNA binding organic molecules, both quantum mechanical and molecular mechanical methods are being used.

The combination of dramatically improved computer hardware and robust, sophisticated, and numerically ef cient modeling software has allowed for employing high levels of theory to examine various aspects of cisplatin chemistry using computational chemistry techniques. The very rst computational studies on cisplatin aimed at better understanding the hydrolysis of cisplatin, because the activation by hydrolysis had long been established as the rate-limiting step (Basch, Krauss et al., 1986). An intriguing question had been the preferential antitumor activity of the *cis* isomer over the *trans* isomer, a fact then attributed to the steric effects of binding DNA bases. It was eventually discovered that the *cis* orientation of the leaving groups allowed binding of two adjacent guanine bases on the same strand, which resulted in a large kink in the DNA helix, causing polymerases to be stalled at the kink. However, it was demonstrated that the *trans* isomer is favored over the *cis* isomer in all cases due to reduction in ligand–ligand repulsion, especially in the case of anionic ligands. These differences become negligibly small when favorable hydrogen bonding interactions are possible between the ammine ligands and the other labile ligands (Basch, Krauss et al., 1986).

There is increasing awareness now that one important reason for cisplatin's performance is associated to the high mobility group (HMG) proteins that bind to DNA and protect the drug–DNA adducts against excision repair (Wang and Lippard, 2005). To enable comparison of the binding of Pt(II) to various positions in the four nucleobases in DNA and to keep computational costs to a minimum, $Pt(NH_3)_3^{2+}$ was used as the fragment that interacted with the bases.

Thermodynamics of hydrolysis of cisplatin and bis(ethylenediamine) dichloroplatinum(II) using a combination of molecular mechanics for obtaining optimized geometries of the reactants and products, and the extended Huckel method for deriving charge distributions and electronic energies were studied . This hydrolysis was studied by several others using various levels of theory, where a common approach adopted has been to use DFT to optimize the geometries of the key intermediates and reevaluate their energies using higher level ab initio methods, and/or adding solvation corrections based on continuum dielectric models. describes the interaction of transplatin and the fragments trans-$PtCl_2(NH_3^+$ and $Pt(NH_3)_3^{2+}$ with G:C and A:T base pairs using DFT, followed by an MP2-based energy analysis.

Other areas of active study on cisplatin are degree of local bending / unwinding upon cisplatin binding, the disruption of base stacking and other local distortions, the thermodynamics of the various possible adducts, the directional preference in the formation of the bifunctional adducts, the ineffectiveness of transplatin, the effect of cisplatin binding

on the dynamics of DNA, and the binding and recognition of HMG domain and/or DNA repair proteins to these adducts (Mantri and Baik, 2006). Computational models have made signi cant contributions to understanding the nature and reactivity of cisplatin and allowed for delineating many features of how it binds to DNA.

Pharmacology action:

The pharmacological action of cisplatin involves its ability to inhibit the growth of cancer cells. It exerts its anti-cancer effects by forming covalent bonds with the DNA molecule within the cancer cells. This binding disrupts the cell's ability to replicate and divide, ultimately leading to cell death.

Cisplatin also induces apoptosis, a process of programmed cell death, in cancer cells. It activates signaling pathways that promote apoptosis, triggering the cancer cells to undergo cell death.

Conclusion:

Cisplatin is one of the most effective anticancer agents widely used in the treatment of solid tumors. It has been extensively used for the cure of different types of neoplasms including head and neck, lung, ovarian, leukemia, breast, brain, kidney and testicular cancers. In general, cisplatin and other platinum-based compounds are considered as cytotoxic drugs which kill cancer cells by damaging DNA, inhibiting DNA synthesis and mitosis, and inducing apoptotic cell death. Several molecular mechanisms of action including induction of oxidative stress as characterized by reactive oxygen species production and lipid peroxidation, induction of p53 signaling and cell cycle arrest, down-regulation of proto-oncogenes and anti-apoptotic proteins, and activation of both intrinsic and extrinsic pathways of apoptosis. However, cisplatin chemotherapy is also associated with substantial side effects that include hepatotoxic, nephrotoxic, cardiotoxic, neurotoxic and/or hematotoxic damage. Also, some patients may relapse from cisplatin treatment with their cancers being refractory to cisplatin regimen. Hence, combination therapies of cisplatin with other drugs are common practice in the treatment of human cancers. Findings of several studies have suggested that other compounds combined with cisplatin constitute the best therapeutic approach to overcome drug resistance and reduce the undesirable side effects. Moving forward, combinatorial strategies which target multiple mechanisms, such as reducing cisplatin uptake and reducing inflammation, may offer the best chance for clinically meaningful prevention.

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