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# THERAUPTIC POTENTIAL OF METAL IN SANMIHITA

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## ABSTRACT

Despite recent encouraging advances against the disease, malaria remains a major public health problem affecting almost half a billion people and killing almost a million per annum. Due to a short arsenal of efficient antimalarial agents and the frequent appearance of resistance to the drugs in current use, which consequently reduce our means to treat patients, there is a very urgent and continuous need to develop new compounds. This forms the foundation for the modern era of the metal-based anticancer drugs. Platinum drugs, such as cisplatin, carboplatin and oxaliplatin, are the mainstay of the metal-based compounds in the treatment of cancer, but the delay in the therapeutic accomplishment of other metal-based compounds hampered the progress of research in this field. Recently, however, there has been an upsurge of activities relying on the structural information, aimed at improving and developing other forms of metal-based compounds and nonclassical platinum complexes whose mechanism of action is distinct from known drugs such as cisplatin.In the present experiment we are discussing regarding the metal in sanmihita.

Keywords: Sanmihita, Cisplatin, Ayurveda.

## INTRODUCTION

To this end, several ligand systems have been developed and dithiocarbamates have emerged as one of the ligand systems of choice for various applications in medicine such as for carbonic anhydrase (CA) inhibitors as well as important compound in cellular metabolism.[5] DTC compounds and its metal complexes have the aptitude of modulating key proteins involved in biological processes such as apoptosis, transcription, oxidative stress and degradation.[6] Coordinated dithiocarbamates are reported to possess potential chemoprotective function,[7] treatment of bacterial and fungal infections, HIV-AIDS, and currently cancer.[8] The effect on tumour cells is ascribed to their reactivity with copper in tumour cells to form complex, which inhibit proteasome and subsequently initiate tumour cell-specific apoptosis. Metal complexes formed by bidentate ligands which dithiocarbamates is an example, forms quite stable molecules. This is because of the so called "chelate effect" and the fact that the possibility of decomposition and ensuing loss of the dithiocarbamato ligand is impossible to occur.[8] In addition, square planner complexes of dithiocarbamates yield more stable complexes due to coordination of additional S-donor moiety such as cysteine, methionine *etc*. The stability has been possible owing to *trans* arrangement of S-donor moiety to the –NCSS moiety resulting from the strong *trans*-influencing effect of the dithiocarbamato sulphur atoms. Consequently, further interactions of the metal centre with other thiol containing biomolecules likely to generate severe side effects, for example, liver, kidney toxicity (hepatotoxicity, nephrotoxicity respectively) *etc*. are prohibited.[8]

Taking into consideration the distinctive attributes and in-depth understanding of the biological properties and recognition phenomena involving dithiocarbamates and biological systems, several dithiocarbamates complexes, nanoparticles, and polymers are currently been developed for therapeutic applications and have shown interesting efficacies. The interest of these dithiocarbamato complexes is gradually growing not only because of their anticancer properties but rather their use for treatment of many other conditions such as: cocaine addiction,[9] inflammation[10] and viral infections.[11] Different metals such as platinum, vanadium, ruthenium, gold, rhodium and many others have been implicated to possess therapeutic properties when conjugated with organic ligands[12,13] Specifically, dithiocarbamates ligand systems have been of interest. The ligand is believed to have the properties to serve as a vehicle for transporting the metal to their intended target site[14] and also has the tendency to reduce toxicity, improve solubility and biocompatibility.[15]

Dithiocarbamates supported gold compounds have been synthesized and exhibited various applications in medicine. Coordinated gold dithiocarbamates are

reported to possess potential chemoprotective function and serve as a means of transporting metal to its active site. Significant improvement is required in the fabrication process from inexpensive to non-toxic materials and technique. This review highlights the importance of dithiocarbamates-based gold metal complexes, polymeric dithiocarbamates gold complexes and dithiocarbamates nano particulate systems towards the development of highly promising therapeutic drugs.

Oxaliplatin was initially launched in France in 1996 and formally available in the countries of Europe in 1999 and the US in 2002.27 This is a platinum-based drug with oxalate and diaminocyclohexane ligand (DACH). The DACH plays a major role in cytotoxicity and protects it against cross-resistance with cisplatin and oxaliplatin. It is licensed to be used as a combination therapy with other chemotherapeutic agents in the management of colon cancer and non-small-cell lung cancer.28 This drug has better safety profile than cisplatin, as such is used in patients who cannot tolerate cisplatin.27

Nedaplatin is a platinum derivative of *cis*-diamine (glycolate), which was formally approved in Japan in 1995. The drug is said to have a better safety profile than cisplatin (less nephrotoxic)29 and is used as a combination therapy in the management of urological tumors.29

Lobaplatin is a derivative of the platinum compound, represented as 1,2-diammino-l-methyl-cyclobutane-platinum(II)-lactate. The antitumor activities of this compound span through the human lung, ovarian and gastric cancer xenografts.27 It has non-cross-resistance to cisplatin, particularly human sensitive cancer cells. Lobaplatin was originally approved for use in the management of patients with chronic myelogenous leukemia, small-cell lung cancer (SCLC) and metastatic cancer.30 Recently, a phase I clinical trial of dose escalation of lobaplatin in combination with fixed-dose docetaxel in the treatment of human solid tumor was established.31 In this study, the maximum tolerable dose of lobaplatin when combined with docetaxel for the treatment of solid tumor, known to have progressed after chemotherapy, was established.31 Positive results from the phase I trial prompted researcher to recommend the same dosage for the phase II clinical trial.31

Picoplatin is a 2-methylpyridine analog of cisplatin (formerly known as ZD0473) originally developed to provide steric cover around the platinum center, thereby providing a steric hindrance to the drug and preventing the attack from nucleophiles. It shields it against DNA-repair pathway that enhanced resistance.32 Preclinical studies33 revealed promising anticancer activities in the resistant cell line to cisplatin.28 However, after the phase II clinical trial was conducted, it was noted that picoplatin offers no superior advantage on the targeted cell line except a significant decrease in neurotoxicities.28 In a related development, picoplatin is still undergoing

phase I and II clinical trials as a treatment for colorectal cancer in combination with 5-fluorouracil (FU) and leucovorin and also in combination with docetaxel for prostate cancer.34

Satraplatin, *bis*-(acetate)-ammine dichloro-(cyclohexylamine) platinum (IV), is the first orally bioavailable platinum drug. This drug exhibits varying pharmacodynamics and pharmacokinetic properties relative to other platinum compounds and hence may possess a different spectrum of anticancer activities.27 The anticancer activities of satraplatin span through platinum-sensitive and resistant cell lines, including cervical, prostate, ovarian and lung cancers.34 Nonlinear pharmacokinetics was one major challenge encountered during the initial studies of satraplatin that led to the study being abandoned.34 Satraplatin has undergone several phases of clinical trials. Phase III clinical trials examined satraplatin and prednisolone combination against refractory cancer.34 Satraplatin is currently targeted in phase I, II and III trials in combination with other drugs such as docetaxel in the treatment of prostate cancer.

Lipoplatin is a liposomal form of cisplatin designed to enhance the pharmacokinetic safety profile and allow dosage manipulation while targeting cancer cells.34 The liposomes are made of dipalmitoyl phosphotidylglycerol, soyphosphatidyl choline, cholesterol and methoxy-polyethylene glycol-distreatoyl phosphatidyl-ethanolamine.34 The presence of liposomes offered a circulatory advantage to the drug. Lipoplatin has undergone phase I, II and III clinical trials with the main focus on its anticancer activity in SCLC.34 It is also being investigated for breast, pancreatic, head and neck anticancers.

References:

Palma G, D'Aiuto M, Rea D, et al. Organo-metallic compounds: novel molecules in cancer therapy. Biochem Pharmacol Open Access. 2014;13(13):1603–1615. [Google Scholar]

Santini C, Pellei M, Gandin V, Porchia M, Tisato F, Marzano C. Advances in copper complexes as anticancer agents. Chem Rev. 2014;114(1):815–862. [PubMed] [Google Scholar]

Khalid H, Hanif M, Hashmi MA, Mahmood T, Ayub K, Monim-Ul-Mehboob M. Copper complexes of bioactive ligands with superoxide dismutase activity. Mini Rev Med Chem. 2013;13(13):1944–1956. [PubMed] [Google Scholar]

Shokohi-pour Z, Chiniforoshan H, Momtazi-borojeni AA, Notash B. A novel Schiff base derived from the gabapentin drug and copper (II) complex: synthesis, characterization, interaction with DNA/protein and cytotoxic activity. J Photochem Photobiol B. 2015;162:34–44. [PubMed] [Google Scholar]

58. Lian W-J, Wang X-T, Xie C-Z, et al. Mixed-ligand copper Schiff base complexes: the role of the co-ligand in DNA binding, DNA cleavage, protein binding and cytotoxicity. Dalton Trans. 2016;45(22):9073–9087. [PubMed] [Google Scholar]

Zou T, Ching A, Lum T, Lok C-N, Zhang J-J, Che C-M. Chemical biology of anticancer gold(III) and gold(I) complexes. Chem Soc Rev. 2015;44:8786–8801. [PubMed] [Google Scholar]

da Silva Maia PI, Deflon VM, Abram U. Gold(III) complexes in medicinal chemistry. Future Med Chem. 2014;6(13):1515–1536.