UNIVERSITI TEKNOLOGI MARA

# MOLECULAR DOCKING STUDIES OF DIOXINS WITH HUMAN ESTROGEN RECEPTORS

SITI ZAIDAH BINTI ROSMAN

**Dissertation submitted in partial fulfillment of the requirements for the Bachelor of Pharmacy (Hons.)**

Faculty of Pharmacy

July 2017

# ACKNOWLEDGEMENT

First and foremost, praised to Allah with his grace; I am given good health throughout completing this study. Herewith, I would like to thank everyone who had assisted me during the completion of this final year project.

I am deeply indebted to my supervisor Dr Siti Azma Jusoh for the help, stimulating suggestions, valuable advices, guidance, encouragement and time spent in all aspects of accomplishing this study. I could not have imagined having a better advisor and mentor for this study.

Furthermore, I would like to express my appreciation to the faculty for the facilities in Bioinformatics Lab. Not to forget my dearest colleagues, Nur Dalilah Anis Hasim and Nur Hafizah Kamal. Thank you so much for your cooperation and willingness to work together during this period of time.

I also would like to thank my friend, Nur Feazira Abdul Kadir, as well as my housemates for their continuous support and motivation in completing this study. Last but not least, I would like to thank all my friends, and other people who are directly or indirectly involved and contributed to this study.

Thank you.

# TABLE OF CONTENT

# ABSTRACT

Dioxins are classified by World Health Organization (WHO) as one of the dangerous chemical groups due to its highly toxic potential. In human, long term exposure of dioxins are associated with immune system, reproductive and developmental problems, as well as cancer. In this study, we used molecular docking method to study binding of dioxins to estrogen receptor -α and -β. The results show all dioxins bound to two binding pockets of estrogen receptor structure in agonistic and antagonistic states. In the primary binding pocket (the known binding pocket of nuclear receptor family), dioxins bound with average affinity of -6.9 kcal/mol. 2-hydroxy-3,7,8-trichlorodibenzo-p-dioxin exhibited the highest binding affinity of -8.3 kcal/mol. In the secondary binding pocket (the binding pocket of second hydroxytamoxifen), the highest binding affinity of dioxin were seen with 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin (HxCDD) with a binding affinity of -6.3 kcal/mol. Furthermore, docking of known ligands, estradiol (human estrogen) and genistein (plant estrogen) showed similar binding affinity. In conclusion, the results indicate that dioxins potentially bind to estrogen receptors and act as endocrine disruptors.



Keywords: Estrogen Receptor-α, Estrogen Receptor-β, dioxins, molecular docking

# CHAPTER 1

# INTRODUCTION

## 1.1 INTRODUCTION

Estrogen receptor (ER) belongs to nuclear receptor family. Nuclear receptors are ligand-regulated transcription factors which are the main function for the body to regulate the expression of hormone-response genes. In case for ER, the natural hormone ligand is the estrogen. Any disruption to the metabolism of the ER may lead to diseases such as cancers (Deroo & Korach, 2006).

Endocrine disrupting chemicals (EDCs) are one of the causes of adverse health effects in human. Generally, an endocrine-disrupting chemical is a compound, either natural or synthetic. If the chemical is inappropriately being exposed, it will alter human hormonal and homeostatic systems. These EDCs are known to exert its activities through nuclear receptors including estrogen receptors. These chemicals are highly heterogeneous and mostly are from synthetic industrial chemicals and their (Diamanti-Kandarakis et al., 2008). Dioxins and Dioxin-like compounds are the examples of EDCs. Based on World Health Organisation (WHO), the high levels of dioxins are found in some soils, sediments and food, especially dairy products, meat, fish and shellfish. Very low levels are found in plants, water and air. A cohort study was done and the results show there are high risk of mortality from cancer and ischaemic heart disease among workers that are highly exposed to dioxins (Kogevinas, 2001).