INTERACTION ENERGIES OF OXALOACETATE AND BINDING SITE OF PHOSPHOENOLPYRUVATE CARBOXYKINASE (PEPCK) BY MP2 CALCULATIONS

INTRODUCTION

Cancer is a class of diseases or disorders in which cells grow and divide without respect to normal limits (aggressive), destroy adjacent tissues (invasive) and sometimes spread to other parts in the body. These abnormalities may be caused by the effects of carcinogens, such as radiation, chemicals, tobacco smoke or infection agents. These carcinogens can make abnormalities in DNA replication. Cancer may affect people at all ages but risk tends to increase with age, for example the most common range of ages that Thai people being cancer are 50-65 years old (Figure 1) (National Cancer Institute, Thailand, 2006).

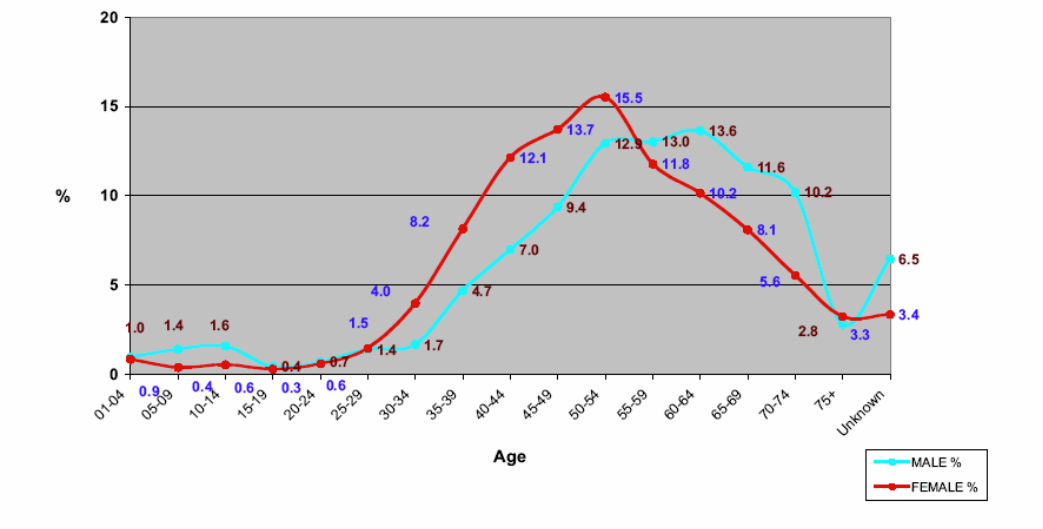

Figure 1 Number by ages-group and sex for all cancer.

Source: National Cancer Institute, Thailand (2006)

The total number of new cancer patients in Thailand in 2006 are 30,853. The most common cancers for Thai male are trachea, bronchus and lung cancer (Figure 2) and for Thai female is breast cancer (Figure 3) (National Cancer Institute, Thailand, 2006).

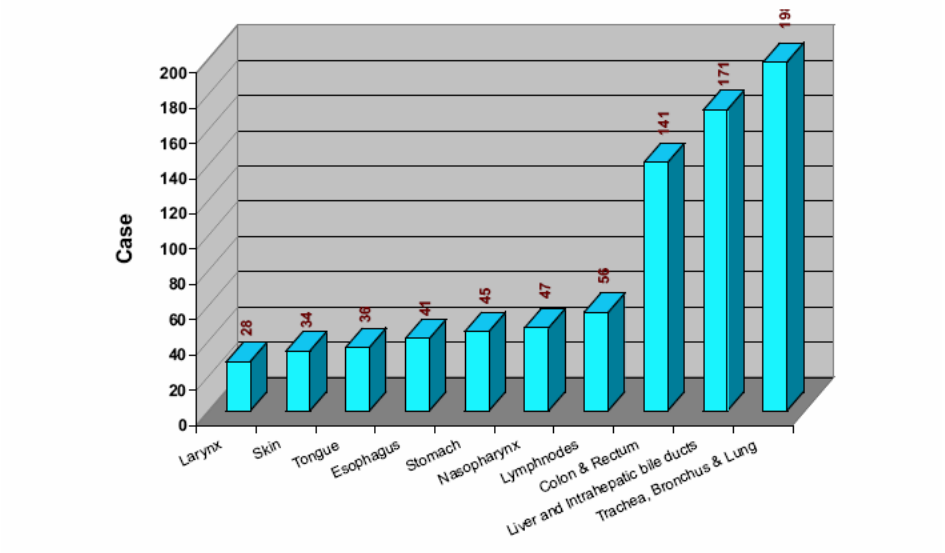

Figure 2 The most common cancer for Thai male.

Source: National Cancer Institute, Thailand (2006)

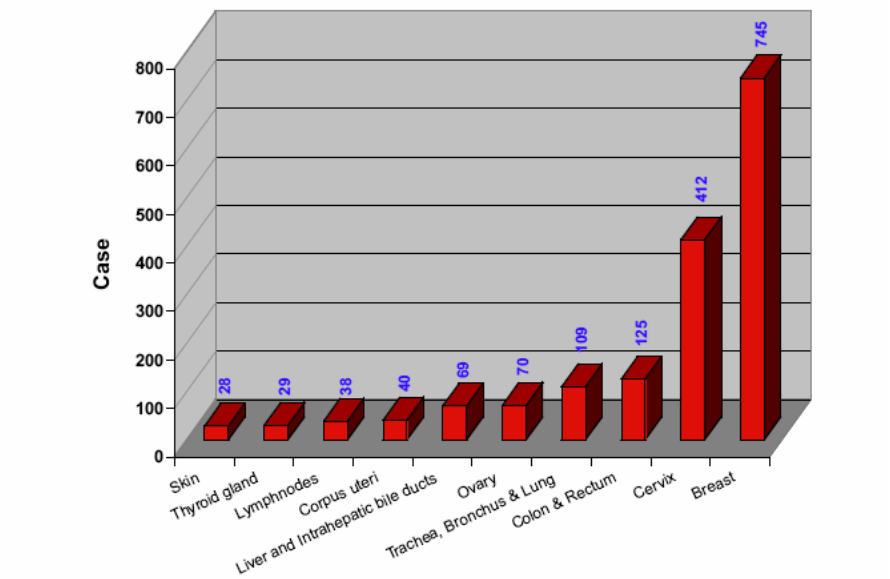

Figure 3 The most common cancer for Thai female.

Source: National Cancer Institute, Thailand (2006)

There are many conventional methods for cancer treatment, such as surgery, chemotherapy and radiation therapy. These methods always damage the healthy cells because they can not distinguish between cancer cells and healthy cells (Table 1).

Table 1 Methods of treatment of cancer site of all cancer.

Methods of treatment	Male		Female		Total	
	n	%	n	%	n	%
Surgery	183	16.2	537	27.4	720	23.3
Radiatherapy	131	11.6	245	12.5	376	12.2
Chemotherapy	185	16.4	223	12.4	408	13.2
Hormone	1	0.1	2	0.1	3	0.1
Surgery+ Radiatherapy	60	5.3	89	4.5	149	4.8
Surgery+ Chemotherapy	56	5	173	8.8	229	7.4
Surgery+Hormone	0	0	7	0.4	7	0.2
Radiatherapy+ Chemotherapy	65	5.8	47	2.4	112	3.6
Radiatherapy+Hormone	0	0	1	0.1	1	0
Chemotherapy+Hormone	0	0	1	0.1	1	0
Surgery+ Radiatherapy+Chemotherapy	8	0.7	30	1.5	38	1.2
Surgery+ Radiatherapy+Hormone	0	0	2	0.1	2	0.1
Surgery+Chemotherapy+Hormone	0	0	3	0.2	3	0.1
Support	315	27.9	442	22.6	757	24.5
Other	63	5.6	71	3.6	134	4.3
Not recorded	62	5.5	87	4.4	149	4.8
Total	1,129	100	1,960	100	3,089	100

Source: National Cancer Institute, Thailand (2006)

So the unconventional methods for example hydrazine sulfate, greentea, 714-X, essiac, etc. can be used to treat cancer (Kaegi, 1998; Ernst *et al.,* 1999). Hydrazine sulfate has been studied as an antitumor/antichacexia agent associated with cancer by Joseph Gold since 1987. It was found that hydrazine sulfate can inhibit gluconeogenesis of cancer cells. Because cancer cells use most of their energy from anaerobic glycolysis (normal cells use their energy from aerobic glycolysis) and produce lactic acid as by product. This lower pH values in cancer tissues via lactic acid formation can induce rapid growth of the cancer cells. However, if we want to stabilize or reduce the growth of cancer, we must decrease the amount of glucose produced by gluconeogenesis process (cancer cells use glucose as the energy source for growing). Gluconeogenesis requires a lot of energy for glucose synthesis that the excessive gluconeogenesis is a major determinant of cancer related cachexia. Hydrazine sulfate inhibits gluconeogenesis (Figure 4) by blocking the conversion of Oxaloacetate (OAA) to Phosphoenolpyruvate (PEP) through Phosphoenolpyruvate carboxykinase (PEPCK) inhibition (Figure 5) (Silverstein *et al*., 1989; Ray *et al*., 1970).

Inhibition of PEPCK enzyme can interfere gluconeogenesis and may be useful in the treatment for cancer related cachexia. In this study, in-dept modeling analysis of inhibition of PEPCK by hydrazine sulfate has been studied.

In order to understand basic structural information of the inhibition, interaction energy between oxaloacetate and PEPCK binding site is performed. Quantum mechanics methods that can now be used to perform calculations on molecular system of real, practical interest are used in this study. There are a lot of quantum mechanics methods for treating molecular systems such as semi-empirical method (AM1, PM3, etc), *ab initio* method (HF, MP2, etc). However, MP2 that is a high accurate method and for ground state study is used to calculate the interaction energy.

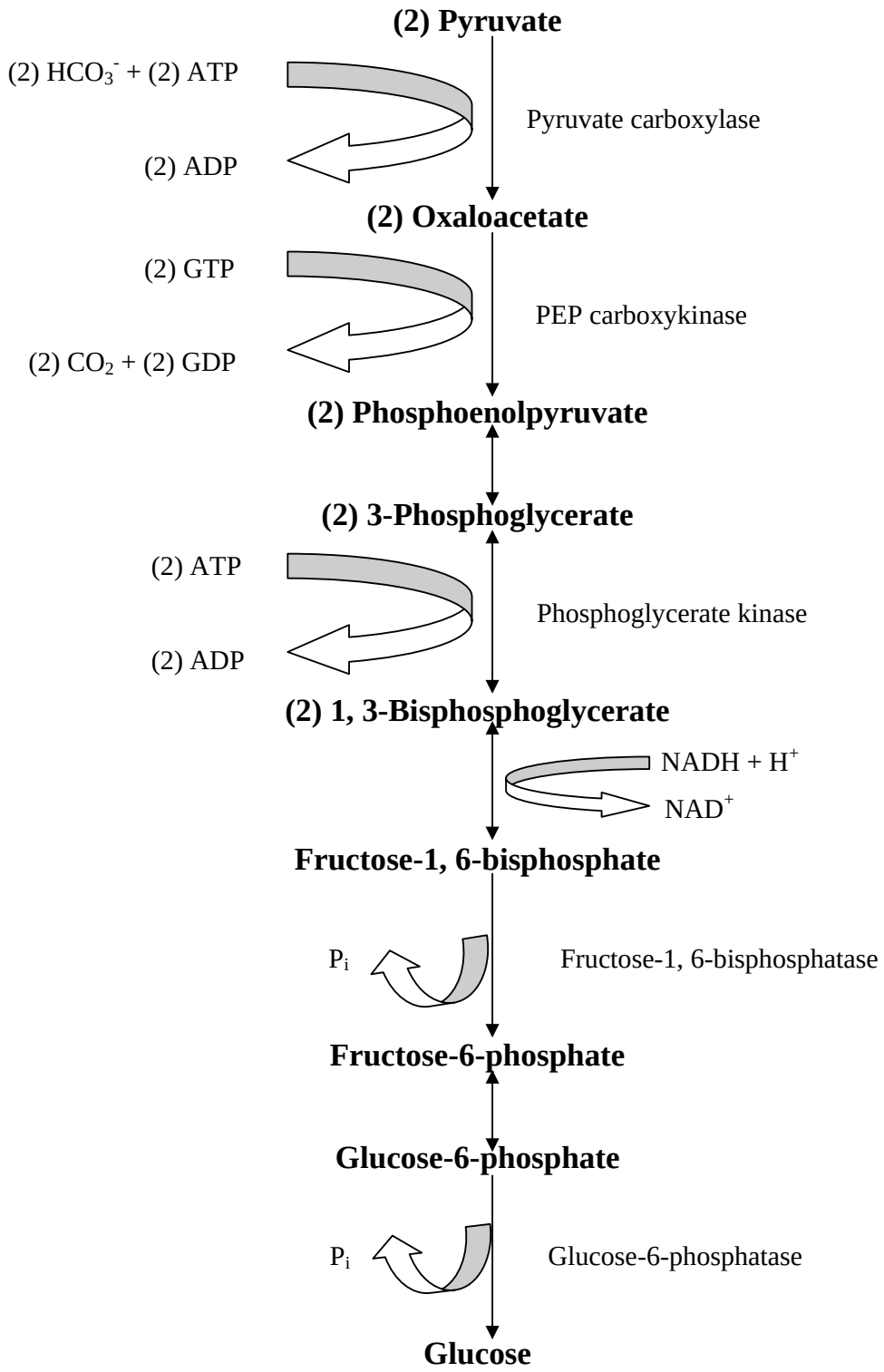

Figure 4 Gluconeogenesis process.

Source: King (1996)

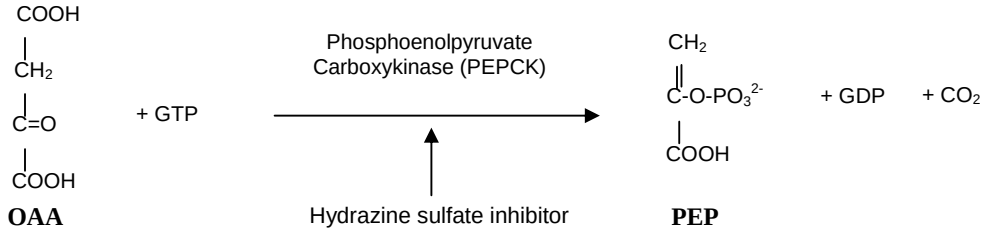

Figure 5 The chemical reaction of inhibition of PEPCK by hydrazine sulfate.

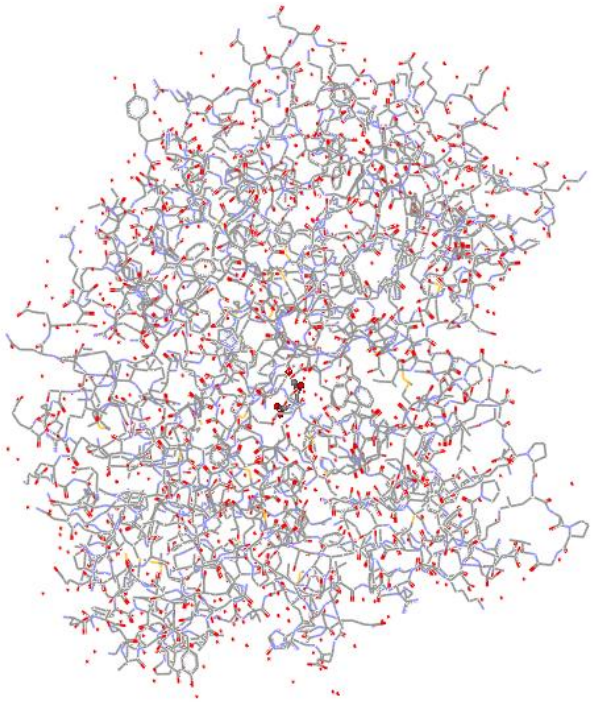

Figure 6 The structure of PEPCK enzyme complexed with OAA.

Source: Protein data bank (code 2QF1)

Therefore, the main objectives of this work are as following;

1. To calculate the interaction energies between oxaloacetate (OAA) and the binding site of phosphoenolpyruvate carboxykinase (PEPCK).

2. To study the structural properties of phosphoenolpyruvate carboxykinase (PEPCK) enzyme complexed with oxaloacetate (OAA).

3. To observe the main amino acids that play an important role in the binding of oxaloacetate in the bound PEPCK complex.