PHARMACOKINETICS, BIODISTRIBUTION AND NEUROPROTECTIVE EFFECTS OF THYMOQUINONE-LOADED NANOSTRUCTURED LIPID CARRIER ON HIGH FAT CHOLESTEROL DIET INDUCED ALZHEIMER'S DISEASE RAT MODEL

By

FATIN HANNANI BINTI ZAKARIAL ANSAR

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

August 2022

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DEDICATION

This thesis is dedicated to

My parents, family and best friends
Who have been my source of inspiration and gave me strength when I thought of giving up, who continually provide their moral, spiritual, and emotional support.

My husband, Muhammad Abu Kadir bin Mubarak Ali
For your endless love, patience and support in the pursuit of my dreams.

&

My son, Muhammad Nael Haris bin Muhammad Abu Kadir
May you never stop learning.

Abstract of 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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FATIN HANNANI BINTI ZAKARIAL ANSAR

August 2022

Chairman : Professor Latifah binti Saiful Yazan, PhD
Institute : Bioscience

Alzheimer's disease (AD) is one of the ultimate forms of dementia in people 65 years of age and older, slowly growing out of slight forgetfulness to the requirement for comprehensive care. Globally, close to 36 million people suffer from Alzheimer's disease or related dementia. In Malaysia, there are approximately 50,000 people with AD. One of the traditional AD risks is hypercholesterolemia. Hypercholesterolemia is commonly linked to oxidative stress and lipid oxidation which play an important role in the development of AD. Currently, there is still no viable cure for AD. Thus, the need for therapies that offer neuroprotective properties is in demand. One of the promising approaches is the use of the natural product. Thymoquinone (TQ), a bioactive compound from *Nigella sativa* that exhibit antioxidant property, can protect the neuron cells from degrading. Nevertheless, TQ has low solubility in blood and poor oral bioavailability. Consequently, a nanostructured lipid carrier (NLC) has been developed as a drug delivery vehicle to overcome the limitations of TQ (herein referred to as TQ-NLC). This study aimed to determine the role of oral and intravenous administration in pharmacokinetics and bioavailability of TQ-NLC as well as the neuroprotective effects of TQ-NLC as a potential drug candidate for the management of AD. The pharmacokinetics and biodistribution study of TQ-NLC was carried out in healthy male Sprague Dawley rats via oral and intravenous administration (100 and 25 mg/kg, respectively) using gamma ray counter and gamma camera. *In vivo* study of neuroprotective effect of TQ-NLC via oral administration (12.5, 25 and 50 mg/kg) includes Morris water maze test, lipid profile level, neurodegenerative features, oxidative stress level and protein expression analysis. Oral administration of TQ-NLC demonstrated improved relative bioavailability compared with intravenous administration. The movement of TQ-NLC through the intestinal lymphatic system is postulated to bypass the first metabolism, thus, increasing the relative bioavailability. However, oral

administration is more slowly absorbed as the $AUC_{0-\infty}$ was 4.539 times lower than intravenous administration. During the Morris water maze test, the animals treated with 25 mg/kg of TQ-NLC showed an increase in the time spent at the targeted quadrant and reduced total cholesterol compared to the negative control (untreated) ($p<0.05$). In addition, the animals treated with 25 mg/kg of TQ-NLC showed shorter escape latency in comparison to the negative control (untreated), but it was not statistically significant. In addition, the animals treated with 50 mg/kg of TQ-NLC showed a reduction in MDA level and protein carbonyl compared to negative control (untreated). Protein analyses in the brain hippocampus revealed reduction in levels of the Aβ, BACE1 and ApoE while enhanced the Aβ clearance and degradation by increasing the level of IDE and LRP1 in the brain. In conclusion, *in vivo* data demonstrated the beneficial effects of TQ-NLC in ameliorating neurodegenerative changes particularly in AD biomarkers through the effects on oxidative stress, Aβ production and improvement in cognitive function. The finding therefore implicates the potential application of TQ-NLC for management of neurodegenerative diseases particularly AD.

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

FARMAKOKINETIK, BIODISTRIBUSI DAN KESAN NEUROPROTEKTIF DARI TIMOKUINON YANG DIMUAT DALAM PEMBAWA LIPID BERSTRUKTUR NANO DALAM MODEL TIKUS BERDIET TINGGI KOLESTEROL DAN LEMAK YANG MENCETUSKAN PENYAKIT ALZHEIMER

Oleh

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Penyakit Alzheimer (AD) adalah salah satu bentuk utama demensia di kalangan orang berumur 65 tahun ke atas, berkembang perlahan-lahan daripada kealpaan ringan kepada keperluan penjagaan secara menyeluruh. Di seluruh dunia, hampir 36 juta orang menghidapi Alzheimer atau yang berkaitan dengan demensia. Di Malaysia, kira-kira 50,000 orang menghidap AD. Salah satu risiko tradisional AD ialah hiperkolesterolemia. Hiperkolesterolemia biasanya dikaitkan dengan tekanan oksidatif dan pengoksidaan lipid yang memainkan peranan penting dalam perkembangan AD. Sehingga hari ini masih tiada penawar yang berkesan untuk AD. Oleh itu, permintaan dalam mencipta terapi yang berkesan dalam menawarkan sifat neuroprotektif adalah sangat diperlukan. Salah satu pendekatan yang menjanjikan keberkesanan tersebut adalah penggunaan produk semula jadi. Timokuinon (TQ), sebatian bioaktif daripada *Nigella sativa* yang mempunyai sifat antioksidan yang luar biasa, boleh melindungi sel-sel neuron daripada kemerosotan fungsi. Namun begitu, TQ mempunyai keterlarutan yang rendah dalam darah dan bioavailabiliti secara oral yang lemah. Akibatnya, pembawa lipid berstruktur nano (NLC) telah dicipta sebagai medium penghantaran ubat untuk mengatasi kelemahan TQ (di sini dirujuk sebagai TQ-NLC). Kajian ini bertujuan untuk menentukan peranan pemberian TQ-NLC secara oral dan intravena dalam farmakokinetik dan pengagihan bio serta kesan neuroprotektif TQ-NLC sebagai calon ubat yang berpotensi untuk pengurusan AD. Kajian farmakokinetik dan biodistribusi TQ-NLC telah dijalankan ke atas tikus Sprague Dawley jantan yang sihat melalui pemberian oral dan intravena (masing-masing 100 dan 25 mg/kg) menggunakan kaunter sinar gamma dan kamera gamma. Kajian in vivo mengenai kesan neuroprotektif TQ-NLC melalui pemberian oral (12.5, 25 dan 50 mg/kg) termasuk ujian maze air Morris, tahap profil lipid, ciri neurodegeneratif, tahap tekanan oksidatif dan

analisis ekspresi protein. Pemberian TQ-NLC secara menunjukkan bioavailabiliti relatif yang lebih besar berbanding dengan pemberian secara intravena. Adalah dipercayai bahawa pergerakan TQ-NLC melalui sistem limfa usus memintas metabolisme pertama dan oleh itu meningkatkan bioavailabiliti relatif. Walau bagaimanapun, pemberian secara oral mempunyai penyerapan yang lebih perlahan berbanding dengan pemberian secara intravena di mana $AUC_{0-\infty}$ adalah 4.539 kali lebih rendah. Semasa ujian Morris, haiwan yang dirawat dengan 25 mg/kg TQ-NLC menunjukkan peningkatan dalam masa yang dihabiskan di kuadran sasaran dan pengurangan jumlah kolesterol berbanding kawalan negatif (tidak dirawat) ($p<0.05$). Di samping itu, haiwan yang dirawat dengan 25 mg/kg TQ-NLC menunjukkan masa menyelamatkan diri yang lebih pendek berbanding kawalan negatif (tidak dirawat), tetapi ia tidak signifikan secara statistik. Walau bagaimanapun, ia tidak signifikan secara statistik jika dibandingkan dengan kumpulan negatif (tidak dirawat). Di samping itu, haiwan yang dirawat dengan 50 mg/kg TQ-NLC menunjukkan pengurangan tahap MDA dan karbonil protein berbanding kawalan negatif (tidak dirawat). Analisis protein dalam hipokampus otak menunjukkan penurunan tahap Aβ, BACE1 dan ApoE disamping meningkatkan degradasi Aβ dengan meningkatkan tahap IDE dan LRP1 dalam otak. Kesimpulannya, data *in vivo* menunjukkan keberkesanan TQ-NLC dalam memperbaiki perubahan neurodegeneratif terutamanya dalam biomarker AD melalui kesan ke atas tekanan oksidatif, pengeluaran Aβ dan peningkatan dalam fungsi kognitif. Oleh itu, penemuan ini memberi implikasi terhadap potensi TQ-NLC untuk pengurusan penyakit neurodegeneratif termasuk AD.

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This thesis was submitted to the Senate of the 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 APPENDICES

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
APP	Amyloid precursor protein
FAD	Familial early-onset form
ROS	Reactive oxygen species
OS	Oxidative stress
DNA	Deoxyribonucleic acid
AChEI	Acetylcholinesterase inhibitors
NMDA	N-methyl-D-aspartic acid or N-methyl-D-aspartate
FAD	Food and Drug Administration
BBB	Blood brain barrier
TQ	Thymoquinone
NLC	Nanostructured lipid carrier
TQ-NLC	Thymoquinone-loaded nanostructured lipid carrier
Aβ	Beta amyloid
NFT	Neurofibrillary tangles
PHT	Paired helical filaments
H&E	Hematoxylin and eosin
SAD	Sporadic Alzheimer's disease
BACE	β-site cleaving enzyme
β-sAPP	β-secretase-cleaved soluble APP
α- sAPP	α-secretase-cleaved site soluble APP
CTF	C terminal fragment
AICD	*Amyloid* precursor protein intracellular domain

PSEN	Presenilin
IDE	Insulin-degrading enzyme
CSF	Cerebrospinal fluid
RER	Rough endoplasmic reticulum
LRP1	Low-density lipoprotein receptor-related protein 1
LDL	Low-density lipoprotein
TC	Total cholesterol
CNS	Central nervous system
APOE	Apolipoprotein E
HDL	High-density lipoprotein
24S-OHC	24S-hydroxycholesterol
$O_2^{\cdot -}$	Oxygen radical superoxide
H_2O_2	Hydrogen peroxide
RNS	Reactive nitrogen species
HNE	4-hydroxy-2-nonenal
NPs	Nanoparticles
API	Active pharmaceutical ingredients
Tc-99m	Technetium
ITLC	Instant thin layer chromatography
AUC	Area under the curve
HFCD	High fat-cholesterol diet
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substances
MDA	Malondialdehyde

TCA	Thichloroacetic acid
RIPA	Radioimmunoprecipitation assay
TBS	Tris-buffered saline
PDI	Polydispersity index
HPLC	High-performance liquid chromatography
EE	Encapsulation efficiency
DCL	Drug loading capacity
$SnCl_2$	Stannous chloride
C_{max}	Maximum peak concentration
$T_{1/2}$	Half-life

CHAPTER 1

INTRODUCTION

1.1 Background

Alzheimer's disease (AD) is an overwhelming neurodegenerative disease that gradually and irreversibly damages thought memory and speech. The presence of senile plaque in several brain regions such as the hippocampus and superior temporal cortex is the main hallmark of AD (Khan *et al*., 2012). The main component of the senile plaque is amyloid β-peptide (Hardy, 1997) that originates from abnormal proteolysis of an integral membrane protein known as the amyloid precursor protein (APP) (Tamagno *et al*., 2003). AD is one of the ultimate forms of dementia in people 65 years of age and older, progressing slowly after a minor oversight. Sadly, elucidative etiology or a viable cure is still unavailable (Liu *et al*., 2005). Globally, close to 47.5 million people are believed to have dementia, and 7.7 million new cases of dementia occur each year that 60-70% of this population have AD (World Health Organization, 2020).

There are two forms of AD, which are the sporadic late-onset form that accounts for more than 90% of the patients (Bertram & Tanzi, 2004) and rare familial early-onset form (FAD) that makes up less than 1% of all cases of AD in which involves gene mutations (Tamagno *et al*., 2012). The mutation of presenilin is the main cause of FAD. This mutation partially loses function in the γ-secretase complex, which affects several downstream signalling pathways. The loss of the role of presenilin causes incomplete digestion of the amyloid β-peptide and might contribute to an increased vulnerability of the brain. Therefore, this mutation explains the early onset of the inherited form of AD (De Strooper, 2007).

The primary non-genetic risk factor associated with the pathogenesis of late-onset sporadic AD is aging that strictly linked to damage caused by reactive oxygen species (ROS) indicators of oxidative stress (OS) (Markesbery and Carney, 1999). The build-up of ROS causes damage to the main cellular components of the brain, including the nucleus, mitochondrial DNA and membranes and cytoplasmic proteins (Harman, 1992). ROS usually attacks the membranous lipid, and lipid peroxidation is the most common oxidative marker that seems to increase during aging. (Zhu *et al*., 2006). Besides that, hypercholesterolemia has been indeed related to enhanced lipid peroxidation (Newairy *et al*., 2009). In this study, diet-induced animal model using high fat-cholesterol diet has been employed to study the development of AD by using adult male Sprague Dawley rats. This animal model has the ability to exhibit the risk of sporadic form of AD that can resulted in disruption in permeability of blood brain barrier, thus, reduced the spatial memory that associated with the risk factor of AD (Ehriclh & Humple, 2012). Ullrich et al. (2010) reported that their study on hypercholesterolemia rats' model related to AD displayed a destruction of the cholinergic system in the basal forebrain that leads to acute spatial learning and long-term memory impairment.

There are two known common types of drugs for the management of AD: acetylcholinesterase inhibitors (AChEI) and NMDA receptor antagonist. Three AChEIs endorsed by the USA Food and Drug Administration (FDA) for treating of mild to moderate AD (Birks, 2006) are donepezil, rivastigmine and galantamine (Liu *et al*., 2005). On the other hand, memantine is the available therapeutic option of NMDA receptor antagonist for intermediate to severe AD (McShane *et al*., 2006). Antipsychotic and antidepressant (olanzapine and fluvoxamine, respectively) treatments for the behavioral symptoms of AD are also being used at the same time as the therapy for AD (Ballard and Corbett, 2010).

Current therapies are symptomatic only to compensate for the disruption of AD neurotransmitters (Yiannopoulou and Papageorgiou, 2013). Therapies do not halt the progression of the disease or provide significant remission (Liu *et al*., 2005). Therefore, there is a demand for therapy that offers neuroprotective properties. To date, more than 98% of drug candidates for neurodegenerative diseases never make it to the clinics (Pardridge, 2007) because of their inability to cross the blood-brain barrier (BBB) at sufficient levels to have a therapeutic effect (Miller *et al*., 2009). In addition, several drawbacks of the current treatments have been reported such as the onset of the treatment during the trials is too late in the disease progression, inaccute dosages of the drugs, incorrect target site of the treatment and poor understanding of the pathophysiological of the disease (Anderson et al., 2017).

To date, different kinds of nanoparticles have been applied to provide a therapeutic amount of drug in the brain for treatment of a variety of neurological disorders. Nanoparticles drug carrier is one of the promising candidates for AD because it has the ability to open the tight junctions (Zhuang *et al*., 2001), crossing the BBB (Smith, 2003), high drug loading capacities and targeting towards the mutagenic proteins of AD (Atwood et al., 2004). The nanoparticles include chitosan-based nanomers, dendrimers, carbon nanotubes, niosomes, beta cyclodextrin carriers, cholesterol-mediated cationic solid lipid nanoparticles, nanostructured lipid carrier, colloidal drug carriers, liposomes and micelles (Upadhyay, 2014).

One of the promising approaches for the management of neurodegenerative diseases is the use of natural products with potent antioxidant properties (Babazadeh *et al*., 2012) that act mainly by scavenging free radical species (Ansari and Khodagholi, 2013). *Nigella sativa* is an important herbal remedies, also called black seed or *habbatus sauda.* Thymoquinone (TQ) is the bioactive component comprising most of the biological activities of *N. sativa* seed (Ahmad *et al*., 2013) such as antioxidant and anti-inflammation (Tahir *et al*., 1993). TQ exhibited neuroprotective activity (Radad *et al*., 2009). Nevertheless, there are few disadvantages of TQ (Ismail *et al*., 2013). TQ has been administered via the intraperitoneal route. However, this route of administration is restricted in preclinical and clinical use by problems of high discomfort, is costly and infertility (Pathan *et al*., 2011). Although administration of TQ via the oral route is

beneficial, it is limited due to its poor solubility in water and bioavailability (Pathan *et al*., 2011; Khader *et al*., 2009).

Nanostructured lipid carriers (NLCs) have been created as drug delivery carriers to compensate for the limitation of the oral route (Mognetti, 2012). NLC provides various advantages as a good drug delivery carrier such as improving the bioavailability of compounds with poor solubility properties, defensing the delicate active compounds and aiding the controlled drugs release mechanism (How *et al*., 2011). Previously, thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) has been developed and produced by the high-pressure homogenization method and it can stable up to two years of storage (Ong et al., 2016). In addition, several properties of TQ-NLC has been reported such as anti-cancer (Ng et al., 2015; Ong et al., 2018; Haron et al., 2018) and wound healing (Alexander et al., 2019). However, the neuroprotective mechanism of TQ-NLC is not established.

1.2 Objectives

1.2.1 General Objective

The general objective of the study was to determine the role of oral and intravenous administration in pharmacokinetics and bioavailability of TQ-NLC as well as the neuroprotective effects of TQ-NLC as a potential therapy for the management of AD.

1.2.2 Specific Objectives

The specific objectives were:

1. to synthesis and characterized the physiochemical properties of TQ-NLC.
2. to determine the pharmacokinetics and biodistribution of TQ-NLC after oral and intravenous administration in healthy male Sprague Dawley rats.
3. to investigate the effects of TQ-NLC on spatial learning and memory, lipid profile and neurodegenerative features of the high fat-cholesterol diet-induced Alzheimer's disease rat model.
4. to determine the oxidative stress level and the effects of TQ-NLC on protein related to Aβ metabolism pathways in high fat-cholesterol diet-induced Alzheimer's disease rat model upon treatment with TQ-NLC.

1.3 Hypotheses

1. TQ-NLC will be absorbed and exhibit greater bioavailability when administered orally compared to the intravenous route. This study will provide the pharmacokinetics and biodistribution profile of TQ-NLC *in vivo.*
2. Treatment with TQ-NLC will improve memory decline observed in high fat-cholesterol diet-induced Alzheimer's disease rat model.
3. Treatment with TQNLC will reduce the lipid levels and decrease the neurodegenerative features in high fat-cholesterol diet-induced Alzheimer's disease rat model.
4. TQ-NLC will reduce the oxidative stress biomarkers level in the brain as well as regulate AD-related biomarker protein of hypercholesteremic rats.

1.4 Significant of study

Previously, the pharmacokinetics and biodistribution of TQ-NLC has yet to be studied. This research will be of great benefit in providing the pharmacokinetics and biodistribution profile of TQ-NLC *in vivo* to assist researcher for clinical use of this drug. The statistical number of people getting AD shows an alarming rate. In addition to the important of study related to common causes and symptoms of AD, the discovery of new treatments for management of AD are in need.

Since the need of therapies which is beneficial for the management of AD is in great demand, the results from this study may be helpful in discovering the potential application of TQ-NLC to manage the of pathophysiological signs of neurodegenerative diseases including AD. This study also helps to uncovered the potential link between hypercholesterolemia and risk of AD.

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