UNIVERSITI TEKNOLOGY MARA

STRUCTURE BASED DRUG MODELING: *MORINDA CITRIFOLIA* L. IN BREAST CANCER TREATMENT

NOR AYUNI BINTI ZULKEFLY

Dissertation submitted in partial fulfillment of the requirements for the Degree Bachelor of Pharmacy

Faculty of Pharmacy

November 2009

ACKNOWLEDGEMENT

First and foremost, I would like to express my deepest appreciation to my very dedicated and caring supervisor, Mr. Ismail Mohd Shah for his guidance, interest and support.

Last but not least, my greatest love to parents and family, for everything that they gave to me and to my friends for their undivided support. Thank You.

TABLE OF CONTENTS

		Page
TITLE PAGE		
APPROVAL		
ACKNOWLEDGEMENTS		ii
TABLE OF CONTENTS		iii
LIST OF TABLES		v
LIST OF FIGURES		vi
LIST OF ABBREVIATIONS		viii
ABSTRACT		ix
CHAPTER ONE (INTRODUCTION)		
1.1	Breast Cancer and Statistics	1
1.2	Etiology of Breast Cancer	2
	1.2.1 Overexpression of Epidermal Growth Factor Receptor (EGFR)	2
1.3	Lapatinib, a Tyrosine Kinase Inhibitor	3
1.4	*Morinda citrifolia* L. (Noni) Plant	5
1.5	Structure-Based Drug Modeling	5
1.6	Statement of Problems	6
1.7	Objectives	7
	1.7.1 General Objectives	7
	1.7.2 Specific Objectives	7
1.8	Significance of Study	8
CHAPTER TWO (LITERATURE REVIEW)		
2.1	Breast Cancer Worldwide	9
2.2	Breast Cancer in Malaysia	11
2.3	Etiology of Breast Cancer	12
	2.3.1 Overexpression of EGFR and ErbB2	12
2.4	Inhibition of Tyrosine Kinase Activity	13
	2.4.1 Lapatinib	13
2.5	Drug Discovery-Structure-Based Drug Modeling	14
2.6	Researches Done Using Structure Based Drug Modeling	15
2.7	*Morinda citrifolia* L. (Noni)	16
	2.7.1 History of *Morinda citrifolia* L. plant.	17
	2.7.2 Therapeutic Effects of *Morinda citrifolia* L. plant	17
	2.7.3 Anticancer Activity of Noni	18
CHAPTER THREE (METHODOLOGY)		
3.1	Preparing Ligands for Docking	21
	3.1.1 Identify Molecular Compounds (Ligands) in Noni	21
	3.1.2 Construct 2D Molecular Structures (Ligands)	22
	3.1.3 Energy Minimization for Ligands	23
	3.1.4 Define Torsions of the Ligand	24
3.2	Preparing Macromolecule Protein for Docking	24

ABSTRACT

Incidence of breast cancer is gradually increasing worldwide, therefore more effective anti-cancer drugs needed to treat this cancer. Focusing on discovering potential inhibitors against cancer-related proteins such as Epidermal Growth Factor Receptors (EGFR) tyrosine kinase that play critical roles in the development of the tumors can be helpful. EGFR tyrosine kinase inhibition by small molecules has been proved effective for cancer treatment. Lapatinib, the existing tyrosine kinase inhibitor has been widely used as chemotherapeutic drug for breast cancer treatment. By using knowledge on structure-based molecular modeling, identifying a new novel tyrosine kinase inhibitors in short timeframe with low cost become more rationale. Several compounds from *Morinda citrifolia* L. (Noni) with possible anti-cancer effects were identified and docking *in silico* approach was carried out. The binding affinity of ligand-protein complex was assessed by energy docking binding, inhibition constant and hydrogen bonding interactions. Amongst the molecular compounds, beta-sitosterol was discovered to have the lowest binding energy and inhibition constant value. Beta-sitosterol also has higher binding affinity than the existing drug, Lapatinib. By this finding, beta-sitosterol might have anti-cancer effects as potent as Lapatinib, thus can lead to the new development of tyrosine kinase inhibitors for breast cancer treatment.

CHAPTER 1

INTRODUCTION

1.1 Breast Cancer and Statistics

Breast cancer refers to a malignant tumor that developed from uncontrolled growth of breast cells. Breast cancer is the most common cancer in most part of the world and the number one cause of cancer death among women in Malaysia. More than 200,000 women in the United States were diagnosed with breast cancer in 2004 (Hortobagyi, 2005). However, in Malaysia, it is difficult to determine the exact number of breast cancer cases due to lack of its registry (Hisham, 2004). Data from the National Cancer Registry of Malaysia for 2004 (Yip, 2006) showed that approximately 1 in 20 women in Malaysia developed breast cancer in their lifetime. However, the rates of getting this disease differed between the three main races, *ie.* Malay, Chinese and Indian, where Chinese women have the highest risk with 1 in 16 women developed breast cancer in their lives followed by Indians and Malays with 1 in 16 and 1 in 28 respectively.