UNIVERSITI PUTRA MALAYSIA

NEUROPROTECTIVE EFFECTS OF THYMOQUINONE-RICH FRACTION AND THYMOQUINONE NANOEMULSIONS IN SPORADIC ALZHEIMER'S DISEASE RAT MODEL

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By

NORSHARINA BINTI ISMAIL

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

January 2019

This thesis is dedicated to

My parents
Allahyarham Ismail Ibrahim & Allahyarhamah Hamiyah Ismail

My brother and sisters
Ismanizami, Nor Radziah & Siti Munirah

My beloved
Ahmad Saifudin Nadin

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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Chairman : Maznah Ismail, PhD
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Increasing life expectancy has produced a dramatic rise in age-associated diseases including Alzheimer's disease (AD). Oxidative stress is one of the most vital risk factor which can potentially lead to the AD pathogenesis such as amyloid-β (Aβ) deposits. The existing treatment of AD only relies on the two types of drug, namely the acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonist. Due to the limitations of these existing drugs, new treatments and therapeutic strategies on AD management are emerging. Despite of the neuropharmacological attributes of *Nigella sativa* (black cumin seeds) and its active constituent, thymoquinone (TQ), limited records are available in relation to AD researches. Thus, the present study was conducted to investigate the neuroprotective effects of thymoquinone-rich fraction (TQRF) and TQ in sporadic AD models, and their underlying mechanistic actions. *In vitro* efficacy of TQRF and TQ was investigated against hydrogen peroxide (H_2O_2)-induced oxidative stress in human neuroblastoma SH-SY5Y cells through cell viability assay, reactive oxygen species (ROS) assay, morphological observation, and gene expression analysis. As a result, TQRF and TQ protected the cells against H_2O_2 toxicity by preserving the mitochondrial metabolic enzymes, reducing intracellular ROS levels, preserving morphology of cells and modulating the expression of antioxidants (SOD1, SOD2 and catalase), and apoptotic signaling (p53, AKT1, ERK1/2, p38 MAPK, JNK and NF-κβ) genes ($p < 0.05$). *In vivo* efficacy of TQRF and TQ was evaluated using a high fat-cholesterol diet (HFCD) model of sporadic AD. The oral bioavailability of poor water soluble TQRF and TQ were improved through nanotechnology approach in the form of nanoemulsion (NE), namely as TQRFNE and TQNE, respectively. The TQRF and TQ conventional emulsions (CE), named as TQRFCE and TQCE, respectively were studied for comparison. Statin (Simvastatin) and non-statin (Probucol) cholesterol-lowering agents, and AD drug (Donepezil) were served as control drugs. The Sprague Dawley rats were fed with HFCD for 6 months, and treated with the intervention groups daily for the last 3 months. The Morris Water Maze learning and memory test, and biochemical analyses (lipid profile, lipid

peroxidation, antioxidant and soluble amyloid-β (Aβ) levels were measured. The neuroprotective mechanistic actions of the intervention groups were determined through gene and protein expression levels. The HFCD-fed rats exhibited hypercholesterolaemia, accompanied by memory deficit, increment of lipid peroxidation and soluble Aβ levels, decrement of total antioxidant status and down-regulation of antioxidants genes expression levels ($p < 0.05$). Nevertheless, TQRFNE diminished those detrimental effects of HFCD through the modulation of Aβ generation (APP, BACE1, PSEN1 and PSEN2), Aβ degradation (IDE), Aβ transportation (LRP1 and RAGE), neuroinflammation genes (CRP, NOS1, TNF-α and PPARγ) ($p < 0.05$), and lessen the hippocampus injury. In conclusion, TQRF has potential to be developed as a nutraceutical product for the management of neurodegenerative diseases owing to oxidative stress including AD.

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

KESAN NEUROPROTEKTIF OLEH NANOEMULSI FRAKSI KAYA-TIMOKUINON DAN TIMOKUINON DALAM MODEL TIKUS PENYAKIT ALZHEIMER SPORADIS

Oleh

NORSHARINA BINTI ISMAIL

Januari 2019

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Peningkatan jangka hayat telah menghasilkan kenaikan dramatik dalam bilangan kes penyakit yang berkaitan dengan usia, termasuk penyakit Alzheimer (AD). Tekanan oksidatif adalah salah satu faktor risiko paling penting yang berpotensi menjurus kepada patogenesis AD seperti pembentukan amiloid-β (Aβ). Rawatan AD yang sedia ada hanya bergantung kepada dua jenis ubat, iaitu penghambat asetilkolinesterase dan antagonis reseptor N-methyl-D-aspartate. Disebabkan terdapat kekangan terhadap ubat sedia ada, rawatan dan terapeutik baru yang strategik bagi pengurusan AD sedang berkembang. Meskipun ciri-ciri farmakologi neuro *Nigella sativa* (biji jintan hitam) dan bahan aktifnya, timokuinon (TQ) telah diketahui, rekod adalah terhad berhubung dengan penyelidikan AD. Dengan itu, kajian ini dijalankan untuk mengkaji kesan perlindungan neuro fraksi kaya-timokuinon (TQRF) dan TQ pada model sporadis AD, dan yang mendasari tindakan mekanistiknya. Keberkesanan *in vitro* TQRF dan TQ telah dikaji terhadap hidrogen peroksida (H_2O_2) yang mengaruh tekanan oksidatif pada sel neuroblastoma manusia SH-SY5Y melalui asai kemandirian sel, asai spesis oksigen reaktif (ROS), pemerhatian morfologi, dan analisis ekspresi gen. Hasilnya, TQRF dan TQ melindungi sel-sel tersebut daripada ketoksikan H_2O_2 dengan memelihara enzim metabolik mitokondria, mengurangkan tahap ROS intraselular, memelihara morfologi sel dan memodulasi pengekspresan gen antioksidan (SOD1, SOD2 dan catalase), dan isyarat apoptosis (p53, AKT1, ERK1/2, p38 MAPK, JNK dan NF-κβ) ($p < 0.05$). Keberkesanan *in vivo* TQRF dan TQ telah dikaji menggunakan model sporadis AD yang tinggi diet lemak-kolesterol (HFCD). Kebolehserapan secara oral oleh TQRF dan TQ yang tidak larut air ditambahbaik melalui pendekatan nanoteknologi dalam bentuk nanoemulsi (NE), masing-masing dinamakan sebagai TQRFNE dan TQNE. Ejen penurunan kolesterol, statin (Simvastatin) dan bukan statin (Probucol), dan ubat AD (Donepezil) digunakan sebagai kumpulan ubat kawalan. Tikus Sprague Dawley diberi makan dengan HFCD selama 6 bulan, dan dirawat dengan kumpulan intervensi setiap hari untuk 3 bulan terakhir. Ujian pembelajaran dan ingatan Morris Water Maze, dan analisis biokimia (profil lipid, peroksidaan lipid, antioksidan dan kadar Aβ larut) diukur. Tindakan mekanisma perlindungan neuro kumpulan intervensi ditentukan

melalui pengekspresan paras gen dan protein. Tikus yang diberi makan HFCD menunjukkan paras kolesterol yang tinggi, disertai dengan kekurangan upaya mengingat, peningkatan peroksidaan lipid dan kadar Aβ larut, penurunan status antioksidan dan pengurangan tahap ekspresi gen antioksidan ($p < 0.05$). Walau bagaimanapun, TQRFNE mengurangkan kesan kerosakan oleh HFCD melalui pengawalaturan penghasilan Aβ (APP, BACE1, PSEN1 dan PSEN2), degradasi Aβ (IDE), pengangkutan Aβ (LRP1 dan RAGE), gen keradangan neuro (CRP, NOS1, TNF-α dan PPARγ) ($p < 0.05$), dan mengurangkan kecederaan hipokampus. Sebagai kesimpulan, TQRF mempunyai potensi untuk dibangunkan sebagai produk nutraseutikal bagi pengurusan penyakit neurodegeneratif akibat tekanan oksidatif termasuk AD.

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

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24S-OHC	24S-hydroxycholesterol
27-OHC	27-hydroxycholesterol
$ABTS^{2-}$	2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)
AD	Alzheimer's disease
ANOVA	One-way analysis of variance
AO	Acridine orange
ApoE	Apolipoprotein E
APP	Amyloid-β precursor protein
Aβ	Amyloid-β
$Aβ_{1-40}$	Amyloid-β fragment length 1-40
$Aβ_{1-42}$	Amyloid-β fragment length 1-42
$Aβ_{25-35}$	Amyloid-β fragment length 25-35
BACE1	β-secretase APP-cleaving enzyme-1
BBB	Blood brain barrier
BHT	Butylated hydroxytoluene
cDNA	Complementary DNA
CE	Conventional emulsion
CEMSS	Lymphoblastic leukemia
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DCFH-DA	2′,7′ dichlorofluorescin diacetate
DG	Dentate gyrus
DLS	Dynamic light scattering
DMEM-F12	Dulbecco's minimum essential Eagle's medium-Ham's nutrient mixture F-12
ELISA	Enzyme-linked immunosorbent assay
FAD	Familial AD
GPx	Glutathione peroxidase
H_2O_2	Hydrogen peroxide
HDL	High density lipoprotein
HFCD	High fat-cholesterol diet
HFD	High fat diet
HL60	Promyelocytic leukemia
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase

HT29	Colon cancer
IDE	Insulin degrading enzyme
JNK	c-Jun N-terminal kinase
LDL	Low-density lipoprotein
LRP1	Low density lipoprotein receptor-related protein 1
LXR	Liver X receptor
MAPK	Mitogen-activated protein kinases
MDA	Malondialdehyde
ME	Microemulsions
$MgCl_2$	Magnesium chloride
MnSOD	Manganese superoxide dismutase
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide
MWM	Morris water maze
N. sativa	*Nigella sativa* Linn
NE	Nanoemulsion
NF-κB	Nuclear factor-κB
NFTs	Neurofibrillary tangles
NMDA	N-methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
O_2^-	Superoxide
PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
PDI	Polydispersity index
PI	Propidium iodide
PSEN1	Presenilin 1
PSEN2	Presenilin 2
RAGE	Receptor for advanced glycation end products
ROS	Reactive oxygen species
RT	Reverse transcription
SAD	Sporadic AD
SFE	Supercritical fluid carbon dioxide extraction
SGD	Serum/glucose deprivation
SLN	Solid lipid nanoparticles
SOD	Superoxide dismutase

TBA	Thiobarbituric acid
TC	Total cholesterol
TCA	Trichloroacetic acid
TGF-β	Transforming growth factor-β
TGs	Triglycerides
TMP	Tetramethoxypropane
TNF-α	Tumor necrosis factor-α
TQ	Thymoquinone
TQCE	Thymoquinone conventional emulsion
TQNE	Thymoquinone nanoemulsion
TQRF	Thymoquinone-rich fraction
TQRFCE	Thymoquinone-rich fraction conventional emulsion
TQRFNE	Thymoquinone-rich fraction nanoemulsion
Triolein	Glycerol trioleate
TrioNE	Triolein nanoemulsion

CHAPTER 1

INTRODUCTION

With an increase in lifespan due to better healthcare and changing population demographics, the incidence of neurodegenerative diseases including dementia is expected to increase significantly in the 21st century (Alzheimer's Association, 2017). It is a disease that develops when nerve cells (neurons) in the brain die or no longer function normally. The death or malfunction of these neurons causes memory loss, behavioral changes and inability to think clearly. An estimated 47 million people worldwide are living with dementia in 2015 (Prince *et al.,* 2015), and this number is projected to triple by 2050 (Prince *et al.,* 2013). In the absence of a disease-modifying treatment or cure, reducing the risk of developing dementia takes on added importance. Even when effective treatments become available, risk reduction will likely remain a fundamental strategy in reducing the number of individuals affected. As for many non-communicable diseases with available treatments (such as diabetes, cancer, and heart disease), risk reduction efforts remain a major component of the campaigns against these diseases (Baumgart *et al.,* 2015).

Alzheimer's disease (AD) is the most common type of dementia, which accounts for 60% to 80% of the cases (Burns and Iliffe, 2009). It is a chronic brain disorder characterized by cognitive impairment, oxidative stress, inflammation, vascular damage, and deposition of amyloid-beta (Aβ) and tau proteins (Ullrich *et al.,* 2010). In AD, these brain changes eventually impair an individual's ability to carry out such basic bodily functions as walking and swallowing (Alzheimer's Association, 2012). Caring for a patient with AD or other dementias poses special challenges as these individuals require increased levels of supervision and personal care. In consequence, the caregivers are experiencing high levels of stress and negative effects on their health, employment, income and financial security (Monin and Schulz, 2009).

Studies indicate that people 65 and older survive an average of four to eight years after a diagnosis of AD, yet some live as long as 20 years with Alzheimer's (Ganguli *et al.,* 2005). This indicates the slow, insidious nature of the progression of Alzheimer's. On average, a person with Alzheimer's will spend more in the most severe stage of the disease than in any other stage (Arrighi *et al.,* 2010). To date, no treatment is available to slow or stop AD progression. The existing five drugs approved by the U.S. Food and Drug Administration had only temporarily improve symptoms, in which their effectiveness varies across the population. None of the treatments available today alters the underlying course of this terminal disease (Alzheimer's Association 2012).

Notably, there is 5% of early onset or familial AD (FAD) caused by mutations in amyloid-β precursor protein (APP) or presenilin 1 or 2 (PSEN1, PSEN2). Up to date, the molecular mechanism of FAD pathology appears to be well understood and numerous transgenic animal models are available. However, another 95% of AD occurrence is categorized under late onset or sporadic AD (SAD) and still limited studies available. Thus, expanding the view on SAD and searching for other possible

causes of the disease that are responsible for its onset are necessary. Recent studies have shown that high cholesterol (i.e. hypercholesterolemia) levels are linked to the pathology of SAD and the accumulation of Aβ, oxidative stress, declined spatial memory, inflammation and induced blood brain barrier (BBB) leakage (Freeman *et al.,* 2014). In line with that, human studies found that statin can reduce the risk of developing AD through several possible mechanisms such as reducing the cholesterol level, thus reducing the production of Aβ, and act as antioxidant and anti-inflammation (Prasanthi *et al.,* 2008; Ehrlich and Humpel, 2012). Nevertheless, more studies are needed to find alternatives for statin from natural products that could have lesser side effects.

The potential of bioactives from natural products for the prevention and treatment of AD are supported by various studies involving diverse mechanisms (i.e inhibition of Aβ accumulation, antioxidant, anti-apoptotic and anti-inflammation). In the current study, the thymoquinone rich fraction (TQRF) extracted from *Nigella sativa* seed is selected as the main ingredient in the proposed nutraceutical product/ drug alternative targeting on the management of AD. *In vitro* study on anti-inflammatory effects of thymol and different quinones (dithymoquinone, thymoquinone and thymohydroquinone) from *N. sativa* suggests that these compounds participate in the general anti-inflammatory activity (Marisk *et al.,* 2005; Mc Namara *et al.,* 2005).

However, delivery of bioactives to the brain still remains highly challenging for the treatment of AD. The development of new practical treatment modalities for the treatment of AD is currently a highly active area of research. The lipid-based nanoemulsion approach has attracted wide attention as a means to improve oral bioavailability of poorly water-soluble bioactives and delivery to the target site. The bioactives can be loaded into the inner phase of these delivery systems and bypassing the enzymes in the gastrointestinal tract and reducing the presystemic clearance and hepatic first-pass metabolism (Chhabra *et al.,* 2011). Due to higher bioactive solubilization capacity, better thermodynamic stability, long self-life, rapid onset of action, and reduced intersubject variability, nanoemulsion becomes a promising technology to achieve optimum targeted drug delivery (Mustafa *et al.,* 2009). Since nanoemulsion is formulated with surfactants, which are approved for human consumption (generally regarded as safe), they can be taken orally.

The general objective of this study was to investigate the neuroprotective effects of thymoquinone-rich fraction (TQRF) and thymoquinone (TQ) nanoemulsions in Sporadic Alzheimer's disease models, and their underlying mechanistic actions.

The specific objectives were:

1. To determine the neuroprotective effects of TQRF and TQ against hydrogen peroxide-induced oxidative stress in differentiated human neuroblastoma SH-SY5Y cell line.

2. To evaluate the neuroprotective effects of TQRF and TQ nanoemulsions on memory deficit, antioxidants genes expression and soluble Aβ levels in high fat-cholesterol diet-induced rat model of Sporadic Alzheimer's disease.

3. To describe the neuroprotective mechanistic actions of TQRF and TQ nanoemulsions on Aβ generation, degradation, transportation and clearance in high fat-cholesterol diet-induced rat model of Sporadic Alzheimer's disease.

4. To assess the neuroprotective mechanistic actions of TQRF and TQ nanoemulsions on neuroinflammation genes and histological changes in high fat-cholesterol diet-induced rat model of Sporadic Alzheimer's disease.

It was hypothesized that:

1. The TQRF and TQ will exhibit the neuroprotective effects against hydrogen peroxide-induced oxidative stress in differentiated human neuroblastoma SH-SY5Y cells.

2. The TQRF and TQ nanoemulsions will reduce the memory deficit and soluble Aβ levels, and increase the expression of antioxidants genes in high fat-cholesterol diet-induced rat model of Sporadic Alzheimer's disease.

3. The TQRF and TQ nanoemulsions will modulate the Aβ generation, degradation, transportation and clearance in high fat-cholesterol diet-induced rat model of Sporadic Alzheimer's disease.

4. The TQRF and TQ nanoemulsions will regulate the neuroinflammation genes and lessen the histological damage in high fat-cholesterol diet-induced rat model of Sporadic Alzheimer's disease.

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