UNIVERSITI PUTRA MALAYSIA

ANTIMIGRAINE ACTIVITY OF *Ficus deltoidea* JACK AQUEOUS EXTRACT IN MICE AND ITS POSSIBLE MECHANISMS

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By

SAFURAA BINTI SALIHAN

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

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Dedicated to my parents.
My mother, Fatimah Abd Majid
My late father, Salihan Juraimin (1947-2014)

Abah, I made it

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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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SAFURAA BINTI SALIHAN

January 2020

Chairman : Associate Prof. Mohamad Aris Mohd. Moklas. PhD
Faculty : Medicine and Health Sciences

Migraine is a disabling headache disorder characterized by throbbing headache and associated with various symptoms namely nausea, vomiting and heightened sensitivity to touch and smell. *Ficus deltoidea* is an herbaceous plant used traditionally in treating pain and headache. As phytomedicine produce alternative therapeutic strategies for migraine pain, the aim of this study is to evaluate the antimigraine properties of *Ficus deltoidea* (var Trengganuensis) aqueous extract (FDA) and its possible mechanisms. In nonspecific antimigraine study, using animal model of nociception, administration of FDA produced significant antinociceptive effect in acetic acid-induced abdominal writhing test, early and late phase of formalin test and in the hot plate test. In specific antimigraine study, nitroglycerin (NTG)-induced migraine model was used. It is the most studied and well accepted model in antimigraine drug testing. Preliminary tests were done verifying and optimizing the use of this model. The effect of FDA was tested in NTG-induced hyperalgesia using formalin and hot plate test. It was found that FDA produced significant inhibition in both early and late phase of formalin test and significant increase in respond latency in hot plate test. In addition, treatment with FDA significantly reduced the NTG-induced c-fos expression in trigeminal nucleus caudalis (TNC), a relay center in migraine. This study also explored the mechanism of FDA through peripheral and central sensitization, and involvement of serotonergic and dopaminergic pathways. The involvement of FDA in peripheral sensitization was done using kainic acid-induced hyperalgesia in hot plate test, showing significant increase in response latency in group receiving FDA compared to control. In study of central sensitization, using NTG-induced mechanical allodynia in von Frey test, FDA group produced significant improvement in paw withdrawal threshold compared to control. Studies on serotonergic and dopaminergic systems involvement was done by studying the effect of FDA on 5-hydroxytryptophan(l-5-HTP)-induced serotonin syndrome and apomorphine-induced climbing behavior. Results showed FDA significantly inhibited l-5-HTP-induced serotonin syndrome and apomorphine-induced climbing activity. In addition, FDA significantly inhibited NTG induced plasma

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CGRP using ELISA. These findings suggested that FDA possessed antimigraine activity through inhibition of peripheral and central sensitization with possibility of involvement of dopaminergic and serotonergic mechanism and CGRP inhibition.

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

AKTIVITI ANTIMIGRAIN DARI SEBATIAN AKUEUS *Ficus deltoidea* JACK DALAM MENCIT DAN MEKANISMANYA

Oleh

SAFURAA BINTI SALIHAN

Januari 2020

Pengerusi : Profesor Madya Mohamad Aris Mohd. Moklas, PhD
Fakulti : Perubatan dan Sains Kesihatan

Migrain merupakan penyakit sakit kepala dicirikan oleh sakit kepala berdenyut dan dikaitkan dengan pelbagai simtom seperti loya, muntah, dan peningkatan tahap pemekaan terhadap deria bau dan sentuhan. *Ficus deltoidea* merupakan tumbuhan herba yang digunakan secara tradisional untuk merawat kesakitan dan sakit kepala. Oleh kerana fitoubatan digunakan sebagai strategi terapeutik alternatif untuk sakit migrain, tujuan kajian ini adalah untuk mengkaji sifat anti-migrain ekstrak aqueus *Ficus deltoidea (var Trengganuensis)* (FDA). Dalam kajian ini, model migrain diaruh nitroglycerin (NTG) digunakan. Ianya merupakan model anti-migrain yang paling banyak digunakan dan diterima untuk ujian ubat-ubatan. Dalam kajian ini, ujian awal telah dijalankan bagi mengesahkan penggunaan model ini. NTG (10mg/kg, secara intraperitoneal (i.p.)) berupaya secara signifikan mengaruh hiperalgesia dan ekspresi c-fos di nukleus trigeminal kaudalis (TNC), iaitu pusat geganti dalam migrain. Aktiviti anti-migrain FDA telah dikaji untuk kesan khusus dan tidak khusus. Dalam kajian kesan tidak khusus anti-migrain, pemberian FDA (50, 100, dan 200 mg/kg, i.p.) menghasilkan kesan anti-nosiseptif signifikan di dalam ujian penggeliutan abdomen diaruh asid asetik dan fasa lewat ujian formalin. Dalam fasa awal ujian formalin dan ujian plet panas, FDA menghasilkan kesan anti-nosiseptif signifikan berbanding kumpulan kawalan. Dalam kajian spesifik anti-migrain, kesan FDA diuji dalam hiperalgesia diaruh NTG menggunakan ujian formalin. FDA menghasilkan perencatan signifikan dalam fasa awal dan lewat. Dalam hiperalgesia diaruh NTG menggunakan ujian plet panas, pemberian FDA (memanjangkan tempoh pendaman secara signifikan terhadap rangsangan haba. Tambahan, pemberian FDA mengurangkan ekspresi c-fos diaruh NTG dalam TNC secara signifikan. Kajian ini juga menyelidik penglibatan FDA melalui pemekaan pusat dan periferi dan mekanisme terlibat, serta penglibatan laluan serotonergik dan dopaminergik. Penglibatan FDA dalam pemekaan periferi diuji menggunakan hiperalgesia diaruh asid kainic dalam ujian plet panas, menujukkan pemanjangan tempoh pendaman secara signifikan dalam kumpulan yang menerima FDA berbanding kumpulan kawalan. Dalam kajian pemekaan pusat,

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menggunakan ‘allodynia’ mekanikal diaruh NTG dalam ujian von Frey, kumpulan menerima FDA menghasilkan pembaikan yang signifikan dalam nilai ambang penarikan tapak kaki berbanding kumpulan kawalan. Kajian ke atas penglibatan sistem serotonergik dan dopaminergik dilakukan dengan mengkaji kesan FDA ke atas sindrom serotonin diaruh 5-hydroxytryptophan dan kelakuan memanjat diaruh apomorfin. Keputusan menunjukkan FDA merencat secara signifikan aktiviti memanjat diaruh apomorfin dan sindrom serotonin diaruh 5-hydroxytryptophan. Tambahan pula, FDA telah secara signifikan merencat kadar CGRP plasma diaruh NTG yang dikaji menggunakan sistem ELISA. Dapatan ini mencadangkan FDA memiliki aktiviti anti-migrain melalui perencatan pusat dan periferi serta kemungkinan penglibatan mekanisme serotonergik, dopaminergik dan perencatan CGRP.

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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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LIST OF ABBREVIATIONS

5HIAA	5-hydroxyindoleacetic acid
5HT	Serotonin
AC	Adenylyl cyclase
ASA	Aspirin/acetylsalic acid
BBB	Blood brain barrier
Ca^{2+}	Calcium ion
cAMP	Cyclical adenosine 3', 5'-monophosphate
cGMP	Cyclical guanosine 3', 5'-monophosphate
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
COX	Cyclooxygenase
CSD	Cortical spreading depression
CSF	Cerebrospinal fluid
DA	Dopamine
DR	Dopamine receptor
EC	Enterochromaffin cells
FD	*Ficus deltoidea*
FDA	Aqueous extract of Ficus deltoidea var trengganuensis
IHS	International Headache Society
HRP	Horseradish peroxidase
K^+	Potassium ion
m-CPP	m-chlorophenylpiperazine
MOA-A	Monoamine oxidase A isoform

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MOR	Morphine
NaCl	Sodium Chloride
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drug
NTG	Nitroglycerin
PET	Positron emission tomography
PGE2	Prostaglandin E2
Po	Posterior thalamic nucleus
PVDF	Polyvinylidene difluoride
PWT	Paw withdrawal threshold
SDS	Sodium dodecyl sulfate
SP	Substance P
SUMA	Sumatriptan
TBST 20	Tris-buffered saline and tween 20
TCC	Trigeminocervical complex
TGVS	Trigeminovascular system
TNC	Trigeminal nucleus caudalis
TPH	Tryptophan hydroxylase
TRPV 1	Transient receptor potential vanilloid 1
VPM	Ventroposteromedial thalamic nucleus
VTA	Ventral tegmental area
YLD	Years lived with disability

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Migraine is defined as disorder of neurological system that is manifests by a unilateral headache, associated with various symptoms namely heightened sensitivity to light (photophobia), sound (phonophobia) and touch (allodynia) (Olesen, 2018). An attack of migraine may begin way before the onset of headache, termed as premonitory phase (Giffin et al., 2003), where migraineurs reported to experience autonomic, affective, and cognitive symptoms (e.g. yawning, nausea and reduced concentration). The attacks can be preceded by aura, termed as migraine aura; or migraine without aura. Migraine with aura was reported in about 30.3% of migraineurs, by which there are changes in cortical excitability that occurred just before the headache phase (Rasmussen et al., 1992). As the headache subsided, migraineurs reported to have tiredness and weakness, termed as postdrome phase (Giffin et al., 2016). The various symptoms present in all phases of migraine suggest the complexity of migraine pathophysiology involving multiple brain area (Borsook et al., 2012). Despite so, there is no known cause of migraine that is uniform for all patients. Although there are several theories on pathogenesis of migraine developed along the years, however, none of these hypotheses able to explain all occurring clinical symptoms in a migraineurs.

Headache disorders, including migraine, are among the most prevalent disorders worldwide (Stovner et al., 2007). In 2016, approximately one billion of individuals was estimated to have migraine, making it one of the most prevalent medical disorders (Stovner et al., 2018). Migraineurs suffered loss of work time and significant reduction in daily activity, making it the sixth highest cause of disability worldwide (Vos et al., 2015). The disability caused will not just burden the patient themselves, but also their families, friends, employers and society. Pharmacological management of migraine is divided into prophylactic and acute abortive medications. An abortive medication is taken when the attack arises to treat the symptoms. It can be divided into non-specific antipain medication such as a nonsteroidal anti-inflammatory drug (NSAID) and opioid; and specific antimigraine medication such as triptans and ergot derivatives. Most of available drugs can only provide temporary alleviation of symptoms, but do not resolve the underlying problem.

The relationship between mankind and plants proven to exists along the development of human themselves (Petrovska, 2012). Human initially consumed plants in their diet and along the way, discovered its medicinal properties. The oldest written evidence on usage of medicinal plant was found from 5000 BC, written on Sumerian clay plate in Nippur (Santic et al., 2017). The application of plants by human as medicine can be defined as ethnomedicine or ethnobotanic medicine (Farnsworth, 1994). The applications are known to be advantageous,

particularly as medicine based on its long-term use by humans. It was estimated that there are about 250,000 plant species on this planet, by which less than 10% screened for possible biological activity. Among these, approximately 15% of it evaluated for its phytochemical activity (Verpoorte, 2000). The reason being is due to matter of approach to find leads in evaluating a particular plants species in comparison to another species (Fabricant et al., 2001). Based on a survey done in Traditional Medicine Centers under WHO supervision, it was found that 80% of a total of 122 pure compounds derived from plants used for its related ethnomedical purposes (Farnsworth et al., 1985).

Malaysia is one of the tropical rainforest countries known for its rich abundance of traditional medicine and herbal plants. *Ficus deltoidea* is one of such plants that is widely used in in Malaysia to treat wound, sores, toothaches and headache (Sulaiman et al., 2008). Locally, it is known as 'mas cotek', 'telinga beruk' or 'serapat angin'. Studies has been done to confirm the application of this herb as anti-inflammatory (Abdullah, Hussain, Ismail, et al., 2009), antidiabetic (Adam et al., 2010), antiulcerogenic (Fatimah et al., 2009) and antioxidant (Omar et al., 2011) remedies.

1.2 Problem Statement

Worldwide, migraine was ranked 6th in causes of years lived with disability (YLD). The burden caused by migraine does not just affect its sufferers alone, but also resulted in significant negative impacts on their surroundings, including family and friends, as well as the society. An attack of migraine can also be very severe that its sufferers will have a fear of the next attack. It was reported that depression and anxiety disorders is more common in migraineurs as compared to healthy individuals (Swanson et al., 2013). Despite its marked prevalence and significant burden, the treatment option for migraine is still limited. Between 1990 and 2016, there was an increase in YLD in concomitant to population growth worldwide. However, the age standardized YLD rates for headache remain unchanged. This suggest a persistent cause of headache, ineffective improvement of headache treatments or its poor availability of the treatment worldwide (Organization, 2011). Furthermore, despite the options in pharmacological approach in treating migraine, 35% of patients were considered as nonresponders to current therapies (Lipton et al., 1999). As for the responders, current medications are still limited due to its side effects and contraindication in certain comorbidities. Therefore, this study is to evaluate antimigraine activity of *Ficus deltoidea* var Trengganuensis as an alternative therapy for migraineurs, by which has also been commonly used by old folks in managing pain including headache, and its possible mechanisms.

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1.3 Significance of the study

The output from this study will provide a new approach in managing pain, specifically migraine, conforming the folkloric use of *Ficus deltoidea*. Natural product as an alternative medicine are generally safer for consumption and cheaper compared to commercialized drug.

1.4 Hypothesis

The hypothesis of the study is that *Ficus deltoidea* var Trengganuensis possess antimigraine activity in nitroglycerin-induced animal model of migraine. *Ficus deltoidea* is hypothesized to act through peripheral and central sensitization of nervous system with the involvement in serotonergic and dopaminergic pathways.

1.5 Objectives

General objective of the study is to evaluate the antimigraine property of *Ficus deltoidea* var Trengganuensis aqueous extract and its possible mechanism underlying its activity.

The specific objectives are:

1. To evaluate the endpoints in nitroglycerin-induced animal model of migraine; nitroglycerin-induced hyperalgesia and c-fos expression
2. To investigate the non-specific antimigraine activity of FDA through animal model of nociception, and specific antimigraine and specific antimigraine activity through nitroglycerin-induced animal model of migraine.
3. To investigate the involvement of *Ficus deltoidea* aqueous extract in peripheral through kainic acid induced hyperalgesia and central sensitization through nitroglycerin-induced allodynia
4. To investigate the involvement of *Ficus deltoidea* aqueous extract in l-5-HTP-induced serotonin syndrome and apomorphine-induced climbing activity, and in CGRP expression induced by nitroglycerin.

To achieve the objectives, this study is divided into three phases; Phase I – concentrated on optimization of animal model of migraine; Phase II – evaluation of antimigraine activity of *ficus deltoidea extract* which was divided into specific and non-specific antimigraine activity; Phase III – elucidation of mechanism on antimigraine activity (Refer Figure 1.1).

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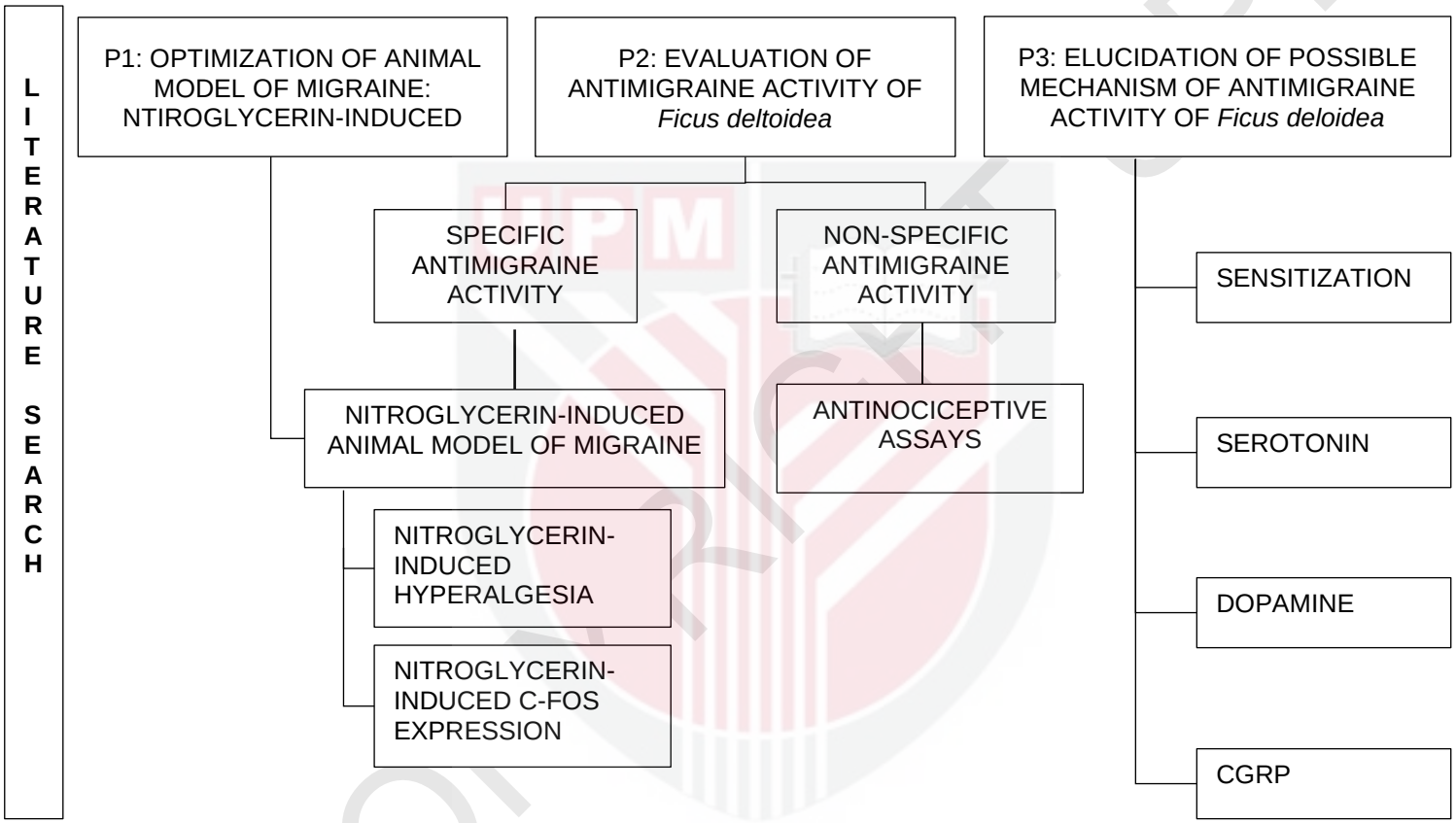

Figure 1.1: Study Design. (P1 = Phase I; P2 = Phase II; P3 = Phase III)

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BIODATA OF STUDENT

My name is Safuraa binti Salihan, was born on 30th July 1986 in Kuala Lumpur. I started my primary school in 1993 at Sekolah Kebangsaan Kajang, Selangor and continued to secondary school in Sekolah Kebangsaan Sultan Abdul Aziz Shah. After rewarded with 9 A's in my PMR, I continued my secondary school study in Sekolah Menengah Agama Maahad Hamidiah Kajang and obtained 7As and 4Bs in my SPM. In pre-university level, I continued my study in Pusat Asasi Sains Universiti Malaya and completed the study with CGPA 3.9. With the result, I entered Universiti Putra Malaysia in Doctor of Medicine, and graduated successfully in 2010. I worked as a house officer in Hospital Tunku Jaafar Seremban and continued as a medical officer there before transferring to Hospital Kajang. In 2015, I started my postgraduate study in Master of Science (Physiology) and managed to convert to Doctor of Philosophy level in 2016.

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PUBLICATIONS

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