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EFFECTS OF AMPELOPSIN E TOWARDS THE INVASIVENESS OF TRIPLE NEGATIVE BREAST CANCER CELL LINE, MDA-MB-231

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By

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

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April 2019

Chairman : Latifah Saiful Yazan, PhD
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Breast cancer is the most common cancer and the second leading cause of cancer-related deaths in women. Its two distinctive hallmarks are rapid abnormal growth and the ability to invade and spread (metastasis). During metastasis, the cancer cells form actin-rich protrusions, called invadopodia, which degrade extracellular matrix. The current breast cancer treatment, in particular chemotherapy, comes with adverse effects like immunosuppression, development of cancer resistance and secondary tumour formation. Hence, naturally-occurring molecules claimed to be less toxic are being studied as new drug candidates. Ampelopsin E, extracted from *Dryobalanops* species, exhibited various pharmacological properties including anticancer and anti-inflammation. Previous study reported that ampelopsin E exhibited strong cytotoxicity against the triple negative breast cancer (TNBC) cell line, MDA-MB-231. However, there is yet any scientific evidence of the effects of ampelopsin E towards metastasis. The objective of this study was to determine the effects of ampelopsin E towards the invasiveness of TNBC cells, MDA-MB-231. To prevent ampelopsin E from causing excessive cell death, the IC_{20} (concentration that caused 20% inhibition of cell growth compared to the untreated group) of ampelopsin E at 24 hours (17.92 ± 2.3 μM) was determined using 3-[4,5-dimethlthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay. Ampelopsin E was proven to halt the rate of migration of MDA-MB-231 cells treated with ampelopsin E through scratch assay at 8, 16 and 24 hours in both untreated group and serum-starved conditions. At 24 hours, a significant ($p<0.05$) reduction pattern was found in the transmigration and invasion of MDA-MB-231 cells when treated with 3.75, 7.5 and 15 μM of ampelopsin E as compared to untreated group. Invadopodia and gelatin degradation assays revealed a significant ($p<0.05$) inhibition effect of ampelopsin E towards invadopodia formation and their gelatin degradation capability in a concentration-dependent manner in all concentrations (1.88, 3.75, 7.5 and 15 μM) when compared to untreated group. Analysis of the proteins involved in metastasis and invadopodia formation showed that ampelopsin E reduced concentration of matrix metalloproteases (MMP2, MMP9 and MMP14) and platelet-derived growth factor (PDGF) in MDA-MB-231 cells treated with ampelopsin

E. In conclusion, ampelopsin E reduced the invasiveness of MDA-MB-231 cells and was proven to be a potential alternative in treating TNBC.

Keywords: Ampelopsin E, triple negative breast cancer, metastasis, invadopodia

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains.

KESAN ANTI-INVASIF AMPELOPSIN E TERHADAP TITISAN SEL KANSER PAYUDARA TRIPLE NEGATIF, MDA-MB-231

Oleh

FRANCIS TIENG YEW FU

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Kanser payudara ialah kanser yang paling kerap berlaku dan punca kedua kematian kanser di kalangan wanita. Kedua-dua ciri khas kanser ialah pertumbuhan yang cepat secara tidak normal dan keupayaan untuk membesar dan merebak (metastasis). Sel-sel kanser yang bermetastasis berupaya membentuk penonjolan atau lebih dikenali sebagai invadopodia. Invadopodia tersebut diperlukan untuk pencerobohan matriks ekstraselular. Rawatan kanser payudara utama, khususnya kemoterapi mempunyai pelbagai kesan negatif seperti imunosupresi, pembentukan rintangan kanser dan tumor sekunder. Oleh itu, molekul semula jadi yang dipercayai merupakan kurang toksik telah dipilih sebagai calon ubatan berpotensi. Ampelopsin E yang diekstrak dari spesies *Dryobalanops*, mempamerkan pelbagai sifat farmakologi termasuk antikanser dan anti-keradangan. Kajian terdahulu melaporkan bahawa ampelopsin E mempamerkan sitotoksiti yang kuat terhadap sel kanser payudara triple negatif, MDA-MB-231. Walau bagaimanapun, setakat ini, tiada bukti saintifik untuk potensinya dalam membentuk metastasis. Objektif kajian ini adalah untuk menyiasat kesan ampelopsin E terhadap sifat invasif sel kanser payudara triple negatif, MDA-MB-231. Untuk mengelakkan ampelopsin E daripada menyebabkan kematian sel yang berlebihan, IC_{20} (kepekatan yang menyebabkan 20% perencatan pertumbuhan sel berbanding dengan kumpulan tanpa rawatan) ampelopsin E pada 24 jam (17.92 ± 2.3 μM) ditentukan menggunakan asai 3-[4,5-dimethlthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT). Ampelopsin E dibuktikan menrendahkan penghijrahan sel MDA-MB-231 yang dirawat dengan ampelopsin E melalui asai calaran pada 8, 16 dan 24 jam dalam keadaan normal dan serum-kelaparan. Pada 24 jam, corak pengurangan signifikasi ($p<0.05$) ditemui di transmigrasi dan pencerobohan sel MDA-MB-231 apabila dirawat dengan 3.75, 7.5 dan 15 μM ampelopsin E berbanding dengan kumpulan tanpa rawatan. Penyelidikan degradasi Invadopodia dan gelatin menunjukkan kesan perencatan yang signifikasi ($p<0.05$) dalam pembentukan invadopodia dan kemampuan degradasi gelatin mengikut penambahan kepekatan ampelopsin E (1.88, 3.75, 7.5 dan 15 μM) berbanding dengan kumpulan tanpa rawatan. Analisis protein yang terlibat dalam metastasis dan

pembentukan invadopodia menunjukkan ampelopsin E mengurangkan konsentrasi metalloproteases matriks (MMP2, MMP9 dan MMP14) dan faktor pertumbuhan dari platelet (PDGF) dalam sel MDA-MB-231 yang dirawat dengan ampelopsin E. Kesimpulannya, ampelopsin E mengurangkan kebolehan invasif sel MDA-MB-231 dan dibuktikan sebagai alternatif yang berpotensi dalam merawat TNBC.

Kata kunci: Ampelopsin E, kanser payudara triple negatif, metastasis, invadopodia

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I certify that a Thesis Examination Committee has met on 23 April 2019 to conduct the final examination of Francis Tieng Yew Fu on his thesis entitled " Effects of Ampelopsin E Towards the Invasiveness of Triple Negative Breast Cancer Cell Line, MDA-MB-231" 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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Name of Member of Supervisory Committee: Norizan Ahmat

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LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
ANOVA	Analysis of variance
Arp	Actin-related protein
ATCC	American type culture collection
A549	Human lung adenocarcinoma epithelial cell
BB-94	Batimastat
BSA	Bovine serum albumin
BHMC	2,6-bis-(4-hydroxy-3-methoxybenzylidine) cyclohexanone
BL	Basal-like
CK	Cytokeratin
DMEM	Dulbecco's modified eagle's medium
DMSO	Dimethyl sulfoxide
Doxo	Doxorubicin
DPPH	1,1-diphenyl-2-picryhydrazyl
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMT	Epithelial-to-mesenchymal transition
ER	Estrogen receptor
FBS	Fetal bovine serum
HEPG2	Human liver cancer cell
HER2	Human epidermal growth factor receptor-2
HL60	Human leukemia cell
IGF-IR	Insulin-like growth factor-1 receptor
IHC	Immunohistochemistry
IL	Interleukin
IM	Immunomodulatory
LAR	Luminal androgen receptor
M	Mesenchymal-like
MCF-7	Human breast cancer cell
MDA-MB-231	Independent-hormonal human breast adenocarcinoma cell
MET	Hepatocyte growth factor receptor
MMP	Matrix metalloproteinase
MSL	Mesenchymal stem-like
MTT	3-[4,5-dimethlthiazol-2-yl]-2,5-diphenyltetrazolium bromide
mTOR	Mammalian target of rapamycin
NGF	Nerve growth factor
N-WASP	Neural Wiskott-Aldrich syndrome protein
OD	Optical density
PARP	Poly (ADP-ribose) polymerase
Pen Strep	Penicillin streptomycin
PD1/PD-L1	Programmed death-ligand 1

PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositide-3-kinase
PR	Progesterone receptor
SEM	Standard error of mean
TGF	Transforming growth factor
TNBC	Triple negative breast cancer
TRITC	Tetramethylrhodamine
Tsk	Tyrosine kinase substrate

CHAPTER 1

INTRODUCTION

1.1 Background

Breast cancer is the cancer that develop in breast regions or tissues such as lobules, connective tissues, ducts, fat and blood vessels as well as lymph nodes (National Cancer Institute, 2017). It is the most popular cancer as well as the second primary cause of cancer-related deaths in women worldwide (Torre et al., 2015). Women over 55 years old (one out of ten) is frequently diagnosed with breast cancer (Lu and Kang, 2007). In 2012, 1.7 million women across the world were diagnosed with breast cancer, with the prevalence of 521,900 death (Torre et al., 2015; Ferlay et al., 2013). According to global cancer statistics 2018, breast cancer accounted for one in every four cancer cases with 2.088.849 new cases and prevalence of 626,679 deaths (Bray et al., 2018).

Breast cancer is a genetically and clinically heterogeneous disease. It has a number of distinct biological entities that is associated with precise morphological and immuno-histochemical features and clinical behaviours, leading towards differences in treatment response patterns and clinical outcomes (Reis-Filho et al., 2005; Simpson et al., 2005; Lacroix et al., 2004). Classification of breast cancer is based on histological appearances and biological features like tumor size, lymph node involvement, patient's age, histological grade and status of hormone receptors. Subtypes of breast cancer are usually classified according to the existence or nonexistence of three receptors: estrogen receptor (ER), progesterone receptor (PR) as well as human epidermal growth factor receptor-2 (HER-2 or c-erbB2) (Kabir et al., 2012). If breast cancer lacks the expression of ER, PR and *HER2,* it is characterized as triple negative breast cancer (TNBC) (Collignon et al., 2016; Brady-West and McGrowder, 2011; Foulkes et al., 2010; Reis-Filho and Tutt, 2008; Brenton et al., 2005).

The term TNBC was first coined by Brenton et al. in October 2005. Generally, 10 to 24% of invasive breast cancers are TNBCs (Viale et al., 2009; Bauer et al., 2007; Morris et al., 2007). Majority of TNBCs consist of high grade tumor, in other words, they are relatively more aggressive, harder to treat and more likely to relapse or reoccur than other breast carcinomas (Gluz et al., 2009; Reis-Filho and Tutt, 2008; Dent et al., 2007; Rakha et al., 2006). Previous molecular profiling studies also suggest that although majority of TNBC (about 70%) is the basal-like subtype, it still consists of different subtypes with distinct biological behaviours, resulting in a heterogeneous entity (Carey et al., 2010; Dent et al., 2007; Kreike et al., 2007). In terms of clinical prognosis, TNBC is characterized by lower overall survival compared with receptor positive breast cancers (Pistelli et al., 2013; Anders and Carey 2009; Nishimura and Arima 2008; Rhee et al. 2008; Tian et al. 2008).

Some of the most common breast cancer treatment strategies are chemotherapy, surgery, radiotherapy, hormone and biological-targeted therapy. However, chemotherapy is still the only routine systemic treatment for TNBC patients (both early and advanced-stages) until today (Bianchini et al., 2017). Chemotherapy, that involves the application of biological agents, anthracyclines, taxanes, ixabepilones, platinum agents, as well as anti-epidermal growth factor receptor drugs, usually comes with adverse effects such as immunosuppression, development of cancer resistance (multidrug resistance) and secondary tumour formation. Even so, it is still in use because of the slack of targeted therapies and poor prognosis of patients with TNBC. Due to this reason, the survival rate of breast cancer patient is very unsatisfactory. Thus, continuous studies have been carried out to discover other possible effective agents or treatments with lower toxicity, better treatment outcomes and lesser adverse effects. One of the examples is the usage of naturally-occurring molecules with chemopreventive and chemotherapeutic properties. Since then, it has always been a rising attention in the discovery of naturally occurring molecules with anti- cancer properties (Seca and Pinto, 2018; Iqbal et al., 2017; Rayan et al., 2017; Kinghorn et al., 2009; Gibbs, 2000).

Natural products have been and are still used especially in developing countries as the primary source of medical treatment. From 1981 to 2014, more than 50% of drugs discovered are designed from natural products and, among them, 75% of anticancer drugs were derived from natural compounds (Newman and Cragg, 2016; Fabricant and Farnsworth, 2001). Examples of the antitumor drugs obtained from plants are colchicine (from *Colchicum autumnale L.*), etoposide (from *Podophyllum peltatum L.*) and monocrotaline (from *Crotolaria sessiliflora L.*) (Farnsworth, 1985), whereas polyphenols, brassinosteroids and taxols are some of natural compounds that are identified and extracted from terrestrial plants (Greenwell and Rahman, 2015). The use of natural products is becoming more popular nowadays due to the fact that they are readily available from the natural environment, less toxic and less severe side effects towards healthy human cells (Greenwell and Rahman, 2015; Unnati et al., 2013). *Dryobalanops* or locally known as 'Kapur' (Dipterocarpaceae family) is usually found only in the area of tropical forests of West Malesia (Sumatra, Peninsular Malaysia and Borneo) (Wibowo and Ahmat, 2015; Ashton, 1983). There are uniquely seven species of *Dryobalanops* worldwide: *D. rappa*, *D. lanceolata, D. aromatica*, *D. beccarii, D. oblongifolia, D. fusca* and *D. keithii*. Similar to the other genus in Dipterocarpaceae family, *Dryobalanops* has been known to have a substantial source of phenolic compounds, especially stilbene oligomers (Wibowo 2012; 2011; Aminah et al., 2010; Syah et al., 2003). Since 2014, approximately 200 oligostilbenoid constituents have been characterized in the Dipterocarpaceae family and ampelopsin E is one of them (Ito et al., 2014). Ampelopsin E was one of the major active compounds extracted from *Dryobalanops* species (Oshima and Ueno, 1993). Ampelopsin E has been proven to be cytotoxic towards breast adenocarcinoma cells, MCF-7 (Wibowo et al., 2014). It also induced apoptosis and G_2/M cell cycle arrest in MDA-MB-231 TNBC cells (Rahman et al., 2016). However, there is yet any scientific evidence on the effects of ampelopsin E towards metastasis.

One defining hallmark of breast cancer is the rapid unusual growing of cells beyond their usual boundaries, with the ability to invade adjoining parts of the body and spread

to other organs, which is referred as metastasis. Tumor metastasis that involves migration and invasion of breast cancer cells is a key step of cancer progression that indicates a more advanced stage with poorer prognosis (Talmadge and Fidler, 2010). The metastatic breast cancer cells can also coordinate extracellular matrix (ECM) degradation and remodeling by secreting proteases through formation of invadosome like invadopodia, which are actin-rich protrusions capable of degrading areas of the cell in contact with ECM (Yamaguchi and Oikawa, 2010; Chen, 1989; Tarone et al., 1985). The ability to form invadopodia is largely correlated with the invasive and metastatic potential of cancer cells (Eckert and Yang, 2011; Huttenlocher and Horwitz, 2011; Yamaguchi and Oikawa, 2010). Many cancer cell lines have the ability to form invadopodia, which is crucial in facilitating the invasive stages of metastasis such as stromal invasion, intravasation, extravasation and colonization of secondary sites (Eckert and Yang, 2011). Thus, targeting invadopodia formation could be an effective way of reducing invasiveness of cancer cells.

1.2 Problem Statement

Breast cancer metastasis was chosen as the target of the study because it remains as the leading cause of cancer-related deaths among women today (Bray et al., 2018). Among these deaths, majority of them were related to metastatic progression (Dent et al., 2017). Invadopodia are thought to play an important role in the metastasis of MDA-MB-231 cells (Weaver, 2006). Since current TNBC treatment is limited to chemotherapy and have many disadvantages, a natural compound, named ampelopsin E, was chosen as an alternative in combating MDA-MB-231 cells in this study. Furthermore, there is yet any scientific evidence on the mechanisms of ampelopsin E towards metastasis and invasiveness of MDA-MB-231 cells.

1.3 Objectives

1.3.1 General Objective

To determine the effects of ampelopsin E towards invasiveness of TNBC cell line, MDA-MB-231.

1.3.2 Specific Objectives

The specific objectives were:

(A) To determine the effects of ampelopsin E on the migration and invasion of MDA-MB-231 cells.
(B) To determine the effects of ampelopsin E on the invadopodia formation and gelatin degradation of MDA-MB-231 cells.
(C) To determine the effect of ampelopsin E on the expression of matrix metalloproteinases (MMP 2, MMP9 and MMP14) and platelet-derived growth factor (PDGF).

1.4 Hypothesis

Ampelopsin E will reduce the invasiveness of line MDA-MB-231 TNBC cells.

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