ANTICOAGULANT ACTIVITY AND TOXICITY PROFILES OF MELASTOMA MALABATHRICUM LINN. LEAF EXTRACT

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DOCTOR OF PHILOSOPHY
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By

CAROLINE MANICAM

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

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DEDICATION

"Be Thou my wisdom, O Lord of my heart; Naught be all else to me save that Thou Art"

To Dad and Ma

You have given me the best of everything in this life and a chance to see this world from an entirely different perspective.

This success would have been impossible without you.

I owe you a debt of gratitude that I can never repay!

In loving memory of Sheba

You may have left us suddenly, but you left your indelible footprints in our hearts.

Thank you, Sheba, for being there for 'akka' in your own silent ways.

I will always miss you!

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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By

CAROLINE MANICAM

September 2011

Chair : Associate Professor Muhajir Hamid, PhD

Faculty : Biotechnology and Biomolecular Sciences

The increased rates of thrombotic diseases contribute to the high number of morbidity and deaths worldwide each year. For many decades, the use of anticoagulant drugs, namely warfarin, heparin and their derivatives in the prevention and treatment of these maladies remain indisputable. Although these anticoagulant agents are efficacious key players in the clinical practice, they are associated with many well-established drawbacks that limit their usefulness. Hence, there exists an unmet need for equally potent but novel anticoagulant agents with improved safety profiles and ease of administration *via* the oral route. This study was, thus initiated in view of the current highlights in the medical realm of anticoagulation and based on the preliminary finding in a screening study of *Melastoma malabathricum* Linn. leaf extract. *Melastoma* leaves gave the highest extract yield (288.0 ± 1.0 g) when extracted with hot water under reflux, compared to cold water (143.0 ± 5.5 g) and organic solvent (189.0 ± 0.9 g) extraction

methods. Hot water extract was also found to possess potent *in vitro* anticoagulant activities, comparable to conventional drug, heparin. Correspondingly, the *Melastoma* leaf extract significantly ($P < 0.001$) prolonged activated partial thromboplastin time (aPTT) (64 - 300 s) in a concentration-dependent manner (100-1000 µg/ ml), but did not affect both prothrombin time (PT) and thrombin time (TT), suggestive of its effect on the intrinsic pathway of coagulation cascade. There were no inter-gender variations in the trends of anticoagulant activities. The nature of the anticoagulation caused by the extract investigated in immediate and timed-incubation mixing studies, demonstrated that the initially prolonged aPTT of test samples spiked with a range of *Melastoma* leaf extract was subsequently corrected to normal clotting time (31.0 – 46.6 s) range when test samples were subjected to 50 % normal human plasma. Subsequent analysis of various coagulation factors in the intrinsic pathway showed that *Melastoma* leaf extract specifically targeted and caused a considerable deficiency in factor VIII (FVIII) levels (23 - 35 %) non-dose dependently. Results from the *in vivo* studies employing suitable animal models of thrombosis corroborated with the findings of *in vitro* clot-based assays and hence, confirmed the inherent anticoagulant properties of *Melastoma* leaf extract. The toxic and hemorrhagic propensity of this extract evaluated in an acute oral toxicity animal study underscored the absence of aberrant effects of the extract *in vivo* when administered at a high, single dose (5 g/ kg) for a short period of 14 days. However, sub-acute toxicity evaluations of the extract administered on a daily-dosing regimen at various lower dosages (50, 75 and 100 mg/ kg) for 28 days, revealed an array of abnormal changes, notably hepatic venous dilatation and congestion, and hemorrhage in renal tissues. Nevertheless, cytotoxicity studies of the extract employing organ-specific cells and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) cell

viability assay proved the absence of direct toxicity, as substantiated by preserved cellular integrity and high 50 % inhibitory concentration (IC_{50}) value of the extract (972 ± 2.57 µg/ml), in comparison to evident cytotoxic manifestations of heparin used as control reference. Collectively, the findings of this study suggested that the hot water extract of *Melastoma* leaves have high potential as an affordable alternative for future development of a potent and safe novel anticoagulant agent of natural origin.

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

AKTIVITI ANTI-BEKU DARAH DAN PROFIL TOKSIK EKSTRAK DAUN *MELASTOMA MALABATHRICUM* LINN.

Oleh

CAROLINE MANICAM

September 2011

Pengerusi : Profesor Madya Muhajir Hamid, PhD

Fakulti : Bioteknologi dan Sains Biomolekul

Peningkatan kadar penyakit trombosis telah menyumbang kepada pertambahan jumlah kematian di seluruh dunia pada setiap tahun. Sejak berdekad, penggunaan ubat anti-beku darah seperti warfarin, heparin dan ubat-ubat terbitan daripadanya dalam langkah pencegahan dan rawatan penyakit sebegini sememangnya tidak dapat dinafikan. Namun demikian, walaupun penggunaan ubat-ubat anti-beku darah dalam rawatan klinikal telah menunjukkan keberkesanan, mereka sering dikaitkan dengan pelbagai kekurangan yang menghadkan penggunaan. Maka, wujud peningkatan permintaan bagi agen anti-beku darah yang baru yang mempunyai ciri-ciri keselamatan yang lebih terjamin serta mudah diambil secara oral. Oleh itu, kajian ini telah dimulakan kerana penyelidikan ubat anti-beku darah kini menjadi salah sebuah isu utama dalam bidang perubatan, serta berdasarkan penemuan aktiviti anti-beku darah ketika saringan ekstrak daun *Melastoma malabathricum* Linn. Daun *Melastoma* yang diekstrak menggunakan kaedah refluks air

panas menunjukkan hasil paling tinggi (288.0 ± 1.0 g), berbanding jika daun diekstrak dengan air sejuk (143.0 ± 5.5 g) atau pelarut organik (189.0 ± 0.9 g). Ekstrak air panas ini juga didapati mempunyai aktiviti anti-beku darah *in vitro* yang poten dan setanding dengan aktiviti anti-beku darah heparin. Di samping itu, ekstrak daun *Melastoma* juga telah memanjangkan masa pembekuan darah dalam ujian aPTT secara signifikan (64 - 300 s) mengikut dos (100-1000 μg/ml), manakala ia tidak memberi kesan ke atas masa pembekuan darah dalam ujian PT dan TT. Keputusan ini menunjukkan bahawa ekstrak daun *Melastoma* mempengaruhi siri intrinsik dalam kitar pembekuan darah. Kesan anti-beku darah ekstrak ini juga didapati tidak dipengaruhi oleh sampel plasma dari jantina berlainan. Dua jenis ujian 'mixing studies' telah dijalankan untuk menentukan cara ekstrak ini memberi kesan anti-beku darah. Masa pembekuan darah aPTT dalam sampel plasma yang telah ditambah dengan ekstrak daun *Melastoma* yang dipanjangkan pada awalnya, telah 'dibetulkan' ke takat masa pembekuan darah yang normal (31.0 – 46.6 s) apabila dicampur dengan 50 % plasma yang normal. Analisa seterusnya mengkaji pelbagai faktor pembekuan darah dalam siri intrinsik, di mana ekstrak *Melastoma* didapati hanya menunjukkan pengurangan paras faktor VIII (FVIII) secara signifikan (23 - 35 %). Keputusan dari kajian *in vivo* menggunakan model thrombosis haiwan yang sesuai pula menyokong hasil keputusan ujian anti-beku darah secara *in vitro,* dan seterusnya mengesahkan kewujudan ciri-ciri anti-beku darah dalam ekstrak daun *Melastoma.* Profil toksik dan kecenderungan insiden pendarahan berpunca daripada pengambilan ekstrak daun ini telah dinilai secara *in vivo* dalam ujian toksik akut ke atas haiwan. Pemberian satu dos tinggi (5 g/kg) ekstrak akuas daun *Melastoma* secara oral untuk jangka masa 14 hari tidak menyebabkan sebarang perubahan mudarat pada haiwan. Walaubagaimanapun, pemberian beberapa dos ekstrak yang rendah (50, 75 dan

100 mg/ kg) bagi jangka masa yang panjang (28 hari) secara berterusan menunjukkan beberapa perubahan abnormal yang ketara, khususnya pengembangan struktur vena tisu hati dan pendarahan tisu buah pinggang berdasarkan ujian sub-akut. Namun demikian, ujian ketoksikan sel menggunakan model sel yang spesifik-organ secara *in vitro* dan ujian 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT), menunjukkan bahawa ekstrak tidak menyebabkan ketoksikan sel. Keputusan ujian ini dibuktikan berdasarkan ketahanan integriti sel dan nilai kepekatan rencatan (IC_{50}) ekstrak yang tinggi (972 ± 2.57 μg/ml) jika dibandingkan dengan kesan toksik ke atas sel oleh heparin yang digunakan sebagai ubat rujukan. Rumusannya, kajian ini memberi bukti kukuh bahawa ekstrak air panas daun *Melastoma* mempunyai potensi yang tinggi sebagai agen anti-beku darah alternatif dari sumber asli, poten dan selamat digunakan secara oral pada masa hadapan.

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To dad and ma – without your unwavering support, love, prayers and values you have instilled within me all these years, I would not have walked down this road boldly.

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I may not have penned down in specific the names of many others who have contributed in a way or another to the successful completion of my Doctorate; but that does not mean you are forgotten. May God bless you abundantly!

I certify that a Thesis Examination Committee has met on 15 September 2011 to conduct the final examination of Caroline A/P Manicam on her thesis entitled "Anticoagulant Activity and Toxicity Profiles of *Melastoma malabathricum* Linn. Leaf Extract" 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 Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

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Date: 22 November 2011

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

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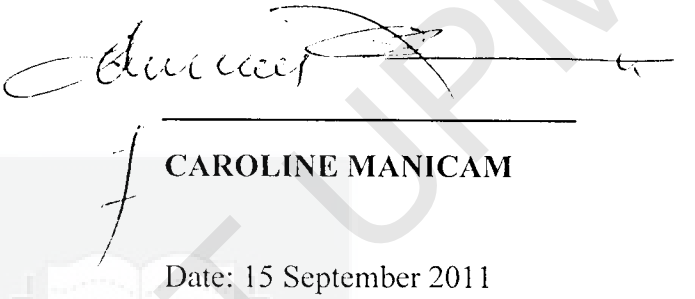
Date: 8 DEC 2011

DECLARATION

I declare that this thesis is my original work except for quotations and citations, which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.



CAROLINE MANICAM

Date: 15 September 2011

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%	percentage
(v/v)	volume per volume
(w/v)	weight per volume
<	Less than
>	More than
°C	degree Celsius
µg	microgram
µm	micrometer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATCC	American type culture collection
BT	Bleeding time
BUN	Blood urea nitrogen
CT	Clotting time
EDTA	Ethylene diamine tetra-acetic acid
FII	Factor II
FIX	Factor IX
FV	Factor V
FVII	Factor VII
FVIII	Factor VIII
FX	Factor X

FXI	Factor XI
g	gram
GGT	Gamma glutamyl transferase
IC_{50}	50% inhibition concentration
IU	International unit
mg	milligram
min	minute
ml	milliliter
NPP	Normal platelet-poor plasma
OECD	Organization for Economic Cooperation and Development
PBS	Phosphate buffer saline
PPP	Platelet-poor plasma
PT	Prothrombin time
s	second
TT	Thrombin time
WB	Whole blood

CHAPTER 1

INTRODUCTION

Vascular and thrombotic diseases represent one of the widespread fatal causes of morbidity and death worldwide (Mousa, 2010; Moura et al., 2011). The major cause underlying the pathogenesis of thrombosis stems from the perturbation in hemostatic balance. Blood coagulation is a highly sophisticated mechanism that is dependent on a series of proteolytic enzymes and co-factors to arrest blood loss and thus, prevent exsanguination of the organism (Tanaka et al., 2009; Vine, 2009). However, if the equilibrium between the pro- and anti-coagulant elements is shifted in favor of blood coagulation and remains unchecked, thrombosis and ultimately thromboemboli occurs (Naderi et al., 2005). This phenomenon has triggered an increased interest in the medical community to prevent lethal thrombus formation, while preserving the fluidity of blood (Sano et al., 2003). Various therapeutic agents are being used extensively in the current medical setting, given the increasing numbers of patients with thromboembolic disorders. Anticoagulant drugs, especially warfarin and heparin and their derivatives used since time immemorial remains the cornerstone of treatment and prevention of thrombotic incidences (Koo et al., 2010; Mousa, 2010).

Numerous novel antithrombotic agents have also emerged over the last several years parallel to the accelerated search for an ideal anticoagulant agent. This is in view of the well-documented drawbacks exhibited by the existing anticoagulant drugs that limit their usefulness, and thus prompt development and discovery of new drugs with

improved pharmacokinetics and safety margin (Lassen and Laux, 2008; Garcia et al., 2010). The most serious complication of all anticoagulant agents is bleeding, especially gastrointestinal and intracranial hemorrhage (Weitz, 2006; Tanaka et al., 2009). Moreover, the mode of administration of most drugs is *via* parenteral routes, with warfarin being the only available potent oral anticoagulant drug in clinical use (Tanaka et al., 2009). Ximelagatran, a novel direct thrombin inhibitor, was first introduced as a potential replacement of warfarin as an oral anticoagulant drug after nearly 60 years. However, this drug hailed as a major breakthrough in oral anticoagulant drug development, elicited severe hepatotoxic manifestations that caused its withdrawal from the market (Haas, 2004).

Therefore, there is an urgent unmet need for new anticoagulant agents with improved attributes over the existing drugs, particularly an anticoagulant agent that can be administered orally, which will represent a crucial improvement over warfarin (Garcia et al., 2010). The overall utility of a novel anticoagulant, however, depends on various other factors that will determine its applicability and efficacy. Conventional drugs in current use, such as vitamin K antagonists and heparins target on multiple factors in the coagulation cascade, hence rendering unpredictable coagulation patterns because each clotting factor targeted has a different plasma half-life (Lassen and Laux, 2008). Thus, an antagonizing new agent that will discretely target on only one coagulation factor is of immense welcome to facilitate predictable pharmacology, negating the inconvenient need for frequent monitoring in patients. In addition, the cost of developing a novel drug is another fundamental factor that needs to be taken into due consideration. Pre-clinical cost to develop synthetic anticoagulant drugs has been estimated to be around $400

million (Ulrich-Merzenich et al., 2010). A cheaper yet potent agent with defined safety profiles, preferably of natural origin would be the ideal attributes of a new anticoagulant.

Plants are the major source of human pharmacopoeia for thousands of years and still represent a vast armamentarium for new drug discoveries (Schmidt et al., 2008). An estimated 25% of drugs used globally are of plant origin and 11% out of the 252 essential medicines prescribed worldwide are derived exclusively from botanicals (Sahoo et al., 2010). Interestingly, an approximately one quarter of the best selling drugs in the world in 2001 and 2002 were derived from natural sources and the number is expected to escalate in years to come (Balunas and Kinghorn, 2005). The history of many major breakthroughs in drug discovery has its foundation firmly rooted in plant sources. An exemplary illustration would be the discovery of the drug that revolutionized cancer treatment, taxol (paclitaxel) from the bark of Pacific yew tree (*Taxus brevifolia* Nutt.) in 1966 (Itokawa et al., 2008; Pitchai et al., 2010). As such, the search for sequestered medicinal properties in plants as potential clinical candidates for novel world-class drugs is gaining momentum after several decades of decline in their usage due to the booming synthetic drug developments (Rishton, 2008; Dev, 2010).

In view of the current clinical phenomenon of the widespread occurrence of vascular thrombotic diseases, as well as the pressing need for oral anticoagulant agents of natural origin with improved safety and benefit dossier to address the pathology, this study was initiated to evaluate the inherent anti-clotting properties of a Malaysian medicinal plant, *Melastoma malabathricum* Linn. The aqueous leaf extract of *Melastoma*, also commonly known as 'senduduk' among the local folks exhibited strong *in vitro* anticoagulation in a screening study and was identified as a potential candidate for

coagulation assessment in an attempt to find a new anticoagulant agent in the present study. The specific objectives of this study were:

1. to determine the *in vitro* anticoagulant properties of *Melastoma* leaf extract and inter-gender variations in its anticoagulant activity,
2. to determine the specific blood coagulation pathway and factor(s) affected by the extract and the nature of its anticoagulant activity,
3. to evaluate the *in vivo* anticoagulant efficacy and comparability of the extract with existing anticoagulant drugs in suitable animal models of thrombosis and thromboembolism,
4. to assess the toxicity of the leaf extract by acute and sub-acute toxicity tests in animals, and cytotoxicity on normal human liver cells *in vitro*

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