UNIVERSITI PUTRA MALAYSIA

ANTI-INVASIVE EFFECTS OF 2,6-BIS-(4-HYDROXYL-3METHOXYBENZYLIDINE) CYCLOHEXANONE AND ITS MOLECULAR TARGETS ASSOCIATED WITH INVADOPODIA FORMATION IN MDA-MB-231 HUMAN BREAST CANCER CELLS

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By

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ANTI-INVASIVE EFFECTS OF 2,6-BIS-(4-HYDROXYL-3METHOXYBENZYLIDINE) CYCLOHEXANONE AND ITS MOLECULAR TARGETS ASSOCIATED WITH INVADOPODIA FORMATION IN MDA-MB-231 HUMAN BREAST CANCER CELLS

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May 2018

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Cancer metastasis is a pathological event occurred in cancer patients where it can colonize the distant organs. In order to metastasize, the tumor cells need to migrate and invade the surrounding tissues. Invadopodia are thought to be specialized actin-rich protrusions formed by the highly invasive cells to degrade the dense meshwork of the extracellular matrix (ECM). This is the initial step employed to drive cancer invasion. Cancer metastasis is deadliest and has affected the survival rate of cancer patients. Current cancer treatment has also produced side effects. Chemotherapy has given rise to the invasion and metastasis while radiotherapy has caused the recurrence of cancer. Identification of compound(s) capable to disrupt the metastasis of cancer especially for hindering the invadopodia formation is important so as to provide anti-metastasis targeted therapy. Curcumin has been demonstrated to produce significant effect as an anti-cancer compound. However, due to its poor bioavailability, some analogues have been formulated. A curcuminoid analogue known as 2,6-bis-(4-hydroxyl-3methoxybenzylidine) cyclohexanone or BHMC has shown good potential in inhibiting inflammation and hyperalgesia. It also possesses anti-tumor effects on 4T1 murine breast cancer cells *in vivo*. However, there is still lack of empirical evidence on how BHMC works in preventing human breast cancer invasion. In this study, we pursued to investigate the role of BHMC on MDA-MB-231 breast cancer cells its underlying mechanism of action to prevent breast cancer invasion especially on the formation of invadopodia.

Analysis revealed that treatment of BHMC at 12.5 μM and below did not interfere with the proliferation of MDA-MB-231 cells. By using scratch migration assay, transwell migration and invasion assays, we found that BHMC at 12.5 μM reduces the percentage of the migration and invasion of MDA-MB-231 cells. The gelatin degradation assay showed that BHMC reduces the number of cells forming invadopodia. Analysis of the proteins involved in invasion showed that there is significant reduction in the expression of Rho guanine nucleotide exchange factor 7 (β-PIX), matrix metalloproteinase-9 (MMP-9) and membrane type 1-MMP (MT1-MMP) in the present of BHMC treatment at 12.5 μM. It can be postulated that BHMC at 12.5 μM is the optimal concentration to prevent the invasiveness of breast cancer cells.

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

KESAN ANTI PENYERANGAN 2,6-BIS-(4-HYDROXYL-3METHOXYBENZYLIDINE) CYCLOHEXANONE DAN SASARAN MOLEKUL BERKAITAN PEMBENTUKAN INVADOPODIA TERHADAP SEL KANSER PAYUDARA MDA-MB-231

Oleh

SITI NOR AINI BINTI HARUN

Mei 2018

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Metastasis (Perebakan) kanser merupakan satu keadaan patologi yang berlaku kepada pesakit kanser yang mana penyakit tersebut mengkoloni organ-organ yang lain. Sel-sel kanser perlu bermigrasi dan menyerang tisu-tisu sekeliling untuk merebak. Invadopodia merupakan bonjolan yang kaya dengan actin dibentuk oleh sel-sel kanser yang tinggi daya serang ini untuk mendegradasi matriks luar sel. Pembentukan ini merupakan langkah pertama berlakunya penyerangan kanser. Perebakan kanser boleh menyebabkan kematian dan telah memberi kesan terhadap jangka hayat pesakit kanser. Rawatan kanser terkini juga menyebabkan kesan-kesan sampingan. Kemoterapi telah menyebabkan berlakunya perebakan kanser manakala radioterapi telah menyebabkan pertumbuhan semula kanser. Proses mengenal pasti suatu kompoun yang boleh bertindak menghalang perebakan sel-sel kanser terutama untuk membantutkan pembentukan invadopodia sangat penting untuk menghasilkan terapi anti-metastasis. Kurkumin telah dilaporkan mempunyai kesan yang sangat memberansangkan sebagai ubat anti-kanser. Walau bagaimanapun, disebabkan oleh tahap ketersediaan bio kurkumin yang rendah, beberapa analog kurkumin telah diformulasi. Satu analog kurkumin yang dikenali sebagai 2,6-bis-(4-hydroxyl-3methoxybenzylidine) cyclohexanone (BHMC) telah menunjukkan potensi yang baik untuk menghalang sitokine keradangan dan hyperalgesia. Ia juga mempunya kesan anti-kanser terhadap sel kanser payudara murin 4T1 *in vivo*. Walaupun begitu, bukti empirikal mengenai tindak balas BHMC untuk menghalang penyerangan kanser payudara masih lagi kurang. Justeru itu, kami mengkaji kesan BHMC terhadap sel kanser payudara MDA-MB-231 dan mekanisme asas BHMC untuk menghalang penyerangan sel kanser terutama terhadap pembentukan invadopodia. Analisis daripada kajian ini menunjukkan

perawatan BHMC pada kepekatan 12.5 μM dan ke bawah tidak memberikan kesan terhadap tahap pertambahan sel MDA-MB-231. Walaupun begitu, eksperimen pergerakan migrasi dan esei migrasi dan invasi transwell, BHMC pada kepekatan 12.5 μM mengurangkan migrasi dan invasi sel MDA-MB-231. Esei degradasi gelatin pula menunjukkan BHMC mengurangkan bilangan sel yang membentuk invadopodia. Analisis kesan BHMC terhadap protein yang berkaitan penyerangan kanser pula menunjukkan BHMC mengurangkan ekspresi Rho guanine nucleotide exchange factor 7 (β-PIX), matrix metalloproteinase-9 (MMP-9) dan membrane type 1-MMP (MT1-MMP) pada kadar kepekatan 12.5 μM dan menyimpulkan bahawa BHMC pada kepekatan 12.5 μM merupakan kepekatan optimum untuk menghalang penyerangan sel kanser payudara.

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I certify that a Thesis Examination Committee has met on 14 May 2018 to conduct the final examination of Siti Nor Aini binti Harun on her thesis entitled "Anti-Invasive Effects of 2,6-Bis-(4-Hydroxyl-3methoxybenzylidine) Cyclohexanone and Its Molecular Targets Associated with Invadopodia Formation in MDA-MB-231 Human 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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2D	Two-dimensional
3D	Three-dimensional
β-arr	β-arrestin
ADAM	A disintegrin and metalloproteinase
ANGPTL	Angiopoietin-like
ANOVA	Analysis of variance
AP 1	Activator protein 1
Arf 6	ADP-ribosylation factor 6
Arp	Actin-related protein
ATP	Adenosine triphosphate
b-FGF	Basic fibroblast growth factor
BCA	Bicinchoninic acid
BHMC	2,6-bis-(4-hydroxyl-3methoxybenzylidine) cyclohexanone
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
BSA	Bovine serum albumin
BSC	Bio safety cabinet
CD63	CD63 antigen
CD9	CD9 antigen
Cdc42	Cell division cycle 42
CIP	Cdc42-interacting protein
CLP	Caecal-ligation puncture
COPD	Chronic Obstructive Pulmonary Disease
CRM	Chromosome region maintenance
CSF	Colony stimulating factor
DMEM	Dulbecco′s modified eagle′s medium
DMOG	Dimethyloxaloylglycine
DMSO	Dimethylsufoxide
DNA	Deoxyribonucleic acid
DNA	Deoxyribonucleic acid
ECL	Enhanced chemiluminescent
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMT	Epithelial mesenchymal transition
EOC	Epithelial ovarian cancer
ER/PR	Estrogen/progesterone receptor
ERRB2	Epidermal growth factor receptor 2
ET	Endothelin
EV	Extracellular vesicles
FA	Focal adhesion
FAK	Focal adhesion kinase
F-BAR	Fer/CIP4 homology-Bin/Amphiphysin/Rvs
FBS	Fetal bovine serum
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GDP	Guanosine diphosphate

GLUT	Glucose transporter
GTP	Guanosine triphosphate
HB	Heparin binding
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
HIF	Hypoxia inducible factor
HNSCC	Head and neck squamous cell carcinoma
HPLC	High performance liquid chromatography
HR	Homology region
HRP	Horseradish peroxidase
IGF	Insulin-like growth factor
IL	Interleukin
kDa	Kilo Dalton
LPS	Lipopolysaccharide
MAPK	p-38 and mitogen-activated protein kinase
MCP	Monocyte chemotactic protein
MLCK	Myosin like-chain kinase
MMP	Matrix metalloproteinase
MT1-MMP	Membrane type-1 matrix metalloproteinase
mTOR	Mammalian target of rapamycin
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5 diaphenyltetrazolium bromide
NF-κB	Nuclear factor κB
NHE	Sodium/hydrogen exchanger
NIC	Notch 1 fragment
N-WASP	Neural-Wiskott Aldrich Syndrome
PBS	Phosphate buffer saline
PCNA	Proliferating cell nuclear antigen
PDGF	Platelet-derived growth factor
PDZ-RhoGEF	postsynaptic density protein 95/disc-large/zonula occludens-RhoGEF
PI3K	Phosphoinositide 3-kinase
PIX	PAK-interacting exchange factor
PKC	Protein kinase C
PTEN	Phosphatase and tensin
PVDF	Polyvinylidene difluoride
RIPA	Radioimmunoprecipitation assay
ROCK	Rho-associated coiled-forming kinase
RSV	Rous sarcoma virus
SDF	Stromal cell derived factor
SDS	Sodium dodecyl sulphate
SDS-PAGE	SDS-polyacrylamide gel electrophoresis
SEM	Standard error of mean
SH	Sulfhydryl
TGF-α	Transforming growth factor α
TGF-β	Transforming growth factor β
TIMP	Tissue inhibitor of metalloproteinase
TLR	Toll-like receptor
TNBC	Triple negative breast cancer
TNF	Tumor necrosis factor
TNF	Tumor necrosis factor

TOM1L	Target of MYB1-like protein
uPAR	Urokinase plasminogen activator receptor
US FDA	United State Food and Drug Administration
VCA	Verprolin-cofilin-acidic
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau
WAVE	WASP family verprolin-homologous protein
WIP	WASP-interacting protein

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Breast cancer is a form of disorder in which the cancer cells can grow either at the lobular, medullary, ductal or sebaceous of the breast tissue. The causes of breast cancer include the mutations of the genes such as epidermal growth factor receptor 2 (ERBB2) (also known as human epidermal growth factor receptor 2 (HER2)), breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) (Lukong, 2017). There are six hallmarks of cancer that have been proposed which encompass of the ability of the cancer cells to sustain the proliferative signaling, resist cell death, induce angiogenesis, evade the growth suppressors, enable the replicative immortality and activate invasive metastasis (Hanahan & Weinberg, 2011). Most of the patients whom endure breast cancer are likely to face mortality once the cancer cells have metastasized to other parts of body. Triple negative breast cancer patients, whom are clinically having less or absent of HER2 receptor (-HER2) and estrogen/progesterone receptor (-ER/PR) are the highly invasive cancer incidence among the patients (Bianchini et al., 2016). These types of patients are having increased likelihood of distant recurrence and believed to be more aggressive compared to other types of breast cancer (Bianchini et al., 2016).

1.2 Problem Statement

Metastatic breast cancer is the major problem in the population as it can affect the survival of breast cancer patients (Lukong, 2017). The ability of the tumor cells to disseminate to other parts of the body such as lungs, brain and bones and only can be diagnosed at an advanced stage has been troublesome as the tumor cells cannot be eradicated totally from the body thus causing the recurrence of cancer (Scully et al., 2012). Once the invasive cancer cells have metastasized, the treatment to reduce the growth of cancer would be challenging as many cancer genes have been up-regulated and also reduce the sensitivity of cancer cells to the treatment (Massagué et al., 2017). There are several treatments used to treat breast cancer including the application of surgery, radio- and chemotherapy. radio- and chemotherapy (Lukong, 2017). However, besides killing the tumor cells, especially radio- and chemotherapy, both radio- and chemotherapy have caused side effects to the patients such as thrombocytopenia, diarrhea, infertility and others (Lukong, 2017).

Curcumin, a diferuloylmethane is a potential compound to target and modulate many proteins linked to cancer (Hasima & Aggarwal, 2012). Curcumin has been reported to have entered the clinical trials but the poor bioavailability

problem that curcumin had has been questioned (Anand et al., 2007). Having promising abilities to target multiple proteins related to cancer has urged the researchers to modify the structure of curcumin but still preserving the methyl and hydroxyl group which are responsible for the anti-proliferation and anti-oxidant properties of curcumin (Nagahama et al., 2016). One of the analogues of curcumin which is 2,6-bis-(4-hydroxyl-3methoxybenzylidine) cyclohexanone or BHMC has been studied in inflammation and hyperalgesic pain (Ming-Tatt et al., 2013; Tham et al., 2010).Recently, BHMC has shown to possess anti-tumor activityin 4T1 murine breast cancer (Razak et al., 2017); . However, BHMC is yet to be studied in human breast cancer. It will be interesting to investigate the effects of BHMC on the migration and invasion of MDA-MB-231 human breast cancer cells and specifically in the formation of invadopodia and their targeted proteins.

1.3 Objectives

This research was conducted to investigate the anti-invasive effects of BHMC and its molecular target(s) on MDA-MB-231 human breast cancer cells.

The specific objectives of the study include the following:

1. To determine the effect of BHMC on the proliferation of MDA-MB-231 human breast cancer cells
2. To determine the effect of BHMC on the migration and invasion of MDA-MB-231 human breast cancer cells
3. To determine the effect of BHMC on the formation of invadopodia in MDA-MB-231 human breast cancer cells
4. To identify the effect of BHMC on expressions of the proteins involved in invasion and invadopodia such as MMP-9, MT1-MMP and β-PIX

1.4 Hypothesis

It is hypothesized that BHMC at non-cytotoxic concentrations will reduce the migration and invasion of MDA-MB-231 human breast cancer cells. In addition, it is expected that BHMC would reduce the number of cells forming invadopodia via down-regulation of MMP-9, MT1-MMP and β-PIX expressions.

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