UNIVERSITI PUTRA MALAYSIA

IN VITRO ANTIPROLIFERATIVE EFFECTS AND UNDERLYING MECHANISMDS OF BISMUTH DITHIOCARBAMATE DERIVATIVES AGAINST BREAST CANCER CELL LINE

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By

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Chair : Roslida Abdul Hamid @ Abdul Razak, PhD
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Drastic increment of cancer incidence in recent years has driven metal complexes including bismuth complexes as a promising approach in anticancer drug development due to its well-known low toxicity, environmental friendliness and medical therapeutic benefits The complexes with R= $(CH_2CH_2OH)(iPr)$, Et_2, $(CH_2)_4$ and $(CH_2CH_2OH)(CH_3)$ in bismuth-dithiocarbamate, $Bi[S_2CN\text{-}R]_3$ labelled as C3, C4, C5 and C9, have been studied, respectively. This study aimed at determining the antiproliferative effect of the bismuth complexes and their underlying mechanism(s) in breast cancer cell (MCF-7) through various *in vitro* assays. The antiproliferative effect of the bismuth complexes was studied using Methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay. Apoptotic cell death activities of C3, C4, C5 and C9 were performed via DNA fragmentation, acridine orange/propidium iodide (AO/PI), Annexin V and caspase activity assays. Whilst, this study further employed Human Cancer Drug Targets RT² Profiler PCR array to study the expression of 84 actively sought targets for anticancer therapeutics and drug development to delineate the underlying mechanism(s). Results showed all tested compounds (C3, C4, C5 and C9) exhibited antiproliferative effects against MCF-7 cell line with IC_{50} of 10.33 ± 0.06 µM, 1.26 ± 0.02 µM, 1.07 ± 0.01 µM and 25.37 ± 0.12 µM, respectively. The morphology of apoptosis including formation of DNA fragments, phosphatidylserine translocation, chromatin condensation, and membrane blebbing was shown. The compounds were found to variably increase reactive oxygen species (ROS) generation thus increased mitochondrial membrane potential (MMP). Consequently, this led to the release of cytochrome c from mitochondria, demonstrated by the data obtained by flow cytometric analysis. All four tested compounds were revealed to induce both intrinsic and extrinsic apoptotic pathways, conferred by the data obtained from Human Cancer Drug Targets RT² Profiler PCR array, along with caspases activities assay. The compounds were also reported to significantly reduce several key gene

expressions such as *AKT1*, BIRC5, *CDK1* and *NFκB1*. The NF-κB signalling pathway was inhibited with the activation of Lys48-linked polyubiquitination thus led to NF-κB degradation. Conclusively, this study evidenced the anticancer property of C3, C4, C5 and C9 against breast cancer by initiating intrinsic and extrinsic apoptosis pathway and lays the foundation in the development of new bismuth based chemotherapeutic drugs.

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

KESAN *IN VITRO* ANTIPROLIFERATIF DAN MEKANISME- MEKANISME TERBITAN BISMUTH DITHIOKARBAMAT KE ATAS SEL KANSER PAYUDARA

Oleh

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Peningkatan kejadian kanser secara drastik kebelakangan ini telah mendorong perubatan kanser yang berasaskan kompleks logam termasuk kompleks bismuth sebagai langkah yang menjanjikan dalam perkembangan drug antikanser, disebabkan ketoksikannya yang rendah, mesra alam sekitar dan bermanafaat sebagai terapeutik perubatan. Terbitan kompleks dengan R= $(CH_2CH_2OH)(iPr)$, Et_2, $(CH_2)_4$ dan $(CH_2CH_2OH)(CH_3)$ dalam bismuth dithiokarbamat, $Bi[S_2CN\text{-}R]_3$ dilabelkan sebagai C3, C4, C5 serta C9, masing-masing telah diuji untuk menentukan kesan anti-proliferatif dan mekanisme-mekanisme sebatian-sebatian tersebut ke atas sel kanser payudara (MCF-7) melalui pelbagai asai *in vitro*. Kesan anti-proliferatif kompleks bismuth dikaji melalui asai Metilthiazolidifenil-tetrazolium bromide (MTT). Kematian sel apoptotik sebatian C3, C4, C5 dan C9 masing-masing dilakukan melalui pemecahan DNA, akridin oren/propidium iodida (AO/PI), asai Annexin V dan asai aktiviti caspase. Sementara itu, kajian ini turut menggunakan pemprofilan RT^2 PCR Sasaran Kanser Manusia untuk mengkaji ekspresi 84 sasaran yang aktif dalam terapeutik antikanser dan perkembangan drug, di samping menjelaskan mekanismanya. Kajian menunjukkan semua sebatian yang diuji (C3, C4, C5 dan C9) menunjukkan kesan anti-proliferatif terhadap sel MCF-7 masing-masing dengan IC_{50} 10.33 ± 0.06 μM, 1.26 ± 0.02 μM, 1.07 ± 0.01 μM dan 25.37 ± 0.12 μM. Morfologi apoptosis menunjukkan perubahan-perubahan termasuk pembentukan pecahan DNA, translokasi fosfatidilserin, kondensasi kromatin, dan pembengkakkan membran. Sebatian-sebatian tersebut juga didapati menyebabkan peningkatan yang berbeza terhadap penjanaan spesies oksigen reaktif (ROS) seterusnya meningkatkan potensi membran mitokondria (MMP). Di samping itu, data yang diperolehi daripada analisis aliran sitometrik juga menunjukkan pelepasan sitokrom c dari mitokondria. Data yang diperolehi daripada pemprofilan RT^2 PCR Sasaran Kanser Manusia bersama-sama

dengan asai aktiviti caspase menunjukkan keempat-empat sebatian yang diuji menyebabkan kematian sel kanser MCF-7 secara apoptosis berperantarakan aruhan laluan intrinsik dan ekstrinsik. Sebatian-sebatian ini juga dilaporkan dapat merendahkan ekspresi beberapa gen utama seperti *AKT1*, BIRC5, *CDK1* dan *NFKB1*. Laluan isyarat NF-κB telah direncat dengan pengaktifan poliubiquitinasi yang dikaitkan dengan Lys48 seterusnya menyebabkan degradasi NF-κB. Kesimpulannya, kajian ini membuktikan sifat anti-kanser C3, C4, C5 dan C9 terhadap kanser payudara melalui laluan apoptosis intrinsik dan ekstrinsik seterusnya menyediakan pengetahuan asas dalam membantu pembangunan drug kemoterapeutik baru yang berasaskan penggunaan logam bismuth.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AO/PI	Acridine orange/propidium iodide
APAF-1	Apoptosis activating factor-1
Apo2L	Apo2 ligand
Apo3L	Apo3 ligand
BAX	BCL2-Associated X Protein
Bcl-2	B-cell lymphoma 2
Bcl-XL	B-cell lymphoma-extra large
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5
BRK	Breast tumour kinase
BSS	Bismuth subsalicylate
Calu-6	Human lung adenocarcinoma cells
CBS	Colloidal bismuth subcitrate
CDKs	Cyclin dependent kinases
CDKIs	Cyclin dependent kinase inhibitors
cFLIP	Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein
DCFDA	5(6)-carboxy-2',7'-dichloroflurescien diacetate
DCIS	Ductal carcinoma in situ
DISC	Death-inducing signaling complex
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOTA	1,4,7,10- tetra-azacylododecane 1,4,7,10-tetraacetate
DR3	Death receptor 3

DR4	Death receptor 4
DR5	Death receptor 5
DTPA	Diethylenetriaminepenta-acetate
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELAM-1	Endothelial leucocyte adhesion molecule-1
ER	Estrogen receptor
ETC	Electron transport chain
ErbB	pidermal growth factor receptor
EtBr	Ethidium bromide
FADD	Fas-associated death domain protein
FasL	Fas ligand
FasR	Fas receptor
FBS	Fetal bovine serum
H. pylori	*Helicobacter pylori*
HER2	Human epidermal growth receptor 2
HRT	Hormone replacement therapy
HSAB	Hard-soft acid–base
IAP	Inhibitor of apoptosis protein
ICAM-1	Intercellular adhesion molecule-1
IDC	Infiltrating ductal carcinoma
IKK	IκB kinase
IL	Interleukin
LCIS	Lobular carcinoma in situ
LPS	Lipopolysaccharides

MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase
MCF-7	Human breast carcinoma cells
MPT	Mitochondrial permeability transition
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NF-κB	Nuclear factor-kappa B
PARP	Poly (ADP-ribose) polymerase
PCD	Programmed cell death
PI3K	Phosphatidylinositol 3-kinase
PPI-based	Proton pump inhibitor-based
PS	Phosphatidylserine
PTPs	Permeability transition pores
RBC	Ranitidine bismuth citrate
ROS	Reactive oxygen species
SHH	Sonic hedgehog
TAE	Tris-acetate-EDTA
TDLU	Terminal ductal lobular units
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor alpha
TNFR1	Tumor necrosis factor receptor 1
TNFR2	Tumor necrosis factor receptor 2
TRADD	TNF receptor-associated death domain
Trx	Thioredoxin
TrxR1	Thioredoxin reductase 1
VCAM-1	Vascular cell adhesion molecule-1
VEGF-1	Vascular endothelial growth factor-1

XIAP	X-linked inhibitor of apoptosis

CHAPTER 1

INTRODUCTION

The development of cancer is a multistep process in which normal and healthy cells in the body go through stages that eventually develop into continual unregulated growth of abnormal cells. Normal cells in the body proliferate to replace worn-out cells. When cancer occurs, cells proliferate in an uncontrolled manner rather than responding appropriately to the signals that control normal cell behavior, invading normal tissues and organs and ultimately spreading throughout the body (Cooper, 2000; National Institutes of Health, 2007).

Cancer is now one of the world's largest killer, ranked top three with number of cases set to explode in coming years as reported in The World Cancer Report 2014 (Stewart and Wild, 2014). Based on GLOBOCAN 2018, cancer has become one of the biggest cause of morbidity and mortality globally with estimated 18.1 million new cases and approximately 9.6 million deaths in 2018 which responsible for nearly 1 in 6 deaths due to cancer (Bray *et al*., 2018). Statistics released shows nearly 65% of the rise in the number of all cancer deaths will occur in less developed regions and simultaneously developing countries will bear the burden of the predicted 23.6 million new cases per year by 2030 (National Cancer Institute, 2018).

Breast cancer is the most common malignancy in women worldwide after lung cancer (Bray *et al*., 2018). It was reported with nearly 1.7 million new cases diagnosed in 2012. This represents around 12% of all new cancer cases and 25% of all cancer cases in women (Ferlay *et al*., 2012). Hence, the change in the global distribution of female breast cancer cases is emerging as a major health issue for women in Asia, Africa and South America.

In Asia, breast cancer incidence has been increasing rapidly in recent years. According to Moore *et al*. (2003), the disease may happen at a relatively young age. Breast cancer is a major cause of morbidity and cancer related mortality among women. Meanwhile, the breast cancer incidence was reported to be increasing in most of the Asian countries. Malaysia is also sharing the same movement.

Health Facts (2013) released by Ministry of Health (MoH) Malaysia stated that cancer is one of the top ten causes of hospitalization and one of the top five

causes of death with an estimation of 30000 cases annually. Furthermore, cancer has overtaken heart disease as the number one killer by 2014 in Malaysia. Based on the report released by Malaysian National Cancer Registry Report (2016), a total of 103507 new cancer cases were diagnosed for the period of 2007-2011 in Malaysia. The top three most common cancers among Malaysians are breast followed by colorectal and lung cancer, with one in 19 Malaysians developing breast cancer, one in 33 developing colorectal cancer and one in 40 developing lung cancer, respectively. Breast cancer appeared to be the most common cancer among female residents in Malaysia which accounted for 32.1%.

Rapid societal and economic transitions have occurred in many countries, any reduction in infection-related cancers has been offset by an increasing number of new cases related to reproductive, dietary and hormonal factors (Bray ***et al***, 2012). Numerous factors that affect the risk of breast cancer have been suggested such as decreased childbearing and breast-feeding, exposure to oestrogen, late menopause, and detrimental dietary and lifestyle changes, including high fat diet and less physical activity (Sun ***et al***., 2017).

There are several types of cancer treatments suggested by medical institutions comprise of surgery, radiotherapy, chemotherapy, endocrine therapy and targeted therapies. The most common method is chemotherapy which uses anti-neoplastic drugs to interact with cancer cells by either eradicating or controlling the growth of cancer. The first developed major metal-based antineoplastic drug is derived from platinum variants such as carboplatin, oxaliplatin, and picoplatin (Donzelli ***et al***., 2004). However, most of the therapeutic agents are associated with severe adverse effects such as significant nausea and vomiting, which indirectly leading to poor compliance with scheduled chemotherapy, eventually leading to poor outcomes.

Previous studies on the bismuth-based compounds do not only reveal the promising outcomes of these compounds in combating several cancers (Köpf-Maier and Klapötke, 1988; Bandyopadhyay ***et al***., 2012; Ishak ***et al***., 2014) but it was also found that the use of bismuth compounds in chemotherapy is able to alleviate the adverse effects of cisplatin by increasing the metallothionein production, without significantly altering the anticancer drug activity (Kondo ***et al***., 1992*). Helicobacter pylori* is believed in causing gastric lymphoma and treatment with bismuth not only resulted in regression but even a cure (Steinbach ***et al***., 1999). Hamer (1986) discovered bismuth subnitrate enhanced the bismuth distribution in kidneys and significantly protected against the toxicity of heavy metals, alkylating agents and free radicals. However, from the foregoing, it is clear that the exploration of the anti-tumor activity of bismuth-based compounds is relatively undeveloped. Hence, elucidation of bismuth dithiocarbamate compounds' cytotoxicity and possible underlying pathway(s) against breast cancer cell line were focused in the current study.

1.1 Problem statements

Breast cancer appears to be one of the main concern and major cause of death in women globally. Cisplatin, was the first platinum based chemotherapy drug discovered by scientists and continues its application in a wide variety of cancer treatments such as breast cancer for about forty years. Notwithstanding, there is drawback in the use of cisplatin to the cancer patients especially its toxicity profile and drug resistance by cancer cells (Kelland and Farrell, 2000; Boyiadzis, 2007; Dasari and Tchounwou, 2014). Other than that, administration of other chemotherapeutic drugs, for instance vinblastine and vincristine may cause immune system and bone marrow suppression, led to decrease amount of white blood cells, red blood cells and platelets, eventually results in anemia, neutropenia and thrombocytopenia (Krzyzanowska *et al*., 2016). Doxorubicin has been used against cancer for more than 30 years. However, it produces a range of adverse effects such as toxicity in heart, kidney and liver (Tacar *et al*., 2013). Lacking of safe and effective chemotherapy regimens against breast cancer, on top of limitations from current treatments including surgery, chemotherapy, radiation or targeted therapies, has led to the new development of chemotherapy regimen. Bismuth-based compound which has been found to be effective in treating a variety of diseases such as peptic ulcer and infection due to *Helicobacter pylori,* which may also lead to gastric lymphoma. Bismuth has also been found to have unusually unexpected low toxicity and is believed to act as protective agent for cancer patients from some of the toxic adverse effects caused by cisplatin, without affecting its anti-cancer activity (Yang *et al*., 2014; Kondo *et al*., 1992).

1.2 Objectives

1.2.1 General objectives

This study aimed at investigating the anticancer potential of four bismuth dithiocarbamate complexes with four different functional groups substitution (isopropyl ethanol, **C3**; diethyl, **C4**; pyrrolidine, **C5** and methyl ethanol, **C9**) against human breast adenocarcinoma cell lines (MCF-7) and its possible underlying molecular mechanisms.

1.2.2 Specific objectives

- To determine the IC_{50} value of bismuth dithiocarbamate complexes with four different functional groups substitution (isopropyl ethanol, C3; diethyl, C4; pyrrolidine, C5 and methyl ethanol, C9) against MCF-7 cell lines.

- To assess the cell death mode induced by bismuth dithiocarbamate complexes and their morphological features.
- To delineate the underlying pathway of breast cancer cell inhibition by bismuth dithiocarbamate complexes through caspase-3, caspase-8, caspase-9, caspase- 10, cytochrome c, cell cycle and reactive oxygen species (ROS)
- To relate the involvement of Nuclear Factor-kappa B (NF-κB) in breast cancer cell inhibition by bismuth dithiocarbamate complexes via ubiquitination activity.
- To construe the cross talk signaling pathway via the gene expression analysis by Human Cancer Drug Targets RT^2 Profile PCR Array.

1.3 Hypothesis

Based on the previous preliminary studies on other cancer cell lines, it is anticipated that bismuth dithiocarbamate coordinated compounds may possess antiproliferative properties on human breast adenocarcinoma cell lines. Apoptosis pathway can be induced through intrinsic and extrinsic apoptosis pathway by mediation of multiple genes expression.

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