INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Anti-Cancer Activity Of Cisplatin And Its Toxicity

Pinki Chandra*, Gagan Panda, Sudhir Kathane, Shruti Rathore

LCIT School of Pharmacy, Bilaspur Chhattisgarh-495220, India

ARTICLE INFO

Received: 04 May 2024
Accepted: 08 May 2024
Published: 17 May 2024
Keywords:
Cancer, Malignancy, Treatment, Melanoma, cisplatin, cancer treatment.
DOI:
10.5281/zenodo.11208084

ABSTRACT

Cancer is a disease in which abnormal cells proliferate in the body. It is a group of various diseases involving uncontrolled multiplication and division of abnormal cells in the body. These abnormal cells form malignant growths which called neoplasm. Nowadays, cancer considered as one of the most prevalent diseases in the world, and its mortality is increasing. It is necessary to investigate new strategies to prevent and treat disease. Nowadays, a lot of research is going on precision medicine for a better future of cancer treatments. The common therapies are given to patient's chemotherapy, radiation therapy, immunotherapy, surgery and hormone therapy and combinations of these therapies. Stem cell transplant is also the best therapy for cancer but it given after the common therapies to recover the patient from blood loss and help in making the patient healthy. Cisplatin and other platinum-based drugs, such as carboplatin, ormaplatin, and oxaliplatin, have been widely used to treat a multitude of human cancers. However, a considerable proportion of patients often relapse due to drug resistance and/or toxicity to multiple organs including the liver, kidneys, gastrointestinal tract, and the cardiovascular, hematologic, and nervous systems. In this study, we sought to provide a comprehensive review of the current state of the science highlighting the use of cisplatin in cancer therapy, with a special emphasis on its molecular mechanisms of action, and treatment modalities including the combination therapy with natural products.

INTRODUCTION

The disease was first named cancer by the Greek physician Hippocrates, Father of Medicine, who applied Greek words "carcinoma" and "Karakinos" to describe a tumor. Cancers are a family of diseases that involve abnormal growth of the cells which spreads to other parts of the body. Cancer was named about the type of tissue from which they arise. Tumors resulting from epithelia are called "carcinomas." In both genders, cancers of the lung, colon, 0and rectum are the most significant problem. Breast cancer is common in women and prostate cancer in men. Breast cancers are not quite as prevalent as these "major four"

***Corresponding Author:** Pinki Chandra
Address: *LCIT School of Pharmacy, Bilaspur Chhattisgarh-495220, India*
Email : pinkichandra050@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

diseases. They include carcinomas of the bladder, stomach, liver, kidney, pancreas, esophagus, and cervix and ovary in women. Epidemiology of cancers is most natural skin cancer. They are rarely deadly, with the important exception of melanoma. Testicular cancer is the most frequent cancer affecting young adult males. Although cancer is a common disease worldwide, its molecular pathology is characterized by a wide spectrum of biological aggressiveness that makes all the difficult of its control, thus a life-threatening disease. Etiologic studies' reports about cancer support that its causal agent(s) could 4 be heterogeneous ranging from genetic mutation (e.g., somatic mutation (s), inherited mutation (s), unavoidable DNA replication errors), to epimutation (hypomethylation of an oncogene (s), tumor suppressor gene silencing through hypermethylation, Chromatin remodeling), to viral infection (Hepatitis B/C, Human Papilloma Virus), exposure to aflatoxin B, etc. However, exogenous risk factors and/or lifestyle could also favor an early onset of certain types of cancers

WHAT IS CANCER ?

Cancer is the uncontrolled growth of abnormal cells anywhere in the body. These abnormal cells are termed cancer cells, malignant cells, or tumor cells. These cells can infiltrate normal body tissues. Many cancers and the abnormal cells that compose the cancer tissue are further identified by the name of the tissue that the abnormal cells originated from (for example, breast cancer, lung cancer, and colorectal cancer). When damaged or unrepaired cells do not die and become cancer cells and show uncontrolled division and growth - a mass of cancer cells develop. Frequently, cancer cells can break away from this original mass of cells, travel through the blood and lymph systems, and lodge in other organs where they can again repeat the uncontrolled growth cycle. This process of cancer cells leaving an area and growing in another body area is termed metastatic spread or metastasis. For example, if breast cancer cells spread to a bone, it means that the individual has metastatic breast cancer to bone.

THE DEVELOPMENT OF CANCER (PATHOGENESIS)

Carcinogenesis is a multistage process. The application of a cancer-producing agent (carcinogen) does not lead to the immediate production of a tumor. There are a series of changes after the initiation step induced by the carcinogen. The subsequent stages tumor promotion may be produced by the carcinogen or by other substances (promoting agents), which do not themselves "produce" tumors. Initiation, which is the primary and essential step in the process, is very rapid, but once the initial change has taken place the initiated cells may persist for a considerable time, perhaps the life span of the individual. The most likely site for the primary event is in the genetic material (DNA), although there are other possibilities. The carcinogen is thought to damage or destroy specific genes probably in the stem cell population of the tissue involved. A compound that reacts with DNA and somehow changes the genetic makeup of the cell is called a mutagen. The mutagens that predispose cells to develop tumors are called initiators and the non-reactive compounds that stimulate tumor development are called promoters. A compound that acts as both an initiator and a promoter is referred to as a 'complete carcinogen' because tumor development can occur without the application of another compound.

Initiation

Initiation is the first step in the two-stage model of cancer development. Initiators, if not already reactive with DNA, are altered (frequently they are made electrophilic) via drug-metabolizing enzymes in the body and are then able to cause changes in DNA (mutations). Since many initiators must be metabolized before becoming active, initiators are often specific to particular

tissue types or species. The effects of initiators are irreversible; once a particular cell has been affected by an initiator it is susceptible to promotion until its death. Since initiation is the result of permanent genetic change, any daughter cells produced from the division of the mutated cell will also carry the mutation.

Promotion

Once a cell has been mutated by an initiator, it is susceptible to the effects of promoters. These compounds promote the proliferation of the cell, giving rise to a large number of daughter cells containing the mutation created by the initiator. Promoters have no effect when the organism in question has not been previously treated with an initiator. Unlike initiators, promoters do not covalently bind to DNA or macromolecules within the cell. Many bind to receptors on the cell surface in order to affect intracellular pathways that lead to increased cell proliferation. There are two general categories of promoters: specific promoters that interact with receptors on or in target cells of defined tissues and nonspecific promoters that alter gene expression without the presence of a known receptor. Promoters are often specific for a particular tissue or species due to their interaction with receptors that are present in different amounts in different tissue types. While the risk of tumor growth with promoter application is dose-dependent, there is both a threshold and a maximum effect of promoters. Very low doses of promoters will not lead to tumor development and extremely high doses will not produce more risk than moderate levels of exposure.

Progression

In mice, repeated promoter applications on initiator-exposed skin produces benign papilloma's. Most of these papilloma's regress after treatment is stopped, but some progress to cancer. The frequency of progression suggests that the papilloma's that progress to cancer have acquired an additional, spontaneous, mutation. The term progression, coined by Leslie Foulds, refers to the stepwise transformation of a benign tumor to a neoplasm and to malignancy. Progression is associated with a karyotypic change since virtually all tumors that advance are aneuploid (have the wrong number of chromosomes). This karyotypic change is coupled with an increased growth rate, invasiveness, metastasis and an alteration in biochemistry and morphology.

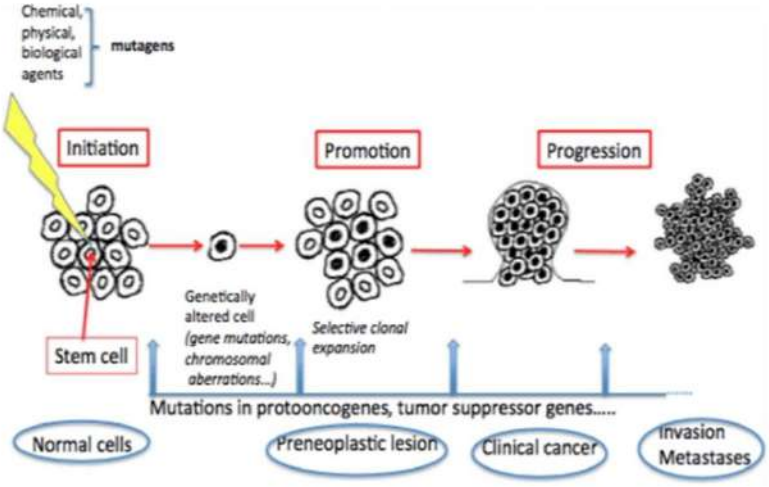

Fig.1: Factors influencing tumor development showing the progression from normal to invasive tumor

OBJECTIVES & METHODOLOGY

Cisplatin-

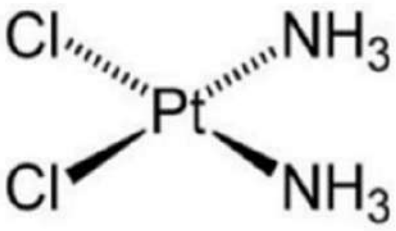

Fig.2: Structure of Cisplatin

Formula – H6Cl2N2Pt

IUPAC Name –

diamminedichloridoplatinum(II)

Mol. Wt.-

300.05 g/mol

Solubility –

Soluble in water, 0.253 g/100 g at 25 °C, 1 mg/mL in 0.9% sodium chloride . Slowly changes from the cis to the trans form in aqueous solution. Soluble in dimethylformamide. Insoluble in most common solvents

Description –

A yellow powder or orange yellow crystals

Category-

Anticancer

Dose-

By intravenous infusion, 15 to 20 mg per sq. m. of body surface daily for 5 days

Synthesis

Cisplatin is a co-ordinate compound that has been widely used since its discovery in 1960 by Rosenberg at the University of Michigan . In addition to testing its antibacterial activity against Escherichia coli, cisplatin's anti-tumor activity in sarcoma and leukemia cell lines was evaluated in 1969 by the same group of researchers. Using this preliminary data, clinical trials were conducted, introducing one of the most potent anticancer drugs to the clinic. In 1845, Michel Peyrone synthesized cisplatin for first time; later, Alfred Werner received the Nobel Prize award for disclosing the isomers of this platinum-based compound after identifying its structure. A rapid method for cisplatin synthesis was developed by Dhara in 1970, and later become a model for the **majority of subsequent cisplatin synthesis.**

ANTI-CANCER ACTIVITY OF CISPLATIN

Cisplatin exerts its anti-tumor activity by covalent binding to DNA-forming adducts and therefore by triggering apoptosis. Upon entry into the blood stream, cisplatin shows high affinity for sulfhydryl groups (proteins) and nitrogen donor atoms (nucleic acids), forming adducts due to aquation, which forms potent electrophiles. The 1,2-intrastrand cross-links of purine bases with cisplatin account for 90% of the adduct formation, leading to its cytotoxicity. Even though DNA repair mechanisms are available, cells often undergo apoptotic or non-apoptotic cell death due to leftover impaired DNA, RNA, and proteins. The mechanism of toxicity is a cascade of events starting with modulation of calcium signaling via copper transporters and therefore induction of oxidative stress. This is followed by mitochondrial dysfunction and the leakage of vital membrane proteins that regulate caspases 8 and 9, thus resulting in activation of downstream or executioner caspases, such as caspases 3 and 7, and inducing apoptosis. Hence, cisplatin interferes with signal transduction and cell regulation mechanisms, such as activation of ERK (extracellular signal-regulated kinase), phosphorylation of p53, upregulation of -p21, 45 kd-growth arrest and DNA damage (GADD45), mouse double minute 2 homolog (Mdm2), and phosphorylation of Bcl-2-associated death promoter (BAD) at ser136 via AKT, resulting in cell cycle arrest. An overview of the molecular mechanisms of cisplatin toxicity is presented in Fig.3

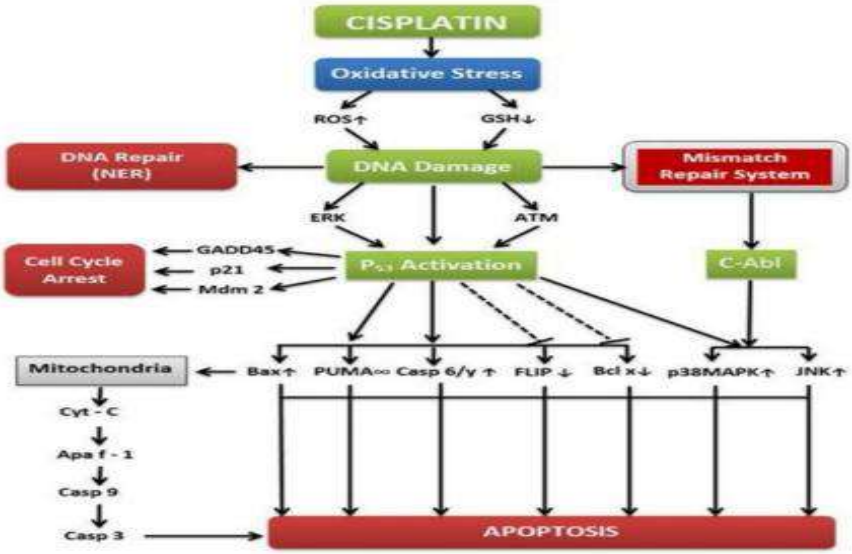

Fig. 3: Overview of the molecular mechanisms of cisplatin in cancer treatment

TOXICITY

Cisplatin has been known for its efficacy towards several types of cancers, such as germ cell tumors, sarcomas, carcinomas, and lymphomas. However, bioaccumulation of cisplatin has been noted, leading to multiple organ toxicity. In this section, we discuss the different types of cisplatin-induced toxicity along with current treatment options to alleviate the damage.

- **Nephrotoxicity:**

Damage to kidneys, being the major organ in the human body for excretion, has been linked to cisplatin treatment due to both tubular secretion and glomerular filtration. Drug efflux out of the body via the kidneys causes disproportionate retention of cisplatin at a rate of about five times that of the serum concentration compared to the liver. The biotransformation of higher cisplatin thiols that trigger a glutathione imbalance is a suggested mechanism of its toxicity. Histopathological studies have revealed proximal tubular damage as an early stage of toxicity, causing an imbalance in the reabsorption of water and sodium. In addition, more than 50% of the kidney tissue was disturbed after cisplatin treatment due to distal tubular damage, causing impaired renal flow of blood and glomerular filtration, which increases the secretion of proteins, enzymes, and electrolytes.

- **Hepatotoxicity:**

The liver is an important organ that is responsible for several biochemical processes. An increase in the levels of malondialdehyde (MDA) and a decrease in antioxidant enzymes in the liver is an indication of liver toxicity to cisplatin treatment. Elevated expression of cytochrome P450-2E1 enzyme leads to high levels of serum alanine transaminase (ALT) and aspartate aminotransferase (AST), and liver caspase-3 activity has been studied due to its cisplatin-induced hepatotoxicity. Therefore, the oxidative stress mechanism could be a potential biomarker of the mitochondrial toxicity leading to liver injury among cisplatin-treated patients. However, several chemical agents have been documented for the prevention of cisplatin-induced hepatotoxicity, such as zinc, selenium, fosfomycin, sodium thiosulfate, N-acetyl-cysteine, methionine, and taurine.

- **Neurotoxicity:**

Cisplatin induces toxicity in the nervous system depending upon the dose level and cumulative dose administered. Studies have shown the presence of DNA adducts in peripheral nerves,

causing peripheral neuropathy with clinical symptoms, such as automatic neuropathy, loss of haring, seizures, Lhermitte's sign, and encephalopathy. In addition, the dorsal root ganglion is considered the primary target of cisplatin-induced neurotoxicity due to its overproduction of reactive oxygen species (ROS). Few neurotropic factors, such as sulfur thiols, free oxygen radical scavengers, and phosphoric acid antibiotics, have been studied to prevent cisplatin-induced neurotoxicity.

- **Cardiotoxicity:**

Cardiotoxicity is a well-known outcome of cancer chemotherapy among long-term cancer survivors after cisplatin treatment. The mechanism of damage includes a significant increase in lactate dehydrogenase, creatine kinase, creatine kinase isoenzyme MB, and plasma cardiac troponin I in the serum plasma concentration, followed by a substantial increase in the MDA level. In addition, significant decreases in the GSH content, SOD activity, and total protein content were observed in myocytes. Clinical symptoms of heart damage induced by cisplatin treatment include cardiac ischemia (bradycardia), diastolic disturbances, hypertension, and microalbuminuria. The use of specific nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase inhibitors seems to have an ameliorative effect on cisplatin-induced cardiotoxicity.

- **Other Organ Toxicity:**

Ototoxicity has been mentioned in the literature as one of the side effects of cisplatin chemotherapy. Studies have shown that about 28% to 77% of patients show altered hearing thresholds after long-term exposure to cisplatin. The mechanism behind such damage appears to be overproduction of ROS in the cochlea, leading to apoptosis of the outer hair cells, spiral ganglion cells, and the stria vascularis. Testicular toxicity is also induced by cisplatin chemotherapy as a long-term effect in few patients. Figure 5.4 provides a schematic presentation of cisplatin-induced multiple-organ toxicity.

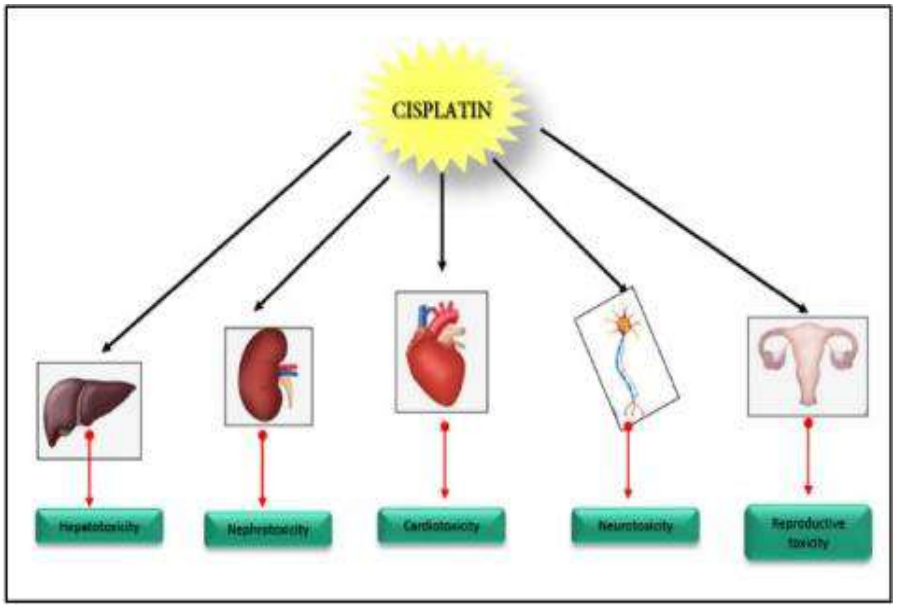

Fig. 4: The current understanding of cisplatin chemotherapy-induced toxicity

CONCLUSION

Cancer is one of the leading causes of death globally. Despite the advances made in the field of cancer treatment, no method is completely effective. Chemoresistance presents a major obstacle in the successful treatment of cancer. Therefore, deciphering the mechanisms involved in chemoresistance is inevitable to understand the complex pathways involved and to develop highly effective therapies. Cisplatin is a potent

chemotherapeutic drug used for the treatment of various human cancers. Its mode of action involves covalent binding to DNA, forming adducts and thereby triggering apoptosis and/or necrosis through a series of biochemical mechanisms that involve oxidative stress, DNA damage, and interference in various signal transduction pathways. However, its usage has been limited due to side effects and chemoresistance. After gaining an understanding of the molecular mechanisms underlying cisplatin resistance and multiple-organ toxicity, the scientific community is now searching for alternatives to enhance the bioactivity of cisplatin and to reduce or eliminate its side effects.

REFERENCES

1. Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, et al. Natural compounds for cancer treatment and prevention. Pharmacol Res 2009;59:365-78.
2. Available from: http://www.who.int/cancer/en/7 March2018.
3. Schulz AW. Cancer Prevention. Molecular Biology of Human Cancers. The Netherlands: Springer; 2007.
4. Thurston ED. Chemistry and Pharmacology of Anticancer Drugs. New York: Marcel Dekker; 2007.
5. Baker S, Silins I, Guo Y, Ali I, Hogberg J, Stenius U, et al. Automatic semantic classification of scientific literature according to the hallmarks of cancer. Bioinformatics. 2016;32(3):432–40. https://doi.org/10.1093/bioinformatics/btv585.
6. Cai Q, Yuan Z. Overview of ınfectious causes of human cancers. Adv Exp Med Biol. 2017;1018:1–9. https://doi.org/10.1007/978-981-10-5765-6_1.
7. De Flora S, La Maestra S. Epidemiology of cancers of infectious origin and prevention strategies. J Prev Med Hyg. 2015;56(1):E15–20.
8. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nat Rev Cancer. 2010;10(12):878–89. https://doi.org/10.1038/nrc2961.
9. https://govatihealth.com/what-is-cancer/
10. Lippert, B. Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug; Wiley-VCH: New York, NY, USA, 2006; ISBN 9783906390420.
11. Rosenberg, B.H.; Vancamp, L.; Trosko, J.E.; Mansour, V.H. Platinum Compounds: A New Class of Potent Antitumour Agents. Nature 1969, 222, 385–386. [CrossRef] [PubMed]
12. Mellor, D.P. The Sterochemistry of Square Complexes. Chem. Rev. 1943, 33, 137–183. [CrossRef]
13. Ramberg, P.J. Alfred Werner and Coordination Chemistry, 1893–1914. In Chemical Structure, Spatial Arrangement; Routledge:London, UK, 2018.
14. Dhara, S.C. A Rapid Method for the Synthesis of Cis-[Pt(NH3)2Cl2]. Indian J. Chem. 1970, 8, 193–19
15. Dasari, S.; Tchounwou, P.B. Cisplatin in cancer therapy: Molecular mechanisms of action. Eur. J. Pharmacol. 2014, 740, 364–378.[CrossRef]
16. Riddell, I.A.; Lippard, S.J. 1. Cisplatin and oxaliplatin: Our current understanding of their actions. In Metallo-Drugs: Development and Action of Anticancer Agents; De Gruyter: Berlin, Germany, 2018.
17. Lin, X.; Okuda, T.; Holzer, A.; Howell, S.B. The Copper Transporter CTR1 Regulates Cisplatin Uptake in Saccharomyces cerevisiae. Mol. Pharmacol. 2002, 62, 1154–1159. [CrossRef]
18. Salvesen, G.S.; Abrams, J.M. Caspase activation—Stepping on the gas or releasing

the brakes? Lessons from humans and flies.Oncogene 2004, 23, 2774–2784. [CrossRef]
19. Salvesen, G.S.; Dixit, V.M. Caspases: Intracellular Signaling by Proteolysis. Cell 1997, 91, 443–446. [CrossRef]
20. Aldossary, S.A. Review on Pharmacology of Cisplatin: Clinical Use, Toxicity and Mechanism of Resistance of Cisplatin. Biomed. Pharmacol. J. 2019, 12, 7–15. [CrossRef]
21. Sarin, N.; Engel, F.; Rothweiler, F.; Cinatl, J.; Michaelis, M.; Frötschl, R.; Fröhlich, H.; Kalayda, G.V. Key Players of Cisplatin Resistance: Towards a Systems Pharmacology Approach. Int. J. Mol. Sci. 2018, 19, 767. [CrossRef]
22. Dulz, S.; Asselborn, N.H.; Dieckmann, K.-P.; Matthies, C.; Wagner, W.; Weidmann, J.; Seidel, C.; Oing, C.; Berger, L.A.;Alsdorf, W.; et al. Retinal toxicity after cisplatin-based chemotherapy in patients with germ cell cancer. J. Cancer Res. Clin. Oncol.2017, 143, 1319–1325. [CrossRef]
23. Rubino, F.M.; Pitton, M.; Brambilla, G.; Colombi, A. A study of the glutathione metaboloma peptides by energy-resolved mass spectrometry as a tool to investigate into the interference of toxic heavy metals with their metabolic processes. Biol. Mass Spectrom.2006, 41, 1578–1593. [CrossRef]
24. Dmitriev, O.Y. Mechanism of Tumor Resistance to Cisplatin Mediated by the Copper Transporter ATP7B. Biochem. Cell Biol. 2011,89, 138–147. [CrossRef]
25. Nematbakhsh, M.; Ashrafi, F.; Pezeshki, Z.; Fatahi, Z.; Kianpoor, F.; Sanei, M.H.; Talebi, A. A histopathological study of nephrotoxicity, hepatoxicity or testicular toxicity: Which one is the first observation as side effect of Cisplatin-induced toxicity in animal model? J. Nephropathol. 2012, 1, 190–193. [CrossRef]
26. Kim, H.-J.; Park, D.J.; Kim, J.H.; Jeong, E.Y.; Jung, M.H.; Kim, T.-H.; Yang, J.I.; Lee, G.-W.; Chung, H.J.; Chang, S.-H. Glutamine protects against cisplatin-induced nephrotoxicity by decreasing cisplatin accumulation. J. Pharmacol. Sci. 2015, 127, 117–126.[CrossRef] [PubMed]
27. Lu, Y.; Cederbaum, A.I. Cisplatin-Induced Hepatotoxicity Is Enhanced by Elevated Expression of Cytochrome P450 2E1. Toxicol.Sci. 2006, 89, 515–523. [CrossRef] [PubMed]
28. Liao, Y.; Lu, X.; Lu, C.; Li, G.; Jin, Y.; Tang, H. Selection of agents for prevention of cisplatin-induced hepatotoxicity. Pharmacol.Res. 2008, 57, 125–131. [CrossRef]
29. Hausheer, F.H.; Schilsky, R.L.; Bain, S.; Berghorn, E.J.; Lieberman, F. Diagnosis, Management, and Evaluation of ChemotherapyInduced Peripheral Neuropathy. Semin. Oncol. 2006, 33, 15–49. [CrossRef] [PubMed]
30. Tlili, N.; Feriani, A.; Allagui, M.S.; Saadoui, E.; Khaldi, A.; Nasri, N. Effects of Rhus tripartitum fruit extract on CCl4-induced hepatotoxicity and cisplatin-induced nephrotoxicity in rats. Can. J. Physiol. Pharmacol. 2016, 94, 801–807. [CrossRef]
31. Salman, M.; Naseem, I.; Hassan, I.; Khan, A.A.; Alhazza, I.M. Riboflavin Arrests Cisplatin-Induced Neurotoxicity by Ameliorating Cellular Damage in Dorsal Root Ganglion Cells. BioMed Res. Int. 2015, 2015, 603543. [CrossRef]
32. El-Awady, E.-S.E.; Moustafa, Y.M.; Abo-Elmatty, D.M.; Radwan, A. Cisplatin-induced cardiotoxicity: Mechanisms and cardioprotective strategies. Eur. J. Pharmacol. 2011, 650, 335–341. [CrossRef]

33. Kucharz, J.; Michalowska-Kaczmarczyk, A.; Zygulska, A.L.; Wojtak, J.; Pawlik, W.; Herman, R.M.; Krzemieniecki, K. Bradycardia as a rare symptom of cisplatin cardiotoxicity: A case report. Oncol. Lett. 2016, 11, 2297–2299. [CrossRef]
34. El-Sawalhi, M.M.; Ahmed, L.A. Exploring the protective role of apocynin, a specific NADPH oxidase inhibitor, in cisplatin-induced cardiotoxicity in rats. Chem. Interact. 2014, 207, 58–66. [CrossRef]
35. Rybak, L.P. Mechanisms of cisplatin ototoxicity and progress in otoprotection. Curr. Opin. Otolaryngol. Head Neck Surg. 2007, 15,364–369. [CrossRef]
36. Osanto, S.; Bukman, A.; Van Hoek, F.; Sterk, P.J.; De Laat, J.A.; Hermans, J. Long-term effects of chemotherapy in patients with testicular cancer. J. Clin. Oncol. 1992, 10, 574–579. [CrossRef] [PubMed

HOW TO CITE: Pinki Chandra, Gagan Panda, Sudhir Kathane, Shruti Rathore, Anti-Cancer Activity Of Cisplatin And Its Toxicity, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 5, 814-822. https://doi.org/10.5281/zenodo.11208084