UNIVERSITI PUTRA MALAYSIA

ZERUMBONE AND SMALL INTERFERENCE RNA INDUCED APOPTOSIS IN MCF-7 CELL AND MAMMARY GLAND TUMOR VIA β-CATENIN PROTEIN INHIBITION

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By

SAFA ABD ELFATAH AMIN FADL

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

July-2013

DEDICATION

Dedicated to Mohamed Ibrahim Saeed for for always keeping a high spirit, and for watching over me.

To the people whose lives have been influenced by breast cancer, and to those who have taken care of them.

To my family specially My mother, friends, and teachers for always believing in me.

To the soul of my father, may Allah send him with his mercy to Elferdus.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for degree of Ph.D.

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Chair: Ahmad Bustamam Bin Abdul, PhD
Faculty: Institute of Bioscience

Extensive research is being conducted to identify therapeutic agents that can inhibit breast cancer cell proliferation through the induction of the apoptotic pathways. Among these is the Wnt/β-catenin pathway, of which β-catenin is one of the main oncogenes of the Wnt signaling pathway implicated in the adhesion of cancer and non-cancer cells. Several studies have shown that there is close linkage between Wnt/β-catenin pathways and tumourigenesis and dysregulation with increased cancer cell growth and survival. In this study, a natural compound, zerumbone (ZER) extracted from *Zingiber zerumbet* Smith was chosen as a potential anticancer compound. The objective of this study is to determine the efficacy of ZER as an inhibitor of breast cancer progression and the role of β-catenin in its anticancer effect. This study was conducted both *in vitro* on MCF-7 cells and *in vivo* in Sprague-Dawley rats induced to develop mammary gland tumor with LA7 and/or β-catenin knockdown LA7 cells. The MCF-7 cells and rats were treated with ZER and the ZER/β-catenin siRNA combination. β-catenin siRNA was used as a positive control to specifically inhibit expression and transcriptional activity of β-catenin. High-throughput screening of 500 apoptosis-related genes of the NFκB and p53 pathways were assessed in treated and untreated MCF-7 cells using the microarray profiles. The microarray analytical results were confirmed by real-time PCR and immunocytochemistry. In both the *in vitro* and *in vivo* studies, there was good correlation between β-catenin inhibition and apoptosis. The MTT assay, flow cytometry, confocal microscopy, and TUNEL assay confirmed that both ZER and siRNA induced apoptosis in MCF-7 cells while not adversely affecting normal cells. In the rat model, immunohistochemistry and real-time PCR also showed that ZER induced apoptosis in mammary gland tumor. The study showed that ZER and β-catenin siRNA treatments markedly decreased β-catenin-dependent gene expression and inhibition of MCF-7 cell proliferation. The study also showed the ZER/β-catenin siRNA combination treatment decreased β-catenin level *in vivo*. The results of this study suggest that both ZER and β-catenin siRNA express anticancer activities via targeting the Wnt/β-catenin signaling pathway. In conclusion, ZER and/or β-catenin siRNA could be used as potential compounds for the treatment of breast cancers.

Abstract tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah PhD

ZERUMBON DAN RNA GANGGUAN KECIL MENGARUH APOPTOSIS DALAM SEL MCF-7 DAN TUMOR MAMA TIKUS MELALUI PERENCATAN PROTEIN β-KATENIN

Oleh

SAFA ABD ELFATAH AMIN FADL
2013

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Banyak penyelidikan telah dijalankan untuk mengenal pasti agen terapeutik yang dapat merencat pemproliferatan sel kanser payudara melalui pengaruhan arah laluan apoptosis. Di antaranya ialah arah laluan Wnt/β-katenin yang di dalamnya ada β-katenin, suatu onkogen arah laluan pengisyaratan Wnt yang terlibat dalam pelekatan sel kanser dan bukan kanser. Beberapa kajian telah menunjukkan ada hubung kait rapat di antara arah lalaun Wnt/β-katenin dengan tumorigenesis dan disperaturan dengan peningkatan pertumbuhan dan kemandirian sel kanser. Dalam kajian ini, suatu sebatian jangkaan antikanser semula jadi, zerumbon (ZER) yang diekstrak daripada *Zingiber zerumbet* Smith dipilih sebagai sebatian antikanser berpotensi. Objektif kajian ini ialah untuk menentukan kemujaraban ZER sebagai perencat pertumbuhan kanser payudaya dan peranan β-katenin dalam kesan antikansernya. Kajian ini dijalankan *in vitro* pada sel MCF-7 dan *in vivo* pada tikus Sprague-Dawley yang diaruh untuk mengembangkan tumor kelenjar mama dengan sel LA7 dan/atau sel LA7 'knockdown' β-katenin. Sel MCF-7 dan tikus diperlakukan dengan ZER dan gabungan ZER/siRNA β-katenin. siRNA β-katenin diguna sebagai kawalan positif untuk merencat secara khusus penyataan dan aktiviti transkripsi β-katenin. Penyaringan daya tinggi 500 gen berkaitan apoptosis untuk arah laluan NFκB, p53 dan reseptor tol dinilai dalam sel terperlaku dan tidak terperlaku mengguna profil mikrotatasusun. Hasil daripada analisis mikrotatasusun disahkan melalui PCR masa nyata dan imunokimia. Dalam kedua-dua kajian *in vitro* dan *in vivo* ini terdapat perkaitan baik di antara perencatan β-katenin dan apoptosis. Assai MTT, sitometri aliran, mikroskopi konfokal, dan assai TUNEL mengesahkan yang kedua-duanya ZER dan siRNA mengaruh apoptosis pada sel MCF-7 sambil tidak memudaratkan sel normal. Dalam model tikus, imunohistokimia dan PCR masa nyata juga menunjukkan yang ZER mengaruh apoptosis dalam tumor kelenjar mama. Kajian ini menunjukkan yang perlakuan ZER dan siRNA β-katenin secara tinggi dapat mengurangkan penyataan gen bersandar β-katenin dan merencat pemproliferatatan sel MCF-7. Kajian ini juga menunjukkan yang perlakuan gabungan ZER/siRNA β-katenin mengurangkan aras β-katenin *in vivo*, dan kesan ini lebih tinggi daripada yang terdapat dengan perlakuan ZER atau siRNA β-katenin sahaja. Perlakuan gabungan ZER/siRNA β-katenin lebih mujarab mungkin kerana kesan sinergi ZER dan siRNA β-catenin. Hasil kajian ini menyarankan yang kedua-dua ZER dan siRNA β-katenin menunjukkan aktiviti antikanser melalui pensasaran arah laluan pengisyaratan Wnt/β-katenin. Kesimpulannya, ZER dan/atau siRNA β-katenin boleh diguna sebagai sebatian berpotensi untuk rawatan kanser payudara.

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APPROVAL SHEET-1

I certify that an Examination committee has met on date of viva voce to conduct the final examination of **safa Abdelfatah Amin Fadl** on her degree thesis entitled "**Zerumbone and Small Interference RNA Induced Apoptosis in MCF-7 Cell and Mammary Gland Tumor Via β-Catenin Protein Inhibition"** in accordance with Universiti Putra Malaysia (Higher Degree) Regulations 1981. The committee recommends that the student be awarded the Ph.D. degree.

Members of the Examination committee were as follows:

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Approval Sheet 2

This thesis was submitted to Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for degree of PhD. The members of the supervisory Committee were as follows:

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Date……

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

SAFA ABD ELFATAH AMIN FADL

Date 9th July 2013

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LIST OF ABBREVIATIONS

AP-1	Activator protein-1
APC	Adenomatous polyposis coli
Bax	Bcl-2 associated X protein
Bcl-2	B-cell leukaemia 2 protein
Bid	BH3 interacting domain death agonist
CamKII	Ca2+/calmodulin-sensitive kinase II
CK	Casein kinase
COX2	Cyclooxygenase-2,
CREB	Cyclic AMP response element binding protein
DR5/Killer	Death receptor 5
Dvl	Dishevelled
Fz	Frizzled
GADD45	Growth arrest and DNA –damage inducible gene 45
GBP	GSK3β binding protein
GSK3β	Glycogen synthase kinase 3β
IC_{50}	Cell proliferation inhibitory concentration to half on cell culture
IGF	Insulin like growth factor
IGF-BP3	Insulin-like growth factor binding protein
IKK	IkB kinases
IκB	Inhibitor of NF-Ķb
LA7	Rat mammary gland carcinoma
LEF1	Lymphoid enhancer-binding factor 1
LRP	LDL-receptor-related protein
MCF-7	Mammary carcinoma/ breast (Michigan Cancer Foundation-7)
MEC	Mammary epithelial cell
MMTV	Mouse mammary tumour virus
NF-κB	Nuclear factor κ-light-chain-enhancer of activated B cells
p90RSK	90kDa ribosomal S6 kinase
PCNA	Proliferating cell nuclear antigen
PCP	Planar cell polarity
PI3K	Phosphoinositide 3-kinase
Pidd	p53 induced protein with a death domain
PKB	Protein kinase B
PKC	Protein kinase C
PP2A	protein phosphatase 2A
PTEN	Protein phosphatase and tensin homology
PUMA	p53 up regulated modulator of apoptosis
RPA	Replication protein A
SFRP4	Secreted Frizzled-related protein 4
TCF	T-cell factor
WAP	Whey acidic protein
Wip1	Wild type p53-induced phosphatase
WISP-1	Wnt1-induced secreted protein
Wnt	Wingless (*Drosophila*)
β-TrCP	β-transducin repeat-containing protein

CHAPTER ONE

1.1 INTRODUCTION AND GENERAL OUTLINE

Among the most frequent cause of death, cancer ranks third in developing countries after infectious parasitic diseases and diseases of the circulatory system and in developed countries it ranks second after diseases of the circulatory system. Among men, lung cancer is the most common cancer, followed by stomach, colon/rectum, prostate, mouth/pharynx and liver cancers. Cancer of the breast represents the leading cancer in women with a frequency of 29.0% followed by cervix, colon-rectum, stomach, lung and mouth/pharynx cancers. In American women, breast cancer is the second major cause of cancer death, with an estimation of 40,000 women expected to die each year (WHO, 1997). The Malaysian National Registry reported that in 2002, among Malaysian females, breast cancer (30.4%) was the most frequent neoplasm followed by cervical cancer (12%). Breast cancer has now become one of the top ten killer diseases, with increasing rate of incidence among the younger age groups (WHO, 2009). Which estimated by 58% cases in 2009 (Ibrahim et al., 2012)

Cancer is caused by defective control in cell proliferation. The inactivation of tumour suppressor genes and deregulated expression of oncogenes are often the cause of cellular transformations. These factors are only partial requirements for the development of cancers. As tumour cells divide, each daughter cell inherits the genetic defects that lead to tumour development and possible progression to malignancy. Tumourigenesis is a multistep process that overcomes the inherent protection against cellular transformation through changes, particularly inactivation of tumour suppressor genes. Thus identification of these genes is essential for understanding the regulation of cell proliferation and development of therapeutic strategies to eradicate cancer. Among these strategies are hormone treatments and chemotherapy. These therapies have been shown to improve survival of patients with breast cancers; nevertheless, there are severe side-effects associated with the lack of specificity of the drugs used. Currently targeted therapy is being investigated, to eliminate these side-effects. The potential of targeted therapy is enormous. However, before these therapies can be instituted, it is important to understand the mechanism/s involved in cell transformation and identify novel molecular targets that could be used in the prevention and treatment of these cancers.

Breast cancer is one of the most debilitating human carcinomas among women, second only to lung cancer in mortality rate (WHO, 2009). There has been an abundance of studies on breast cancers, and recent advances in genetic and biochemical investigations have facilitated the understanding of molecular pathways involved in breast cancer development. For example, the Wnt signaling pathway has long been known to play a critical role in normal adult cell regulation. However, inappropriate activation of this pathway may drive cell proliferation resulting in cancers (Furuuchi et al., 2000; Spink et al., 2000). Thus this signaling pathway is a good target for development of anticancer drugs. The Canonical WNT pathway controls expression of target genes by modulating intracellular content of β-catenin and is considered to be the core molecule of the Wnt pathway. β-Catenin is a membrane-associated protein involved in cell–cell adhesion (Barth et al., 1997; Jamora and Fuchs, 2002; Steinberg and and McNutt, 1999). β-catenin attaches to the carboxyl terminus of E-cadherin. This complex associated with α-catenin and other structural proteins facilitate the cell-cell adherence. β-catenin is also a transcription co-activator for Wnt signaling. This plasma membrane-bound

multifunctional protein mediates the intercellular adhesion through the Wnt signaling pathway (Polakis, 2000).

In this study β-catenin selected as target molecule for zerumbone (ZER) to act upon the treatment of breast cancers. As many studies have showed, ZER can delay the progression of tumour including breast cancers, while showing minimal effects on normal cells(Murakami et al., 2002, Hoffman M. et al, 2002). These studies focused on how ZER influences β-catenin expression in breast cancer cells especially those related to apoptosis. The study also investigated the ability of ZER to alter β-catenin nuclear function through the transformation or alteration in behavior of breast cancers toward a more normal phenotype.In addaition, we also utilised small interfering RNA (siRNA) as an inhibitor for β-catenin, with and without ZER treatment, to determine whether or not breast cancer cells will continue to proliferate in a state of β-catenin deficiency. Zerumbone/siRNA was also used to determine whether or not siRNA improves the ability of ZER to decrease nuclear activity of β-catenin.

1.1 Issues of the study

Wnt-1 was first identified as a customary site of integration by the mouse mammary tumour virus (MMTV) and its over-expression in MMTV-infected glands had led to mammary tumours development. Although many researches have made great strides in elucidation of the mechanisms in cancer development, the role of Wnt signaling in the mammary gland is not understood. The Wnt proteins now are well known as a large family of secreted signaling molecules that are expressed in various tissues and reported to regulate cell proliferation, growth, and differentiation (Larue et al., 2003). Consequently, aberrant regulations of the Wnt-1 signaling pathway had been associated with tumour progression, most probably by enhancing cell growth and proliferation. Thus, the final assumption that Wnt signaling that maintains cell survival could be the target in the facilitation of chemotherapeutic agent-induced apoptosis. Wnt-mediated cell survival is dependent on the activation of β-catenin/TCF transcription. The inhibition of β-catenin/TCF transcription will block Wnt downstream components that mediate cell survival, rendering these cells sensitive to apoptotic stimuli. Therefore, β-catenin chosed as the target to investigate the functional consequence of down-regulation of the β-catenin gene associated with apoptosis. In this study, a known anti-cancer agent, ZER was chosen as a potential inhibitor of β- catenin and siRNA. The models for the study were the normal MCF-7 and the β-catenin knockdown MCF-7 cell lines. The expression profile of apoptotic gene on treated and untreated cells was examined by microarray analysis. The main objective of the study was to determine whether or not targeting or knockdown of β-catenin by ZER or siRNA can induce apoptosis *in vitro* at least partially through the p53 pathway and inhibit tumour growth in rats induced to develop mammary gland tumour and MCF-7 the breast cancer cell.

1.2 Hypothesis

Previous studies showed that Zerumbone can reduce breast cancer cell growth. ZER also down regulate many genes and proteins associated with increasing cell growth like Survivin, Cyclin D and COX2. Most of these genes are known targets for β-catenin. Therefore, the hypotheses of this study are:

a. Zerumbone exerts its antiproliferation activity through the modulation of β-catenin expression.
b. Zerumbone targets β-catenin apoptosis-related gene in the murine mammary gland tumour and MCF-7 human cancer cell.

1.3 Objectives

The objectives of this study are:

1. To determine the *in vitro* effect of ZER and siRNA on the expression of β-catenin in the human breast cancer cell line (MCF-7 cells).

2. To identify genes involved in the apoptosis and regulated by wnt/β-catenin in the MCF-7 cells treated by ZER.

3. To determine the effect of ZER and β-catenin siRNA treatments on the apoptosis of MCF-7 cells.

4. To investigate the effect of ZER and β-catenin siRNA on the β-catenin expression and signaling consequences in rats induced to develop mammary gland tumour.

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