UNIVERSITI PUTRA MALAYSIA

CYTOTOXICITY OF THYMOQUINONE AND THYMOQUINONE-LOADED NANOSTRUCTURED LIPID CARRIER ON CERVICAL CANCER CELLS (SiHa AND HeLa)

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By

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Chairman : Latifah Saiful Yazan, PhD

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Cancer is a life-threatening disease and a major leading cause of death worldwide. Drug resistance and adverse effects impede the success of chemotherapy. Hence, searching for anti-cancer bioactive compounds with low toxicity from natural products is now in demand. Thymoquinone (TQ), the bioactive compound of *Nigella sativa*, has been reported to exert anti-cancer properties. Nevertheless, TQ exhibits poor oral bioavailability. Therefore, nanostructured lipid carrier (NLC), provides an alternative delivery system for TQ to overcome the limitations. The objective of the study was to determine the cytotoxicity and mechanisms of action of TQ and TQ-NLC towards cervical cancer cells (SiHa and HeLa). The cytotoxicity of TQ towards SiHa and HeLa was determined by MTT assay. Cell cycle and mode of cell death was performed by using flowcytometry. The expression of p53, Bcl-2 and Bax, and caspases was studied by using Western blot and ELISA, respectively. Thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) was synthesized by high pressure homogenization method. Physicochemical characteristics of TQ-NLC were determined. Cytotoxicity of TQ-NLC_4 towards SiHa and HeLa cells was evaluated by MTT assay. *In vitro* drug release kinetic, gastrointestinal digestion, absorption and bioavailability studies of TQ-NLC_4 were performed. Result shows that TQ was cytotoxic towards SiHa and HeLa cells by inducing cell cycle arrest and apoptosis in the cells. Elevation of Bax to Bcl-2 ratio and expression of caspase-3 and -9 were noted in SiHa cells while in HeLa cells, elevation of Bax to Bcl-2 ratio and expression of caspase-3, -8 and -9 were noted. Physicochemical analysis revealed that average diameter of TQ-NLC_4 was less than 100 nm. TQ-NLC_4 was found stable up to 24 months. High EE and DLC of TQ-NLC_4 were achieved. TQ-NLC_4 was cytotoxic towards SiHa and HeLa cells. TQ was released from NLC in a zero-order manner. Degradation and aggregation of TQ-NLC_4 occurred in simulated intestinal fluid. *In vitro* absorption and bioavailability studies indicated that bioavailabilty of TQ-NLC_4 was high. In conclusion, TQ was cytotoxic against the cervical cancer cells by modulating the apoptotic pathways. NLC conferred drug controlled release, protection and enhanced bioavailability to TQ. Hence, TQ-NLC_4 may be a promising anti-cancer agent against cervical cancer.

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

KESAN SITOTOKSIK TIMOKUINON DAN PEMBAWA LIPID BERSTRUKTUR NANO DIMUAT TIMOKUINON TERHADAP SEL KANSER SERVIKS MANUSIA (SiHa DAN HeLa)

Oleh

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Kanser merupakan sejenis penyakit yang mengancam nyawa dan punca kematian utama di seluruh dunia. Oleh itu, pencarian sebatian bioaktif anti-kanser dengan ketoksikan yang rendah atau tiada ketoksikan daripada produk semulajadi menjadi tumpuan. Timokuinon (TQ), sebatian bioaktif daripada *Nigella sativa*, telah dilaporkan mempunyai ciri anti-kanser. Namun demikian, TQ mempunyai keterbiosediaan oral yang rendah. Oleh itu, sistem penghantaran ubatan koloid berasaskan lipid seperti pembawa lipid berstruktur nano (NLC) menyediakan sistem penghantaran alternatif untuk TQ bagi menyelesaikan masalah tersebut. Objektif kajian ini adalah untuk menentukan kesitotoksikan dan mekanisma aksi TQ dan TQ-NLC terhadap sel kanser serviks (SiHa dan HeLa). Kesitotoksikan TQ ke atas SiHa dan HeLa ditentukan oleh asai MTT. Analisis kitaran sel dan cara kematian dilaksanakan dengan menggunakan sitometer aliran. Kesan TQ ke atas pengekspresan p53, Bcl-2 dan Bax, dan caspase dikaji dengan pemblotan Western dan ELISA, masing-masing. Pembawa lipid berstruktur nano dimuat timokuinon (TQ-NLC) disintesis dengan kaedah penghomogenan tekanan tinggi. Ciri-ciri fizikokimia TQ-NLC ditentukan. Kesitotoksikan TQ-NLC terhadap sel SiHa dan HeLa ditentukan dengan asai MTT. Kinetik pembebasan TQ-NLC_4 secara *in vitro*, pencernaan dalam gastrousus, penyerapan dan keterbiosediaan TQ-NLC secara *in vitro* telah dijalankan. Keputusan menunjukkan TQ adalah sitotoksik terhadap sel SiHa dan HeLa dengan mengaruhkan penahanan kitaran cell dan apoptosis. Peningkatan dalam pengekspresan p53, caspase-3 dan -9, tetapi penurunan pengekspresan Bcl-2 dalam sel SiHa telah dikesan. Walau bagaimanapun, dalam sel HeLa, peningkatan nisbah Bax kepada Bcl-2, dan pengekspresan caspase-3, -8 dan -9 telah dikesan. Analisis fizikokimia menunjukkan bahawa TQ-NLC_4 mempunyai purata diameter zarah kurang daripada 100 nm. TQ-NLC_4 didapati stabil sehingga 24 bulan (2 tahun). EE dan DLC TQ-NLC_4 yang tinggi telah dicapai. TQ dibebaskan daripada NLC mengikut kinetik tertib sifar. Simulasi pencernaan gastrousus menunjukkan bahawa pencernaan dan pengumpulan TQ-NLC_4 berlaku di dalam SIF. Kajian penyerapan dan keterbiosediaan TQ secara *in vitro* menunjukkan bahawa TQ-NLC_4 mempunyai keterbiosediaan yang tinggi. Kesimpulannya, TQ adalah sitotoksik terhadap sel kanser serviks tersebut dengan memodulasikan laluan apoptosis. NLC memberi TQ pembebasan yang terkawal, menyediakan perlindungan dan peningkatan keterbiosediaan. Oleh demikian, TQ-NLC_4 adalah agen anti-kanser serviks yang berpotensi.

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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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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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DLC	drug loading capacity
DSC	differential scanning calorimetry
EE	encapsulation efficiency
ELISA	enzyme-linked immunosorbent assay
GIT	gastrointestinal tract
GRAS	generally recognized as safe
HPO	hydrogenated palm oil
MWCO	molecular weight cut-off
NLC	nanostructured lipid carriers
P_{app}	permeability coefficient
PDI	polydispersity index
R^2	correlation coefficient
SGF	simulated gastric fluid
SIF	simulated intestinal fluid
SLN	solid lipid nanoparticle

CHAPTER 1

INTRODUCTION

1.1 Background

Malignant tumour or cancer is a family of genetic and epigenetic diseases in which a single cell in the body overrides the normal controls of mitosis and cell division (Richards & Hawley, 2011; Riley & Anderson, 2011). It is characterized by a deregulated proliferation of cells with the consequences of an abnormal increase of the cell number in particular organs, invasion of the surrounding tissues, formation of metastasis and eventually choking off the life (Schwab, 2011).

Globally, vast effort and innumerable researches have been conducted to improve the miserable outcomes of cancer. Nonetheless, cancer remains as one of the most hazardous and fast propagating diseases of the current century. In the past 30 years, the overall mortality rates from cancer have shown no significant decline (Ameta *et al*., 2012; Zhao *et al*., 2010). In 2004, cancer stayed as the second leading cause of death worldwide (following heart diseases), accounted for 12.6% of the total death cases. Globally, one in eight deaths is due to cancer and cancer causes more deaths than total death cases caused by AIDS, tuberculosis and malaria (American Cancer Society, 2011; Jemal *et al*., 2011). In 2012, malignant neoplasms, which accounted for 14.9% of the total death cases (8.2 million death cases) have overtaken the ischemic heart disease (7.4 million death cases) as the first leading cause of death worldwide, ahead of other causes of death such as stroke (6.7 million death cases), chronic obstructive pulmonary disease (3.1 million death cases) and AIDS (1.5 million death cases) (Ferlay *et al*., 2015; WHO, 2014; Ferlay *et al*., 2013).

According to the report of the GLOBOCAN project (GLOBOCAN-2012), there were 14.06 million estimated new cancer cases reported worldwide (increase by 10.24% as compared to year 2008), of which 6.05 million (43.03%) and 8.01 million (56.97%) cases occurred in economically developed countries and economically developing countries, respectively, in 2012. Meanwhile, a total of 8.20 million cancer deaths (about 22,500 cancer deaths per day) were estimated worldwide, with 2.88 million in economically developed countries and 5.32 million in economically developing countries. Due to the growth and aging of the population, it is expected that the global cancer burden is going to increase to 23.98 million new cancer cases and 14.63 million cancer deaths by 2035, if the current trends continue. Worldwide, lung (12.42 million cases, 16.8%), prostate (1.09 million cases, 14.8%), colorectal (7.46 million cases, 10.1%), stomach (6.31 million cases, 8.5%) and liver cancer (5.54 million cases, 7.5%) were the five most commonly diagnosed cancer among men, while breast (16.71 million cases, 25.1%), colorectal (6.14 million cases, 9.2%), lung (5.83 million cases, 8.8%), cervix uteri (5.28 million cases, 7.9%) and corpus uteri cancer (3.20 million cases, 4.8%) among women (Ferlay *et al*., 2015; Ferlay *et al*., 2013).

In 2012, cancer (11.64%) was ranked as the fourth leading cause of death in the Ministry of Health Malaysia Hospitals after cardiovascular diseases (24.69%), diseases of pulmonary circulation (18.80%) and infectious and parasitic diseases (17.17%) (Ministry of Health Malaysia, 2013). A total of 37,426 new cancer cases (increase by 105.4% as compared to year 2007) were reported in the year 2012, comprising 18,125 males (48.43%) and 19,301 females (51.57%) in Malaysia. In the meantime, a total of 21,678 cancer deaths were estimated in Malaysia, of which 11,281 (52.04%) and 10,397 (47.96%) cases occurred in male and female, respectively. Lung cancer (17.88%) was the most frequently diagnosed cancer among Malaysian males in 2012, followed by colorectal (14.14%), nasopharynx (8.20%), prostate (6.54%) and stomach cancer (6.49%). Meanwhile, the five most commonly reported female cancers were breast (28.03%), cervix uteri (11.11%), colorectal (10.24%), lung (6.03%) and ovarian cancer (5.69%) (Ferlay *et al*., 2013; Zainal Ariffin & Nor Saleha, 2011).

High rate of mitosis and uncontrolled proliferation of the cervical cells result in the development of cervical cancer (Chang *et al*., 2010b). Primarily, due to the introduction of Papanicolaou (PAP) smear screening programme, the cervical carcinoma incidences and mortality rates have gradually declined. Nevertheless, it remains one of the third most prevalent gynaecologic malignancies and major causes of cancer death in women around the world (Zagouri *et al*., 2012). Cervical squamous cell carcinoma, which is more common than cervical adenocarcinoma, accounts approximately for 80% of all invasive cervical neoplasia (Katanyoo *et al*., 2012). Due to the high oncogenic human papilloma virus (HPV) infection rates, the absence of screening programmes and the lack of access to affordable HPV vaccination programmes, cervical cancer causes a major health problem in the developing countries (Diaz-Padilla *et al*., 2013).

Approximately, 528,000 new cases (83,000 cases in developed countries and 445,000 cases in developing countries) and 266,000 cancer deaths (36,000 deaths in developed countries and 230,000 deaths in developing countries) were attributed to cervical cancer worldwide in 2012. Cancer of the cervix was the second most commonly diagnosed cancer (11.11% of total female cancers) among women in Malaysia in 2012. There were a total of 2,145 new cases (increase by 153.2% as compared to year 2007) of cervical neoplasia diagnosed in Malaysia, with the age-standardized incidence rate (ASR) of 15.6 per 100,000 population (Ferlay *et al*., 2013; Zainal Ariffin & Nor Saleha, 2011).

Cis-diamminedichloroplatinum(II) or cisplatin-based chemoradiotherapy is the commonest, well known and promising regime used to manage cervical cancer. Despite of its capability of destroying the rapidly growing cancer cells, it damages the non-targeted, proliferating normal healthy cells as well. Cisplatin shows undesirable adverse-effects that include mild myelosuppression, ototoxicity and neurotoxicity. However, the most significant dose-limiting toxicity caused by cisplatin is renal dysfunction (Singh *et al*., 2013b; Jiang *et al*., 2012). Moreover, emergence of multidrug resistance (MDR) in cervical cancer patients hinders the success of the cisplatin-based chemoradiotherapy (Lo & Wang, 2013).

Natural products, including plants, have become the most significant natural resources for the discovery of anti-cancer compounds (Kitdamrongtham *et al*., 2013; Zhang *et al*., 2013b; Zhao *et al*., 2013). It is believed that natural products or bioactive compounds derived from natural products usually exhibit low toxicity, inexpensive and are well tolerated by the human body (Greenlee, 2012; Wu *et al*., 2011). Due to the advance in analytical chemistry and chemical biology, characterizations of commonly used herbs or

herbal formulation from natural products provide the possible discoveries of bioactive ingredients or entities (Li & Zhang, 2013). Since 1981 to 2010, over 74.8% of the approved drugs were derived from natural products (Newman & Cragg, 2012; Nobili *et al*., 2009). The success stories of vinca alkaloids (vinblastine and vincristine) from *Catharanthus roseus* (Madagascar periwinkle) as well as paclitaxel (Taxol®) from *Taxus brevifolia* (Pacific Yew tree) encourage a continuous research and discovery on potential anti-cancer candidates from natural products (Zhang *et al*., 2013b; Manosroi *et al*., 2012).

Nigella sativa (also known as black seed or *habbatus sauda*) appears as one of the important herbs among various medicinal plants. Majority of the biological activities of *Nigella sativa* are associated with the presence of thymoquinone (TQ), the major bioactive compound found in the seeds of the plant (Ahmad *et al*., 2013). *N. sativa* and TQ are well known with their biological activities that include anti-cancer (Peng *et al*., 2013; Mahmoud & Torchilin, 2012; Woo *et al*., 2011), anti-oxidant (Bourgou *et al*., 2012; Umar *et al*., 2012), anti-inflammatory (Alemi *et al*., 2013; Chehl *et al*., 2009), hepatoprotective (Zafeer *et al*., 2012; Yildiz *et al*., 2008) and renal protective (Saleem *et al*., 2012; Ulu *et al*., 2012; Yildiz *et al*., 2010) properties.

Among all the route of administrations, non-invasive oral route is the most preferred route for chemotherapy. Nevertheless, oral administration of 50% of the drug compounds is hampered by the lipophilic property of the drugs. In fact, among the newest drug candidates, 40% exhibit low water solubility, resulting in poor oral bioavailability (Dey *et al*., 2012; Katteboina *et al*., 2009). Most of the time, these poor water solubility anticancer candidates are dissolved in surfactants or in organic solvents such as dehydrated alcohol which cause adverse side effects to the patients. These side effects include neurotoxicity, nephrotoxicity and cardiotoxicity (Mognetti *et al*., 2012). Similar trends are expected from TQ as it is lipophilic in nature with relatively low water solubility (Khader *et al*., 2009). Therefore, oral delivery of TQ will be limited by the solubility-related poor oral bioavailability (Pathan *et al*., 2011).

In order to overcome the low solubility and low bioavailability of the active anticancer compounds, lipid based nano-drug delivery systems particularly solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are utilised as potential carriers for hydrophobic and lipophilic drugs (Zhuang *et al*., 2010). Both SLNs and NLCs confer many advantages including capability of increasing the bioavailability of poorly soluble compounds, providing protection for sensitive active compounds and facilitating controlled release of drugs (Müller *et al*., 2000). NLC is the second-generation of lipid based nanoparticles which are developed from SLN. NLC overcomes the limitations of SLN, which include low drug loading capacity and drug expulsion during storage (Fang *et al*., 2008).

Although has been documented to exhibit cytotoxic effects in several cancer cell lines, the cytotoxicity and mechanisms of action of TQ from *Nigella sativa* towards cervical cancer cells (HeLa and SiHa) have not been investigated yet. Furthermore, the formulation and characterisation of thymoquinone-loaded nanostructure lipid carrier (TQ-NLC) as well as its cytotoxicity have not been performed before.

1.2 Objective

1.2.1 General Objective

The general objective of the study was to determine the cytotoxicity of TQ and TQ-NLC towards cervical cancer cells (SiHa and HeLa).

1.2.2 Specific Objectives

The specific objectives were:

(1) to determine the cytotoxicity of TQ towards cervical cancer cells (SiHa and HeLa) and the mode of cell death induced by TQ,
(2) to study the mechanisms of action underlying cytotoxicity of TQ,
(3) to formulate and synthesize TQ-NLC,
(4) to characterize the physicochemical properties, drug release profile and *in vitro* bioavailability of TQ-NLC and
(5) to evaluate the cytotoxicity and mode of cell death induced by TQ-NLC.

1.3 Hypotheses

TQ will be cytotoxic towards all the selected cancer cell lines by inducing cell cycle arrest and apoptosis. The induction of apoptosis by TQ will involve p53-dependent intrinsic pathway.

TQ-NLC will be formulated. NLC will confer drug controlled release, protection, and enhanced bioavailability and cytotoxicity to TQ.

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