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INDUCTION OF APOPTOSIS AND THE SIGNALLING PATHWAYS INVOLVED BY Dillenia suffruticosa DICHLOROMETHANE ROOT EXTRACT IN MCF-7 AND MDA-MB-231 BREAST CANCER CELLS

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By

FOO JHI BIAU

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INDUCTION OF APOPTOSIS AND THE SIGNALLING PATHWAYS INVOLVED BY *Dillenia suffruticosa* DICHLOROMETHANE ROOT EXTRACT IN MCF-7 AND MDA-MB-231 BREAST CANCER CELLS

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Chairman : Latifah Saiful Yazan, PhD

Faculty : Institute of Bioscience

Dillenia suffruticosa has been used traditionally to treat cancerous growth. Previous study reported that dichloromethane extract of *D. suffruticosa* root (DCM-DS) was the most cytotoxic towards breast cancer cells. The present study investigated the mode of cell death and the signalling pathways involved in MCF-7 and MDA-MB-231 breast cancer cells treated with DCM-DS. DCM-DS was obtained by sequential solvent extraction. The cytotoxicity of DCM-DS was determined by using MTT assay. The mode of cell death was evaluated by using an inverted light microscope and Annexin-V/PI-flow cytometry analysis. Cell cycle analysis and measurement of intracellular reactive oxygen species (ROS) level were performed by using flow cytometry. The cells were co-treated with DCM-DS and antioxidants α-tocopherol or ascorbic acid to evaluate the involvement of ROS in the cytotoxicity of DCM-DS. Effect of DCM-DS on the expression of antioxidant, apoptotic, growth, survival genes and proteins were analysed by using GeXP-based multiplex system and Western blot, respectively. The compounds in DCM-DS were isolated by various chromatography techniques. The structure of the compounds was elucidated by using nuclear magnetic resonance analysis. DCM-DS was cytotoxic to the MCF-7 and MDA-MB-231 cells in a time-and dose-dependent manner. Cell cycle analysis revealed that DCM-DS induced G_0/G_1 and G_2/M phase cell cycle arrest in MCF-7 and MDA-MB-231 cells, respectively. DCM-DS induced apoptosis and oxidative stress in these two cell lines. Treatment with α-tocopherol reduced the cytotoxicity of DCM-DS at 50 µg/mL in the cells, suggesting that DCM-DS induced lipid peroxidation to destroy the cancer cells. Therefore, DCM-DS can be employed as a pro-oxidant agent to treat breast cancer. The induction of apoptosis in MCF-7 and MDA-MB-231 cells by DCM-DS is possibly due to the activation of pro-apoptotic JNK1 and down-regulation of anti-apoptotic ERK1 and AKT1, which in turn down-regulates anti-apoptotic BCL-2 to increase the BAX/BCL-2 ratio to initiate the mitochondrial apoptotic pathway. The induction of cell cycle arrest in MCF-7 and MDA-MB-231 cells is possibly via p53/p21-dependent and p53-independent but p21-dependent pathway, respectively. A total of seven triterpene compounds were isolated. Betulinic acid (BA) appears to be the major and most cytotoxic compound in DCM-DS. Therefore, BA could be used as a mean for standardisation of herbal product from *D. suffruticosa*. In conclusion, the data suggest the potential application of DCM-DS in the treatment of breast cancer.

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ARUHAN APOPTOSIS DAN LALUAN ISYARAT TERLIBAT OLEH EKSTRAK DIKLOROMETANA AKAR *Dillenia suffruticosa* TERHADAP SEL KANSER PAYUDARA MCF-7 DAN MDA-MB-231

Oleh

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Dillenia suffruticosa telah digunakan secara tradisional untuk merawat pertumbuhan kanser. Kajian terdahulu melaporkan bahawa ekstrak diklorometana dari akar *D. suffruticosa* (DCM-DS) adalah yang paling sitotoksik terhadap sel kanser payudara. Kajian ini menyiasat cara kematian sel dan laluan isyarat yang terlibat dalam sel kanser payudara MCF-7 dan MDA-MB-231 dirawat dengan DCM-DS. DCM-DS diperolehi melalui pengekstrakan berurutan pelarut. Sitotoksisiti DCM-DS ditentukan oleh asai MTT. Cara kematian sel ditentukan dengan mikroskop keterbalikan dan analisis aliran sitometri dengan *Annexin-V/PI*. Analisis kitaran sel dan pengukuran paras spesies oksigen reaktif (ROS) intrasel dilaksanakan dengan aliran sitometri. Sel kanser tersebut dirawat dengan DCM-DS dan antioksidan α-tokoferol atau asid askorbik untuk menentukan penglibatan ROS dalam sitotoksisiti DCM-DS. Kesan DCM-DS terhadap pengekspresan gen dan protein untuk antioksidan, apoptosis, pertumbuhan dan daya tahan hidup dianalisis dengan menggunakan sistem multipleks GeXP dan Western blot, masing-masing. Sebatian dalam DCM-DS diasingkan menggunakan pelbagai teknik kromatografi. Struktur sebatian dikenalpasti dengan resonans magnetik nuklear (NMR). DCM-DS adalah sitotoksik terhadap sel MCF-7 dan MDA-MB-231 secara bersandar pada masa dan dos. Analisis kitaran sel mendedahkan bahawa DCM-DS mengaruh penahanan fasa G_0/G_1 dan G_2/M kitaran sel terhadap sel MCF-7 dan MDA-MB-231, masing-masing. DCM-DS mengaruh apoptosis dan tekanan oksidatif terhadap kedua-dua jujukan sel tersebut, Rawatan dengan α-tokoferol mengurangkan sitotoksisiti DCM-DS pada 50 µg/mL dalam sel tersebut. Ini mencadangkan bahawa DCM-DS mengaruh pengoksidaan lipid untuk memusnahkan sel kanser tersebut. Justeru itu, DCM-DS boleh diguna sebagai agen pro-oksidan untuk merawat kanser payudara. Aruhan apoptosis dalam sel MCF-7 dan MDA-MB-231 oleh DCM-DS berkemungkinan disebabkan oleh pengaktifan JNK1 pro-apoptotik dan penurunan ERK1 dan AKT1 anti-apoptotik, seterusnya menurun BCL-2 anti-apoptotik dan meningkat nisbah BAX/BCL-2 untuk memulakan laluan apoptotik mitokondria. Penahanan kitaran sel dalam sel MCF-7 dan MDA-MB-231 dirawat DCM-DS berkemungkinan melalui laluan bergantung p53/p21 dan tidak bergantung p53 tetapi bergantung p21, masing masing. Sejumlah tujuh sebatian triterpin telah diasingkan. Asid betulinic (BA) merupakan sebatian yang paling banyak dan paling sitotoksik dalam DCM-DS. Oleh itu, BA boleh digunakan untuk tujuan pemiawaian produk herba dari *D. suffruticosa*. Sebagai penutup, data mencadangkan potensi aplikasi DCM-DS dalam rawatan kanser payudara.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACTB	Beta-actin
AKT	Protein kinase B
APT	Attached proton test
BRCA1	Breast cancer 1
BRCA2	Breast cancer 2
CASP-3	Caspase-3
CAT	Catalase
CDK	Cyclin-dependent kinase
CK5/6	Cytokeratin 5/6
COSY	^{1}H-^{1}H correlation spectroscopy
DCFH-DA	Dichlorodihydrofluorescein diacetate
FITC	Fluorescein isothiocyanate
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ER	Oestrogen receptor
ERK	Extracellular signal-regulated kinase
HER2	Human epidermal growth factor receptor 2
HMBC	Heteronuclear multiple bond correlation
HSQC	Heteronuclear single quantum correlation
IκB	Inhibitor of κB
IKK	IκB kinase
JNK	c-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
MAPKK	MAPK kinase
MAPKKK	MAPKK kinase
MPTP	Mitochondrial permeability transition pores
NF-κB	Nuclear factor-kappa B
NMR	Nuclear magnetic resonance
PARP	Poly (ADP-ribose) polymerase
PKC	Protein kinase C
PMSF	Phenylmethanesulfonyl fluoride
p38MAPK	p38 Mitogen-activated protein kinase
PR	Progesterone receptor
PS	Phosphatidylserine
SOD	Superoxide dismutase
TCM	Traditional Chinese medicine
T-DM1	Trastuzumab-DM1
TEY	Thr-Glu-Tyr
TGY	Thr-Gly-Tyr
TNBC	Triple-negative breast cancer
TNF	Tumour necrosis factor
TNM	Tumour, nodes and metastasis
TPY	Thr-Pro-Tyr
TRAIL	TNF-related apoptosis inducing ligand

CHAPTER 1

INTRODUCTION

Breast cancer is the leading cause of cancer death among females worldwide (Jemal *et al.*, 2011). There were approximately 1.7 million and 500,000 of new cases and deaths due to breast cancer, respectively, in 2012 worldwide. It is also estimated that one in eight women will develop breast cancer at some point in her lifetime (GLOBOCAN, 2012).

Breast cancer patients can be treated by chemotherapy, surgery and radiotherapy. Chemotherapy is the most common treatment that uses chemicals to kill or stop cancer cells from growing (Coates *et al*., 2012). Nevertheless, the mortality rate of women with breast cancer is still relatively high due to recurrence and metastasis. The main cause for cancer recurrence is that the cancer cells have acquired resistance to the chemotherapy due to dysregulation of multiple genes and multiple cell signalling pathways, rendering the initial successful chemotherapy becomes ineffective (Holohan *et al*., 2013; Curigliano, 2012; Marquette and Nabell, 2012; Dhillon *et al*., 2011). In addition, chemotherapeutic drugs such as tamoxifen, trastuzumab, doxorubicin and cisplatin for the management of breast cancer (Silver *et al.*, 2010; Subik *et al.*, 2010; Adams *et al.*, 2006) have been reported to cause adverse effects such as increased incidence of endometrial cancer (Wysowski *et al.*, 2002), cardiotoxicity (Ichikawa *et al.*, 2014) (Cardinale *et al.*, 2010), and hematotoxicity (Pearcey *et al.*, 2002). Therefore, there is an urgent need to seek for other remedies for the management of breast cancer.

In contrast to the conventional single molecule-single target approach, being able to target two or more pathways at once or a few players in the same pathway would be a more effective therapy for cancer (Verpoorte, 2012; Dolgin, 2011). Thus, evidence-based herbal medicines might be one of the starts for these approaches. The mixture of active compounds in the herbal medicines may have synergistic effect on cancer such as targeting on several pathways, reducing adverse side effects, and altering drug metabolism and excretion (Liu and Cheng, 2012; Cao *et al.*, 2011).

Dillenia suffruticosa (Griffith ex Hook. F. and Thomson) Martelli (Family: Dilleniaceae), commonly known as "*Simpoh air*", is found abundantly in the secondary forest and swampy ground of Malaysia. This plant is traditionally used for the treatment of cancerous growth (Ahmad and Holdsworth, 1995). Previous studies revealed that the root hot water extract of *D. suffruticosa* has anti-cervical (Said, 2010) and anti-colon cancer properties (Husain, 2010). In addition, root dichloromethane extract of *D. suffruticosa* (DCM-DS) from sequential solvent extraction exhibited strong cytotoxicity towards human MCF-7 and MDA-MB-231 breast cancer cells (Armania *et al.*, 2013). Therefore, *D. suffruticosa* has a great potential to be developed as evidence-based complementary and alternative medicine for the treatment of breast cancer

The general objective of this study was to determine the mode of cell death and the signalling pathways involved in MCF-7 and MDA-MB-231 breast cancer cells treated with DCM-DS.

The specific objectives of this study were:

1. To determine the cell cycle profile and mode of cell death of DCM-DS treated MCF-7 and MDA-MB-231 breast cancer cells.
2. To determine the involvement of ROS in the cytotoxicity of DCM-DS towards MCF-7 and MDA-MB-231 cells.
3. To determine the expression of apoptotic, growth, survival genes and proteins of MCF-7 and MDA-MB-231 breast cancer cells treated with DCM-DS.
4. To isolate and identify the compounds in DCM-DS.

It was hypothesised that DCM-DS will induce cell cycle arrest, apoptosis and generation of ROS to induce cell death in MCF-7 and MDA-MB-231 breast cancer cells via multiple signalling pathways. The compounds in DCM-DS will be isolated and identified.

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