UNIVERSITI PUTRA MALAYSIA

APOPTOTIC-RELATED SIGNALLING PATHWAYS IN MCF-7 CELLS TREATED WITH ETHYL ACETATE EXTRACT OF Dillenia suffruticosa, AND ISOLATION OF ITS MAJOR COMPOUNDS

TOR YIN SIM

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By

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Chairman : Latifah Saiful Yazan, PhD

Faculty : Institute of Bioscience

Breast cancer is the most prevalent cancer among women worldwide. The trend for breast cancer treatment has shifted towards the use of natural product such as herbal medicine as an alternative and complementary medicine. *Dillenia suffruticosa* (Griff) Martelli that belongs to the family Dilleniaceae has been traditionally used to treat cancerous growth. In this study, the anti-cancer activity of ethyl acetate extract of *D. suffruticosa* (EADs) root was examined on breast cancer cells, MCF-7. EADs was prepared from the root of *D. suffruticosa* by using sequential solvent extraction. MTT assay was used to determine the cytotoxicity of EADs, which was demonstrated to be dose- and time-dependent, with IC_{50} of 39 ± 3.6 µg/mL at 72 hours. Flow cytometry cell cycle analysis displayed that EADs induced non-phase specific cell cycle arrest. EADs induced mainly apoptosis in MCF-7 cells in Annexin-FITC/PI analysis. The use of general caspase-inhibitor Z-VAD-FMK indicated that EADs-induced apoptosis was caspase-independent. EADs was found to promote oxidative stress that will lead to cell death because the pre-treatment with antioxidants α-tocopherol and ascorbic acid significantly reduced the cytotoxicity of the extract ($P<0.05$). DCFH-DA assay revealed that treatment with EADs attenuated the generation of intracellular ROS. The use of JC-1 dye reflected that EADs caused disruption in the mitochondrial membrane potential. Up-regulation of p53 and p21, is believed has led to EADs-induced non-phase specific cell cycle arrest ($P<0.05$). Elevation of Bax/Bcl-2 ratio and the depolarization of mitochondrial membrane potential indicated that EADs-induced apoptosis was mitochondrial-dependent.The expression of oxidative stress–related proteins AKT, p-AKT, ERK, and p-ERK was downregulated with upregulation of JNK and p-JNK suggesting that induction of apoptosis by EADs is mediated by inhibition of AKT and ERK, and activation of JNK. The major compounds of EADs were then isolated using column chromatography and elucidated using nuclear magnetic resonance analysis producing a total of 6 compounds. The cytotoxicity of the isolated compound was determined using MTT assay. Gallic acid was found to be most cytotoxic against MCF-7 cell line compared to others, with IC_{50} of 36 ± 1.7 µg/mL ($P<0.05$). In summary, EADs induced cell cycle arrest, oxidative stress and apoptosis in MCF-7 cells Thus, EADs has the potential to be developed as an anti-cancer agent against breast cancer.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan ijazah Doktor Falsafah

LALUAN ISYARAT BERKAITAN APOPTOSIS DALAM SEL KANSER PAYUDARA MCF-7 DIRAWAT DENGAN EKSTRAK ETIL ASETAT *Dillenia suffruticosa*, DAN PENGASINGAN SEBATIAN UTAMANYA

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Kanser payudara adalah kanser paling lazim di kalangan wanita seluruh dunia. Kaedah rawatan kanser payudara telah beralih kepada penggunaan hasilan semulajadi seperti perubatan herba sebagai perubatan alternatif dan pelengkap. *Dillenia suffruticosa* (Griff) Martelli yang berasal dari keluarga Dilleniaceae telah digunakan untuk merawat pertumbuhan kanser secara tradisional. Dalam kajian ini, ciri-ciri anti-kanser ekstrak etil asetat akar *D. suffruticosa* (EADs) terhadap sel payudara, MCF-7, dinilai. EADs disediakan daripada akar *D. suffruticosa* menggunakan pengekstrakan berurutan pelarut. Asai MTT digunakan untuk menentukan kesitotoksikan EADs, yang ditunjukkan bersandar kepada dos dan masa, dengan IC_{50} = 39 ±3.6 μg/mL pada 72 jam. Analisis sitometri kitaran sel menunjukkan bahawa EADs mengaruh penahanan fasa tak spesifik kitaran sel. Mengikut analisa sitometri annexin-FITC/PI, EADs mengaruh apoptosis terhadap sel MCF-7. Penggunaan perencat umum caspase Z-VAD-FMK menunjukkan pengaruhan apoptosis oleh EADs adalah tidak bersandar kepada caspase. EADs didapati menggalakkan tekanan oksidatif yang menyebabkan kematian sel. Asai DCFH-DA mendedahkan bahawa rawatan dengan EADs melemahkan penjanaan spesies oksigen reaktif intrasel. Penggunaan JC-1 menunjukkan EADs mengakibatkan gangguan kepada potensi membran mitokondria. Peningkatan dalam pengekspresan p53 dan p21 dipercayai telah mendorong kepada penahanan fasa tidak spesifik kitaran sel aruhan EADs ($P<0.05$). Peningkatan nisbah Bax/Bcl-2 dan penyahkutuban potensi membran mitokondria menunjukkan apoptosis aruhan EADs adalah bersandar kepada mitokondria. Pengekspresan protein yang berkaitan dengan tekanan oksidatif AKT, p-AKT, ERK, dan p-ERK yang diturunkan berikutan dengan peningkatan JNK dan p-JNK mencadangkan bahawa aruhan oleh EADs disebabkan oleh perencatan AKT dan ERK, dan pengaktifan JNK. Pengasingan sebatian utama EADs dijalankan dengan menggunakan kromatografi turus dan dikenalpasti dengan analisa resonans magnetik nuclear menghasilkan sejumlah enam sebatian. Kesitotoksikan sebatian yang diasingkan ditentukan dengan asai MTT. Asid galik adalah paling sitotoksik kepada sel MCF-7 berbanding dengan sebatian lain, dengan IC_{50} = 36 ± 1.7 μg/mL ($P<0.05$). Secara ringkas, EADs mengaruh penahanan kitaran sel, tekanan oksidatif and apoptosis melalui pengawalan pelbagai gen dan protein yang terlibat dalam laluan isyarat apoptosis. Justeru itu, EADs mempunyai potensi dijadikan agen anti-kanser terhadap kanser payudara.

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

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LIST OF ABBREVIATIONS

^{13}C-NMR	Carbon nuclear magnetic resonance
1D-NMR	One dimensional NMR
^{1}H-NMR	Proton nuclear magnetic resonance
2D-NMR	Two-dimensional NMR
AIF	Apoptosis inducing factor
AKT	Protein kinase B
APT	Attached proton test
CAT	Catalase
CDK	Cyclin-dependent kinase
DCFH-DA	Dichlorodihydrofluorescein diacetate
DCIS	Ductal carcinoma *in situ*
EGFR	Epidermal growth factor receptor
EMT	Epithelial to mesenchymal transition
ER	Oestrogen receptor
ERK	Extracellular signal-regulated kinase
FITC	Fluorescein isothiocyanate
GSH-Px	Glutathione peroxidase
HER-2	Human epidermal growth factor receptor-2
IARC	International Agency for Research on Cancer
IDC	Invasive ductal carcinoma
IKK	IκB kinase
IκB	Inhibitor of κB
JNK	c-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
MPT	Membrane permeability transition
MPTP	Mitochondrial permeability transition pores
NF-κB	Nuclear factor-kappa B
NMR	Nuclear magnetic resonance
p38MAPK	p38 mitogen-activated protein kinase
PARP	Poly (ADP-ribose) polymerase
PgR	Progesterone receptor
PKC	Protein kinase C
RCS	Reactive chlorine species
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SAPK	Stress-activated protein kinase
SOD	Superoxide dismutase
TCM	Traditional Chinese medicine
TNF	Tumour necrosis factor
Z-VAD-FMK	Benzyloxycarbonyl-ValAla-Asp(O-methyl) fluoromethylketone
ΔΨm	Mitochondrial membrane potential

CHAPTER 1

INTRODUCTION

The burden of cancer is expanding at an alarming rate. As in 2012, approximately 14.1 million cancer cases and 8.8 million cancer deaths were reported worldwide. It is expected that in coming two decades, the cancer incidence will grow more than 70% (Ferlay *et al.*, 2015). Breast cancer is the most commonly diagnosed life-threatening cancer in women. Breast cancer is heterogeneous and associated with a combination of risk factors that includes hereditary, reproductive factors, hormonal and environmental factors (Althuis *et al.*, 2004; DeBruin and Josephy, 2002). There were approximately 522,000 deaths due to breast cancer in 2012 that ranked as the fifth cause of overall cancer cases (Ferlay *et al.*, 2015).

Apart from surgery, radiotherapy and hormonal therapy, chemotherapy is one of the most common treatments for breast cancer (ACS, 2014). Chemotherapy is a systemic treatment, which refers to the use of one or more anti-cancer drugs circulating throughout the body to eliminate cancer cells. Unfortunately, the treatment will also inevitably affect the surrounding normal cells, thus causing adverse effects to the breast cancer patients (Breakthrough-Breast-Cancer, 2013) that include cardiac toxicity, secondary cancers, hand-foot syndrome, premature menopause, altered cognitive function and neurotoxicity (ACS, 2014; Azim *et al.*, 2011). Thus, alternative medication with alleviated adverse effects is indeed crucial.

Cancer is a complex disease characterized by the alteration in dynamic signaling pathways that modulate cell growth, survival, differentiation and invasion. Occurrence of cancer often involves deregulation of multiple genes that confers growth advantages and unlimited proliferative ability to cancer cells. Altered genes are commonly involved in signaling pathways such as mitogen-activated protein kinase (MAPK), protein kinase B (AKT) (Paraiso *et al*., 2010) and NF-κB pathway (Mauro *et al*., 2009). Therefore, the emergence of anticancer agents that are aiming multiple pathways or targets has promising future to cure cancer (Sebolt-Leopold and English, 2006).

Currently, combination therapy or multi-target anticancer agent is used to target multiple cancer-related molecules simultaneously. The purpose of this approach is to activate or to suppress the diverse signaling processes responsible for the survival of tumor (Giordano and Petrelli, 2008). The same concept applies to phytotherapy, where plant extract contains a variety of bioactive compounds that could exert synergistic therapeutic effect by acting or targeting on different receptors of different signaling pathways (Bhatt *et al.*, 2010). Phytotherapy practitioners assert that a whole extract performs better than equivalent dosage of isolated compounds (Nelson and Kursar, 1999). The examples of popular phytotherapy are Indian Medicine (Ayurveda) and Traditional Chinese Medicine. The interaction of compounds within the extract is associated with the improvement in efficiency, declination of undesirable effect, increment in the bioavailability and stability, and sufficient therapeutic effect with less doses (Biavatti, 2009).

The paradigm of cancer therapy has been drifted towards the use of natural products particularly herbal medicine. It is evidenced through the sale of plant-derived chemotherapeutic drugs such as taxanes derivatives (paclitaxel and doxetacel) and camptothecin derivatives (topotecan and irinotecan), which accounted for one third of the total chemotherapeutic drug sales globally, reaching 4 billion dollar in year 2007 (Demain and Vaishnav, 2011).

Deregulation of molecules involved in apoptotic pathway renders unlimited replicative ability to the cancer cells. Many anticancer agents exploit the abnormalities to halt the tumor progression (Ghobrial *et al.*, 2005; Kasibhatla and Tseng, 2003). Plant extracts have been reported to modulate the apoptotic-related pathways in cancer cells. Therefore, they can be served as promising apoptosis-inducing cancer therapeutic agents (R ós, 2015). The apoptotic pathways can be classified into mitochondrial-dependent and mitochondria-independent pathway. The regulation of mitochondrial pathway is controlled by the family of Bcl-2 (Brunelle and Letai, 2009). Another important regulator of apoptosis is the tumor suppressor, p53, which can also incite DNA repair and cellular senescence (Fridman and Lowe, 2003). p53 can also control the transcription of the members of Bcl-2 family especially Bcl-2 and Bax. Literature has shown that many plant-derived extracts are capable to induce apoptosis in cancerous cells by governing p53, Bax and Bcl-2 in the apoptotic signaling pathway (Ryu *et al.*, 2012; Gao *et al.*, 2011; Cheng *et al.*, 2008).

Dillenia suffruticosa (Griffith ex Hook. F. and Thomson) Martelli (Family: Dilleniaceae), locally known as "Simpoh air", is found abundantly in the secondary forest and swampy ground in Peninsular Malaysia to Papua New Guinea and Solomon Islands. The fruit of the plant is traditionally used for the treatment of cancerous growth (Ahmad and Holdsworth, 1995). Aside from that, the plant has been reported to possess antibacterial (Wiart *et al.*, 2004) and antiviral (Muliawan, 2008) activities. The hot water extract of the root of *D. suffruticosa* has anti-cervical (Said, 2010) and anti-colon (Husain, 2010) properties. This study was carried out as the ethyl acetate extract of *D. suffruticosa* was reported to be cytotoxic toward the breast cancer cell line, MCF-7 by Armania *et al.* (2013). In addition, the chemistry profile of ethyl acetate extract of *D. suffruticosa* has never been reported before.

The general objective of this study was to determine the mode of cell death of ethyl acetate extract of *D. suffruticosa* (EADs) and the signaling pathways involved in MCF-7 breast cancer cells.

The specific objectives of this study were:

1. To determine the mode of cell death and cell cycle profile in MCF-7 breast cancer cells treated with EADs.
2. To ascertain the involvement of oxidative stress in MCF-7 breast cancer cells treated with EADs.
3. To elucidate the signaling pathways related to apoptosis, survival and growth in MCF-7 breast cancer cells treated with EADs.
4. To isolate and identify the compounds in EADs.

It was hypothesized that:

1. EADs will show cytotoxic effect and induce cell cycle arrest in MCF-7 breast cancer cells.
2. EADs will induce oxidative stress in MCF-7 breast cancer cells.
3. EADs will induce apoptosis in MCF-7 breast cancer cells through the activation and inhibition of several apoptotic-related signaling pathways.
4. The compounds in EADs will be isolated and identified.

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