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A brief review on bioactivity of platinum therapeutics

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Abstract

The present review includes a brief introduction over deferent platinum anticancer drugs and their mechanism of action as well as their applications and limitations. Various recently studied Pt(II) complexes are also discussed herein. It also highlights the different possible DNA binding mode for a chemical substance as well as intracellular or extracellular platinum-sulfur interactions.

Keywords: Platinum complexes; Anticancer drugs; Pt-Sulphur adduct; Inorganic metal complexes; DNA binding mechanisms

1. Introduction

Inorganic metal complexes have versatile applications in the field of drug design where platinum (Pt) complexes have a story of success in cancer therapy [1,2]. Cisplatin, carboplatin, and oxaliplatin [3] are the three Pt based therapeutics which are endorsed worldwide for the cancer treatment in humans while few countries approved nedaplatin, lobaplatin and heptaplatin in medicinal use. After the insertion of cisplatin into the testicular cancer treatment, more than 95% cure rates have been recorded for the disease [4]. Since few decades, in testicular, ovarian, bladder and neck cancer treatment cisplatin are being continuously used. However, different side effects of these therapeutics restrict their uses in chemotherapy. Among them nephrotoxicity, neurotoxicity, ototoxicity and drug resistance are found to be major. Carboplatin has been listed on the World Health Organization's model list of essential medicines [5,6]. Because of the feeble cooperation with proteins, carboplatin is generally discharged through bio-waste [7]. It is additionally found to hamper the suitable activity of bone marrow [8]. Then again, oxaliplatin chemotherapy causes neurotoxicity as its aftereffects [9]. Accordingly, there are perpetually rising desire on the planning of platinum based anticancer medications having comparative or more noteworthy cytotoxic action on malignant growth cells yet lower harmfulness on typical cells in human body contrasted with the right now utilized Pt(II) based chemotherapeutics. Investigations throughout few decades have been performed by chemists, biologists and physicians to understand the mechanism of action of Pt(II) based anticancer drugs for improvement of their efficacy. Various metal complexes closely resembling cisplatin have been orchestrated which are unbiased and square-planar with two cis amines and two cis anionic ligands. The amine ligands in Pt(II) buildings can be chelating or nonchelating in nature and stay bound to the metal community over the span of intracellular changes and in this way named as "carrier ligands". On the contrary, the non-amine ligands which are monodentate or chelating in nature and are subsequently replaced by different bioactive molecules are called leaving groups. Strategies have been developed to modify the carrier ligands as well as leaving groups. However, a new platinum anticancer drug with reduced toxicity has not been approved worldwide over a decade and requires more exploration in the relating field of platinum (Pt) based anticancer medication plan.

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2. Mechanism of therapeutic action of cisplatin

The generalized mechanism of cisplatin involves (i) incretion of it within the cell; (ii) aquation and activation; (iii) interaction of these active species with different thiols, thio-ethers, peptides *etc.* (iv) DNA binding and (v) different cellular activity leading to cell death [10]. The cellular insertion of cisplatin (Figure 1) has been taken place through two different roots. Among these one is passive diffusion where plasma membrane is used to penetrate. Other one uses membrane proteins and called active transport [6,11]. Before binding to DNA it undergoes ligand substitution reaction where the chloride leaving groups have been replaced by intra cellular water to form monoaqua or diaqua species followed by the interaction with different sulphur containing bioactive molecules. The positively charged platinum complexes can be attracted by the negatively charged nuclear DNA which initially facilitates the Pt-DNA adduct formation.

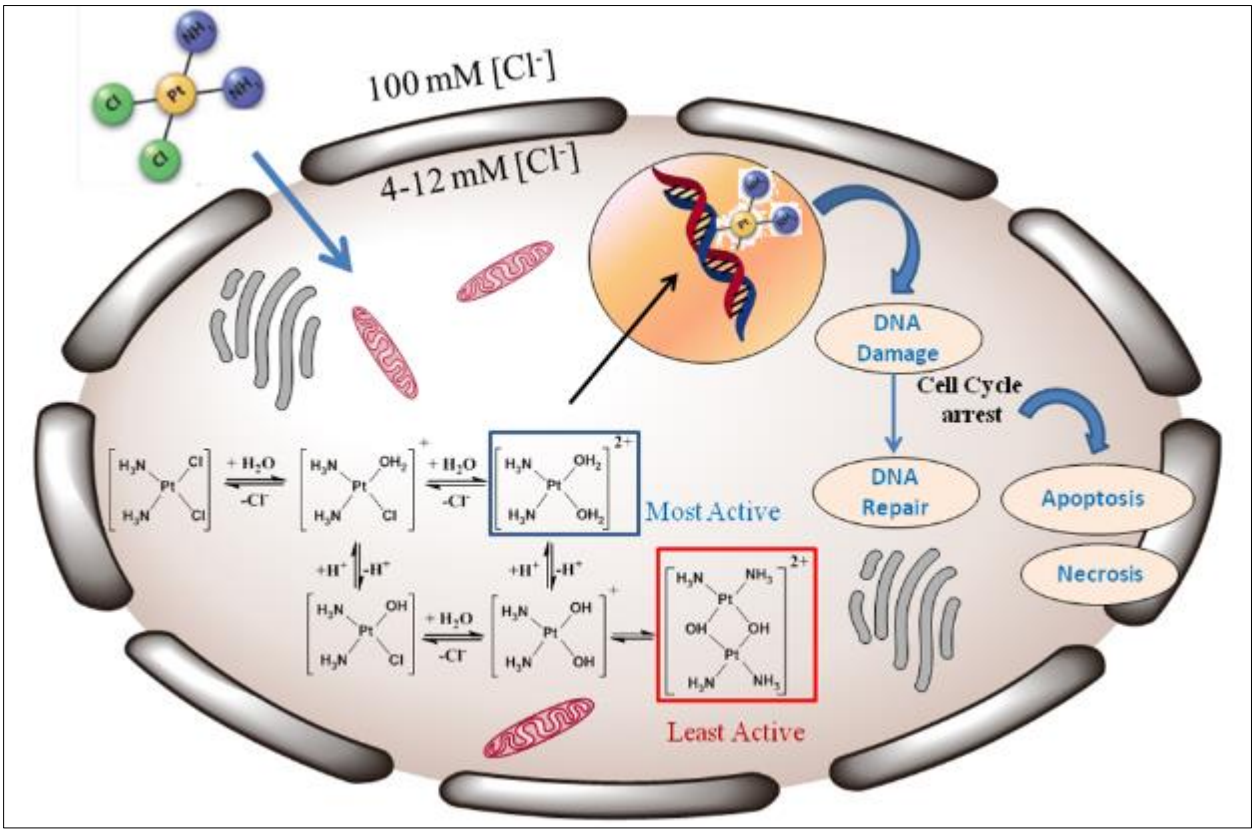

Figure 1 Mechanistic action of cisplatin

The diaqua species enters into the nucleus where the heterocyclic DNA bases coordinate to Pt(II) followed by the substitution of the ligated water molecules. Pt being electrophilic in nature attacks N7 atoms of the bases guanine and adenine as at this site the nucleophilicity is maximum. It is evident from ^{195}Pt NMR spectroscopic data [12] that cisplatin initially interacts with DNA to form monofunctional adduct followed by platination of the second guanine base which produce a cross linking on DNA. These DNA adducts produce a substantial distortion in DNA structure. Subsequently the cell cycle has been arrested at G2/M phase and attempts have been taken to repair the DNA [13].

3. Next generation Anticancer drugs

In modern oncology Pt-based therapeutics (Figure 2) are among the widely prescribed chemotherapeutics either alone or in association with other compounds. Platinum therapeutics shows their activity towards wide range of solid tumors, including bladder, colon, ovarian, testicular, lung, head and neck. Unfortunately, cisplatin chemotherapy produces several major side effects including nephrotoxicity and ototoxicity which has driven the field of research towards the development of cisplatin like next generation anticancer agents.

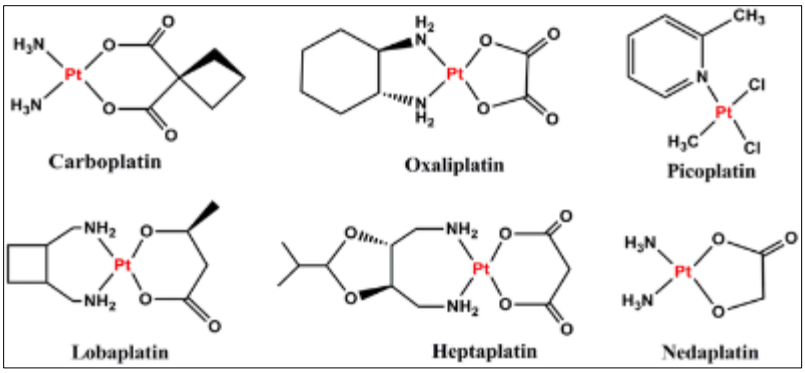

Figure 2 Next generation anticancer drugs

- ***Carboplatin*:** It got its approval in the year 1989. It is a second-generation Pt(II) anticancer drug that holds cyclobutane-1,1-dicarboxilate as its leaving group in place of the more labile chlorides in cisplatin. The chemical name of it is [cis-diammine(1,1-cyclobutanedicarboxyla to) platinum(II) and marketed in its trade name Paraplatin. Carboplatin forms similar type of DNA adducts as cisplatin does. It causes the complex activation kinetics much slower [14] and thus produces lower toxicity than cisplatin. It has a prolonged effect (a retention half-life of 30 hour) compared to cisplatin (1.5–3.6 hour) as the higher stability of carboplatin provides more time to interact with the targeted biomolecules [15]. Interestingly, it produces reduced side-effects, particularly negligible nephrotoxicity than cisplatin.
- ***Oxaliplatin*:** It is a third generation Pt(II) drug containing a bidentate 1,2-diaminocyclohexane stable carrier ligand (instead of two monodentate ammine carrier ligands as in cisplatin and carboplatin) and a bidentate oxalate leaving group. The chemical name and trade name of is [(*1R*,2*R*)-cyclohexane-1,2-diamine](ethanedioato-*O*,*O*′)platinum(II) and Eloxatin respectively. It is approved in the year 2002. Oxaliplatin containing weaker leaving groups than cisplatin facilitates much slower hydrolysis and the solutions of it are found to be stable towards equation over a period of time. The high activity and less toxicity of this third-generation drug make it a better chemotherapeutics. In some cases, like the treatment of colorectal cancer, oxaliplatin is administered jointly with leucovorin and fluorouracil colorectal, gastric and ovarian cancers [16]. Recently, many oxaliplatin derivatives including dinuclear complexes comprising of a cisplatin like moiety [17] are being synthesized worldwide to test the modified cytotoxicity in comparison to oxaliplatin [18–20]. These complexes have produced acceptable results such as similar cytotoxicity in ovarian cancer with higher tolerance level.
- ***Picoplatin*** {*cis*-(amminedichloro-2-methylpyridine) platinum(II)}**:** It was designed by replacing one amine of cisplatin by comparatively bulkier group 2-methylpyridine to overcome glutathione mediated platinum resistance [21,22]. Picoplatin is active upon oral administration. Due to the presence of 2-methylpyridine, binding to glutathione occurs through a dissociative substitution pathway. In this regard it also differs to Cisplatin which follows associative one. Thus the substitution becomes too slow to allow glutathione mediated resistance [23]. The drug is found to be active on various cisplatin, carboplatin and oxaliplatin resistant cancer [24, 25] such as hormone-refractory prostate, colorectal, small cell lung cancer with reduced toxicity. Investigations regarding oral versus intravenous administration of the drug have revealed that in case of oral administration linear and dose dependent plasma exposure with sufficient bioavailability has been achieved [26]. Moreover, significant potential for the drug has also been shown in combination therapies.
- ***Lobaplatin*** {cis-[(1R,2R)-1,2-cyclobutanebis(methylamino)-N,N'][(2*S*)-2-hydroxypropanoato(2-)-O1,O2]platinum(II)}**:** It is a platinum(II) complex having 1,2-bis(aminomethyl)cyclobutane as carrier ligand. Here lactic acid is present as leaving group. Lobaplatin mainly interacts with DNA to form Guanine-Guanine and Adenine-Guanine intra-strand cross-linking. The drug is active in a wide range of human tumours and in some of the cases it is found to overcome tumor resistance to cisplatin and carboplatin. Dose-limiting toxicity (thrombocytopoenia) for the drug has been noticed after Phase I clinical trials through different administration schedules where maximum tolerated doses have been recorded as 60 mg/m^2 per 3-4 weeks [27]. Lobaplatin is found to be active in patients with a variety of tumor types after Phase II trials.
- ***Heptaplatin*:** It is a Pt(II)-based anticancer chemotherapeutic compound developed by Sunkyong Industry Research Centre in Korea under the name SKI 2053R. The chemical name of it is cis-malonato-(4R,5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II). In 1990, the compound entered in clinical trials and got its approval from "Korean Food and Drug Administration" in 1999. Currently the drug is marketed in South Korea in the name of SunPla for gastric cancer treatment [6,28]. Combination of Heptaplatin and 5-fluorouracil

exhibits anti-proliferative activity in models of head and neck squamous cell cancers. After phase I clinical trial, the maximum tolerated dose (MTD) for Heptaplatin has found to be 480 mg/m^2 once every 4 weeks.

- ***Nedaplatin*** {cis-diammine(glycolato)platinum(II)}**:** The discovery of nedaplatin had been done by Shionogi Pharmaceutical Co. and approved in 1995 in Japan, the only country where the drug has its therapeutic use. Nedaplatin has regulatory approval, which was granted in 1995 [29,30]. The drug contains same carrier ligands as in cisplatin where glycolate is present as chelating leaving group, which enhances its water solubility than cisplatin. Primarily it has been used [31,32] for the treatment of head, neck, esophagus, small cell as well as non-small cell lung cancers. Continuous clinical trials are still going on to explore its expanded clinical applications [32].

4. DNA-Drug interactions

DNA is the prime target for the platinum based anticancer therapeutics. In DNA double helix structure each complementary strands are paired through H-bonding between A–T double bond and G–C triple bond. This helical structure consists of a major and minor groove which provides locations of attachments for tiny therapeutics [33]. These two grooves vary significantly in their dimension, shape, electrostatic potential, hydration and H-bonding sites [33,34]. There are many factors, for example, base pair arrangement, salt density and existing DNA binders which promptly impact the sugar puckering and overall DNA configuration [35]. Various substances having potentiality for DNA binding can interact with DNA through various potential binding including intercalation, irreversible covalent interactions or reversible grove binding [36]. The selectivity for these binding depends on the transition metal, the corresponding state of oxidation, ligand coordination, all over size and shape of the transition metal complexes [37]. Binding activity largely depends on the complex geometry. For example, complexes with square planar geometry such as Pt(II) compounds allow more profound entry within DNA compared to the other octahedral or tetrahedral metal complexes.

4.1. Covalent binding

The most familiar method of interaction for anticancer drug-DNA complex formation is covalent binding where direct covalent bond has been formed between the DNA constituent mainly nitrogenous base and the metal center of the drug molecule. The first clinically approved platinum based anticancer drug cisplatin undergoes covalent binding with DNA. This covalent binding causes unwinding of double helix and subsequently inhibit DNA transcription [36] followed by the cell death through apoptosis [38]. Next generation Pt(II) based anticancer drugs, analogous to cisplatin are capable of forming various DNA adduct (Figure 3) such as monofunctional, 1,2-intrastrand adducts, 1,3-intrastrand adducts and interstrand adducts. In monofunctional adduct formation one coordination site of the metal is occupied by N-bases of DNA and the other coordination site of the metal covalently interacts with surrounding water or protein molecules [39]. 1,2-intrastrand adducts which is the most common type of DNA interaction shown by the Pt-based anticancer drugs, involve the bond formation on the same strand between consecutive base pairs while in 1,3-intrastrand adducts, bond formation occurs with the base pairs which are one base pair apart. In inter-strand adduct formation covalent interactions have been established on opposite side of the double helix [39]. The next generation drugs are also binding with DNA through similar mechanisms as followed by cisplatin [40,41]. The limitations and side effects of these compounds have motivated the researcher to design the platinum complexes with different carrier ligands and leaving groups which will allow the complexes to interact with DNA in a different way.

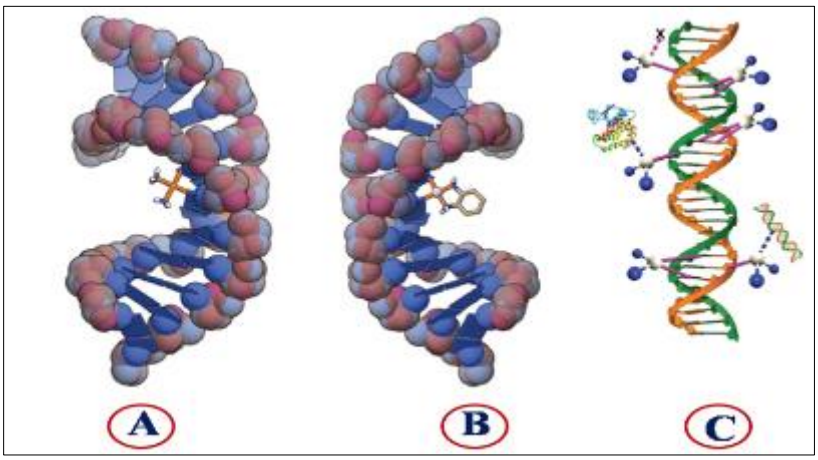

Figure 3 Covalent interaction of (A) cisplatin and (B) oxaliplatin with B-DNA. (C) Model of various type of possible DNA adduct formations (Image source: [37])

4.2. Noncovalent binding (Groove binding and intercalation)

Intercalation {Figure 4(A)} refers to the insertion of planar aromatic moiety of an organic molecule or metal complex between two adjacent base pairs of DNA structure [42]. This stabilizes the DNA by π–π stacking between the π –electron clouds of aromatic ring compounds and DNA base pairs [43]. However, binding strength depends on the depth of insertion of the molecule between DNA base pairs. It is an interaction of reversible nature which is stabilized by variety of possible binding forces [44–46]. The organic molecules or metal complexes containing π-electron rich moieties such as benzimidazole [47], phenanthrolines [48], anthracenes [49], anthraquinones [50], phenanthridines [51], acridines [51] and ellipticines [52] are known to act as good DNA intercalator.

In general platinum complexes which intercalate with DNA typically show anticancer property [37]. These type of complexes intercalate into the minor groove of DNA which as a whole lengthened and rigidified the DNA helix [53,54]. The positively charged complexes show better selectivity for binding to DNA with negatively charged backbone [55,56]. Additionally, it has been reported that independent properties of the ligands attached to metal center can influence both the biological activity and DNA affinity [57-60]. For example, few Pt-phen (phen= phenanthroline) complexes with methyl substituents in 5/6 position of phen had been developed and their cytotoxic efficiency are known at their nanomolar concentrations [61,62]. Complexes containing 5,6-dimethyl-1,10-phenanthroline had also been found to produce higher DNA binding efficacy than the complexes with phen without any substituent.

4.3. Bimodal - intercalation and covalent binding

Bimodal binding {Figure 4 (B)} represents a special type of DNA interaction where a substance undergoes intercalation in major or minor groove followed by covalent binding with DNA base pairs [37]. In literature the complex $[Pt(terpy)Cl]^+$ (where terpy is terpyridine) was reported [63] to show this type of interaction with DNA. The complex first undergoes intercalation and subsequently forms bonds with DNA base pairs after the removal of labile chloride leaving ligands. However, sulphur coordination to the Pt-center prevents the hydrolysis and leads the therapeutics to undergo intercalation alone [64]. There are so many complexes available in literature which can intercalate and subsequently bind covalently with DNA. Mostly the complexes that contain an intercalating carrier ligands and labile leaving groups are capable of this type of binding. Platinum complexes with the general formula $[Pt\{AO(CH_2)n(en)\}Cl_2]Cl$ where AO represents acridine orange bonded with ethylenediamine (en) through a polymethylene chain (n= 3 or 6) are found to show this type of dual binding [65] with DNA. These complexes show cytotoxicity in their micromolar level on different type of cancer cell lines. Nanomolar cytotoxicity on non-small-cell lung cancer has been shown by a new series of Pt-acridinylthiourea complexes which has been reported to simultaneously intercalate and forms covalent bonds with DNA base pairs.

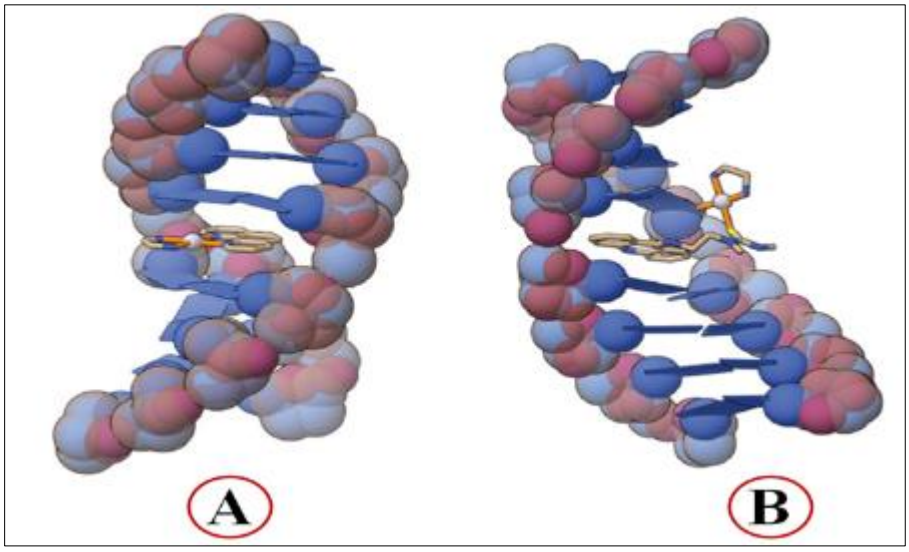

Figure 4 (A) A model for intercalative mode of binding (B) A model for the bimodal (intercalation and covalent) binding (Image source: [37])

5. Platinum-sulphur interaction

In cancer therapy platinum-sulfur interaction is no doubt a complicated concern due to the large abundance of sulfur-containing bio-molecules either inside or outside the human cells. These intracellular or extracellular associations are straightforwardly associated with the metabolism, toxicity and drug resistance of platinum-based anticancer medications in human body. In physiological frameworks, adequate bio-particles, for example, thio-ether and thiols are accessible for both kinetic and thermodynamic competition [66-69] with DNA for Pt(II) attributable to their high fondness towards the metal. Notwithstanding, the capability of these S-containing bio-molecules is questionable [70]. On one hand, sulfur rich proteins and amino acids are considered to block and deactivate the Pt(II) drug before it arrives at its cell target DNA causing side effects like gastrointestinal, nephro-, oto-and neurotoxicity [71,72]. Then again, Pt(II)-S collaborations are related with positive results, for example, conveyance of active species to cells and filling in as a medication repository for extreme platination to DNA [73]. In this way, clarification of the component of collaboration of Pt(II) buildings with organically pertinent S-containing particles by active and hypothetical examinations is of gigantic pertinence in the field of drug design.

5.1. Intracellular interaction

Mechanistic investigation of cisplatin and other related Pt(II) based anti-tumor drugs reveals that the active species of the drugs, generated from the intracellular hydrolysis enter into the nucleolus core and attaches to DNA. It ultimately triggers cell-cycle arrest and apoptosis. However, intracellular glutathione (a sulphur containing molecules) would compete for cisplatin with DNA. These sulphur binding may cause cisplatin resistance and its inactivation. As a consequence, the efficiency of Pt-based anticancer drugs largely depends on the balance between DNA target and sulphur triggered metabolism system [74,75]. After cellular insertion of cisplatin, a large amount of it (60%) has been arrested by GSH in cytoplasm [76] to give Pt-GSH adduct. The presence of Pt-GSH adduct has been confirmed both in a cancer cell-free system and in L1210 leukemia cells by detecting the related chelate bis-(glutathionato)-platinum [76]. Other cisplatin analogues drugs have also formed similar Pt-GSH adducts that have also been confirmed [77]. Again, in positive outcome platinum-sulfur adduct formation of hydrolyzed cisplatin derivatives with sulfur containing ligands generate a pro-drug which slowly releases the active form of the drug and modulates the kinetics of platination to DNA [78]. Hence, the examinations of connection of Pt(II) buildings with S-contributor bio-particles can assist the analysts with acquiring better understanding in the fate of anti-tumor drugs in the cells after their take-up, as well as to get more data about the internal cell processes which are impacted by drug administration within the body

5.2. Extracellular interaction

The metallo drug interacts with the most abundant plasma protein Human serum albumin (HSA) which could crucially determine its bioavailability and toxicology. The interaction of HSA with platinum-based anticancer drugs is related to its metabolism, efficacy, and distribution along the physiological system [79]. In blood, about 65–98% of cisplatin binds quasi irreversibly with HSA which is responsible for its transportation to targeted tumor calls. Methionine residues in HSA appear to be the most active binding site for Pt(II) rather than the previously believed Cys34 [80]. Among the six methionine residues, i.e. 87, 123, 298, 329, 446 and 548, Met298 appears to be the most surface accessible residue and thus becomes the main binding site for cisplatin. The apparent pseudo first-order rate constant (k_{app}) is linearly correlated with [albumin] by the following relation

$$k_{app} = 0.263 + 0.405\ [\text{albumin}]$$

Oxaliplatin reveals [81] quite better protein binding nature than either cisplatin [82] or carboplatin [83], while other next generation drugs such as lobaplatin [84] or nedaplatin [85] exhibited poor plasma protein interactions. Administration of cisplatin with HAS in human body increases the platinum concentrations in tumor cells [86] which causes a reduction of laryngeal carcinoma [87]. Chemotherapeutic activity of carboplatin could also be increased by albumin [88].

6. Conclusion

The present review highlights the mechanistic understanding of DNA binding, interaction of the different thiol or thio-ether and cytotoxicity which will offer a workable source for planning of new metal based anticancer therapeutics with reduced side effects and enhanced specificity. This review holds the information of the platinum based cytotoxic complexes which have prospect of becoming good antitumor therapeutics after advance examination of physiological and pharmacological investigations on living systems.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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