UNIVERSITI PUTRA MALAYSIA

ANTIOXIDANT PROPERTIES OF Morinda citrifolia L. AND THEIR EFFECTS ON HAEMOSTASIS PARAMETERS

MOHD ARIF BIN ABDUL KARIM

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By

MOHD ARIF BIN ABDUL KARIM

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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Hadith related by Ibn-Abbas; the Prophet (s) said,

"Grab five things before five others: your youth before your decrepitude, your health before your illness, your wealth before your poverty, your leisure before your work, and your life before your death." (al-Hakim in al-Mustadrak)

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

ANTIOXIDANT PROPERTIES OF *Morinda citrifolia* L. AND THEIR EFFECTS ON HAEMOSTASIS PARAMETERS

By

MOHD ARIF BIN ABDUL KARIM

June 2014

Chairman : Sabariah Md Noor, MD, MPath

Faculty : Medicine and Health Sciences

This study aims to determine the antioxidant properties of *Morinda citrifolia (M. citrifolia)* fruit crude extracts and its effects on the blood haemostasis parameters. Extracts used in this study were *M. citrifolia* fruit crude aqueous and ethanolic extracts (MFCAE and MFCEE). 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging and β-carotene bleaching assay were conducted to determine antioxidant activity. Ascorbic acid (ASA) and butylated hydroxytoluene (BHT) were used as standard antioxidants. Total phenolic content was determined spectrometrically according to the Folin-Ciocalteu's method and expressed as Gallic acid equivalent (GAE). The effects on blood haemostasis parameters were determined by using *in vitro* and *in vivo* models. *In vitro* model was done by determination the effect on haemostasis tests which include prothrombin time (PT), activated partial thrombosplastin time (APTT), and platelet aggregation tests where the human blood samples were treated with different concentrations (10, 20, 30, 40, 50mg/mL) of MFCAE and MFCEE. Blood collected from 58 respondents were prepared to obtain platelet rich plasma (PRP) and platelet poor plasma (PPP) for coagulation (PT, APTT), and platelet aggregation test respectively. In *in vivo* model, 48 Sprague Dawley rats were treated with different dosage (7.5, 75, 750mg/kg) of MFCAE. Their blood samples were subjected for

haemostasis parameter tests which include full blood count, PT, APTT, platelet aggregation, and bleeding time. The highest percentage of inhibition by MFCAE against DPPH radicals was 27.21 ± 1.24%, 61.78 % lower when compared to ASA. β-carotene bleaching assay showed the percentage of antioxidant activity of MFCAE was 78.96%, 13.6% lower than BHT. Total phenolic content of MFCAE was 281.83 ± 14.78mg GAE/100g. *In vitro* model showed that MFCAE and MFCEE were significantly prolonged the PT and APTT in dose dependant manner. The highest measureable value was at the concentration of 40mg/mL. The highest PT and APTT were 55.97 ± 14.54 and 114.74 ± 11.53 seconds for MFCAE; and 58.27 ± 15.69 and 118.03 ± 10.18 seconds respectively for MFCEE. However this anticoagulant property for the *in vivo* model was not significantly observed as *in vitro* model. MFCAE exhibits some antiplatelet activity in both *in vitro* and *in vivo* model. This study showed MFCAE contains some antiplatelet activity with dose dependant manner when collagen was used as an agonist. Briefly, the findings suggest that *M. citrifolia* extracts may become a potential plant based anticoagulant and antiplatelet which should be effective and safe for patients with cardiovascular disorders. The presence of total phenolic in the extract may be partly responsible for the observed effects.

Abstrak tesis yang dikemukakan kepada Senat Universti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

SIFAT ANTIOKSIDAN *Morinda citrifolia* L. DAN KESANNYA KE ATAS PARAMETER HAEMOSTASIS

Oleh

MOHD ARIF BIN ABDUL KARIM

Jun 2014

Pengerusi : Sabariah Md Noor, MD, MPath

Fakulti : Perubatan dan Sains Kesihatan

Kajian ini bertujuan untuk menilai ciri-ciri antioksidan ekstrak buah *Morinda citrifolia (M. citrifolia)* dan kesannya terhadap parameter haemostasis darah. Ekstrak digunakan dalam kajian ini ialah ekstrak akueus dan etanolik mentah buah *M. citrifolia* (MFCAE dan MFCEE). Ujian radikal bebas yang stabil 2,2-difenil-1-pikril hidrazil (DPPH) dan ujian pelunturan β-karotena telah dijalankan untuk menentukan aktiviti antioksidan. Asid askorbik (ASA) dan hidroksi toluena dibutilkan (BHT) telah digunakan sebagai antioksidan piawai. Jumlah kandungan fenol ditentukan secara spektrometrik mengikut kaedah Folin-Ciocalteu dan diekspresikan sebagai Asid galik setara (GAE). Kesan ke atas parameter haemostasis darah ditentukan dengan menggunakan model *in vitro* dan *in vivo.* Dalam model *in vitro*, penentuan kesan terhadap ujian haemostasis seperti masa protrombin (PT), masa tromboplastin separa teraktif (APTT), dan ujian pengagregatan platelet telah dilakukan di mana sampel darah manusia dirawat dengan MFCAE dan MFCEE yang berlainan kepekatan (10, 20, 30, 40, 50mg/mL). Darah yang diambil daripada 58 orang responden telah diproses untuk mendapatkan platelet kaya plasma (PRP) bagi ujian koagulasi (PT, APTT), dan platelet kurang plasma (PPP) bagi ujian pengagregatan platelet. Dalam model *in vivo*, 48 ekor tikus Sprague Dawley telah dirawat dengan MFCAE yang berlainan dos (7.5, 75, 750mg/kg). Sampel darah tikus terbabit telah diuji untuk menilai kiraan darah lengkap, PT, APTT, pengagregatan

platelet dan masa pendarahan. Peratusan perencatan tertinggi bagi MFCAE daripada radikal DPPH adalah 27.21 ± 1.24 %, 61.78 % lebih rendah jika dibandingkan dengan ASA. Ujian pelunturan β-karotena menunjukkan peratusan aktiviti antioksidan MFCAE adalah 78.96 % , 13.6 % lebih rendah daripada peratusan dicatat BHT. Hasil kandungan jumlah fenol adalah 281.83 ± 14.78mg GAE/100g. Model *in vitro* menunjukkan bahawa MFCAE dan MFCEE dengan ketara melanjutkan tempoh PT dan APTT. Nilai tertinggi yang dapat dicatat adalah pada kepekatan 40mg/mL. Nilai tertinggi PT dan APTT masing-masing adalah 55.97 ± 14.54 and 114.74 ± 11.53 saat bagi MFCAE; dan 58.27 ± 15.69 and 118.03 ± 10.18 saat bagi MFCEE. Namun begitu, kesan antikogulan dalam model *in vivo* tidak menunjukkan kesan yang signifikan seperti model *in vitro*. MFCAE mengandungi sedikit aktiviti antiplatelet bagi kedua-dua model *in vitro* dan *in vivo*. MFCAE menunjukkan sedikit antiplatelet aktiviti apabila kolagen digunakan sebagai agonis. Secara ringkasnya, kajian menunjukkan bahawa ekstrak *M. citrifolia* mempunyai potensi sebagai antikoagulan dan antiplatelet berasaskan tumbuhan yang seharusnya berkesan dan selamat untuk pesakit jantung. Kehadiran sejumlah fenol dalam ekstrak berkemungkinan bertanggungjawab untuk kesan seperti diperhatikan.

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I certify that a Thesis Examination Committee has met on 9 June 2014 to conduct the final examination of Mohd Arif Bin Abdul Karim on his thesis entitled **"Antioxidant Properties of *Morinda citrifolia* L. and Their Effects on Haemostasis Parameters"** in accordance with the Universities and University College Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

Asmah binti Rahmat, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Norhaizan binti Mohd Esa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Norhafizah binti Mohtarrudin, PhD
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Ainoon Othman, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Sains Islam Malaysia
(External Examiner)

_____

NORITAH OMAR, PhD
Assoc. Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 21 July 2014

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Sabariah Md Noor, MD, MPath
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Zainina Seman, MD, MPath
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Eusni Rahayu Mohd Tohit, MBBS, MPath
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Faridah Idris, MBBS, MPath
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

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This is to inform that:

- the research conducted and the writing of this thesis was under our supervision;
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Signature: _____	Signature: _____
Name of Chairman of Supervisory Committee: Sabariah Md Noor, MD, MPath	Name of Member of Supervisory Committee: Zainina Seman, MD, MPath
Signature: _____	Signature: _____
Name of Member of Supervisory Committee: Eusni Rahayu Mohd Tohit, MBBS, MPath	Name of Member of Supervisory Committee: Faridah Idris, MBBS, MPath

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADP	adenosine diphosphate
AF	atrial fibrillation
APTT	activated partial thromboplastin time
BHT	butylated hydroxyl toluene
BT	bleeding time
CAD	coronary artery disease
CVDs	cardiovascular diseases
DPPH	2,2-diphenyl-1-picrylhydrazyl
ET	electron transfer
FBC	full blood count
FRAP	ferric reducing antioxidant power
GAE	gallic acid equivalent
HAT	hydrogen atom transfer
Hb	haemoglobin
Hct	haematocrit
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MI	myocardial infarction
MOH	Ministry of Health
NO	nitric oxide
ORAC	oxygen radical absorbance capacity
PAI	plasminogen activator inhibitor
PAR	protease-activating protein

PPP	platelet poor plasma
PRP	platelet rich plasma
PGI_2	prostacyclin
PT	prothrombin time
RBC	red blood cell
RNS	reactive nitrogen species
ROS	reactive oxygen
TF	tissue factor
TIA	transient ischemic attack
t-PA	tissue-type plasminogen activator
TPC	total phenolic content
TxA_2	thromboxane
vWF	von Willebrand factor
WBC	white blood cell
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

The uses of alternative medicine based on herbal formulations and medicinal plant extracts have been growing rapidly throughout the world. Green plants synthesize and preserve a various biochemical constituents. Several secondary metabolites of plant are commercially important and used in a number of pharmaceutical compounds (Joy et al., 2001). The chemical constituents of the medicinal plants such as polyphenols and flavonoids are found to have curative effect against several diseases and illness (Vickers and Cassileth, 2001). Tropical fruits are rich in antioxidants properties such as polyphenols, vitamins and carotenoids (Corral-Aguayo et al., 2008).

Phenolics compounds can be categorized into simple phenols, phenolic acids, hydroxycinnamic acid derivatives and flavonoids. Studies show that consumption of antioxidant-phenolic compounds does have benefits in prevention of chronic disease such as cancer, diabetes and cardiovascular disease (CVDs) (Sherman and Billing, 1999). *Morinda citrifolia* Linn. (*M. citrifolia*) has been considered as a potential medicine CVDs where it has being used for hypertension, atherosclerosis and dyslipidemia (Mandukhail et al., 2010).

The haemostatic system is a complex cascade of events. It consists of six major components like platelet, vascular endothelium, procoagulant plasma protein factors, natural anticoagulant proteins, fibrinolytic proteins, and anti-fibrinolytic proteins (Deitcher and Gardner, 1999). Haemostatic system has evolved to maintain blood in a fluid state under physiological conditions, and also to react rapidly to vascular trauma by sealing defects with fibrin clots. The formation of fibrin can be initiated through either of two converging cascades which are the extrinsic pathway and the intrinsic pathway (Colman, 2006). Deficiencies of coagulation factor in this cascade such as factor VIII, IX, and XI can lead to bleeding disorders (Maas et al., 2008).

Abnormal clotting frequently occurs in CVDs and can lead to heart attacks or stroke (Gregg and Goldschmidt-Clermont, 2003). Platelets play an important role as both for the formation of blood clots, where platelet aggregates are an essential constituent of the thrombus formation, and platelet as a platform for activation of coagulation proteins (Colman, 2006). Platelets first become activated at sites of vascular injury when they

encounter matrix proteins exposed by injury to the vessel wall. It arrest on the exposed sub-endothelial surface, become activated, and secretes or generates soluble mediators, such as ADP, thromboxane A2, and thrombin (Woulfe et al., 2004).

Numbers of therapeutic agents are available for management of patient with platelet hyper-aggregability. Aspirin, an anti-platelet drug, is commonly used to reduce the risk of ischaemic events in patients with CVDs. Aspirin acts by irreversibly binding to cyclooxygenase and blocking the synthesis of thromboxane A2 (Wong et al., 2004).

Vitamin K antagonists and heparin have been the main anticoagulant drugs for decades. Warfarin, a vitamin K antagonist, is the most widely used oral anticoagulant in clinical practice for treatment of venous thromboembolism as well as for prevention of systemic embolism in patients with atrial fibrillation and prosthetic heart valves. Warfarin exerts anticoagulant effect by interfering with the cyclic conversion of Vitamin K, thus, inhibiting the activation of the Vitamin K-dependent coagulation factors (II, VII, IX and X) and inhibitors (protein C and protein S) (Sun et al., 2006). Besides, heparin is the most commonly used intravenous anticoagulant. Heparin prevents the formation of clots and extension of existing clots within the blood and normally it does not affecting the platelets (Baroletti and Goldhaber, 2006).

Recently, uses of *M. citrifolia* as a food and dietary supplement have increased greatly worldwide (Müller et al., 2008 and West et al., 2006). It is a native plant from Southeast Asia to Australia and is cultivated in Polynesia, India, Central and northern South America (Chan-Blanco et al., 2006). *M. citrifolia* has been reported to possess antidiabetic, antiseptic and antibiotic properties, anti-cancer activity, hypotensive and anticoagulant activities (Sukardi et al., 2005). Mature *M. citrifolia* fruits are good sources of dietary antioxidants (Yang et al., 2011). Antioxidants may help prevent CVDs by aiding in the repair of the damage that free radicals cause to the blood vessels (LoBisco, 2011).

M. citrifolia leaves and especially the fruit are consumed in different forms by various communities throughout the world (Chan-Blanco et al., 2006). *M. citrifolia* leaf extracts were used to curb excessive blood flow and slow formation of blood clots. *M. citrifolia* fruit juice extract the anti-inflammatory potential, suggesting there is a high probability for therapeutic effectiveness of the fruit juice against some inflammatory conditions (McKoy et al., 2002).

The bioactive compounds that was found in *M. citrifolia* as included scopoletin (7-hydroxy-6-methoxycoumarin), nitric oxide, vitamin C, acetyl derivatives of asperuloside, fiber, alkaloids and sterols (Chan-Blanco et al., 2007). Scopoletin is a coumarin derivative. It can be used as a relatively specific marker of *M. citrifolia* exposure in the blood and particularly in urine (Issell et al., 2008).

1.2 Problem Statement

The increasing use of *M. citrifolia* products as dietary supplements suggested an urgent requirement to check for their advocated effect for quality control purposes. However, scientific evidence for the benefits and precise mechanism of action of different part of *M. citrifolia* extract remains unclear.

Nowadays, concerns over health are gaining attention across the Malaysian community. In 2005, the CVDs have been the principle cause of death in Malaysia accounting for 11.5% medically certified and 5.7% not medically certified of deaths (DOS, 2009). Current available medication including anticoagulant and antiplatelet agents seems unable to reduce the statistics when CVDs still remain leading cause of death in Malaysia.

Some of these anticoagulant and antiplatelet agents have a lot of side effects and patients need to be monitored conscientiously. Therefore, there is a need to have an alternative medication. In addition, some medications like heparin are derived from porcine based polysaccharide. Hence, there is a need to search for an alternative approach or medicine particularly for Muslim community.

This research study the effect of *M. citrifolia* fruit crude extracts on blood haemostasis system in *in vitro* and *in vivo* models. The focus was on the effects of *M. citrifolia* fruit crude extracts onto full blood count parameters, blood coagulation, platelet aggregation and bleeding time. In *in vivo* model and antioxidant determination, the focus was on *M. citrifolia* fruit crude aqueous extract since there were abundant of *M. citrifolia* products consumed as drinks. With the new knowledge acquired from this study, it is hope to supplement users about the side effects onto the blood haemostasis system and also it might be used as an alternative approach in managing patients with cardiovascular diseases.

1.3 Significance of study

The importance of this study can be viewed from the limited research on effects of *M. citrifolia* fruit crude extract on haemostasis parameters on *in vitro* and *in vivo* models. Up to the time this thesis was written, there had been no previously reported study on this matter. Hence, this study was conducted to fill the information gap. The results from this study can be used as a reference to provide the impetus for future prospective and interventional research in the related field.

1.4 Objectives

1.4.1 General objective

To determine the antioxidant properties of *M. citrifolia* fruit crude extracts and its effects on the blood haemostasis parameters.

1.4.2 Specific objectives

1. To determine the antioxidant properties and total phenolic content of *M. citrifolia* fruit crude extract using free radical scavenging activity measurement (DPPH), β-carotene bleaching assay and Folin-Ciocalteu's method.

2. To determine the effect of *M. citrifolia* fruit crude extracts on the blood coagulation tests i.e: Activated partial thrombin time (APTT) and Prothrombin time (PT) of *in vitro* and *in vivo* models.

3. To determine the effects of *M. citrifolia* fruit crude aqueous extract on the full blood count parameters and bleeding time of *in vivo* model.

4. To determine the effect of *M. citrifolia* fruit crude aqueous extract on platelet aggregation test of *in vivo* model.

1.5 Hypotheses

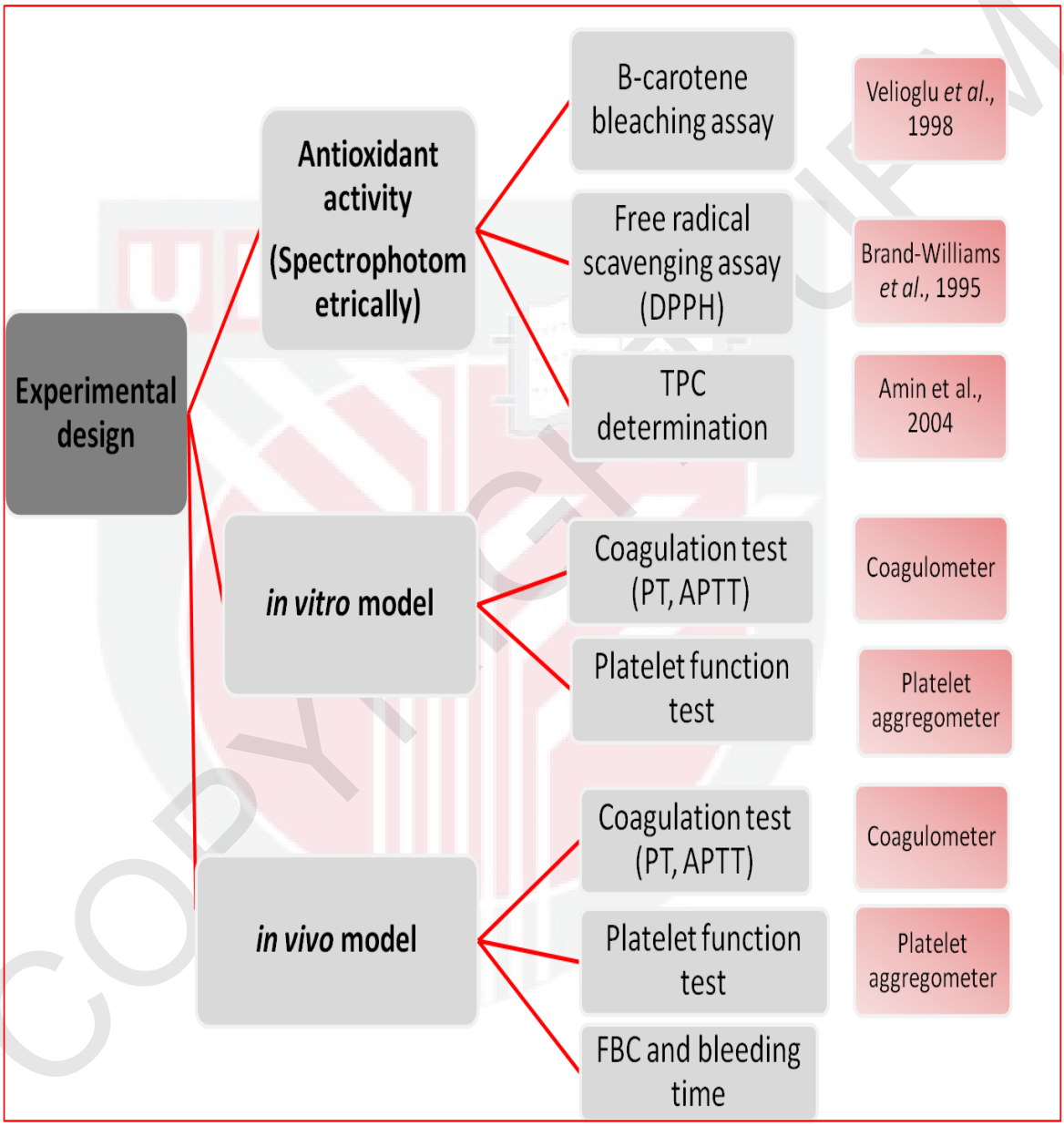
Null hypotheses

1. There is no significance difference between different concentrations of *M. citrifolia* fruit crude extracts with APTT and PT on *in vitro* and *in vivo* models.

2. There is no significance difference between different dosages of *M. citrifolia* fruit crude aqueous extract with the full blood count parameters and bleeding time of *in vivo* model.

3 There is no significance difference between different dosages of *M. citrifolia* fruit crude aqueous extract with platelet aggregation test of *in vivo* model

1.6 Conceptual framework



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