EFFECT OF THYMOQUINONE AND THYMOQUINONE-LOADED NANOSTRUCTURED LIPID CARRIER IN *IN VITRO* WOUND HEALING MODEL

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the degree of Master of Science

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Chairman : Sharifah Sakinah Syed Alwi, PhD
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Wound healing is the body's natural response to wounding. It comprises of four highly integrated phases (haemostasis, inflammation, proliferation and remodelling) resulting in a scar. When there is an impairment to any of the healing components, the healing process gets disrupted and chronic wound ensue. Impaired wound healing is one of the major problems in diabetic patients due to persistence of inflammatory cells and increased apoptosis throughout the healing process. A constant influx of inflammatory cells releases a high level of free radicals such as reactive oxygen species that results in chronic wound. Although the exact mechanism that causes poor wound healing in diabetic patients is unclear, numerous factors have been associated with it, including wound infection, chronic inflammation, sensory neuropathy and hypoxia. Thus, new prospect for therapy to favour speed and optimal healing are emerging. In this study, thymoquinone (TQ), a bioactive compound found in *N. sativa* seed was loaded into a colloidal drug carrier known as a nanostructured lipid carrier (NLC) producing a compound known as thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) (PATENT NO: PI2012001818). The rapidly progressing nanotechnology today set a new alternative carrier to enhance and favour the speed of healing process. This study aimed to determine the effect of TQ and TQ-NLC on cell proliferation and migration, the mode of cell death and the antioxidant levels in normal and diabetic cell models, 3T3 and 3T3-L1. Cytotoxicity of TQ and TQ-NLC was determined by MTT assay. Based on the MTT assay, the IC_{10} obtained for 3T3-L1 treated with TQ and TQ-NLC for 24 hours were 5.3 ± 0.6 and 4.7 ± 3.3 µM respectively. As for 3T3 cell, the IC_{10} obtained for TQ and TQ-NLC at 24 hours were 3.9 ± 2.05 and 4.3 ± 0.17 µM. TQ-NLC was seen to increase the number of healthy cells (89-95%) and gradually decrease early apoptotic cells in time and dose dependant manner compared to TQ in 3T3-L1 cell in the Annexin V analysis. At 72 hours, 3 µM of treatment with TQ-

NLC resulted in the highest number of healthy cells. In 3T3-L1 cells treated with TQ, the apoptotic cells decreased from 16.5% to 11.5 % after 72 hours. 3T3-L1 treated with TQ-NLC showed the lowest number of apoptotic cells and a significant increase in healthy cells compared to control at 48 and 72 hours. In the proliferation and migration assay, 3T3-L1 treated with TQ-NLC showed a higher proliferation and rate of migration ($p< 0.05$) compared to TQ treated cells. In the antioxidant assay, TQ-NLC acted as antioxidant by reducing ROS levels in both the cells after injury at concentration as low as 3 µM. Both the cells treated with TQ-NLC showed a significantly lower level of ROS ($p< 0.05$) compared to treatment with TQ. Thus, this study demonstrated that TQ-NLC performed better compared to TQ especially on the diabetic mimic cell, 3T3-L1. TQ-NLC accelerated the migration and proliferation of cells while reducing the ROS produced in the wounded cells confirming its ability as a good antidiabetic and antioxidant agent.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan ijazah Master Sains

KESAN THYMOQUINONE DAN THYMOQUINONE BERNANOSTRUKTUR PEMBAWA LIPID DALAM MODEL *IN VITRO* PENYEMBUHAN LUKA

Oleh

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Penyembuhan luka adalah tindak balas semula jadi tubuh apabila luka berlaku. Ia terdiri daripada empat fasa yang sangat bersepadu (haemostasis, keradangan, proliferasi dan pembentukan semula tisu) yang menghasilkan parut. Apabila terdapat kerosakan pada komponen penyembuhan, proses penyembuhan akan terganggu dan luka kronik berlaku. Penyembuhan luka terjejas adalah salah satu masalah utama pesakit kencing manis akibat ketegangan sel-sel radang dan peningkatan apoptosis sepanjang proses penyembuhan. Kemasukan sel-sel yang menyebabkan inflamasi ini membebaskan paras radikal bebas yang tinggi seperti spesies oksigen reaktif yang mengakibatkan luka kronik. Walaupun mekanisme tepat yang menyebabkan penyembuhan luka yang lemah dalam pesakit diabetes tidak jelas, banyak faktor telah dikaitkan dengannya, termasuk jangkitan luka, keradangan kronik, neuropati deria dan hipoksia. Oleh itu, prospek baru untuk terapi bagi menggalakkan penyembuhan luka yang optimum semakin meningkat. Dalam kajian ini, thymoquinon (TQ), sebatian bioaktif yang terdapat dalam benih *N. sativa* dimasukkan ke dalam pembawa dadah koloid yang dikenali sebagai pembawa lipid nanostruktur (NLC) yang menghasilkan sebatian yang dikenali sebagai pembawa lipid nanostruktur yang dimodilkan thymoquinone (TQ-NLC) PATEN NO: PI2012001818). Nanoteknologi yang berkembang pesat hari ini menetapkan pembawa alternatif baru untuk meningkatkan dan memihak kepada proses penyembuhan yang cepat. Kajian ini bertujuan untuk menentukan kesan TQ dan TQ-NLC terhadap percambahan dan penghijrahan sel, cara kematian sel dalam model sel normal dan diabetik dan tahap antioksidan di dalam sel 3T3 dan 3T3-L1. Sitotoksiti TQ dan TQ-NLC ditentukan oleh ujian MTT. Berdasarkan ujian MTT, IC_{10} yang diperolehi untuk 3T3-L1 yang dirawat dengan TQ dan TQ-NLC selama 24 jam masing-masing adalah 5.3 ± 0.6 dan 4.7 ± 3.3 μM. Bagi sel 3T3 pula, IC_{10} yang diperolehi untuk TQ dan TQ-NLC pada 24 jam ialah 3.9 ± 2.05 dan 4.3 ± 0.17 μM. TQ-NLC dilihat meningkatkan jumlah sel yang sihat (89-95%) dan secara beransur-ansur menurunkan sel-sel apoptosis awal dalam masa dan dos berbanding

dengan TQ di dalam sel 3T3-L1 berdasarkan analisis Annexin V. Pada 72 jam, rawatan 3 μM dengan TQNLC menghasilkan bilangan sel yang paling sihat. Dalam sel 3T3-L1 yang dirawat dengan TQ, sel apoptosis menurun dari 16.5% hingga 11.5% selepas 72 jam. 3T3-L1 yang dirawat dengan TQ-NLC menunjukkan bilangan sel apoptotik yang paling rendah dan peningkatan yang ketara dalam sel-sel sihat berbanding dengan kawalan ($p<0.05$) pada 48 dan 72 jam. Untuk ujian luka, kepekatan TQ-NLC sebanyak 3 μM menunjukkan kesan yang ketara pada kedua-dua 3T3 dan 3T3-L1 berbanding kawalan ($p<0.05$). Sel 3T3-L1 yang dirawat dengan TQ-NLC menunjukkan percambahan dan kadar penghijrahan yang lebih tinggi berbanding sel-sel yang dirawat dengan TQ. Dalam ujian antioksidan, TQ-NLC bertindak sebagai antioksidan dengan mengurangkan tahap ROS dalam kedua-dua sel selepas kecederaan pada kepekatan serendah 3 μM. Kedua-dua sel yang dirawat dengan TQ-NLC menunjukkan tahap ROS yang lebih rendah berbanding rawatan dengan TQ. Oleh itu, kajian ini menunjukkan bahawa TQ-NLC lebih berkesan berbanding dengan TQ terutama pada sel yang mimik diabetes, 3T3-L1. Rawatan dengan TQ-NLC mempercepat penghijrahan dan pembiakan sel serta mengurangkan ROS yang dihasilkan di sel-sel yang cedera mengesahkan keupayaannya sebagai ejen antidiabetik dan antioksidan yang baik.

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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 Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ANOVA	One-Way Analysis of Variance
ATCC	American Type and Culture Collection
CO_2	Carbon dioxide
DCFH	2',7'-dichlorofluorescein
DCF-DA	2′,7′-Dichlorodihydrofluorescein Diacetate
DHTQ	Dihydrothymoquinone
DM	Diabetes mellitus
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EGF	Epidermal growth factor
FBS	Fetal Bovine Serum
FGF	Fibroblast growth factor
FITC	Fluorescein isothiocyanate
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
H_20_2	Hydrogen peroxide
IC_{10}	Inhibitory Concentration of 10% Cell Viability
MDA	Malondialdehyde
MMPs	Matrix metalloproteinases
MTT	3-(4,5-dimethythiazol- 2-yl)-2,5-diphenyl tetrazolium bromide
N. *sativa*	*Nigella sativa*
NLC	Nanostructured lipid carrier
O_2	Oxygen
PBS	Phosphate Buffered Saline

PDGF	Platelet-derived growth factor
PI	Propidium Iodide
PS	Phosphatidylserine
ROS	Reactive oxygen species
SD	Standard Deviation
SEM	Standard error of mean
SLN	Solid lipid nanoparticles
STZ	Streptozotocin
TGF	Transforming growth factor
THQ	Thymohydroquinone
TQ	Thymoquinone
TQ-NLC	Thymoquinone-loaded nanostructured lipid carrier
VECs	Vascular endothelial cells
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

Wounds are physical insults that result in a break or opening of the skin (Yamini & Gopal, 2016) and are a major cause of physical disability (Nagori & Solanki, 2011). Wounds are generally classified into two types: acute and chronic wound. Acute wounds usually repair themselves in an orderly manner which causes both functional and anatomical restoration (Martin, 1997). Any alterations that interrupt the timely controlled healing processes would prolong tissue damage and the repair process, consequently contributing to chronic wound (Kurahashi & Fujii, 2015) and complications usually entail. Chronic wounds are wounds that display impaired healing. They usually have failed to progress through the normal stages of healing (Guo et al., 2010) and get trapped in a permanent inflammatory stage due to an imperfect or uncoordinated healing process (Briquez et al., 2015; Velnar et al., 2009; García Orue et al., 2016). Wound healing is the body's natural reaction that leads to repair of the injured tissue (Ammar et al., 2015) and is comprised of four highly integrated and overlapping phases (haemostasis, inflammation, proliferation and remodelling of tissue) (Dunill et al., 2015; Shah et al., 2012).

Diabetes mellitus (DM) is a group of metabolic disease characterized by high glucose level in the blood. This can be a result of insulin resistance, absence of insulin or inadequate levels of insulin released due to the destruction of β-cells that are responsible for insulin production (Reece, 2010). Patients with DM often suffer from various metabolic abnormalities including delayed wound healing that usually results in leg amputations. (Cakirca et al., 2014; Asmat et al., 2016). The cause of chronic ulcers in DM patients has been attributed to a variety of abnormal biological mechanisms: ischemia, neuropathy, infection, prolonged inflammatory response, cytokine and growth factors deficits (Falanga, 2005; Medina et al., 2005; Hu & Lan, 2016).

Since ancient times, preparations from plants were used to speed up the process of wound healing (Schmidt et al., 2009; Fronza et al., 2009). Usage of medicinal plants dates from the earliest years of men's evolution (Dattner, 2003). They have been extensively used to prepare herbal medicines as they are known to be safer than most modern medicines (Ahmad et al., 2013). Examples of medicinal plants used for wound healing are *Morinda citrifolia* (Nayak et al., 2007), *Radix paeoniae* (Malviya et al., 2009), *Lawsonia alba* (Mandawgade & Patil., 2003) *and Ginko biloba* (Bairy & Rao, 2001). The use of natural products to replace man-made drugs has risen significantly in the last decade as there are concerns about side effects of conventional medicine (Darakshan et al., 2015).

Nigella sativa Linn., (N. *sativa*) is an annual flowering plant belonging to Ranunculaceae family (Khan et al., 2011). It is an amazing herb with a rich historical background (Ng et al., 2011). It is native to North Africa, Southern Europe and Southwest Asia (Ahmad et al., 2013). N. *sativa* is also known as Habbatus Sauda, black seed, roman coriander and kalonji (Hussain and Hussain, 2016). Black seed has been extensively used as spice, condiment (Yarnell & Abascal, 2011) and was one of the earliest cultivated plants in human history (Desai et al., 2015). It also has been utilized as herbal medicine by various cultures to treat various ailments (Butt & Sultan, 2010; Khan et al., 2015) including high blood pressure, headache, fever, dizziness and influenza (Baharetha et al., 2013; Agbaria et al., 2015). The principle active ingredient isolated from the essential oil of N. *sativa* is thymoquinone (TQ) (Mahfouz & El-Dakhakhany, 1960; Hajhashemi et al., 2004). TQ is responsible for the therapeutic properties of this plant (Ahmad et al., 2013). The pharmacological investigation of the seed extracts reveals a variety of activities including antihypertensive (El Tahir et al., 1993), anti-inflammatory (Ali et al., 2003; Houghton et al., 1995), antihistaminic (Mahfouz et al., 1965), antimicrobial (El-Alfy et al., 1975; Kouidhi et al., 2011), antioxidant (Staneik & Gille, 2010) and antidiabetic (Al-Hader et al., 1993; Abdelmeguid et al., 2010).

Many studies on N. *sativa* and TQ have been previously recorded to find a solution for diabetes mellitus yet none have been carried out to observe the effect of TQ on wounds in diabetic patients. Although TQ is known for its varied functions, because its bioavailability is poor, its clinical use is limited (Pathan et al., 2011). Therefore, to overcome this problem, together with the rapidly progressing nanotechnology today, it is indeed important to look at a new alternative can effectively reach beneath the skin to speed the healing process.

Nanostructured lipid carrier (NLC), a colloidal drug carrier is tagged to a compound or extract that has trouble with bioavailability or absorption in the body. As Ng et al. (2015) previously described, thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) (PATENT NO: PI201200181) was produced through a hot high-pressure homogenization method and yielded remarkable physicochemical properties. With high encapsulation efficiency, and a particle size of less than 50 nm in diameter, TQ-NLC has a stability of up to two years (Ng et al., 2015). It presents a larger surface area for reaction with its target component and also minimizes the probability of it being phagocytosed by macrophages (zur Mühlen et al., 1998; Ong et al., 2016). TQ-NLC has a huge potential to be used for wounds of diabetic patients. With all the attributes of NLC and the effectiveness of TQ as an anti-oxidant, anti-inflammation and antidiabetic agent, TQ-NLC may be an effective agent for diabetic wound healing.

1.2 Problem statement

Diabetic patients develop wounds that are prone to infection and display impaired wound healing that leads to many other complications such as chronic ulceration, and resultant limb amputation (Bowling et al., 2015). A great deal of effort has gone into developing treatments for diabetic wounds. Still, current treatment for diabetic wound comes with adverse side effects that lead to further problems such as damage to the large blood vessels of the heart and kidney complication (Chaudhury et al., 2017). Therefore, it is crucial to discover an alternative treatment to accelerate the healing of diabetic wound with lesser side effects. One target has been the reduction of chronic inflammation by restoring levels of endogenous antioxidants and reducing the level of reactive oxygen species (Griffith et al., 2009). TQ was reported to significantly reduce the levels of reactive oxygen species and act as a good antioxidant (Badary, 2003). It was also found to be a good anti-diabetic agent through numerous studies (AI-Trad et al., 2016; Al Wafai et al., 2013). Hence, with the integration of the new advance nanotechnology together with the anti-diabetic and anti-oxidant property of TQ, we decided to look at the beneficial effect of TQ-nanostructured lipid carrier to enhance healing process, not only in normal condition but also in prolonged tissue damage of diabetic patients. There are no previous reports on the *in vitro* wound healing properties of TQ and TQ-NLC.

1.3 Objectives

1.3.1 General objective

To elucidate the healing effect of TQ and TQ-NLC in normal and diabetic cell models.

1.3.2 Specific Objectives

1. To measure cell viability upon treatment with TQ and TQ-NLC using MTT assay
2. To examine the mode of cell death in both the cell lines using Annexin V assay
3. To evaluate the effect of TQ and TQ-NLC on cell migration in normal and diabetic models using scratch assay.
4. To evaluate the ROS level of both compounds toward human skin fibroblast 3T3 and 3T3-L1 cells.

1.4 Hypothesis

It is hypothesized that TQ-NLC is a better candidate and have better healing properties by enhancing the proliferation and migration process as well as reducing the ROS levels compared to TQ.

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