UNIVERSITI PUTRA MALAYSIA

APOPTOSIS AND CELL CYCLE ARREST OF MCF-7R BREAST CARCINOMA CELLS BY BIS(PHOSPHANE)COPPER(I) THIOCARBAMIDES DERIVATIVE COMPOUNDS

OOI KAH KOOI

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By

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APOPTOSIS AND CELL CYCLE ARREST OF MCF-7R BREAST CARCINOMA CELLS BY BIS(PHOSPHANE)COPPER(I) THIOCARBAMIDES DERIVATIVE COMPOUNDS

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July 2017

Chair: Abdah Md. Akim, PhD
Faculty: Medicine and Health Sciences

Previous studies on coordinated gold compounds namely phosphanegold(I) thiocarbamides exhibited promising anti-cancer activities through induction of apoptosis. To a greater extent, current research was advanced to study copper(I) derivatives, namely bis(phosphane)copper(I) thiocarbamides, $(Ph_3P)_2Cu[S=C(O\mathbf{R})N(H)Ph]Cl$, with R referring as three different substituent group: methyl (**Compound 1**), ethyl (**Compound 2**), and isopropyl (**Compound 3**); on breast cancer. Among the aggressive cancers reported, breast cancer exhibited poor response to chemotherapy owing to its high cellular glutathione (GSH) levels, high mitochondrial thioredoxin reductase (TrxR) activities and over-activation of NF-κB; hence, contributed for reduced drug's efficacy and resistance to death-signals. Thus, regulation on GSH, TrxR and NF-κB are suitable targets in current study. The tested copper(I) compounds demonstrated *in-vitro* cytotoxicity against MCF-7R breast carcinoma cells with micromolar potency. Meanwhile, cytotoxicity testing on normal cells (kidney, breast and heart) suggest **Compound 1**–**3** are less potent towards normal cells and selective towards breast cancer cells. Inhibition of TrxR yield increase of cellular level of reactive oxygen species and further mitochondria membrane polarization, indicating **Compound 1**–**3** inhibit mitochondrial function via oxidative stress. The detailed mechanistic studies demonstrated **Compound 1**–**3** induced both intrinsic and extrinsic pathway of apoptosis through upregulation of p53/p73 genes and interaction with cell-death receptor. Also, **Compound 1**–**3** arrest the cell cycle of MCF-7R cells through activation of S-phase cell cycle checkpoint via modulation of cyclins and cyclin-dependent kinases. The NF-κB pathway is also down-regulated by **Compound 1**–**3** through the regulation of Lys48- and Lys63-linked polyubiquitination. From the summary of apoptosis and cell cycle pathway, it can be concluded different mechanisms are mediated by differing the nature of substituent groups in compounds hence they possess potential as anti-cancer agents.

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

ISYARAT KEMATIAN DAN RENCATAN KITARAN SEL KANSER PAYUDARA MCF-7R OLEH SEBATIAN TERBITAN BIS(PHOSPHANE)COPPER(I) THIOCARBAMIDES

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Kajian terdahulu mengenai sebatian terkoordinasi terbitan emas ke-atas phosphanegold(I) thiocarbamides mempamerkan aktiviti anti-kanser yang berkesan melalui induksi isyarat kematian. Untuk ke tahap yang lebih lanjut, penyelidikan ini diteruskan bagi mengkaji sebatian terkoordinasi terbitan kumprum(I), $(Ph_3P)_2Cu[S=C(O\mathbf{R})N(H)Ph]Cl$, dengan **R** sebagai pengganti kepada tiga kumpulan subsituen yang berlainan: metil (**Sebatian 1**), etil (**Sebatian 2**), dan isopropil (**Sebatian 3**) terhadap kanser payudara. Antara kanser agresif yang dilaporkan, kanser payudara mempamerkan gerakbalas lemah terhadap kemoterapi kerana ia mempunyai tahap glutation (GSH) dan tahap enzim reduktesa thioredoxin mitokondria (TrxR) yang tinggi, disertai dengan pengaktifan lebihan daripada NF-κB; justeru menyumbang kepada kekurangan kesan ubat dan rintangan terhadap laluan isyarat kematian. Oleh itu, pengawalan ke-atas GSH, TrxR dan NF-κB merupakan sasaran yang sesuai dalam pengajian ini. Sebatian kuprum(I) yang dikaji menunjukkan sitotosisiti *in-vitro* ke-atas sel karsinoma payudara MCF-7R dengan nilai potensi secara mikromolar. Selain itu, kajian sitotosisiti ke-atas sel biasa (buah pinggang, payudara dan jantung) mencadangkan bahawa **Sebatian 1—3** adalah kurang berkesan terhadap sel biasa dan lebih berkesan terhadap sel kanser. Perencatan ke-atas reduktesa thioredoxin mitokondria menyebabkan pengingkatan tahap spesis oksigen reaktif (ROS) dan memberi kesan bahawa polarisasi membran mitokondria, justeru ia membuktikan bahawa **Sebatian 1—3** menginduksi tekan oksidatif untuk merencat fungsi mitokondria. Berdasarkan analisa aliran ke-atas RT^2 PCR isyarat p53/kematian, **Sebatian 1—3** mempamerkan isyarat kematian secara intrinsik dan ekstrinsik melalui peningkatan kawal atur gen p53/p73, dan interaksi dengan reseptor kematian sel. Selain itu, **Sebatian 1—3** menahan kitaran sel MCF-7R di fasa S melalui pengawalan siklin dan aktiviti kinase siklin berdasarkan analisa aliran ke-atas RT^2 PCR isyarat siklin dan kitaran sel. Lintasan NF-κB juga diturun-atur oleh **Sebatian 1—3** melalui modulasi Lys48- and Lys63-pautan polyubiquinasi. Sebagai kesimpulan, hasil kajian daripada laluan isyarat kematian dan laluan kitaran sel memberikan bukti bahawa perubahan kumpulan subsituen dalam

struktur sebatian akan mengubah mekanisme tindakan secara ketara oleh itu ia dicadangkan mempunyai potensi sebagai ubat anti-kanser.

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I certify that a Thesis Examination Committee has met on 19 July 2017 to conduct the final examination of Ooi Kah Kooi on his thesis entitled "Apoptosis and Cell Cycle Arrest of MCF-7R Breast Carcinoma Cells by Bis(Phosphane)Copper(I) Thiocarbamides Derivative Compounds" 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 Doctor of Philosophy. Members of the Thesis Examination Committee were as follows:

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LIST OF ABBREVIATIONS

Ag	Silver
AIDS	Acute Immune Deficiency Syndrome
AO	Acridine orange
ATP	Adenosine triphosphate
Au	Gold
BRCA1	Breast cancer 1
BRCA2	Breast cancer 2
CAM	Cell adhesion molecules
CCN	Cyclin
CcO	Cytochrome c oxidase
CDK	Cyclin-dependent kinase
cDNA	Complementary DNA
Cl^-	Chloride
CTR1	Copper transporter 1
CTR2	Copper transporter 2
Cu	Copper
DAPI	4',6-diamidine-2-phenylindole dihydrochloride
DISC	Death inducing signaling complex
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonuclease acid
EGFR	Endothelial growth factor receptor
Et	Ethyl
FBS	Fetal bovine serum
FDA	Food and Drug Association
G_2	Gap 2
G_o/G_1	Gap 1
H^+	Hydrogen
HNPCC	Hereditary non-polyposis colorectal cancer
IARC	International Agency for Research on Cancer
IC_{50}	Inhibitory concentration of 50%
IKK	NF-κB inhibitor
IL	Interleukin
IMM	Inner mitochondrial membrane
iPr	Isopropyl
JNK	Jun amino terminal kinase
Lys	Lysine
M	Mitotic
MAPK	Mitogen activated protein kinase
Me	Methyl
MMP	Matrix metalloproteinase
mRNA	Messenger RNA
mTOR	Mechanistic target of rapamycin
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NF-κB	Nuclear factor kappa B
OMM	Outer mitochondrial membrane
PBS	Phosphate buffered saline
Ph_3P^+	Triphenylphosphine
PI	Propidium iodide

PI3K	Phosphatidylinosityl-3-kinase
PS	Phosphatidylserine
Pt	Platinum
RNA	Ribonuclease acid
ROS	Reactive oxygen species
S	Synthetic
SOD	Superoxide dismutase
TGF-β	Tumor growth factor β
Trx	Thioredoxin
TrxR	Thioredoxin reductase
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
XIAP	X-linked apoptotic protein

Note: Most of the abbreviation of genes can be found in Table L1 and L2.

CHAPTER 1

INTRODUCTION

Modernization and industrialization of world during 20th century brought significant improvement in lifestyles yet it is resulting several general health problems such as cancer. Based on the information provided by Cancer Facts and Figures published by American Cancer Society in 2017, the group of authors estimated there are 14.1 million of new cancer cases reported yet caused 8.2 million of death in 2016. The high occurrence and high mortality rate of cancer make it ranked the third leading cause of death worldwide, beyond the cardiovascular diseases (e. g. myocardial infraction, stroke and hypertension) and infectious disease (e. g. HIV/AIDS, tuberculosis and malaria) (Siegel *et al*., 2017 in the Cancer Facts and Figures 2017; *together with* Torre *et al*., 2015 in the Global Cancer Facts and Figures 2015). Referring to the statistic in Figure 1.1, the top leading cancers of male are lung, prostate and colorectal cancer in comparison with top leading cancers of female are breast, colorectal and lung cancer.

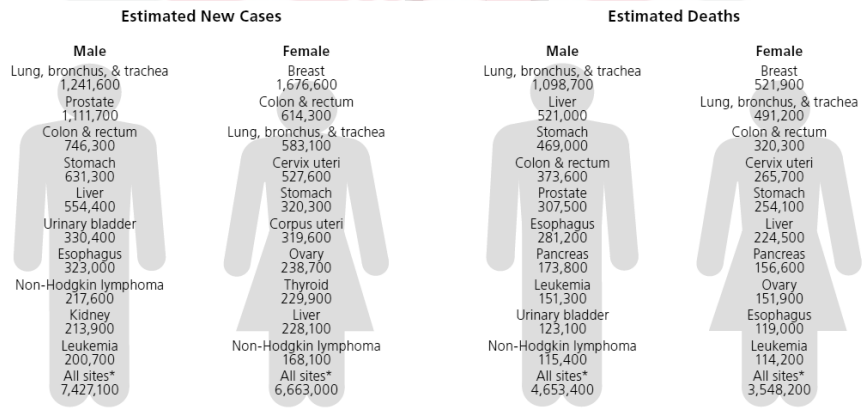

Figure 1.1: The estimated number of new cases and estimated deaths for top-leading cancers worldwide in 2016. (Source: Cancer Facts and Figures 2017)

Note: The estimated number of new cases and deaths are sum across high-income, middle-income and low-income nations.

In contrast with colorectal and lung cancers, breast cancer is the most commonly diagnosed cancer among female population (Figure 1.1). In the case of female who born with familial inherited mutation of tumor suppressor genes BRCA1 and BRCA2, the lifetime risk to develop breast cancer and the associated illness are up to 65% (Karin *et al*., 2005; Woolston, 2015). The most common type of breast cancer is the epithelial carcinoma which derived from epithelial cells of mammary glands' duct (Castaneda *et al*., 2017). Carcinogenesis on epithelial cells of breast resulting it gained oncogenic features such as high rate of proliferation, resistant to death signals, silenced from immunosurveiliance and vascular invade into distant location (Yang *et al*., 2017). Despite advancement of technology greatly improved survival rate of breast cancers' patient through surgery, chemotherapy, radiotherapy, hormonal therapy and recently the targeted immunotherapy (Yang *et al*., 2017; 2017). Nevertheless, chemotherapy remained as first choice and widest approach applied due to the effectiveness in inhibiting proliferation of cancer cells (Tozawa *et al*., 2003), however it is often militated by several factors including drug resistance, non-selectivity actions from chemotherapeutic drugs and high proliferation rates in breast cancer cells (Chen *et al*., 2001).

Breast cancer is associated with activation of several signaling pathways to enhance their proliferation, survival, invasion and metastasis capability, such as Nuclear Factor-kappaB (NF-κB) pathway, Wingless and T-cell factor-β-Catenin (WnT-β-Catenin) pathway, estrogen receptor kinases/mitogen-activation protein kinases (ERK/MAPK) pathway and mTOR pathway (Shafiee *et al*., 2016). Among of these, NF-κB was targeted in present study owing to its significant roles in regulating cell cycle, cell survival and cell death (Liang *et al*., 2013). Activation of oncogenes upon mutations or increased activity of mitochondria eventually activate NF-κB and promote its translocation into nucleus and subsequent binding to DNA leads to expression of cytokines, such as interleukin-6 (IL-6) and interleukin-8 (IL-8). The two interleukins in return enhanced NF-κB activity to express cancer cell survival and metastasis factors, e. g. BIRC5 (survivin), BIRC6, XIAP etc. (Schmitz *et al*., 2016). Therefore, the discovery of potent drugs that targeting programmed cell death and inhibitory effect towards NF-κB pathway are both highly importance (Shao *et al*., 2015). Here in, these factors contributed for the problem statements of current study.

Continued from statement above, chemoresistance of breast cancer are complex results from increased mitochondrial thioredoxin reductase (TrxR) enzymatic activities and increased cellular glutathione (GSH) levels (Tanaka *et al*., 2016). Thioredoxin reductase, an enzyme located in mitochondria was over-activated in cancer cells thus contribute for cancer cells proliferation and metastasis capability (Carlson *et al*., 2012). Despite GSH was reported with their antioxidant functions, high levels of GSH in breast cancer cells reduced efficacy of chemotherapeutic compounds, particularly the metal compounds, e. g. gold and copper due to their high affinity towards sulfhydryl-domain of GSH which eventually increase efflux of compounds from the host cells hence reducing overall treatment outcome (You *et al*., 2015).

Recent studies on sister compounds of this project, phosphanegold(I) thiocarbamides exhibited promising anti-cancer activities in terms of induction of apoptosis, cell cycle arrest, inhibition of cell invasion and inhibition of NF-κB in colorectal cancer cells (Yeo *et al*., 2013; Ooi *et al*., 2015; 2017). Given the increased interests in developing copper complexes as anti-cancer agents, a full range of copper complexes were synthesized and studied regarding their anti-cancer potential, through coordination with phosphine ligands (Santini *et al*., 2014), thiosemicarbazone ligands (Palanimuthu *et al*., 2013), and thiocarbamate ligands (Biersack *et al*., 2012). Hence it seemed a logical extent to develop this chemistry to include copper, which lead to the synthesis of $(Ph_3P)_2Cu[S=C(O\mathbf{R})N(H)Ph]Cl$, with **R** referring as different substituent substitution, namely methyl substitution (**Compound 1**), ethyl substitution (**Compound 2**), and isopropyl substitution (**Compound 3**).

As mentioned, these series of trial copper compounds are phosphanecopper(I) derivatives which carrying the binary (Gandin *et al*., 2015) and mixed ligand systems (Porchia *et al*., 2013). They were synthesized after auranofin [tetraacetyl-β-D-thiogluchosegold(I) triethylphosphine], one of the most successful anti-cancer compound. In accord, the respective chemical properties of candidate copper(I) compounds had been reported previously (Yeo *et al*., 2014; Zukerman-Schpector *et al*., 2016), hence the current study focuses upon the investigation of the response of human breast carcinoma MCF-7R cells to **Compound 1**–**3**, in terms of cell death and the cell cycle arrest mechanism pathways through RT^2 PCR microarray analysis. In addition, the inhibitory activities of **Compound 1**–**3** towards the NF-κB signalling pathway were determined through the study of Lys48/Lys63-linked polyubiquitination, cell invasion assay and the expression of relevant genes.

1.1 Hypothesis

It is expected the bis(phosphane)copper(I) thiocarbamides series, $(Ph_3P)_2Cu[S=C(OR)N(H)Ph]Cl$, with R = Methyl, Ethyl, and Isopropyl [named as **Compound 1**, **Compound 2** and **Compound 3** respectively throughout the thesis] are able to exhibit anti-cancer effects on breast carcinoma cells by inducing both intrinsic and extrinsic apoptosis.

1.2 Objectives

1.2.1 General objective

To investigate anticancer activities of bis(phosphane)copper(I) thiocarbamides compounds against MCF-7R breast carcinoma cells.

1.2.2 Specific objectives

1. To determine IC_{50} dosage of bis(phosphane)copper(I) thiocarbamides derivatives against MCF-7R cancer cells.
2. To investigate possible toxicity profile of bis(phosphane)copper(I) thiocarbamides by using *in-vitro* normal cells models.
3. To investigate the morphology and mechanism of apoptosis carried by bis(phosphane)copper(I) thiocarbamides towards MCF-7R cells.
4. To identify mechanism of cell cycle arrest induced by bis(phosphane)copper(I) thiocarbamides towards MCF-7R cells.
5. To investigate ability of bis(phosphane)copper(I) thiocarbamides in inhibition of mitochondrial thioredoxin reductase enzyme and cellular glutathione levels, thus overcome the chemoresistance of breast cancer.
6. To determine inhibitory activity of bis(phosphane)copper(I) thiocarbamides towards NF-κB via detection of Lys48- and Lys63-polyubiquitination.

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