UNIVERSITI PUTRA MALAYSIA

ANTI-ATHEROTHROMBOTIC EFFECTS OF Berberis vulgaris L., Teucrium polium L. AND Orthosiphon stamineus BENTH EXTRACTS In Vitro AND Berberis vulgaris L. EXTRACTS In Vivo

NURUL HUDA MOHD NOR

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By

NURUL HUDA MOHD NOR

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

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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

ANTI-ATHEROTHROMBOTIC EFFECTS OF Berberis vulgaris L., Teucrium polium L. AND Orthosiphon stamineus BENTH EXTRACTS In Vitro AND Berberis vulgaris L. EXTRACTS In Vivo

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July 2017

Chairman : Prof. Fauziah Othman, PhD
Faculty : Medicine and Health Sciences

Coronary artery disease is a group of diseases that includes stable angina, unstable angina, myocardial infarction and sudden cardiac death. Coronary artery disease is a leading cause of mortality and morbidity worldwide. The pathogenesis mainly due to atherosclerosis, plaque rupture and platelet thrombus formation. The main risk factors for coronary artery diseases are obesity, hypercholesterolemia, smoking, diabetes and high blood pressure. As part of disease management, anticoagulant and antiplatelet drugs are the options of treatment together with lipid-lowering medication.

In combating this disease, medicinal plants comprised of anti-atherothrombotic effects can be options other than drug therapies that may be considered to have lesser adverse effects. Nevertheless, the effectiveness of medicinal plants in treating coronary atherothrombotic disease has yet to be fully explored. Therefore, the haematological, biochemical, gross and histological effect of *Berberis vulgaris* L, *Teucrium polium* Land *Orthosipohon stamineus* Benth extracts in preventing and treating coronary atherothrombotic disease were studied at the *in vitro* (phase I) *and in vivo* (phase II) level.

In phase I, three types of extraction including aqueous, methanol and polysaccharide of the *B. vulgaris, T. polium* and *O. stamineus* were studied for antiplatelet and anticoagulant effect using human whole blood. All extracts were subjected to the prothrombin time (PT) and activated partial thromboplastin time (APTT) test for anticoagulant activity and then investigated using an electrical impedance method for antiplatelet activity. *B. vulgaris* aqueous extract (BVAE), *B. vulgaris* polysaccharide extract (BVPE) *T. polium* aqueous extract (TPAE) and *T. polium* polysaccharide extract (TPPE) were found to significantly prolong the coagulation time in a concentration dependent manner ($p<0.05$). In addition, phytochemical screening revealed that aqueous extract of all three medicinal plants contained polysaccharides. Hence, it was

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concluded that the present of polysaccharides in the medicinal plants, especially in *B. vulgaris* and *T. polium* but not in *O. stamineus* played a role in prolonging blood clotting in coagulation activity. However, this current study on also proved that not all polysaccharides gave equal effects on coagulation test. Though, for antiplatelet activity, the BVAE was the most effective sample against platelet aggregation caused by arachidonic acid (AA) and collagen. These effects are probably due to the present of berberine content in *B. vulgaris* and higher total phenolic compound thus inhibit platelet aggregation activity.

In continuation of result in phase I, BVAE was proceeded for phase II *(in vivo*) due to its optimum effect of anticoagulation and antiplatelet activity. Phase II was divided into two parts, preventive and treatment studies. Atherosclerotic-induced male New Zealand white rabbits were divided into nine groups and antihyperlipidemic effect, anti-inflammatory effect, antiplatelet properties, anticoagulation properties, liver function test and renal profile were studied. After the treatment period for preventive study (10 weeks) and treatment study (12 weeks) were completed, the rabbits were sacrificed for gross and histological analyses (H&E, Masson trichrome and Modified Verhoeff stains), immunohistochemistry analyses (RAM 11) and biochemistry analyses were performed on extracts and control groups in both studies. All data were analysed using one-way ANOVA followed by LSD's post-hoc test. The values were considered significant when p value is less than 0.05.

The current study provided biochemical and histological evidences that BVAE possesses antihyperlipidemic effect through significant reduction on total cholesterol, triglyceride and low-density lipoproteins levels, and histologically for intima-media ratio and collagen score compared to control ($p<0.05$). For the anti-inflammatory effect, BVAE was shown to attenuate inflammatory cells biochemically including TNF-alpha and interleukin-6 levels, and significant reduction on macrophages cells number in concentration dependent manner ($p<0.05$).

Toxicity analysis showed both concentrations of the extracts had no effect on the liver and renal function biochemically and histologically These finding provide an important evidence that BVAE is safe to use, and possible to proceed for further testing in a clinical setting. In conclusion, *B. vulgaris* had been proven to have anti-atherothrombotic properties and can be considered as a safe option for anti-atherothrombotic agent.

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

KESAN-KESAN ANTI-ATHEROTHROMBOSIS DALAM EKSTRAK *Berberis vulgaris* L., *Teucrium polium* L. DAN *Orthosiphon stamineus* BENTH KE ATAS MODEL *In Vitro* DAN EKSTRAK *Berberis vulgaris* L. KE ATAS MODEL *In Vivo*

Oleh

NURUL HUDA MOHD NOR

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Pengerusi : Prof. Fauziah Othman, PhD
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Penyakit koronari arteri adalah penyakit jantung termasuklah angina yang stabil, angina tidak stabil dan infarksi miokardium. Penyakit koronari arteri adalah penyebab utama kematian dan morbiditi di seluruh dunia. Patogenesis utamanya adalah disebabkan oleh aterosklerosis plak dan pembentukan thrombus platelet. Faktor-faktor utama bagi penyakit atherothrombotik koronari adalah obesiti, hyperkolesterolemia, merokok, diabetik dan tekanan darah tinggi. Antikoagulan dan antiplatelet adalah pilihan rawatan untuk penyakit ini bersama-sama dengan ubat kolesterol.

Dalam memerangi penyakit ini, tumbuh-tumbuhan perubatan yang mempunyai kesan anti-atherothrombotic boleh menjadi pilihan selain daripada rawatan yang mempunyai kesan sampingan yang lebih rendah. Walau bagaimanapun, keberkesanan tumbuhan dalam merawat penyakit atherotrombotik koronari masih belum diterokai sepenuhnya. Oleh itu, kesan hematologi, biokimia, makroscopik dan histologi ke atas *Berberis vulgaris* L, *Teucrium polium* L dan *Orthosipohon stamineus* Benth ekstrak dalam mencegah dan merawat penyakit atherotrombotik koronari dikaji di peringkat *in vitro* (fasa I) dan *in vivo* (fasa II).

Dalam fasa I, tiga jenis ekstrak termasuk air, metanol dan polisakarida dari *B. vulgaris*, *T. polium* dan *O. stamineus* telah dikaji untuk kesan antiplatelet dan antikoagulan menggunakan sampel darah manusia. Semua ekstrak telah dikaji untuk aktiviti antikoagulan melalui ujian masa prothrombin (PT) dan masa tromboplastin (APTT) dan juga menggunakan kaedah impedans elektrik untuk aktiviti antiplatelet. Ekstrak air *B. vulgaris* (BVAE), ekstrak polisakarida *B. vulgaris* (BVPE) ekstrak air *T. polium* (TPAE) dan ekstrak polisakarida *T. polium* (TPPE) didapati memanjangkan masa pembekuan mengikut kepekatan ($p< 0.05$). Di samping itu, pemeriksaan phytokimia juga mendedahkan bahawa ekstrak air dari ketiga-tiga tumbuhan ubatan ini

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mengandungi polisakarida. Oleh itu, disimpulkan bahawa polisakarida dalam tumbuhan perubatan, terutama di *B. vulgaris* dan *T. polium* tetapi tidak pada *O. stamineus*, memainkan peranan dalam memanjangkan pembekuan darah dalam aktiviti pembekuan. Walau bagaimanapun, kajian semasa ini juga membuktikan bahawa tidak semua polisakarida memberi kesan yang sama pada ujian koagulasi. Untuk aktiviti antiplatelet pula, BVAE adalah sampel yang paling berkesan terhadap agregasi platelet yang disebabkan oleh asid arakidonik (AA) dan kolagen. Kesan-kesan ini mungkin disebabkan oleh kandungan berberine dalam *B. vulgaris* dan sebatian fenolik yang lebih tinggi sekali gus menghalang aktiviti agregasi platelet.

Kesinambungan dengan keputusan dalam fasa I, BVAE diteruskan untuk fasa II (*in vivo*) disebabkan oleh kesan optimum aktiviti antikoagulasi dan antiplatelet. Fasa II dibahagikan kepada dua bahagian, kajian pencegahan dan kajian rawatan. Arnab jantan jenis New Zealand yang bewarna putih diaruhkan kepada arterosklerosis dan kesan antihyperlipidemik, kesan anti-radang, antiplatelet, antikoagulasi, ujian fungsi hati dan profil renal dikaji. Selepas tempoh rawatan untuk kajian pencegahan (10 minggu) dan kajian rawatan (12 minggu) telah selesai, arnab dikorbankan untuk analisis makroskopik dan histologi (H&E, Masson trichrome dan Modified Verhoeff noda), analisis imunohistokimia (RAM 11) dan analisis biokimia dilakukan pada ekstrak dan kumpulan kawalan dalam kedua-dua kajian. Semua data dianalisis dengan menggunakan satu arah ANOVA diikuti oleh ujian post-hoc LSD. Nilai dianggap bererti apabila nilai p kurang dari 0.05.

Kajian semasa menyediakan bukti biokimia bahawa BVAE mempunyai kesan antihyperlipidemik melalui pengurangan jumlah kolesterol, trigliserida dan tahap lipoprotein berketumpatan rendah, dan secara histologi untuk nisbah intima-media dan skor kolagen berbanding dengan kawalan ($p<0.05$). Untuk kesan anti-radang, BVAE ditunjukkan untuk menurunkan sel-sel radang secara biokimia termasuk tahap TNF-alpha dan interleukin-6, dan secara histologi melalui pengurangan ketara pada jumlah sel makrofaj mengikut kepekatan ($p <0.05$).

Analisis toksik menunjukkan kedua-dua kepekatan ekstrak tidak memberi kesan ke atas fungsi hati dan buah pinggang secara biokimia dan histologikal. Penemuan ini memberikan bukti penting bahawa BVAE adalah selamat untuk digunakan dan dilanjutkan ke ujian secara klinikal. Kesimpulannya, *B. vulgaris* telah terbukti mempunyai sifat anti-atherotrombotik dan dapat dianggap sebagai pilihan yang selamat untuk agen anti-atherotrombotik.

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I certify that a Thesis Examination Committee has met on 24 July 2017 to conduct the final examination of Nurul Huda binti Mohd Nor on her thesis entitled "Anti-Atherothrombotic Effects of *Berberis vulgaris* L., *Teucrium polium* L. and *Orthosiphon stamineus* Benth Extracts *In Vitro* and *Berberis vulgaris* L. Extracts *In Vivo*" in accordance with the Universities and University Colleges 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.

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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

15-R-HETE	15- R- hydroxyicosatetraenoic acid
5-HT	5- hydroxytryptamine
AA	Arachidonic Acid
ACS	Acute Coronary Syndrome
ADP	Adenosine Diphosphate
AGE	Advance Glycation End- product
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BV	*Berberis vulgaris*
BVAE	*Berberis vulgaris* L Aqueous Extract
BVME	*Berberis vulgaris* L Methanol Extract
BVPE	*Berberis vulgaris* L Polysaccharide Extract
CAD	Coronary Artery Disease
cAMP	Cyclic adenosine monophosphate
CHD	Coronary Heart Disease
COX	Cyclooxygenase
CRP	C-reactive Protein
CVD	Coronary Vascular Disease
ELISA	Enzyme Linked Immunosorbent Assay
FBC	Full blood count
FGF- 2	Fibroblast growth factor 2
GBD	Global Burden of Disease Study
GPIa	Glycoprotein Ia
GPIIa/IIIb	Glycoprotein IIb /IIIa
H&E	Haematoxylin and Eosin
HDL	High Density Lipoprotein
HK	High Molecular Weight Kininogen
ICAM	Intercellular Cell Adhesion Molecule
IFN-γ	Interferon-gamma
IHC	Immunohistochemistry
IHD	Ischemic Heart Disease
IL	Interleukin
INR	International Normalized Ratio
IU/L	International Unit per Liter
LDL	Low Density Lipoprotein
LOX	Lipooxygenase
MI	Myocardial Infarction
MOH	Ministry of Health
NCD	Non-communicable Disease
NO	Nitric Oxide
OS	*Orthosiphon stamineus* Benth
OSAE	*Orthosiphon stamineus* Benth Aqueous Extract
OSME	*Orthosiphon stamineus* Benth Methanol Extract
OSPE	*Orthosiphon stamineus* Benth Polysacharide Extract
oxLDL	Oxidize Low Density Lipoprotein

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PAF	Platelet Activating Factor
PFGF	Platelet- derived Growth Factor
PG	Prostaglandin
PK	Prekallikrein
PT	Prothrombin Time
ROS	Reactive Oxygen Species
SGOT	Serum Glutamic Oxaloacetic Transaminase
SMC	Smooth Muscle Cell
TF	Tissue Factor
TIA	Transient Ischemic Attack
TNF-α	Tumour Necrosis Factor-alpha
TP	Teucrium polium
TPAE	Teucrium polium L Aqueous Extract
TPME	*Teucrium polium* L Methanol Extract
TPPE	*Teucrium polium* L Polysaccharide Extract
TXA2	Thromboxane A2
VCAM	Vascular Cell Adhesion Molecule
VSMC	Vascular Smooth Muscle Cell
vWF	Von Willebrand
WBC	White Blood Cell
WHI	Woman Health Initiative
WHO	World Health Organization

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The World Health Organization (World Health Organization, 2011) reported that coronary artery diseases (CADs) are the leading causes of death and disability in the world. Globally, it is estimated about 17.3 million people died from CADs in 2008 and by 2030, approximately 23.6 million of the world population will die from this disease (Lee, 2006). The risk factor for CADs is mainly due to atherosclerosis which leads to arterial thrombosis.

The pathogenesis of atherothrombosis started with endothelial disturbance by many noxious stimuli, including oxidised LDL cholesterol, glycation end-products, smoking, hypertension and others leading to inflammation, oxidation of more lipoproteins, smooth muscle cell proliferation, platelet activation, hypercoagulation and thrombosis formation. Hypercholesterolemia with high LDL causes release of more platelet-activating factor that, in turn, increased the production of inflammatory factors including activation of macrophages and released of cytokines. The process encompasses chronic progressive atherosclerosis punctuated by acute processes such as plaque rupture and platelet thrombus formation in areas of progressive stenosis. The final pathway to arterial thrombosis is atherosclerosis plaque rupture, thus the effective way to treat or to prevent this event is limiting or eradicating platelet-dependent thrombus formation.

Anticoagulant and antiplatelet drugs together with lipid lowering medication are the cornerstone in the management of coronary artery diseases. An ideal anticoagulant should be effective, safe, lack of serious toxicity, and have a wide therapeutic window with less monitoring. It should be also available orally (for long-term use), safe during pregnancy, at low cost and a short half-life for drugs used in the acute setting of thrombosis or has long half-life for prophylaxis (Moll and Roberts, 2002). Aspirin is the most commonly used antiplatelet drug worldwide in both primary and secondary prevention of CVDs. However, the antiplatelet effects of aspirin may vary between individuals. A proportion of patients prescribed aspirin suffer recurrent thromboembolic vascular events (‘aspirin resistance’) or had increased risk of bleeding (Hankey and Eikelboom, 2006).

The pharmaceutical industry uses animal polysaccharides on a large scale, especially for treatment of CADs. Heparin is an example of an animal based, widely used as anticoagulant for the treatment and prevention of thrombotic diseases and for maintaining blood fluidity in extracorporeal devices (Johnell et al., 2002). Unfortunately, the main complication with heparin as an anticoagulant includes occasionally life-threatening bleeding and heparin-induced thrombocytopenia (Greinacher and Warkentin, 2006).

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Medicinal plants serve as a greater resource for new medication and their potential is now becoming a topic of interest for researchers all over the world. WHO has recommended medicinal plants to be used more effectively in the healthcare system (Lee, 2006).

Three plants named *Berberis vulgaris* L, *Teucrium polium* L and *Orthosiphon stamineus* Benth are herbs that had been used widely in Asia in daily diets or medicinal purposes. These plants have well-known benefits toward human health (Esmaeili, Zohari and Sadeghi, 2009; Fatehi-Hassanabad et al., 2005; Yuliana et al., 2009). The promising properties from *B. vulgaris, T. polium and O. stamineus* lead this study to determine their potential anti-atherothrombotic properties. Polysaccharides isolated from higher plants do not contain sulphate groups and their anticoagulant activity is due to the presence of hexuronic acids residues, like GlcA or GalA, and its derivatives (Yoon et al., 2002).

All three plants have been studied for various cardiovascular effects that play important roles in CAD management. These include antihyperlipidemia, cardiotonic and antiarythmia effects for *B. vulgaris* (Imanshahidi and Hosseinzadeh, 2008), anti-inflammatory effect for *T. polium* (Passos et al., 2007) and antihyperlipidemia effects for *O. stemineus* (Sriplang et al., 2007). All these cardiovascular effects suggest possible potentials of the plant to be investigated for anti-atherothrombotic properties.

This research resulted to determine the medicinal plants effects of *B. vulgaris, T. polium and O. stamineus* on atherothrombotic diseases as an herbal treatment. As compared to current synthetic medicine, herbal therapy has shown lower toxicity, easier availability and better acceptability, thus patients with CAD favour to use complementary and alternative medicine (Kristoffersen et al., 2017). Therefore, this study aims to determine the use of *B. vulgaris, T. polium and O. stamineus* in phase I and *B. vulgaris* aqueous extract as a treatment in atherothrombotic diseases.

1.2 Research Hypothesis

It is hypothesized that the three medicinal plants, *B. vulgaris* fruits, *T. polium* and *O. stamineus* leaves possess potential anti-atherothrombotic effects *in vitro* and *in vivo* experiments. These plants seem as complementary agent with no side effect, to the current medicines which are known with adverse side effects.

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1.3 Research Objectives

1.3.1 General Objective

To determine anti-atherothrombotic effects of *B. vulgaris*, *T. polium*, and *O. stamineus* extracts *in vitro* and *in vivo* animal models.

1.3.2 Specific Objectives

1. To determine the effect of aqueous extract, methanol extract and polysaccharides crude extract of *B. vulgaris* fruits, *T. polium*, and *O. stamineus* leaves on the basic blood coagulation (Prothrombin Time and Activated Partial Thrombiplastin Time) in human plasma and platelet function test in human whole blood.

2. To identify specific monosaccharides from aqueous extracts of *B. vulgaris*

3. To investigate the anti hyperlipidemia effect of *B. vulgaris* aqueous extract (BVAE) on lipid profile (HDL, LDL, TG and Cholesterol) in atherosclerotic-induced rabbits.

4. To determine the antiplatelet and anti-coagulation effects of BVAE on haematological parameters (full blood count, basic coagulation test and platelet function test) using *in vivo* model.

5. To determine the anti-inflammatory effect of BVAE on interleukin-6, tumor necrosis factor alpha (TNF- α) and macrophages in the atherosclerotic plaque in atherosclerotic-induced rabbits.

6. To investigate the effects caused by BVAE on gross anatomical and histological changes of aorta and vital organs of *in vivo* model.

7. To determine toxicity effect of BVAE on liver function test (ALT, AST and ALP), kidney function (RP and creatinine).

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