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APOPTOSIS AND CELL CYCLE MECHANISMS OF AMPELOPSIN E ON TRIPLE NEGATIVE BREAST CANCER CELLS

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By

NAPSIAH ABD RAHMAN

Thesis Submitted to the School of Graduate Studies,
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APOPTOSIS AND CELL CYCLE MECHANISMS OF AMPELOPSIN E ON TRIPLE NEGATIVE BREAST CANCER CELLS

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Chairman : Latifah Saiful Yazan, PhD
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Cancer remains as the second leading cause of death after cardiovascular disease, worldwide. Approximately 14.1 million new cancer cases and 8.2 million cancer deaths were reported in 2012. Breast cancer is the most common cancer among women with 522,000 deaths in 2012 alone. There are a few treatment modalities for breast cancer that include chemotherapy, mastectomy, biological therapy and hormone replacement therapy. Chemotherapy remains as the main treatment, but it comes with severe side effects such as immunosuppression and formation of secondary tumor. Therefore, people now are turning to natural products that include the use of plant as an alternative for management of the cancer. Indeed, plants have been a good source of a few anticancer drugs such as taxol, vincristine and vinblastine. *Dryobalanops* or also known as Kapur can be found in tropical rain forest of West Malesia (Peninsular Malaysia, Borneo and Sumatra). There are only seven species of *Dryobalanops,* which are *D. rappa, D. aromatica, D. lanceolata, D. beccari, D. fusca, D. keithii* and *D. oblongifolia*. Resveratrol oligomer is a major group of bioactive compounds that can be found in *Dryobalanops* species was reported to exhibit antioxidant, antifungal, anti-HIV, anti-platelet aggregation, tyrosinase and cyclooxygenase I and II inhibitory properties. The objective of this study was to determine the cytotoxicity of resveratrol oligomers (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D and nepalensinol E) from *Dryobalanops species* towards non-hormone dependent (MDA-MB-231) and hormone dependent (MCF-7) breast cancer, human colorectal adenocarcinoma cancer (HT-29), alveolar carcinoma (A-549), cervical adenocarcinoma (HeLa), non-tumorigenic epithelial breast (MCF-10A) and mouse embryonic fibroblast (NIH/3T3) cells. The cytotoxicity was determined by MTT assay. The cells were treated with the compounds (0.94-30 µM) for 72 hours. The mode of cell death was evaluated by using an inverted light microscope and annexin V/PI flow-cytometry analysis. Cell cycle analysis was performed by using a flow cytometer. Effects of ampelopsin E on the expression of NF-κB, p53, p21, Cyclin A, Cyclin B1, CDK1, Bax and Bcl-2 were analysed by using Western blotting. Data showed that ampelopsin E was most cytotoxic towards MDA-MB-231 cells with the IC_{50} (50% inhibition of cell viability compared to the control) of 14.5±0.71 µM. Cell shrinkage, membrane blebbing and formation apoptotic bodies characteristic of apoptosis were

observed following treatment with ampelopsin E. The annexin V/PI flow cytometric analysis further confirmed that ampelopsin E induced apoptosis in MDA-MB-231 cells. Cell cycle analysis revealed that ampelopsin E induced G_2/M phase cell cycle arrest in the cells. The expression level of Bax and p21 was significantly up-regulated ($p<0.05$), whereas, the expression level of NF-κB, p53, Cyclin A, Cyclin B1, CDK1 and Bcl-2 was significantly down-regulated ($p<0.05$) after treatment with ampelopsin E. In conclusion, ampelopsin E induced apoptosis and cell cycle arrest in MDA-MB-231 cells. It is postulated that the induction of apoptosis is via NF-κB p53/p21 and intrinsic pathways, and the G_2/M arrest is via p53-independent/p21 pathway. Therefore, ampelopsin E has the potential to be developed into an anticancer agent for the treatment of triple negative breast cancer.

Abstrak thesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan ijazah Master Sains

MEKANISMA APOPTOSIS DAN KITARAN SEL OLEH AMPELOPSIN E DI KANSER PAYUDARA *TRIPLE NEGATIVE*

Oleh

NAPSIAH ABD RAHMAN

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Pengerusi : Latifah Saiful Yazan, PhD
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Kanser kekal sebagai punca kedua utama kematian selepas penyakit kardiovaskular di seluruh dunia. Kira-kira 14.1 juta kes baharu dan 8.2 juta kes kematian akibat kanser dilaporkan pada tahun 2012. Kanser payudara merupakan kanser yang paling kerap dikalangan wanita dengan 522,000 kes kematian pada 2012 sahaja. Terdapat beberapa kaedah rawatan untuk kanser payudara termasuklah kemoterapi, mastektomi, terapi biologi dan terapi penggantian hormon. Kemoterapi kekal sebagai rawatan utama, tetapi ia hadir dengan kesan sampingan yang teruk seperti penekanan sistem imun dan pembentukan tumor sekunder. Oleh itu, masyarakat kini beralih kepada produk semulajadi termasuklah penggunaan tumbuh-tumbuhan sebagai alternatif untuk pengurusan kanser. Hakikatnya, tumbuh-tumbuhan telah menjadi sumber utama bagi beberapa ubatan anti-kanser seperti taxol, vincristine dan vinblastine. *Dryobalanops* atau dikenali juga sebagai pokok Kapur boleh ditemui di dalam hutan hujan tropika Barat Malesia (Semenanjung Malaysia, Borneo dan Sumatera). Terdapat hanya tujuh spesis *Dryobalanops* iaitu *D. rappa, D. aromatica, D. lanceolata, D. beccari, D. fusca, D. keithii* dan *D. oblongifolia.* Resveratrol oligomer adalah kumpulan utama sebatian bioaktif yang boleh ditemui daripada spesis *Dryobalanops* yang dilapor mempamerkan ciri-ciri antioksidan, anti-kulat, anti-HIV, anti-pengumpulan platelet, *tyrosinase* dan *cyclooxygenase* I dan II. Objektif kajian ini adalah untuk menentukan kesitotoksikan resveratrol oligomer (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D dan nepalensinol E) daripada spesis *Dryobalanops* terhadap kanser payudara tidak bergantung kepada hormon (MDA-MB-231) dan bergantung kepada hormon (MCF-7), kanser kolorektal (HT-29), kanser paru-paru (A-549), kanser servik (HeLa), sel bukan kanser payudara (MCF-10A) dan fibroblas embrio tikus (NIH/3T3). Kesitotoksikan ditentukan oleh asai MTT dirawat dengan sebatian (0.94-30 μM) selama 72 jam. Cara kematian sel telah ditentukan dengan mikroskop cahaya keterbalikan dan analisis sitometri aliran dengan Annexin-V/PI. Analisis kitaran sel telah dilaksanakan dengan sitometri aliran. Kesan ampelopsin E terhadap pengekspresan NF-κB, p53, p21, Cyclin A, Cyclin B1, CDK1, Bax dan Bcl-2 telah dianalisis dengan menggunakan pemblotan Western. Data menunjukkan ampelopsin E paling sitotoksik terhadap sel MDA-MB-231 dengan IC_{50} (50% perencatan kemandirian sel berbanding kawalan) 14.5±0.71 μM. Pengecutan sel,

pembengkakan membran dan pembentukan badan apoptotik telah diperhatikan berikutan rawatan dengan ampelopsin E. Analisis sitometri aliran dengan Annexin-V/PI mengesahkan bahawa ampelopsin E mengaruh apoptosis terhadap sel MDA-MB-231. Analisis kitaran sel pula mendedahkan bahawa ampelopsin E mengaruh perencatan kitaran sel di fasa G_2/M. Tahap ekspresi p21 dan Bax ditingkatkan secara ketara ($p<0.05$), manakala, tahap ekspresi NF-κB, p53, Cyclin A, Cyclin B1, CDK1 dan Bcl-2 diturunkan secara ketara ($p<0.05$) selepas rawatan dengan ampelopsin E. Kesimpulannya, ampelopsin E mengaruh apoptosis dan merencat kitaran sel dalam sel MDA-MB-231. Ianya dicadangkan bahawa aruhan apoptosis adalah melalui laluan NF-κB p53/p21 dan intrinsik, dan perencatan di fasa G_2/M adalah melalui laluan tidak bersandar p53/p21. Oleh itu, ampelopsin E mempunyai potensi untuk dibangunkan sebagai agen anti-kanser payudara tiga kali ganda negatif.

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I certify that a Thesis Examination Committee has met on 20 December 2017 to conduct the final examination of Napsiah binti Abd Rahman on her thesis entitled "Apoptosis and Cell Cycle Mechanisms of Ampelopsin E on Triple Negative Breast Cancer Cells" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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

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I hereby confirm that:

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This is to confirm that:

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LIST OF ABBREVIATIONS

BRCA1	Breast cancer 1
CDK	Cyclin-dependent kinase
CHK	Checkpoint kinase
CKI	Cyclin-dependent kinase inhibitor
DR	Death Receptor
ER	Estrogen receptor
E2F	Genes encoding transcription factor
IKK	IκB kinase
NF-κB	Nuclear factor-kappa B
PMSF	Phenylmethanesulfonyl fluoride
PR	Progesterone receptor
PS	Phosphatidylserine
P21	Potent cyclin-dependent kinase inhibitor
P53	Tumour protein p53 (TP53)
RB	Retinoblastoma protein
TNBC	Triple negative breast cancer
TNF-α	Tumor necrosis factor-α
TRAIL	TNF-related apoptosis inducing ligand
TUNEL	Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End labeling assay

CHAPTER 1

INTRODUCTION

1.1 Background

There have been approximately 14.1 million cancer cases recorded worldwide in 2012 and 8.2 million were cancer-related deaths. Breast cancer is the second most commonly diagnosed cancer with 1.7 million cases (11.9%) after lung cancer with 1.8 million cases (13%). Approximately 522,000 cases of breast cancer deaths in females were reported, which 324,000 cases occurred in less developed regions and 198,000 cases in more developed regions (Ferlay et al., 2015).

Cancer is an uncontrolled growth of cells that results from genetic mutations and it can invade to other tissues. Breast cancer is a heterogeneous disease with several biological subtypes, which are normal-like, luminal A, luminal B, basal-like and $HER2^+$ enriched (Glück, 2014). There are two factors that lead to development of breast cancer, which are external factors such as viruses, diet, radiations, chemicals and infectious organisms and internal factors such as hormones, immune conditions, inherited mutations and abnormal occurrence from metabolism due to loss of tumor suppressor genes (Parsa, 2012).

Currently, there are several treatments of breast cancer, such as chemotherapy (the use of tamoxifen, raloxifene and taxol), radiation therapy (brachytherapy), surgery (mastectomy), hormone therapy (aromatase inhibitor) or targeted therapy (herceptin). Chemotherapy is the most commonly used breast cancer treatment. Nevertheless, it comes with some adverse effects such as immunosuppression (Chapman et al., 2013), formation of secondary tumour (Powe et al., 2010) and development of cancer resistance (Glück, 2014). Therefore, alternative management for breast cancer is crucial to minimise the adverse effects.

The elimination of cancer cells is possible via induction of apoptosis and inhibition of cell cycle phase. Apoptosis is a programmed cell death, which is important in animal development, tissue homeostasis and other disease process (Yu et al., 2015) as the common response of cell stress induced by physiological changes, drugs, agents or toxins (Gerl and Vaux, 2005). The alterations of normal apoptotic pathways result in the process of neoplastic transformation, progression and metastasis (Elumalai et al., 2012). Apoptosis is a more preferred mode of cell death than necrosis because it is a programmed cell death and does not trigger inflammation (Millan and Huerta, 2009). Most of the antibreast cancer drugs induced apoptosis such as paclitaxel and doxorubicin (Lee et al., 2013), disulfiram (Chen et al., 2006), cannabidiol (Shrivastava et al., 2011), platinum II (Muscella et al., 2013) and tamoxifen (Liu et al., 2014).
There are two types of apoptotic pathways, which are intrinsic and extrinsic pathway (Dasgupta et al., 2017; Ricci and Zhong, 2006). The extrinsic or receptor pathway is

initiated by binding of an extracellular ligand (such as FasL and TNF-α) to its receptor (such as FasR and TNFR). Next, an adaptor protein (such as FADD, TRADD and RIDD) transmits the activating signal to an initiator caspase (such as caspases-2, -8 and -10) (Dasgupta et al., 2017; Riedl and Shi, 2004). TNF-α is a potent cytokine in response to injury, inflammation, infection and other environmental challenges that result in apoptosis (MacParland et al., 2016; Baud and Karin., 2001). TNF-α is frequently detected in human cancer tissues such as breast, ovarian and renal cancer. TNF-α activation promotes a recruitment of adaptor protein and NF-ƙB pathway (MacParland et al., 2016; Choi et al., 2013). NF-ƙB participates in the development, survival, proliferation and metastasis in cancer (Park and Hong, 2016; Pandey et al., 2008). The free NF-ƙB will be translocated from cytoplasm to the nucleus and bound to specific DNA sequences, which are related to tumor development and metastases (Park and Hong, 2016).

The intrinsic or mitochondria pathway is initiated within the cell by a few factors such as hypoxia, genetic damage, extremely high concentration of Ca^{2+} and severe oxidative stress via outer mitochondrial membrane permeabilization (Dasgupta et al., 2017; Wong, 2011; Riedl and Salvesen, 2007). Bcl-2 family of proteins initiates the mitochondrial apoptotic pathway by down-regulation of anti-apoptotic (such as Bcl-2, Bcl-X_L, Bcl-W, Bfl-1 and Mcl-1) and up-regulation of pro-apoptotic (such as Bax, Bak, Bad, Bcl-Xs, Bid, Bik, Bim and Hrk) protein (Wong, 2011). In both pathways, they will result in the activation of family cystein proteases (caspases) that act in proteolytic cascade to dismantle and remove the dead cells (Czerski and Nunez, 2004). There are two classes of caspases, which are the initiator caspases (such as caspase 2, 8, 9 and 10) and the effector caspases (such as caspase 3, 6 and 7) (Kawai et al., 2004). Initiator caspases will initiate the caspase-cascade and activates the effector caspases that results in apoptosis (Faleiro et al., 1997). At the same time, apoptosis will eliminate the cancer cells (Dasgupta et al., 2017).

In cell cycle regulation, cyclin-dependent kinases (CDKs) and cyclins play the most critical role to control the growth and proliferation of cancer cells (Dasgupta et al., 2017). The disruption of the enzymes and proteins to form a complex by CDK inhibitor can facilitate apoptotic death (Dasgupta et al., 2017; Rastogi and Mishra, 2012).

Natural products are employed in the management of variety of ailments and diseases including cancer for thousands of years (Dias et al., 2012). Approximately, 75% of novel anticancer agents derived from natural products from 1981 to 2010 (Newmann and Cragg, 2012). Indeed, plants have been a good source of a few anticancer agents, especially for breast cancer treatment, such as vindesine from *Catharanthus roseus* (Cragg and Newman, 2005), taxol from *Taxus brevifolia* (Kingston, 2007), beta-lapachone from *Tabebuia avellanedae* (Li et al., 2000; De Almeida, 2009), berberine from *Berberineeris* species (Wang et al., 2011), genistein from *Glycin max* (Kinghorn et al., 2009) and silvestrol from *Aglaia foveolata* (Moon et al., 2006). The potential of natural compounds in readjusting the balance in cancer to favor apoptosis has caused people to turn to natural products as an alternative to chemotherapeutic drugs for the management of cancer (Boik, 2001).

Dryobalanops or locally known as Kapur is a type of flowering plant from *Dipterocarpaceae* family. There are only seven species worldwide restricted to West Malesia (Peninsular Malaysia, Borneo and Sumatra), which are *D. rappa, D. aromatica, D. beccarii, D. lanceolata, D. fusca, D. keithii* and *D. oblongifolia* (Ashton and Flora, 1983). This genus is a rich source of resveratrol oligomers (trans-3,4',5-tryhydroxystilbene), which possess various bioactivities such as antioxidant (Fauconneau et al., 1997), anticancer (Dai et al., 1998) and antifungal (Pacher et al., 2002). There are several resveratrol oligomers isolated from *Dryobalanops sp* such as ampelopsin E (Oshima and Ueno, 1993), ampelopsin F (Takaya et al., 2002), flexuosol A (Li et al., 1998), laevifonol (Hirano et al., 2003), Malaysianol A (Wibowo et al., 2011b), Malaysianol D (Wibowo et al., 2014) and nepalensinol E (Yamada et al., 2006). Malaysianol A and ampelopsin E from *D. beccarii* were cytotoxic towards breast adenocarcinoma cell line, MCF-7 (Wibowo et al., 2014) but the mechanism of action is not yet studied.

1.2 Objective

1.2.1 General Objective

This study was conducted to determine the cytotoxicity of resveratrol oligomers of Dryobalanops species (ampelopsin E, ampelopsin F, flexuosol A, laevifonol, Malaysianol A, Malaysianol D and nepalensinol E) towards non-hormone dependent (MDA-MB-231) and hormone dependent (MCF-7) breast cancer, human colon cancer (HT-29), alveolar carcinoma (A-549), cervical adenocarcinoma (HeLa), non-tumorigenic epithelial breast (MCF-10A) and mouse embryonic fibroblast (NIH/3T3) cell lines.

1.2.2 Specific Objective

1. To determine the most cytotoxic resveratrol oligomer and the most sensitive cell line.

2. To determine the morphological changes of the most sensitive cell line treated with the most cytotoxic resveratrol oligomer.

3. To evaluate the mode of the cell death and cell cycle arrest induced by the most cytotoxic resveratrol oligomer in the most sensitive cell line.

4. To determine the effects of the most cytotoxic resveratrol oligomer on the expression of NF-κB, p53, p21, Cyclin A, Cyclin B1, CDK1, Bax and Bcl-2 in the most sensitive cell line.

1.3 Hypothesis

All of the resveratrol oligomers of *Dryobalanops* species will exhibit cytotoxicity towards the cancer cell lines. The most cytotoxic resveratrol oligomer will induce apoptosis and cell cycle arrest in the the most sensitive cell line. The expression level of NF-κB, p53, Cyclin A, Cyclin B1, CDK1 and Bcl-2 will decrease, whereas the expression level of p21 and Bax will increase following treatment with the most cytotoxic resveratrol oligomer.

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