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Medicinal Applications of Transition Metals and some Platinum (II) based anti-cancer Drugs

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Abstract

In this review paper, the characteristic properties of the transition of metals applied for its medicinal application have been discussed in detail with relevant references. The fundamental properties of transition metals like the bonding of transition metals in biological systems applied to the treatment of various diseases, Ligand exchange Properties utilized for drugs designing, inhibition of enzyme activity by substrate and metabolite mimics to prevent the diseases, development of some new important redox-active drugs, applications of transition metal complexes in radio imaging and therapy with radiometals and radioactive agents for the treatment of various types of cancers and tumors, Paramagnetic behavior applied to use as MRI contrast agents, Catalytic potential of certain metal complexes applied to design and development of catalytic drugs and some platinum-based anti-cancer drugs such cis-platin, Oxaliplatin, Carboplatin, their discovery with the mechanism of action and side effect has also been discussed.

Keywords: Transition metals, Chemotherapy, anticancer drugs, and mechanism of action.

1. Introduction

Transition Metal-based compounds were widely used in the treatment of disease for decades, [1-10] but the lack of clear knowledge between the therapeutic and toxic limits was a major challenge for current medical science. In 1960 when the discovery of cisplatin was done by Barnett Rosenberg, a milestone in the history of metal-based compounds used in medical science in the treatment of various types of cancers was noticed. This led to the basic foundation for the recent era of the transition metal-based anticancer drugs. Platinum metal-based drugs, such as cisplatin, carboplatin, and oxaliplatin, are the basis of the transition metal-based compounds in the treatment of cancer, but the delay in the discovery of many other metal-based compounds obstructed the progress of research in this crucial medical field. Nowadays, demand for transition metal-based compounds in the treatment of different types of cancer needs more attention. This may be due to the scourge of cancer and, to a greater extent, the level of in vitro cytotoxic effect exhibited by some transition metal-based complexes, particularly those synthesized recently. Besides these, ligand interchange and modification of existing chemical structures led to the synthesis of a wide variety range of transition metal-based compounds, many of

which have demonstrated an increased cytotoxic and pharmacokinetic profile. Nowadays a new approach of cytotoxic drug design has recently been applied which involves conjugating metallic compounds with bile acid, steroid, peptide, or sugar to allow direct drug delivery to the targeted cancer cells. The objective of this review paper is to provide an overview of previous reviews on the certain properties of transition metals useful for their use in the medical field, analysis of recent new pharmaceutically important drugs, designing of certain important drugs applied to various diseases, certain platinum-based drugs, use in the treatment of different types of cancers occurring in different body parts, their cytotoxic effect on the cancer cells, as well as on new approach to metal-based drug design in cancer therapy.

2. Characteristic Properties of transition metal and compounds utilized for medical applications

2.1 Covalent bonding in biological systems applied to recent drug designing

The wide applications of metal complexes in medicine to diagnose or treat patients with different medical conditions are well established. The mechanism involves the formation of covalent bonds to essential biomolecules such as proteins, enzymes, DNA, etc., with transition metal ions, which inhibit their function and lead to cell death through different cellular pathways. In the case of platinum-based anticancer drugs, after intravenous injection, after entry inside the living cell, the complex undergoes aquation reaction which results in ligand interchange reaction between, one or two of the chloro ligands and water molecules. The newly formed Pt(II) complexes are activated and will then go to bind to nuclear DNA, preferentially to the N7 position of guanine base, to produce largely Intra and inter-strand crosslinking. These crosslinking blocks the replication process and cell division by interfering with DNA processing. [1,2]. Such a pattern of bonding of transition metals with the biological system has opened the door for the development of various new drugs for various diseases.

2.2 Ligand exchange Properties of transition metals used in various new medicines

The ligand exchange reactions of transition metal complexes, have been the subject of considerable interest for a number of decades. An extensive series of complexes, substituted with N-,O-,S-, and P-donor ligands have been synthesized, The substitution products of transition metal complexes are significant due to their widespread applications as antitumor [3], antiamoebic [4], antileukemic [5,6], DNA binders [7,8], anticancer [9,10], antimetastatic [11], antifungal and immunosuppressant [12]. One of the key characteristics of a number of transition metal complexes is their considerable ligand exchange chemistry, which is responsible for the mode of action of the most well-studied transition metal-based drugs approved in the clinic, namely the anticancer Pt(II) complexes cisplatin, oxaliplatin, and carboplatin (Figure 1A), as well as other drugs including the gold-based antiarthritic drug auranofin.

2.3 Inhibition of enzyme activity by substrate and metabolite mimics by transition metal complexes applied to the treatment of diseases

Many transitions metal-based medicines inhibit the activity of the enzyme by mimicking substrates and metabolites without the formation of direct coordinate bonds between the central transition metal ion and the enzyme. like vanadium-oxo species, which exhibit versatile and complex speciation and aqueous chemistry. This property of transition metals makes them useful for their application in enzyme activity inhibition. This property of transition metals has been used in the development of many recent drugs.

2.4 Transition metals applied to develop new Redox-active drugs.

Most transition metals have multiple oxidation states since it is relatively easy to lose electrons for transition metals. The oxidation state of a transition metal ion strongly influences its ligand interchange kinetics,38 which implies that it may be less reactive in one oxidation state but more reactive in some different oxidation state, which provides an intrinsic activation mechanism until the redox change is within the biologically accessible range. In other words, the low toxic active species is given to the patient, and upon activation by oxidation or reduction, the compound is able to exert its activity. This

characteristic, property of certain transition metal complexes, reduces the potential side effects of a drug, and further, the approach has been extensively studied in cancer treatment. Redox drug is activated by both oxidations as well as reduction processes. Both pathways have been applied successfully, but the latter is much more common.

2.5 Radiological applications of transition metal complexes

Radioactive metals have essential applications in radio-imaging and radiotherapy, useful in the detection and further treatment of some lethal diseases. Radiological applications comprise a large fraction of all clinically approved metal complexes in medicine. Radiometals also called radioactive metals to have some properties that have become essential to use in clinical medicine, which provides information that can lead to a concise diagnosis of some disease and therapy. [13,14] For imaging, radioisotopes that emit a detectable quantity of photons arising from direct gamma emission or positron decay are employed.

2.6 Paramagnetic behaviour of transition metals applied to use as MRI contrast agents

Transition metal ion and complexes having unpaired electrons in (n-1) d subshell shows paramagnetic behaviour i.e. They are attracted by the magnetic field. The paramagnetic metal ion has the potential to alter the transverse and longitudinal relaxation of the nuclear spin of protons of water molecules in a magnetic field was recognized soon after the discovery of NMR as a suitable technique for 3D imaging. Potential enhancers for in vivo proton relaxation were further developed, and initial work included the investigation of the various paramagnetic metal ions, like Fe(III), Cu(II), Cr(III), Mn(II), and Gd(III).[15] MRI contrast agents are now categorized by their composition and mechanism of action with respect to relaxation enhancement.

2.7 Catalytic potential of certain metal complexes used in certain catalytic drugs

In medical science certain transition metal complexes have been used as catalytic drugs by using the catalytic capability of certain transition metal complexes. Generally, drugs based on the catalytic property of transition metal can be broadly classified into two main categories, first, those that mimic the catalytic processes of naturally occurring metalloenzymes, and other, those that contain non-essential metals and catalyse abiotic transformations for having no enzymatic counterparts. In both above-said cases, however, small-molecule catalysts are generally preferred over large metalloenzyme-like structures. [16]. Transition Metal-based drugs that operate via catalytic mechanisms have been applied in clinical trials, and some other experimental complexes proposed to operate via a catalytic mechanism have been already reported. many metal complexes show the catalytic activity ex vivo and very few act via a catalytic mechanism in vitro or in vivo.

3. Transition Metal Compounds in Cancer Treatment:

Transition Metals and their compounds widely used in medicinal chemistry. Transition metals are represented by the d block element and their d subshells are in process of filling with an increase in atomic numbers. Because of small size and high charge density, and the presence of vacant (n-1) d orbitals having appropriate energy to accept lone pair and unshared electron pair from the ligands for bonding, Transition metals form a number of complexes that have wide applications in medicinal chemistry. The beginning reports for therapeutic application of transition metal complexes in cancer and leukemia date from the sixteenth decades. In 1960 the anti-tumor activity of an inorganic complex commonly called cisplatin was discovered. Cisplatin has developed into one of the most frequently used and most effective cytostatic drugs for the treatment of solid carcinomas. Other metals like gallium, germanium, tin, bismuth, titanium, ruthenium, rhodium, iridium, molybdenum, copper, gold were also shown effective against several kinds of tumors and cancers in humans and animals.

3.1 Some Platinum-based anticancer drugs:

3.1.1 Cisplatin

The compound cis-[Pt(NH3)2Cl2] or cis–diamminedichloroplatinum(II) , used as a chemotherapy drug, was first described by Italian chemist Michele Peyrone in 1845, and known for a long time as Peyrone's salt.[17] The structure of this complex was deduced by Alfred Werner in 1893. (Figure 1(a,b))[18] It is used to treat several kinds of cancers like testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancer, oesophageal cancer, lung cancer, mesothelioma, brain tumors, and neuroblastoma.[19] It is a non-organic platinum (II) containing drug having alkylating properties. It causes cross-linking of DNA and RNA chains. It has been shown that cisplatin binds primarily at N7 of two neighboring deoxyguanylates to DNA, which causes the inhibition of its replication.

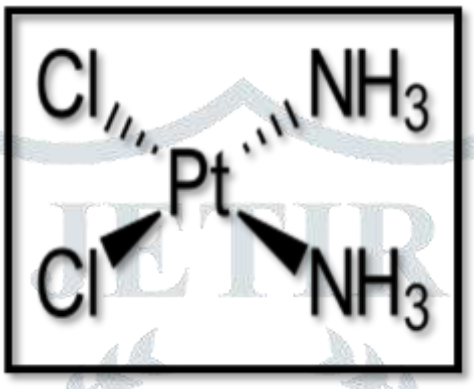


Figure 1a. Structure of Cisplatin

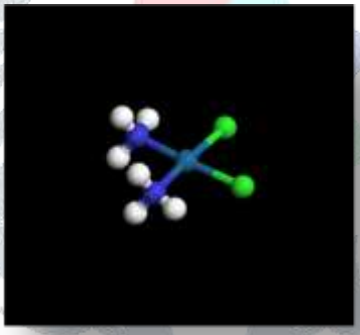


Figure 1b. Structure of Cisplatin (Ball and Stick)

3.1.1.1 Mechanism of action

It is given by injection into a vein and moves into the cell through diffusion and active transport. Inside the cell, it causes platination of DNA strand, which involves interstrand and intrastrand cross-linking as well as the formation of adducts, usually through guanine, (Figure 2.) as it is the most electron-rich site and hence, easily oxidized. The formation of cisplatin DNA adducts causes distortion and results in the inhibition of DNA replication. This ability of cisplatin to crosslink with purine bases to form adduct causes DNA damage and further induction to apoptosis within the cancer cells. [20,21]

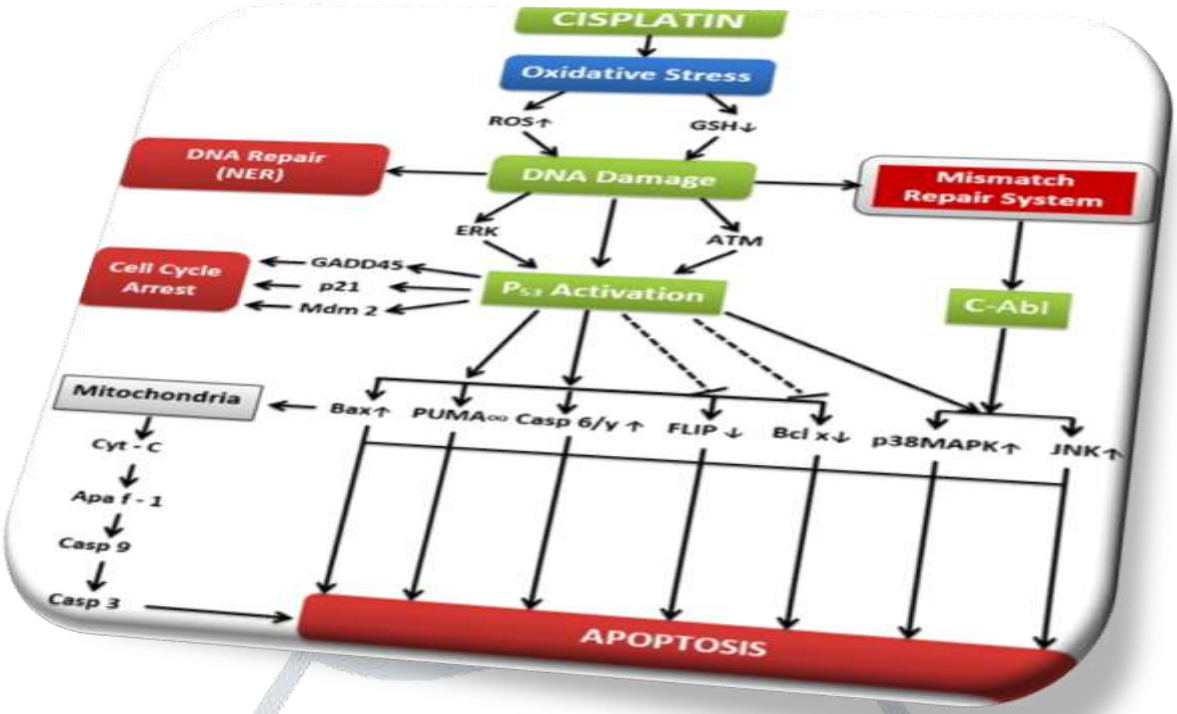


Figure 2. Adopted and modified from Dasari, S., Bernard Tchounwou, P., Cisplatin in cancer therapy: Molecular mechanisms of action. Eur J Pharmacol (2014),

3.1.1.2 Side effects

Cisplatin has a number of side effects that can limit its use including nephrotoxicity is a major concern. [22], Common side effects of cisplatin include visual perception and, Nausea and vomiting, diarrhea hair loss, loss of inability to taste food, dry mouth, dark urine, decreased sweating, dry skin, and other signs of dehydration, loss of vision, eye pain, chest pain or pressure, fever, sore throat, chills, or other signs of infection, unusual bleeding or bruising, black and tarry stools, red blood in stools, bloody vomit, Ototoxicity 23], hypomagnesemia, hypokalaemia, hypocalcemia and Hemolytic anemia [24]

3.1.2 Oxaliplatin

Oxaliplatin (Figure 3 a,b) was discovered in 1976 at Nagoya City University by Professor Yoshinori Kidani, is cancer treatment drug, given by injection into a vein. used to treat colorectal cancer. Generic oxaliplatin was approved in the United States in August 2009.[25] The drug was patented in 1976 and given approved for medical use in year 1996 and is in the World Health Organization's List of Essential Medicines.[26]

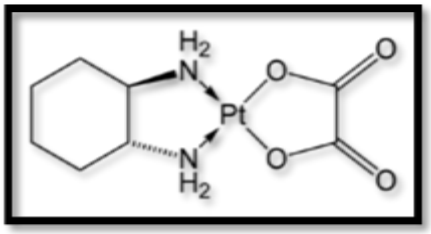


Figure 3 a. Structure of Oxaliplatin

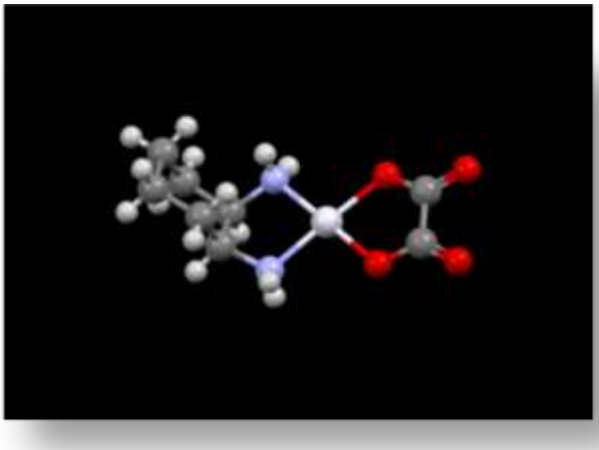
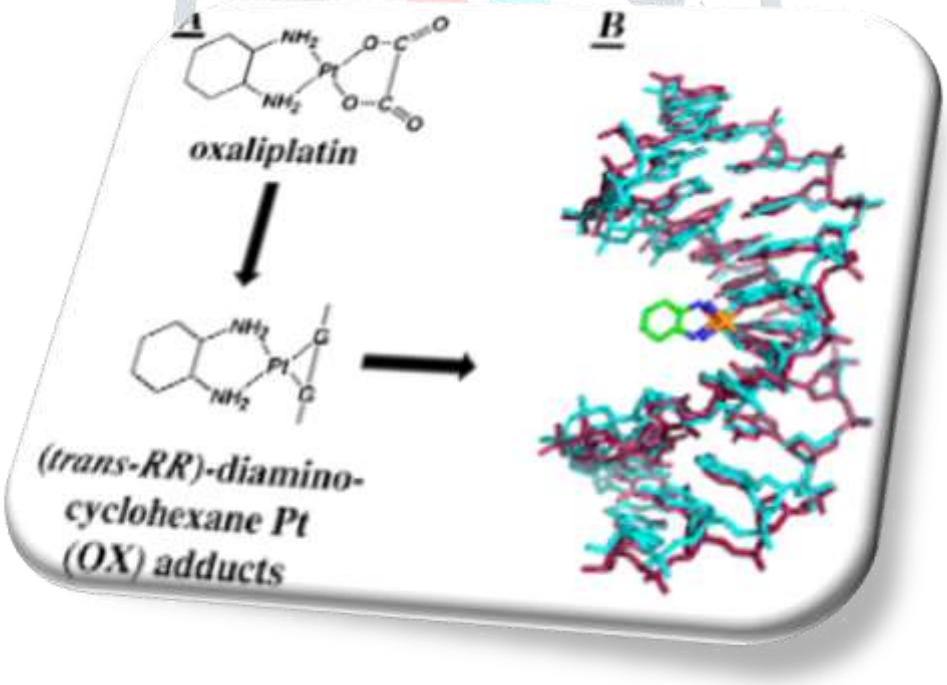


Figure 3b. Structure of Oxaliplatin (Ball and Stick)

3.1.2.1 Mechanism of action

The drug has a square planar geometry having platinum (II) as a central metal atom., oxaliplatin features the bidentate ligand trans-1,2-diaminocyclohexane and also features a bidentate oxalate group. in vivo studies suggest that oxaliplatin fights carcinoma of the colon through non-targeted cytotoxic effects. Similar to other platinum complexes, its cytotoxicity is thought to result from inhibition of DNA synthesis in cells. It forms both inter-and intra-strand cross-links in DNA,[27] which prevent DNA replication and transcription, leading to cell death



(Figure 4.). Figure 4. Oxaliplatin bonded to cancer cells (Adopted and modified from Google image)

3.1.2.2 Side effects

Oxaliplatin can cause a severe or life-threatening allergic reaction on the patient. Some people receiving it have had a reaction to the infusion within minutes after the medicine is injected into the vein. Common side effects include numbness, feeling tired, nausea, vomiting, diarrhea, tingling, burning pain, decreased blood cell counts.[28,29] abnormal liver function tests; mouth sores, or feeling tired. Besides these, Other serious side effects include allergic reactions and harmful to the baby in pregnancy are also noticed.[28,29,30]

3.1.3 Carboplatin

Carboplatin, (Figure 5 a,b) an effective chemotherapy drug, used to treat different forms of cancer, including ovarian cancer, lung cancer, head and neck cancer, brain cancer, and neuroblastoma [31], that had the same benefits of cisplatin but have lesser side effects were discovered at Michigan State University, by Dr. Tom Connors and Dr. Ken Harrap of in the 1970s. [32] and was developed at the Institute of Cancer Research in London.Carboplatin was patented in 1972 and approved for medical use by Food and Drug Administration (FDA), under the brand name Paraplatin, in March 1989. [33] Later, the generic versions of the drug became available in October 2004 and It is on the World Health .

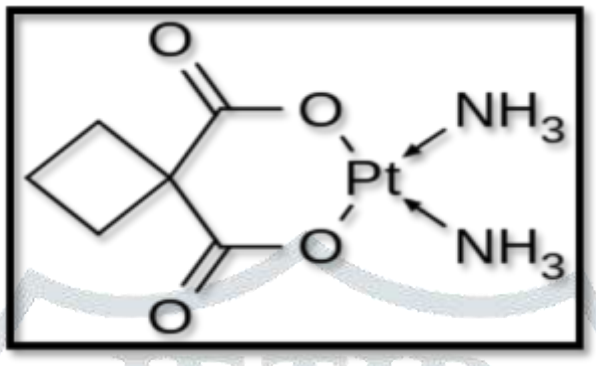


Figure 5a. Structure of Carboplatin

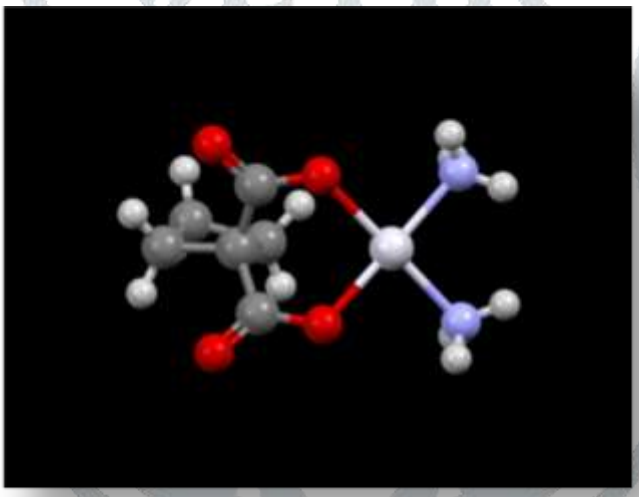


Figure 5b. Structure of Carboplatin (Ball and Stick)

3.1.3.1 Mechanism of action

It is very similar to cisplatin as it binds with DNA and affects the replication process. Carboplatin undergoes activation inside cells and acts by attaching alkyl groups to the nucleotides, leading to the formation of reactive platinum complexes that cause the intra- and inter-strand cross-linkage of DNA molecules within the cell. This modifies the DNA structure and inhibits DNA synthesis. This may affect a cell in all the phases of its cycles and can induce a number of different mutations.[35]

3.1.3.2 Side effects

Carboplatin is often favored because it has fewer side effects that are relatively common including vomiting within 24 hours of injection, fatigue, hair loss, changes in taste, abnormal magnesium levels, and low blood cell counts in more than 30 % of patients. In fact, some people don't experience any side effects at all. Besides these, abdominal pain, constipation or diarrhea, infection, mouth sores, kidney problems, hearing loss, and abnormal electrolyte and enzyme levels also have been recorded in 10-29% of patients. In Some cases, patients experience peripheral neuropathy, which is a very uncommon side effect.

4. Conclusions

Transition Metals were widely used in the treatment of diseases for centuries in different forms, among them platinum (II) based transition metal complexes are used for the treatment of different types of cancers since their discovery. Cisplatin is a very effective anticancer agent used for the treatment of several kinds of cancers which include the head and neck, lung, ovarian, leukemia, breast, brain, kidney, testicular, and many more varieties of cancers. generally, platinum-based complexes are considered cytotoxic drugs causing the death of cancer cells by damaging DNA, inhibiting DNA replication and mitosis, and inducing apoptotic cell death. Different mechanisms of action include oxidative stress, induction of signaling and cell cycle arrest, down-regulation of proto-oncogenes and anti-apoptotic proteins, and activation of intrinsic and extrinsic pathways for apoptosis. However, the platinum-based chemotherapy technique is also associated with certain fatal side effects that include hepatotoxic, nephrotoxic, cardiotoxic, neurotoxic, hematotoxic damage, and also many more common side effects. Recent studies have suggested that combination therapies of platinum-based drugs with other drugs, constitute the best therapeutic approach to overcome drug resistance and reduce the side effects. Moving forward, combinatorial strategies which target multiple mechanisms may offer the best chance for clinically meaningful prevention and cure for different types of cancers.

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