**SANI SADIQ**

**16/SCI03/012**

**410 ASSIGNMENT**

1. ROLE OF CISPLATIN AS ANTI CANCER AGENT

Cisplatin (CAS No. 15663-27-1, MF-Cl2H6N2Pt; 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 stemperature. It is slightly soluble in water and soluble in dimethylprimanide and *N,N*-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the *trans*-isomer . Cisplatin has a molecular weight of 301.1 gm/mol, a density of 3.74 g/cm3, a melting point of 270° C, a log Kow of -2.19 and a water solubility of 2.53 g/L at 25° C (HSDB 2009).

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 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.

Cisplatin has been especially interesting since it has shown anticancer activity in a variety of tumors including cancers of the ovaries,' testes,' and solid tumors of the head and neck. It was discovered to have cytotoxic properties in the 1960s, and by the end of the 1970s it had earned a place as the key ingredient in the systemic treatment of germ cell cancers. Among many chemotherapy drugs that are widely used for cancer, Cisplatin is one of the most compelling ones. It was the first FDA-approved platinum compound for cancer treatment in 1978 . This has led to interest in platinum (II) - and other metal-containing compounds as potential anticancer drugs .

Cisplatin is clinically proven to combat different types of cancers including sarcomas, cancers of soft tissue, bones, muscles, and blood vessels. Although such cancers have recently received better prognosis and therefore have become less life threatening, significant challenges remain with regard to their cure. Also, because of drug resistance and considerable side effects, combination therapy of cisplatin with other cancer drugs have been applied as novel therapeutic strategies for many human cancers. In this research, we aim to provide a comprehensive review of the physicochemical properties of cisplatin and related platinum-based drugs, to discuss its uses (either alone or in combination with other drugs) for the treatment of various human cancers, to examine its molecular mechanisms of action, and to discuss it potential side effects.

ROLE OF SELENIUM AS ANTI CANCER AGENT

Selenium is an essential micronutrient for human and animals. The function of selenium has been mainly attributed toits presence in selenoproteins . Selenium was first proposedas an antitumorigenic trace element in the late 1960s, a decadelater than it was identified as a nutritional essential, based on ecological associations of cancer mortality rates and crop se-lenium contents in the United States. Since then, a large body of scientific evidence indicated that selenium can play a role in cancer prevention. This is supported by an extraordinarily consistent body of discoveries from studies with animal tumor and cell culture models, and by some, but not all epidemiologic studies. Both inorganic and organic selenium-compounds can be anti-tumorigenic at doses greater than those required to support the maximal expression of the selenoenzymes that are generally regarded as discharging the nutritional effects of the element. The evidence for selenium as a cancer preventive agent includes that from geographic , animal, prospective and intervention studies. Newly-published prospective studies on oesophageal, gastic-cardia and lung cancer have reinforced previous evidence, which is particularly strong for prostate cancer. Interventions with selenium have shown benefit in reducing the risk of cancer incidence and mortality in all cancers combined, and specifically in liver, prostate, colon rectal and lung cancers. The effect seems to be strongest in those individuals with the lowest selenium status. As the level of selenium that appears to be required for optimal effect is higher than that previously understood to be required to maximize the activity of selenoen-zymes, the questions has been raised as to whether selenoproteins are involved in the anti-cancer process. However, re-cent evidence showing an association between selenium ,reduction of DNA damage and oxidative stress together with data showing an effect of selenoprotein genotype on cancer risk implies that selenoproteins are indeed implicated. The likelihood of simultaneous and consecutive effects at different cancer stages still allows an important role for anti-cancer selenium metabolites such as methyl selenol formed from gama-glutamyl-selenomethyl-SeCysand selenomethyl-SeCys,components identified in certain plants and selenium-enriched yeast or garlic that haveanti-cancer effects. Several cancerpreventive mechanisms have been described and it is likely that selenium acts through multiple pathways including inhi-bition of cell proliferation, induction of cell apoptosis, inhibition of angiogenesis, the anti-oxidative, and anti-inflammatory effects mediated through activity of selenoenzymes. Genetic variation in selenoenzymes may modify thepotential chemopreventive effect of selenium and need to be further investigated. Current primary and secondary preven-tion trials of selenium are underway in the USA, including theSelenium and Vitamin E CancerPrevention Trial relatingto prostate cancer. It will be important to further evaluate the potential chemopreventive effect of selenium. The anticarcinogenic effects of selenium compoundsconstitute intermediate mechanisms with several underly-ing chemical/biochemical mechanisms such as redox cy-cling, alteration of protein-thiol redox status and me-thionine mimicry. The results from all of three differentlevels of research, clinical trial, animal model and cul-tured cells, have confirmed that selenium can be recog-nized as a cancer preventive agent to reduce the risk ofsolid cancers of several organ sites. The significant inter-action between baseline selenium and the efficacy of theselenium-yeast for reducing cancer risk, if validated, hasimportant implications for the tailor-designing of deliv-ery of selenium of target populations for cancer preven-tion. Studies in mechanisms have indicated that the me-tabolite pool of methylselenol has a lot of desirable at-tributes for chemoprevention bytargeting both epithelialand vascular endothelial cells of cancers.

**VANADIUM AS AN ANTIDIABETIC AGENT**

Compounds of the trace element vanadium have been shown to mimic insulin in *in vitro* and *in vivo* systems. These compounds have been found to exert anti-diabetic effects in rodent models of type 1 and type 2 diabetes mellitus as well as in a limited number of studies in human diabetic subjects. Thus, vanadium compounds have emerged as agents for potential use in diabetes therapy. However, treatment of diabetic animals with inorganic vanadium salts has also been associated with some toxic side-effects such as gastrointestinal discomfort and decreased body weight gain. In addition, vanadium salts have been reported to exert toxic effects on the liver and kidney. More recently, it was shown that organic vanadium compounds were much safer than inorganic vanadium salts and did not cause any gastrointestinal discomfort, hepatic or renal toxicity.

The increased plasma free fatty acid levels due to the deregulated lipolysis in adipocytes are considered as one of the major risk factors for developing type II diabetes. Vanadium compounds are well-known for their antidiabetic effects both on glucose and lipid metabolism, but the mechanisms are still not completely understood. There is a present study which suggests a mechanism for how vanadium compounds exert antilipolytic effects. It demonstrates that all the three vanadium compounds, bis(acetylacetonato)-oxovanadium(IV) (VO(acac)2), bis(maltolato)-oxovanadium(IV) (VO(ma)2) and sodium metavanadate (NaVO3), attenuated basal lipolysis in 3T3L1 adipocytes in a dose- (from 100 to 400 μM for VO(acac)2and VO(ma)2, 1.0 to 4.0 mM for vanadate) and time-dependent (from 0.5 to 4 h) manner using the glycerol release as a marker of lipolysis. In addition, the three compounds inhibited lipolysis to a different extent. Among them, VO (acac)2 (from 100 to 400 μM) exerted the most potent effect and reduced the lipolysis to ∼60–20% of control after 4 h treatment. The antilipolytic effects of vanadium compounds were further evidenced by a decrease of the levels of phosphorylated HSL at Ser660 and phosphorylated perilipin, which were counteracted by inhibitors of PI3K or Akt but not by an MEK inhibitor. This indicates that though both Akt and ERK pathways are activated by the vanadium compounds, only Akt activation contributes to the antilipolytic effect of the vanadium compounds, without the involvement of ERK activation. We previously demonstrated that VO(acac)2 can block cell cycle progression at the G1/S phase *via* a highly activated ERK signal in human hepatoma HepG2 cells. Together with this study, we show that similar activated pathways may lead to differential biological consequences for cancer cells and adipocytes, indicating that vanadium compounds may be used in the prevention and treatment of both diabetes and cancer.