UNIVERSITI PUTRA MALAYSIA

PHYSICOCHEMICAL CHARACTERIZATION OF PALLADIUM-, PLATINUM-, SILVER-DOPED MAGNESIA NANOPARTICLES AND *IN VITRO* CYTOTOXICITY IN A549 (LUNG) AND HT29 (COLON) CANCER CELL LINES

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By

MOHAMMED QASIM KHLAIF

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

January 2019

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DEDICATION

I wish to dedicate this thesis to my mother (Samerah Obaid) and father (Qasim K. Al-Fahdawi) for their love and giving me the genes for research. They have always believed in me and have always encouraged me not only during this PhD period but throughout life.

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

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January 2019

Chairman : Professor Rasedee Abdullah, PhD
Faculty : Institute of Bioscience

Cancers are one of the main causes of death in the developed countries. Currently, there is ongoing search for innovative therapeutics and strategies to combat the disease. This study was conducted to prepare three noble metal complexes, namely, palladium-, platinum-, and silver-doped magnesia designated Pt/MgO, Pd/MgO, and Ag/MgO nanoparticles, respectively, and to determine their cytotoxic potentials. These nanoparticles were prepared by hydrothermal impregnation method followed by calcination. The chemical compositions, functional groups, and optical properties of these nanoparticles were determined using X-ray diffraction (XRD), thermal gravimetric analysis (TGA), Fourier transform infrared spectroscopy (FT-IR), and Brunner-Emmett-Teller (BET) surface area measurements. The sizes, size distribution, and morphology of nanoparticles have been determined by zetasizer. Transmission (TEM) and scanning electron (SEM) microscopy were also used to determine their ultrastructure and estimate the size of the nanoparticles. The cytotoxicity of these nanoparticles against the human colon (HT29) and lung cancer (A549), and normal human colon (CCD-18Co) and lung (MRC-5) cell lines was evaluated using the (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The caspase-3, -8 and -9, activities, and Bax, Bcl-2 and p53 protein expressions were also determined in cancer cells treated with Pt/MgO, Pd/MgO, and AG/MgO nanoparticles.

The Pd/MgO, Pt/MgO, and Ag/MgO nanoparticles prepared in this study were pure and crystalline and cuboid in structure with physical and thermal stability. The size of these nanoparticle ranged from 30 to 80 nm. The Pt/MgO, Pd/MgO, and Ag/MgO were relative innocuous to normal cells. However, the nanoparticles variably induced apoptosis of HT29 and A549 cells via the caspase-3/7- and caspase-9-

dependent mitochondrial signaling pathway. The Pd/MgO nanoparticles did not induce receptor-mediated (extrinsic) apoptotic pathway in colon cancer HT29 cells. The Ag/MgO nanoparticles had least effect among nanoparticles on the cancer cell receptor-mediated apoptotic pathway. All three nanoparticles expressed pro-apoptotic Bcl-2 protein and induce anti-tumour effect through the activation of the tumour suppressor protein, p53.

In conclusion, Pt/MgO, Pd/MgO, and Ag/MgO nanoparticles have anti-colon and anti-lung cancer cell effects through the induction of apoptosis. All three metal-doped nanoparticles have potential to be developed into efficacious anti-cancer compounds.

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

PENCIRIAN FISIKOKIMIA NANOZARAH MAGNESIA TERDOP PALADIUM, PLATINUM, AND ARGENTUM DAN KETOKSOKIKAN *IN VITRO* PADA TITISAN SEL KANSER A549 (PARU-PARU) DAN HT29 (KOLON)

Oleh

MOHAMMED QASIM KHLAIF

Januari 2019

Pengerusi : Profesor Rasedee Abdullah, PhD
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Kanser adalah antara penyebab utama kematian di negara maju. Kini, banyak penyelidikan yang dijalankan untuk menemui terapeutik and strategi yang inovatif untuk rawatan penyakit ini. Kajian ini dijalankan untuk menyediakan tiga kompleks logam nobel, iaitu, nanozarah magnesia terdop paladium, platinum, dan argentum yang masing-masing dinamakan nanozarah Pd/MgO, Pt/MgO, dan Ag/MgO, dan untuk menentukan potensi kesitotoksikannya. Nanozarah ini disediakan mengguna kaedah impregnasi hidroterma diikuti dengan kalsinasi. Komposisi kimia, kumpulan fungsian, dan sifat optik nanozarah ini ditentukan melalui belauan sinar-X (XRD), analisis gravimetri terma (TGA), spektroskopi inframerah transformasi Fourier (FT-IR), dan sukatan kawasan permukaan Brunner-Emmett-Teller (BET). Saiz, taburan saiz, dan morfologi nanozarah ditentukan mengguna zetasizer. Mikroskopi elektron pancaran (TEM) and imbasan (SEM) juga diguna untuk menentukan ultrastruktur dan saiz nanozarah tersebut. Kesitoksikan nanozarah terhadap titisan sel kanser kolon (HT29) and paru-paru (A539), sel kolon (CCD-18Co) dan paru-paru (MRC-5) normal dinilaikan mengguna asai (4,5-dimetiltiazol-2-yl)-2,5-difenyitetrazolium bromida (MTT). Aktiviti kaspase-3, -8, -9, penyataan protein Bax, Bcl-2, and p53 juga ditentukan pada sel kanser terperlaku nanozarah Pd/MgO, Pt/MgO, dan Ag/MgO.

Nanozarah Pd/MgO, Pt/MgO, dan Ag/MgO yang disediakan dalam kajian ini adalah murni dan berstruktur kristal and kuboid dan stabil fisikal dan terma. Saiz nanozarah adalah pada julat 30 hingg 80 nm. Nanozarah Pd/MgO, Pt/MgO, dan Ag/MgO tidak memberi kesan buruk terhadap sel normal. Bagaimanapun, nanozarah secara berbeza mengaruh apoptosis pada sel HT29 dan A549 melalui laluan pengisyaratan mitokondrion bersandarkan kaspase-3/7 dan kaspase-9. Nanozarah Pd/MgO tidak mengaruh arah laluan apoptosis berantara reseptor (ekstrinsik) pada sel kanser kolon,

HT29. Di kalangan nanozarah ini, kesan Ag/MgO terhadap arah laluan apoptosis berantarakan reseptor sel kanser adalah yang paling kurang. Ketiga-tiga nanozarah ini menyatakan protein Bcl-2 dan mengaruh kesan anti-tumor melalui pengaktifan protein penindas tumor, p53.

Kesimpulan, nanozarah Pt/MgO, Pd/MgO, and Ag/MgO mempunyai kesan antikanser kolon dan paru-paru melalui pengaruhan apoptosis. Ketiga-tiga nanozarah terdop logam ini berpotensi untuk dikembangkan sebagai sebatian antikanser yang mujarab.

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Thank you.

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

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LIST OF ABBREVIATIONS

ATCC	The American Type Culture Collection
CO_2	Carbon dioxide
DMEM	Dulbecco's modified Eagle's medium
DMSO	Dimethyl sulphoxide
DTT	Dithiothreitol
dUTP	2'-deoxyuridine 5'-triphosphate
EDTA	Ethylendiaminetetraacetic acid
ELISA	Enzyme-linked Immunosorbent Assay
EtOH	Ethanol
FBS	Fetal bovine serum
XRD	X-ray diffraction
TGA	Thermogravimetric analysis
FTIR	Fourier transform infrared
TEM	Transmission electron microscopy
HCl	Hydrochloric acid
IC_{50}	Inhibition concentration at 50 percent
KCl	Potassium Chloride
KH_2PO_4	Potassium dihydrogen phosphate
LDH	Lactate Dehydrogenase
BET	Brunauer, Emmett and Teller analysis
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NaCl	Sodium Chloride
NADH	Nicotinamide adenine dinucleotide
NaHPO4	Disodium hydrogen phosphate anhydrous

NaOH	Sodium hydroxide
PBS	Phosphate buffer saline
A549	Human lung cancer cell line
HT29	Human colorectal adenocarcinoma cell line
CCD-18Co	Human normal colon cell line
MRC-5	Human normal lung cell line

CHAPTER 1

INTRODUCTION

1.1 Background

Cancer, or malignant tumour, is a disease caused by abnormal cell growth (Daniel *et al.*, 2001, Colditz and Stein, 2004, Jaggi, 2005). Excessive proliferation of tissue cells will eventually damage neighbouring healthy cells with lethal outcomes (Srivastava *et al.*, 1999). Cancer is one of the deadliest and most complicated diseases in medicine (Badve and Gökmen-Polar, 2016, Loda *et al.*, 2016, Dalgleish and Browning, 1996) and it is the result of mutations in DNA responsible for the synthesis of cellular proteins (Knowles and Selby, 2005, Yousef and Jothy, 2014, Franks and Teich, 1997). In cancer, DNA abnormalities result in normal production of proteins (Ruddon, 2010), which are harmful to the organism (Pecorino, 2012, Macdonald *et al.*, 2004).

Colon cancer is the third most common cancer worldwide, accounting for over 9% of all cancer incidences (Haggar and Boushey, 2009). In Malaysia, it is the second most common type of tumour accounting for 14.1% of all malignant tumours in men and 10.2% in women (Haggar and Boushey, 2009). Recently bowel screening was introduced by the International Agency for Research on Cancer for people in the high risk age group of 60 to 69 years, to aid early detection of tumours and increase survivality (Cancer, 2012).

Lung tumours are largely a disease of the elderly, where almost 70% of suffers were more than 65 years old (Siegel *et al.*, 2013). Approximately 90% of lung tumours are due long-term tobacco usage. Patients with lung cancers survives better if the cancer is detected early (Siegel *et al.*, 2016).

1.2 Problem Statement

The current first-line lung cancer therapies use cisplatin and gemcitabine (Macbeth *et al.*, 1996). Cisplatin induces its anticancer effects by forming DNA adducts and subsequently activating apoptotic pathways via p53. Sometimes, pemetrexed is used in combination with cisplatin for first-line therapy (Reckamp, 2016). However, treatment with cisplatin is plagued with reduced drug uptake, drug inactivation, and increased DNA damage.

Treatment of colon cancers is traditionally with surgery, radiotherapy, and chemotherapy (Baxter, 2014). Chemotherapeutic agents are used following surgery if there is evidence of spread of the tumour to neighbouring lymph nodes or features suggestive of cancer spread (Saltz, 2007). Among chemotherapeutics that have been

used in the last 10 years include Oxaliplatin, Irinotecan, anti-epidermal growth factor receptor agents such as Cetuximab in select patients, Bevacizumab, Aflibercept and Regorafenib, and Fluorouracil (Skeel and Khleif, 2011).

Cancer chemotherapy may be applied intravenously or orally (Skeel and Khleif, 2011). Chemotherapeutic drugs targets actively dividing cells causing side effects (Chu and DeVita, 2006, Doroshow, 2006). These side effects are dependent of the type, dose, and duration of the drug therapy. Among side effects of chemotherapies are mouth sores, nausea, diarrhoea, susceptibility to infection, bruising, loss of appetite, bleeding, hair loss, and vomiting (Perry, 2008). For these reasons, there is ongoing search for more selective anticancer drugs with minimal side effects (Seddon and Workman, 2014).

Among new strategies employed in the development of new therapeutic regimen is nanotechnology and nanomedicine (Jain *et al.*, 2014). Nanomedicine is a rapidly evolving field with the objective to improve disease treatment outcomes by enhancing diagnostic procedures and treatments (Jain, 2017, Tibbals, 2017). Nanomedicine refers to the use nanoscale materials to improve human health and well-being (Prasad, 2012). Nanoparticles with loaded or entrapped therapeutic agents have the characteristics of prolonged circulation time (Duzgunes, 2012), increased tissue targeting and uptake (Mishra, 2013), and decreased toxicity (Pan, 2014).

Due to their unique chemical and physical properties, noble metals such as gold, silver, palladium and platinum are now being investigated for their potential in diagnostic and therapeutic applications in cancers. Noble metals based-nanoparticles are easier and more convenient to engineer than non-metal drug carriers. The noble metal nanoparticles can be engineered to exhibit multifunctional or synergistic effects in the treatment of diseases (Jain *et al.*, 2008, Giljohann *et al.*, 2010, Bijur *et al.*, 2001). Noble metal-containing nanoparticles also have fewer side effects and cheaper to produce than currently available chemotherapeutic compounds (Merchant, 1998, Conde *et al.*, 2012).

In this study, three noble metals-based nanoparticles, palladium-doped (Pd/MgO), platinum-doped (Pt/MgO), and silver-doped magnesia (Ag/MgO) nanoparticles were developed as potential anticancer compounds. The anticancer properties of these nanoparticles were determined on the human colorectal adenocarcinoma (HT29), and lung adenocarcinoma (A549) cells. Application of these nanoparticles as chemotherapeutic agents are governed by the following: suitability of hydrothermal impregnation method in the synthesis of noble metals-containing nanoparticles, cytotoxicity towards cancer cells, selectivity of the nanoparticles for cancer cell lines, and the death pathway by which the nanoparticles exert their actions.

1.3 Objectives

1.3.1 General objective:

To prepare, physicochemically characterise and detemine the anticancer cell effects of Pt/MgO, Pd/MgO, and Ag/MgO nanoparticles.

1.3.2 Specific objectives:

The specific objectives of the study are to

1. synthesize and characterise the physiochemical properties of, Pt/MgO, Pd/MgO, and Ag/MgO nanoparticles,
2. determine the *in vitro* cytotoxicity of Pt/MgO, Pd/MgO, and Ag/MgO nanoparticles on human colon cancer (HT29) and lung cancer (A549) cell lines,
3. determine the in vitro effect of apoptotic pathway markers in HT29 and A549 after treatment with Pt/MgO, Pd/MgO, and Ag/MgO nanoparticles.

1.4 Hypothesis

Based on existing literature, we hypothesise that palladium-, platinum-, and silver-doped magnesia are both thermal-stable and nanoparticulated. These nanoparticles will serve as potent chemo-preventative agents towards lung and colon cancer development. The anticancer effect of the magnesia-doped nanoparticles on lung and colon cancers is postulated to occur through the induction of oxidative stress and apoptosis.

1.5 Limitation of study

One obvious limitation of this study was the use absence of an animal model to confirm the anticancer effects of noble metal-doped magnesia in in situ tumour. In addition, in the study the molecular anticancer mechanisms of the nanoparticles were only superficially investigated. This limits the ability to conclude on the potential of the nanoparticles as anticancer agents.

Further research is needed to determine the effect the nanoparticles in combination chemotherapies. There is also need to determine the effect of nobel metal doped magnesias on other cancers besides colon and lung cancers.

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LIST OF PUBLICATIONS

Journal Paper

Al-Fahdawi, M., Rasedee, A., Alhassan, F. H., Al-Qubaisi, M. S., Rosli, R., El Zowalaty, M. E.,Taufiq-Yap, Y. H. (2015). Cyctotoxicity and physicochemical characterization of palladium magnesia nanoparticles. Future Medicine: Nanomedicine. *In press*.

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