UNIVERSITI PUTRA MALAYSIA

MOLECULAR MECHANISMS UNDERLYING ANTIPROLIFERATIVE EFFECT OF TRICYCLOHEXYLPHOSPHINE GOLD (I) MERCAPTOBENZOATE DERIVATIVES ON HUMAN BREAST AND OVARIAN CARCINOMA CELL LINES

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FPSK(p) 2018 5

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

October 2017

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

MOLECULAR MECHANISMS UNDERLYING ANTIPROLIFERATIVE EFFECT OF TRICYCLOHEXYLPHOSPHINE GOLD (I) MERCAPTOBENZOATE DERIVATIVES ON HUMAN BREAST AND OVARIAN CARCINOMA CELL LINES

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Breast and ovarian cancers are in the list of top three female cancers. Hormonal problem and family genetic background play important role in these two types of cancer. In cancer research, p53 deems to be the key regulator in the apoptosis events (intrinsic and extrinsic). Many studies have been focusing on the therapeutic effects of the metal complexes including gold complexes due to its potential in exhibiting various medical therapeutic benefits. Thus, a series of gold complexes has been synthesized from the precursor tricyclohexylphosphine gold (I) and mercaptobenzoic acid ligands. The Tricyclohexylphosphinegold (I) R-mercaptobenzoate derivatives are yielded at different ligand position of ortho (2), meta (3) and para (4), labelled as CAU2, CAU3 and CAU4, respectively. The antiproliferative effect and their underlying mechanism(s) were investigated on both breast (MCF-7R) and ovarian (A2780) cancer cell lines via various *in vitro* assays. Molecular mechanisms of p53 of both cells upon treatments were analysed via Human p53 signaling pathway RT^2 profiler PCR array with all other supportive parameters such as cell proliferation, DNA fragmentation, cell invasion, cell cycle analysis, Anexin V/FITC and caspases (3, 8, 9 and 10). All compounds (CAU2, CAU3 and CAU4) exhibited strong cytotoxicity against MCF-7R and A2780 cell lines with IC_{50} of 8.14 µM, 7.26 µM and 9.03 µM against the former cell lines and 1.19 µM, 2.28 µM and 0.785 µM against the latter cell lines, respectively. Apoptotic cell death was confirmed by DNA fragmentation and Annexin V assay, respectively. The treated compounds also induced caspases (caspase-3/7, -8, -9, -10) expressions at both cancer cells which led to apoptosis. Both types of cancer cells were arrested at S-phase checkpoint upon treatment with the treated compounds. All treated compounds were shown to induce both intrinsic and extrinsic apoptotic pathways, supported and confirmed by the data obtained from

Human p53 signaling pathway RT^2 profiler PCR array and caspases activities assay, respectively. The compounds were also able to significantly modulate several important gene expressions such as *p53*, *p73* and *Bax* via upregulation whilst simultaneously downregulated key anti-apoptotic gene *bcl-2*. Downregulation of *MDM2* gene has also been observed, as it served as the destructive factor for *p53* gene. The compounds also inhibited the NF-κB signaling pathway via activation of Lys48-linked polyubiquitination thus led to NF-κB degradation. Furthermore, the accumulation of reactive oxygen species (ROS) was observed upon the compounds' treatment, indicating the ROS generation thus led to the increment of mitochondrial membrane potential (MMP). Consequently, this led to the increase of cytochrome c releases from mitochondria, manifested by the results obtained by flow cytometric analysis. In conclusion, CAU2, CAU3 and CAU 4 exhibited significant anticancer effects against both breast and ovarian cancer by inducing intrinsic and extrinsic apoptotic cell death, respectively. These findings shed a light for furthering the research in the new discovery of novel chemotherapeutic agents.

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

KESAN PROLIFERATIF DAN MEKANISME KOMPLEKS EMAS TERHADAP SEL MCF-7 DAN A2780

Oleh

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Kanser payudara and ovary merupakan kanser utama di kalangan wanita. Masalah hormon dan latar belakang genetik keluarga memainkan peranan penting dalam kedua-dua jenis kanser. Dalam penyelidikan kanser, gen p53 dianggap sebagai pengatur utama dalam laluan apoptosis (intrinsik dan ekstrinsik). Banyak kajian telah memberi tumpuan kepada kesan terapeutik kompleks logam termasuk kompleks emas kerana potensinya mempamerkan pelbagai manfaat terapeutik perubatan. Oleh itu, satu siri kompleks emas telah disintesis daripada prekursor emas (I) trisikloheksilfosfina dan ligan asid merkaptobenzoik. Terbitan emas (1) triskiloheksilfofina R-merkaptobenzoat dihasilkan pada kedudukan ligan yang berbeza iaitu pada kedudukan ortho (2), meta (3) dan para (4), dilabelkan sebagai CAU2, CAU3 dan CAU4. Kesan anti-proliferatif dan mekanisma sebatian-sebatian tersebut telah dikaji ke atas sel kanser payudara (MCF-7R) dan ovari (A2780) melalui pelbagai asai *in vitro*. Mekanisme molekul gen *p53* pada kedua-dua sel kanser selepas rawatan dengan terbitan komples emas dianalisis melalui pemprofilan RT^2 PCR laluan isyarat p53 manusia dan kesemua parameter sokongan lain seperti kesan sitotoksik sel, pemecahan DNA, perebakan sel, analisis kitaran sel, Anexin V / FITC dan caspases (3, 8, 9 dan 10). Semua sebatian (CAU2, CAU3 dan CAU4) telah menunjukkan kesan sitotoksik terhadap sel-sel MCF-7R dan A2780 dengan nilai IC_{50} masing-masing pada 8.14, 7.26 dan 9.03 μM terhadap sel MCF-&R dan 1.19, 2.28 dan 0.785 μM ke atas sel A2780. Kematian sel apoptotik disahkan oleh pemecahan DNA dan asai Annexin V. Semua sebatian yang dirawat menunjukkan keupayaan mengaruh laluan intrinsik dan ekstrinsik apoptosis, dan ini disokong dan disahkan melalui data yang diperolehi daripada pelbagai pemprofilan RT^2 PCR laluan isyarat p53 manusia dan asai aktiviti caspase. Terbitan kompleks emas juga telah mengaruh ekspresi caspases (caspase-3/7, -8, -9, -10) pada kedua-dua jenis sel kanser dans eterusnya menyebabkan apoptosis. Kedua-dua jenis sel kanser telah menunjukan

kematian sel pada fasa-S selepas rawatan dengan terbitan kompleks emas. Sebatian-sebatian tersebut juga berupaya memodulasi secara ketara beberapa ekspresi gen yang penting seperti *p53*, *p73* dan *Bax* melalui peningkatan regulasi dan pada masa yang sama menurunkan regulasi gen utama anti-apoptosis *bcl2*. Penurunan regulasi gen *MDM2* juga dipamerkan kerana ia berfungsi sebagai faktor pemusnah gen *p53*. Sebatian-sebatian ini juga merencat laluan isyarat NF-κB melalui pengaktifan poliubikuitinasi berkaitan Lys48 seterusnya membawa kepada penguraian NF-κB. Tambahan pula, rawatan menggunakan sebatian-sebatian tersebut juga menyebabkan pengumpulan spesis oksigen reaktif (ROS) yang ditunjukkan melalui penjanaan ROS dan seterusnya menyebabkan peningkatan keupayaan membrane mitokondria (MMP). Akibatnya, ini membawa kepada peningkatan pengeluaran sitokrom c dari mitokondria, yang ditunjukkan oleh hasil yang diperolehi oleh analisis aliran sitometrik. Secara keseluruhannya, CAU2, CAU3 dan CAU4 mempamerkan kesan antikanser yang ketara terhadap kedua sel payudara dan ovari dengan mengaruh kematian sel apoptosis intrinsik dan ekstrinsik. Hasil daripada kajian ini akan memberi harapan untuk meneruskan penyelidikan dalam penemuan baru agen kemoterapi yang ulung.

ACKNOWLEDGEMENTS

First and foremost, it is a genuine pleasure to deliver my deep sense of thanks and gratitude to my supervisor Associate Professor Dr. Roslida, her dedication and keen interest as well as her overwhelming attitude to help her students had contributed for the completion of my works and thesis. Her timely advice, scholarly advice and scientific approach have helped me to a very great extend in the accomplishment of this task.

Besides, I would like to express my sincere thanks to the panel members of my supervisory comittee, Associate Professor Dr. Abdah, Associate Professor Dr. Cheah Yoke Kqueen and Distinguished Professor Dr. Edward Tiekink. Not forgetting their kind hands delivered to me when I was facing tough time at the beginning of my PhD candidature. Without the precious compounds and financial support of the research materials from Professor Dr. Edward Tiekink, it is impossible for me to complete my bench work and deliver my thesis today.

I would like to deliver my deepest thanks to Dr. Samuel Ooi and Dr. Ally Yeo for their assistance and advise during my experimental stage and write up. Without their kind help, it is not possible for me to come to this stage smoothly. Special thanks to Dr. Mohd Islahuddin for his moral support and time too during the difficult time.

My appreciation also extends to my friends and fellow colleagues, Jassy Lim and Dr. Arulselvan who provided me plenty of support, flexibility and advise for the completion of the thesis as well as publication.

Lastly, the greatest appreciation of thanks to be delivered to my family members, especially my dearest mother, a person who bless me all the time and never fail in providing her immeasurable support, encouragement, help and her care to me during the tough time of my candidature.

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

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LIST OF ABBREVIATIONS

APAF-1	Apoptosis protease activating factor-1
BRCA1	Tumor suppressor gene BRCA 1
BRCA2	Tumor suppressor gene BRCA 2
BRK	Breast tumor kinase
ATM/ATR	Ataxiatelangiectasia mutated/Ataxia-telangiectasia mutated and Rad related
CAD	Caspase activated DNase
CDK	Cyclin-dependent kinase
CDKI	Cyclin-dependent kinase inhibitors
DISC	Death-induced signaling complex
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ER	Estrogen receptor
ERK	Extracellular regulated kinase
EtBr	Ethidium bromide
FADD	Fas-associated death domain protein
FasLG	Fas-ligand
FasR	Fas receptor
FBS	Fetal bovine serum
FLICA	Flurochrome inhibitors of caspase
HER2	Human epidermal growth receptor-2
ICAD	Inhibitor caspase activated DNase
ICAM-1	Intracellular adhesion molecule-1
IL	Interleukin
JNK	jun Amino-terminal Kinases
Lys	Lysine
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MDM2	Mouse double minute 2 homolog
mg	Miligram

MIP-1	Macrophage inflammatory protein-1
mM	Milimolar
MMP	Matrix metalloproteinase
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
MTT	Dimethyl thiazolyl dephenyl tetrazolium
NF- κB	Nuclear factor kappa-B
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PDGF B	Platelet derived growth factor subunit B
RIP	Ribosome-inactivating protein
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SD	Standard deviation
TAE	Tris-acetate-EDTA
TAK1	Mitotic Activated Protein Kinase Kinase Kinase
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
TRADD	TNF receptor-associated death domain protein
TrxR	Thioredoxin reductase
uM	Micromolar
uPA	Urokinase-type plasminogen activator
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

CHAPTER 1

INTRODUCTION

1.1 Research Background

The world of 21st century changes the diet lifestyle and living habits of people, which actually causes several health problems. Among the health problems, cancer is considered one of the most major public health issues. Up to date, there are total of 14.1 million of the new cancer cases has been reported and the mortality rate of cancer is 9.1 million at the year of 2012 (Globocan, 2017).

According to the figures obtained from global cancer statistic of the year 2012, three of the top leading cancers in females is breast, ovarian and cervical cancer. Environmental exposure, hormonal and family genetic backgrounds are closely correlated to an increased risk for breast cancer and ovarian.

According to the latest Health Facts (2013) released by the Ministry of Health Malaysia, cancer is one of the top five causes of death in both government and private hospitals. Besides, cancer has overtaken coronary heart disease as the 1st killer in 2014. In Malaysia, the rate of new cancer incidence has been increased from 32,000 in year 2008 to approximately 37,000 cases in year 2012. The mortality rate of cancer in Malaysia also increased from 20,100 death cases in year 2008 to 21,700 death cases in 2012.

Breast cancer is a major global health issue and also the killer among women of all ethnic backgrounds. In Malaysia, breast cancer affected 1 in every 19 Malaysian women whom are diagnosed with breast cancer by the age of 85. Approximately, 4000 women are diagnosed each year and it commonly affects the women aged between 35 to 60 and 40% of the incident rate age d below 50 years old. The risk factors of breast cancer including early menarche or late menopause, late stage at first full term pregnancy, high body mass index after menopause and exposure to ionizing radiation (Almutlaq *et al*., 2017).

Ovarian cancer is the 4th most common cancer amongst Malaysian women. The statistic shows about 500 women were diagnosed with the disease each and every year. The known risk factors of ovarian cancer including nulliparity, late menopause, early menarche, use of infertility drugs and personal or family history of breast or ovarian cancer (Keng *et al*., 2015).

Genetic cancer syndromes including mutations of BRCA1 or BRCA2 genes have been associated with an increased risk in both ovarian and breast cancer. Women with BRCA1 and BRCA2 mutations possess an estimated risk of 85% for breast cancer, 20% - 40% of the chances of developing ovarian cancer (Petrucelli *et al*., 2010).

Several treatments for cancer are usually adopted by most of the medical institutions including radiotherapy, surgical removal and chemotherapy. Surgical resection of the tumour is very risky as it may cause severe pain and may also lead to organs dysfunction, post-operative infection and even death. Radiotherapy kills cancer cells by using the principle of radiation; at the same time, it harms the normal cells due to the accuracy and persistency to target the tumour spot for the delivery of radiation (Sharma *et al.,* 2001). Whereas, the most common therapy is chemotherapy that usually adopts anti-neoplastic drugs in killing rapid dividing cancer cells and further suppresses their proliferation.

In cancer research, the apoptosis and p53 are closely related as most of the time apoptosis is meadiated by p53 (Volgerstein *et al*., 2000). Besides, p53 capable of intervene apoptosis mechanisms of cancer at both intrinsic and extrinsic apoptosis pathways (Haupt *et al*., 2003). Tumour suppressor gene – p53 also criticallly involved in cell cycle checkpoint and also activation of caspases that lead to apoptosis (Schuler *et al*., 2000). Hence it is important for us to study the molecular mechanisms of the treated compounds in related to p53 as well as apoptosis.

Therefore, each of the elements in involved in both intrinsic and extrinsic apoptosis pathways are to be studied in this research project. Cytochrome c, *Bcl-2, ATM, ATR, Apaf1, Bax*, caspase-3 and -9 are to be involved in intrinsic pathway of apoptosis. Whereby, caspase-3, -8 and -10, Bid, TNF/TNF-R and FAS/FADD are involved in extrinsic pathway of apoptosis (Ooi *et al*., 2017).

1.2 Problem Statement

Most of the antineoplastic-based chemotherapy drugs are the metal-based drugs. Most commonly used metal-based antineoplastic drugs are made of platinum complexes. Platinum complexes are a family of metal-based drugs showing anti-cancer properties. Cisplatin, the conventional antineoplastic drug of this family is one of the most widely used and most effective cytotoxic agent in the treatment of solid tumours such as breast and ovarian cancers with the cure rate of 70% - 80% (Brezdan *et al*., 2000; Donzelli *et al.,* 2004; Taguchi *et al*., 2005). However, there is a limitation in the application of cisplatin to the cancer patients due to the development of resistance by tumour cells (Boulikas and Vougiouka, 2003).

Auronafin, [triethylphosphinegold (I) tetraacetathioglucose] is the gold based anti-inflammatory compound serendipitously discovered for it's potential inhibitory activity on malignancies. The discovery of this gold compound inspired the researchers to determine and discover more anti-cancer potential from gold complexes. A hypothesis was made from the presence of phosphine ligand on gold complexes, which demonstrated significant cytotoxicity on cancer cells (Tiekink, 2002).

Tricyclohexylphosphine gold (I) R-mercaptobenzoate (R= 2, 3, 4) complexes were synthesized with the inclusion of cyclophosphine ligand and mercaptobenzoic acid ligand at different location on the structure. Based on the aforementioned justification, tricyclohexylphosphine gold (I) R-mercaptobenzoate (R= 2, 3, 4) complexes were successfully synthesized to investigate their potential in anticancer by determining their apoptosis pathway profile against human breast adenocarcinoma cell line (MCF-7R) and human ovarian carcinoma cell lines (A2780) in this current study. R is referred to the ligand position at the ortho (2), meta (3) and para (4), respectively.

1.2.1 Cells selection

Human ovarian carcinoma cell line (A2780) and human breast adenocarcinoma cell line - drug resistance (MCF-7R) were selected to be used as cell culture model in this experiment.

In this study, cisplatin was used as the drug control and A2780 cells are sensitive towards the drug control. Besides, A2780 is a very common cell line used in most of the ovarian cancer research yet can be compared the efficacy and sensitivity of the cancer cells with treated compounds (Hunakova *et al*., 2005).

Apart from this, MCF-7R was selected to be the cell line used for breast cancer study, where this cell line is multi-drug resistant. This cell line is selected to compare the sensitivity of the cells with drug control (cisplatin) over the treated compounds (Bichat *et al*., 1997). Besides, the chemoresistance mechanism could be elucidated too from the study.

1.3 Objectives

1.3.1 General objective

To investigate the anticancer potential of tricyclohexylphosphine gold (I) R-mercaptobenzoate (R= 2, 3, 4) complexes against human breast adenocarcinoma cell lines (MCF7-R and human ovarian carcinoma cell lines (A2780) and its underlying molecular mechanism(s).

1.3.2 Specific objectives

1. To determine and compare IC_{50} values of tricyclohexylphosphine gold (I) R-mercaptobenzoate (R=2,3,4) compounds against MCF-7R and A2780 cell lines, respectively.
2. To evaluate the cell cycle analysis and mode of cells death on MCF-7R and A2780 cell lines when treated with tricyclohexylphosphine gold (I) R-mercaptobenzoate (R=2,3,4).
3. To assess the influence of caspases (caspase-3, caspase-8, caspase-9, caspases-10), cytochrome c and inducer of apoptosis in the pathway of apoptosis
4. To investigate the activity of Nuclear Factor-kappa B (NF- κB) in apoptosis through ubiquitin-detection a well as its tyrosine kinase activities
5. To manifest the cross talk signaling events amongst the biomarkers assessments with gene expression analysis of p-53 pathway via Human p-53 RT^2 Profiler PCR Array.

1.4 Hypothesis

Based on the principles and knowledge established on auronafin and platinum complexes, thus it is anticipated that tricyclohexylphosphine gold (I) R-mercaptobenzoate (R= 2, 3, 4) series may possess anti-proliferative activities on human breast adenocarcinoma cell lines and human ovarian carcinoma cell lines by inducing both intrinsic and extrinsic apoptosis pathway via modulation of multiple gene expressions

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