LITERATURE REVIEW

Dr. Joseph Gold, an American research oncologist now at the Syracuse Cancer Research Institute is an original proponent and important developer of hydrazine sulfate for cancer treatment. He studied of hydrazine sulfate alone or in combination with other chemotherapeutic agents. He was influenced by research of Dr. Otto Warburg, a 1931 Nobel prize winner who had proposed that an important distinguishing feature of cancer cells is their propensity to obtain energy through the anaerobic, rather than the aerobic, metabolism of glucose (Warburg, 1956). Otto's work was confirmed by Gold and other investigators (Macbeth *et al.,* 1962; Gold, 1966). Gold reported that hydrazine sulfate can improve appetite and reduced weight loss (Gold, 1975, 1981). In addition, hydrazine sulfate could inhibit tumour growth and increase survival in rats with transplanted tumours (Gold, 1974).

The x-ray structure of hydrazine sulfate, $[N_2H_6][SO_4]$, was studied by Thomas *et a*l (Thomas *et al.,* 1996). They showed that the configuration of sulfate anion is an almost regular tetrahedron with S-O distances of 1.47-1.49 Å. The hydrazinium cation may be considered to be of the trans type, the N-N distance being 1.44 Å.

Inhibition by hydrazine of gluconeogenesis in the rat was studied by Ray *et al* (Ray *et al.*, 1970). They showed the metabolic crossover point between oxaloacetate and phosphoenolpyruvate which indicated that hydrazine inhibited the conversion of oxaloacetate to phosphoenolpyruvate. By using enzyme kinetics methods, they reported that hydrazine inhibited phosphoenolpyruvate carboxykinase noncompetitively with respect to oxaloactate.

Phosphoenolpyruvate carboxykinase (PEPCK) is an enzyme which requires metal for activity. Mn^{2+} is the best activator for mPEPCK, with Co^{2+} and Mg^{2+} also providing activation but lesser extent (Lee *et al.,* 1981). The important role of PEPCK is the formation of PEP in the first step of gluconeogenesis and glyceroneogenesis. Because of its role in gluconeogenesis, the importance of PEPCK is the maintenance of blood glucose levels (Consoli *et al.,* 1989; Magnusson *et al.,* 1992).

There are two mechanisms of action which have been proposed for hydrazine sulfate to explain its potential anticachexia properties. Both mechanisms relate to the utilization of glucose which is the cells' energy. In the first mechanism, hydrazine sulfate is an inhibitor of the enzyme phosphoenolpyruvate carboykinase (PEPCK) and blocking the conversion of oxaloacetate to phosphoenolpyruvate (PEP) (Ray *et al.,*1970; Silverstein *et al.*, 1989). Blocking gluconeogenesis, and interfering with the supply of nutrients to tumor, has been proposed to inhibit tumor growth and to prevent cachexia (Ray *et al*., 1970). In the second mechanism, hydrazine sulfate inhibits tumor necrosis factor-alpha (TNF-alpha) activity (Hughes *et al.,* 1989). TNF-alpha, which is known as chachectin, is a substance produced by white blood cells of the body in response to infection by microorganisms and in response to other stimuli such as tissue damage. There is more TNF-alpha production in white blood cells obtained from cancer patients (Jia *et al*., 1994). It has been suggested that higher-than-normal levels of TNF-alpha can cause the anorexia, the increased energy expenditure, and the increased muscle protein breakdown seen in cancer patients (Bruera, 1992). Inhibition of TNF-alpha activity might inhibit tumor growth and prevent cachexia.

There are many clinical observations for treating cancer by using hydrazine sulfate treatment. Early clinical studies, there are four studies in 1975 about initial clinical results with hydrazine sulfate treatment. The first, a phase II controlled clinical trail. 58 percent demonstrated antichachexia response and 35 percent showed antitumor response. (Seits *et al*., 1975). The second, 84 terminal and preterminal patients with different type of cancer demonstrated a 59 percent anti chachexia response and 17 percent antitumor response (Gold, 1975). The third, a small study of 29 patients, totally uncontrolled patient selection, found no long-term improvement (Ochoa *et al*., 1975). The fourth, the effect of hydrazine on gluconeogenesis by measuring blood glucose, lactate and pyruvate. These findings demonstrate that hydrazine inhibited gluconeogenesis and simultaneously caused hypoglycemia and elevated blood lactate and pyruvate (Fottney *et al.,* 1967). In 1979, 225 cancer patients were studied, controlled for patient selection, performance status, dosage protocol. This study showed the results of 65 percent antichachexia response and 44 percent antitumor response (Gershanovich *et al*., 1979). The cancerous rat was treated by hydrazine sulfate and it showed that hydrazine sulfate may influence to carbohydrate metabolism at the level of selected liver enzymes not only with respect to gluconeogenesis (Silverstein *et al*., 1989). Lung cancer patients were received hydrazine sulfate (60 mg. three times daily) for 30 days. After one month, the result showed that serum albumin was unchanged in the hydrazine group. Administration of hydrazine sulfate to reduce amino acid flux may influence to the abnormal metabolism in cancer cachexia (Tayek *et al*., 1987). More than 400 hydrazine analogs were screened for antitumor actity. Hower, there are 7 hydrazine compounds which showed activity against human cancer. Among 7 compounds, only N-isopropyl-alpha-(2-methylhydrazino)-p-toluamide HCl (procarbazine,natulan) was completed testing in human (Toth, 1996).

There are many researches in the field of theoretical chemistry that studied on the interaction energy. The particular interactions between efavirenz and the HIV-1 reverse transcriptase binding site based on the B3LYP/6-31G(d,p) and ONIOM2 methods were studied by Hannongbua *et al.* (Hannongbua *et al*., 2005a). They showed that the interaction between efavirenz and LYS101 was the strongest interaction due to they formed two hydrogen bonds between benzoxazin-2-one, and the backbone carbonyl oxygen and the back bone amino hydrogen of LYS101. These hydrogen bond interactions play an important role in the bound efavirenz/HIV-1 RT complex. In the same year, Hannongbua *et al*. performed two-layered and three-layered ONIOM calculations to compare the binding energies of 8-Cl *TIBO* inhibitor when bound into the human immunodeficiency virus reverse transcriptase binding pocket and a Y181C variant (Hannongbua *et al*., 2005b). They calculated the interaction energies between 8-Cl *TIBO* with individual residues surrounding the binding pocket by MP2/6-31G(d,p) and B3LYP/6-31G(d,p) levels of theory and they found that Pro95, Leu100, Tyr181 and Tyr318 were the larger repulsive interaction in the Y181C mutant system, compared with wild-type system. Next year, Hannongbua *et al*. investigated on intermolecular interactions between ethanol and ethylene forming H---π complex systems by using B3LYP, MP2 and ONIOM methods with a 6-31G(d,p) basis set (Kuno *et al*., 2006). All binding energies were corrected by counter poise method of Boys-Bernardi approach.

Equilibrium geometries, interaction energies and charge transfer for the intermolecular interactions between BrF and H_nX (HF, H_2O and NH_3) at the MP2/6-3111++(3d,3p) level wrer calculated by Wu *et al*. (Wu *et al*., 2007). The calculated interaction energies with basis set superposition error (BSSE) correction showed that the halogen-bonded structures are more stable than the corresponding hydrogen-bonded structures.

The complexes between tert-butanethiol (BSH) and water were studied by Wierzejewska and Sompolski (Wierzejewska and Sompolski, 2008). They calculated the interaction enrgy between BSH and water by using the MP2 method with 6-3111++G(2d,2p) basis set and matrix isolation FTIR spectroscopy. The interaction energies for the complexes were corrected for both basis set superposition error (BSSE) and for zero-point vibrational energy (ZPE).

Gang *et al*. investigated the interaction between water molecules and amino acid cation based ionic liquids (ILs), by quantum chemistry calculations on the system composed of $HGlyBF_4$ (Gly, glycine) IL molecule and one wter molecule (Gang *et al*., 2008). Geometry optimizations on the system in gas phase were performed with B3LYP/6-31+G(d,2p), B3LYP/6-311++G** and and MP2/6-3111++G** methods. The interaction energies between $HGlyBF_4$ and water molecule were calculated with the basis set superposition error (BSSE) was corrected by counterpoise method (CP).