UNIVERSITI PUTRA MALAYSIA

ANTI-INFLAMMATORY ACTIVITIES IN Stachytarpheta jamaicensis (L.) VAHL ETHYL ACETATE LEAF EXTRACT

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ANTI-INFLAMMATORY ACTIVITIES IN *Stachytarpheta jamaicensis* (L.) VAHL ETHYL ACETATE LEAF EXTRACT

By

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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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October 2017

Chairman : Yong Yoke Keong, PhD
Faculty : Medicine and Health Sciences

Objective: Inflammation is regarded as a complicated pathophysiology process that triggered by direct activation of receptors or by the secretion of inflammatory mediators. However, if prolonged, can lead to tissue damage as well as pathogenesis of fatal diseases. Inflammation is currently treated by non-steroidal anti-inflammatory drugs (NSAIDs). Unfortunately, these drugs caused severe side effects, such as gastrointestinal bleeding and cardiovascular diseases. *Stachytarpheta jamaicensis* (L.) Vahl has been used traditionally as herbal remedy in the treatment of inflammatory diseases. Nevertheless, little is known on the anti-inflammatory benefits of this plant. Thus, this research work aimed to scientifically evaluate and validate the anti-inflammatory activities of an ethyl acetate extract of *Stachytarpheta jamaicensis* (L.) Vahl (EASJ) as agents for treating inflammatory complications, using *in vitro* and *in vivo* models of inflammation. This study was also designed to investigate the possible molecular mechanisms involved in this activity. **Methodology:** EASJ was prepared by overnight soaking of the oven-dried powdered leaves in ethyl acetate. The extract was then filtered and evaporated to dryness. This study was determined using two different inducers (lipopolysaccharides, LPS and hydrogen peroxide, H_2O_2) and two different cell lines (RAW 264.7 murine macrophages and human umbilical veins endothelial cells, HUVECs). The cytotoxicity of EASJ on both RAW 264.7 murine cells and HUVECs was evaluated by MTT assay. As in all the subsequent experiments, the cells were pre-treated with EASJ (10, 50 and 75 µg/mL) followed by stimulation with LPS or H_2O_2. The anti-inflammatory properties of EASJ were evaluated by measuring NO production, expression of soluble cell adhesion molecules (CAMs) and *in vivo* vascular permeability (Miles assay) induced by LPS. Additionally, the effect of EASJ on *in vitro* vascular permeability, actin cytoskeleton rearrangement, VE-cadherin expression, reactive oxygen species

(ROS) production and cAMP signalling activity were also determined in H2O2-stimulated HUVECs. **Results:** EASJ was able to significantly reduce the excessive NO production. Collectively, FITC-dextran permeation in HUVECs as well as vessel leakage in the skin of mice, in response to the inflammatory factors LPS and H_2O_2, were reduced by EASJ treatment. In addition, pre-treatment with EASJ significantly inhibited actin stress fibers formation and VE-cadherin disruption on H_2O_2-challenged HUVECs. EASJ showed a significant reduction in inhibiting ROS level in a dose-dependent manner. However, EASJ did not inhibit the increased expression of soluble ICAM-1 and VCAM-1 in HUVECs triggered by LPS. Interestingly, EASJ was able to upregulate the concentrations of cAMP level. **Conclusion:** Based on these observed activities, it was showed that EASJ exhibited protective effects against LPS-induced inflammation and H_2O_2-induced oxidative stress. This activity was related to the upregulation of cAMP signaling activity. This mechanism contributed, at least in part, to the anti-inflammatory actions showed by this plant.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

AKTIVITI-AKTIVITI ANTI-RADANG DALAM EKSTRAK DAUN ETIL ASETAT *Stachytarpheta jamaicesis* (L.) VAHL

Oleh

PEARL MAJORIE LIEW

Oktober 2017

Pengerusi : Yong Yoke Keong, PhD
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Objektif: Radang ialah dianggap sebagai proses patofisiologi rumit yang dicetuskan pleh pengaktifan langsung reseptor atau oleh rembesan pengantara-pengantara inflamasi. Bagaimanapun, jika berlanjutan, boleh menjurus kerosakan tisu serta patogenesis penyakit yang membawa maut. Radang kini dirawat oleh ubat anti-radang bukan steroids (NSAIDs). Malangnya, ubat ini menyebabkan kesan-kesan sampingan yang teruk, seperti pendarahan gastrousus dan penyakit kardiovaskular. *Stachytarpheta jamaicensis* (L.) Vahl telah digunakan secara tradisional sebagai ubat herba dalam rawatan penyakit radang. Walau bagaimanapun, kurang diketahui di faedah-faedah anti radang tumbuhan ini. Maka, kerja penyelidikan ini menyasarkan untuk secara saintifik menilai dan mengesahkan aktiviti-aktiviti anti-radang ekstrak etil asetat *Stachytarpheta jamaicensis* (L.) Vahl (EASJ) sebagai ejen untuk merawat komplikasi inflamasi, menggunakan model-model keradangan *in vitro* dan *in vivo*. Kajian ini juga direka bentuk untuk menyiasat kemungkinan mekanisme molekul terlibat dalam kegiatan ini. **Metodologi:** Serbuk EASJ telah disediakan oleh perendaman semalaman yang keringan ketuhar dalam etil asetat. Ekstrak ini kemudian ditapis dan disejatkan kepada kekeringan. Kajian ini ditentukan menggunakan dua induser berbeza (lipopolisakarida, LPS dan hidrogen peroksida, H_2O_2) dan dua jenis sel kultur yang berbeza (RAW 264.7 murin makrofaj dan sel endotelium vena umbilikus manusia, HUVECs). Ujian ketoksikan EASJ di kedua-dua RAW 264.7 sel murine dan sel HUVECs dianalisasikan oleh asai MTT. Sebagai dalam semua eksperimen-eksperimen berikutnya, sel dipra-rawat dengan EASJ (10, 50 and 75 µg/mL) diikuti oleh ransangan dengan LPS atau H_2O_2. Ciri-ciri anti-radang EASJ telah dinilaikan dengan mengukur pengeluaran NO, ekspresi molekul adhesi sel dan ketelapan vaskular *in vivo* (asai Miles) yang dirangsang oleh LPS. Tambahan pula, kesan-

kesan EASJ ke atas ketelapan vaskular *in vitro,* penyusunan semula rangkasito aktin, ekspresi VE-cadherin, pengeluaran spesies oksigen reaktif (ROS) dan isyarat aktiviti cAMP juga dikaji dalam HUVECs dirangsang H_2O_2. **Keputusan:** EASJ menunjukan penurunan secara signifikan dalam penghasilan NO yang berlebihan. Secara kolektif, penelapan FITC-dekstran dalam HUVECs serta kebocoran vesel di atas kulit tikus, sebagai respons kepada factor-faktor inflamasi LPS dan H_2O_2, juga telah dikurangkan oleh rawatan EASJ. Sebagai tambahan, pra-rawat dengan EASJ menghalang pembentukan serat tekanan aktin dan perpecahan VE-cadherin di HUVECs dicabar oleh H_2O_2. EASJ menunjukkan satu pengurangan signifikan dalam menghalang tahap ROS dengan bergantung kepada dos. Bagaimanapun, EASJ tidak menyekat ekspresi larutan ICAM-1 dan VCAM-1 yang meningkat dalam HUVECs disebabkan oleh LPS. Menariknya, EASJ mampu meningkat tahap kepekatan cAMP. **Kesimpulan:** Berdasarkan aktiviti-aktiviti diperhatikan ini, ia menunjukkan bahawa EASJ menunjukkan kesan perlidungan terhadap keradangan yang dirangsang oleh LPS dan tekanan oksida dirangsang oleh H_2O_2.Kegiatan ini berkaitan dengan kegiatan pengisyaratan aktiviti cAMP yang tinggi. Mekanisme ini menyumbang, sekurang-kurangnya sebahagian, kepada tindakan-tindakan anti-radang yang ditunjukkan oleh tumbuhan ini.

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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 Master of Science. The members of the Supervisory Committee were as follows:

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Ang-II	Angiotensin II
ANOVA	Analysis of variance
Ca^{2+}	Cytosolic calcium
$C3_a$	Complement component 3
$C5_a$	Complement component 5a
CAMs	Cell adhesion molecules
cAMP	Cyclic adenosine monophosphate
DAPI	4′,6-diamidino-2-phenylindole
DCFH-DA	Dexamethsaone, 2′, 7′-dichlorodihydrofluorescein diacetate
DDA	Disc diffusion assay
DMSO	Dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
EASJ	Ethyl acetate extract of *Stachytarpheta jamaicensis* (L.) Vahl
ELISA	Enzyme Linked Immuno-Sorbent Assay
ENOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
F-actin	Filamentous-actin
FAK	Focal adhesion kinase
FGF	Fibroblast growth factor
FITC	Fluorescein-isothiocyanate dextran
FRAP	Ferric Reducing Ability of Plasma
H_2O_2	Hydrogen peroxide

HDLC	HDL-cholesterol
HUVECs	Human umbilical vein endothelial cells
ICAM-1	Intracellular adhesion molecule-1
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-8	Interleukin-8
LPS	Lipopolysaccharides
MIC	Minimum Inhibitory Concentration assay
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
n-$C_{29}H_{60}$	Nonacosane
n-$C_{30}H_{62}$	Triacontane
n-$C_{32}H_{66}$	Dotriacontane
n-$C_{31}H_{64}$	Hentriacontane
n-$C_{33}H_{68}$	Tritriacontane
n-$C_{34}H_{70}$	Tetratriacontane
n-$C_{35}H_{72}$	Pentatriacontane
NO	Nitric oxide
NSAIDS	Non-steroidal anti-inflammatory drugs
O_2^-	Chemical formula of superoxide anion
OH	Chemical formula of hydroxyl radical
PBS	Phosphate buffer saline
PECAM-1	Platelet endothelial cell adhesion molecule-1
Rac1	Ras-related C3 botulinum toxin substrate 1

RAW264.7	murine macrophage derived from Abselon Leukemia virus-induced tumour
ROS	Reactive oxygen species
S1P	Sphingosine 1-phosphate
sCAMS	Soluble cell adhesion molecules
S.E.M	Standard error of mean
sICAM-1	Soluble Intracellular adhesion molecule-1
SJ	*Stachytarpheta jamaicensis* (L.) Vahl
SPSS	Statistical Package for Social Sciences
sVCAM-1	Soluble Vascular cell adhesion molecule-1
TC	Total cholesterol
TG	Plasma triglycerides
TNF-α	Tumor necrosis factor alpha
UPM	Universiti Putra Malaysia
VCAM-1	Vascular cell adhesion molecule-1
VE-cadherin	Vascular Endothelial-cadherin
VEGF	Vascular endothelial growth factor

CHAPTER 1

GENERAL INTRODUCTION

1.1 Research background

Inflammation is a protective mechanism of the body to eliminate the harmful invaders as well as initiates the healing process for the injured tissues. However, when the injury is persistent and the resolution of inflammation is inadequate, the state of inflammation becomes chronic and irreversible (Serhan et al., 2008). Recent evidence suggested that inflammatory processes are thought to lie in the pathogenesis of many serious diseases, such as cardiovascular disease, cancer, diabetes and sepsis, that have been leading to death to the human population in the world today and are still worrying as the prevalence increases comprehensively (WHO, 2014). This fact indeed emphasized the importance of understanding the inflammatory mechanisms and the necessity of development of potent anti-inflammatory therapies. The result of inflammation-related diseases is an unwarranted inflammatory response, characterized by a cascade of reaction with flares of increased inflammatory activity (Bröms, 2015).

The loss of control over inflammatory response can be provoked by either exogenous stimulus (such as lipopolysaccharides, LPS) or endogenous stimulus (such as reactive oxygen species, ROS). At higher concentrations, these stimuli cause the excessive production of pro-inflammatory mediators, which in turn altered the cellular phenotype from a quiescent state to an activated state, resulting in the activation of inflammatory signalling events (Larsen and Henson, 1983).

The current treatment of chronic inflammation with non-steroidal anti-inflammatory drugs (NSAIDs) have been showing high efficacy in subduing inflammation. Unfortunately, these medicines have been reported to induce severe side effects such as cardiovascular disease (Arfè et al., 2016) and gastric ulceration (Dhikav et al., 2003) which can be fatal. And hence, the need to explore alternative approach is required for the treatment of inflammation-related diseases.

Natural products have been and are still continue to be used in every country of the worldwide. Owing to the fact that traditional medicines are accessible, offer good efficacy and display little side effects, there has been an emerging attention and interest in discovering the potentiality of traditional medicines. *Stachytarpheta jamaicensis* (L.) Vahl (SJ), which is known as "Jolok Cacing"

locally, has been traditionally used as a remedy against numerous disorders (Okwu and Ohenhen, 2010). In addition, this plant also has been employed as anti-inflammatory agent (Sulaiman et al., 2009).

The anti-inflammatory properties of SJ were confirmed by a study conducted by Sulaiman et al. (2009) on animals where animals were exposed to acute and chronic inflammation. SJ exerted potential antinoiceptive and anti-inflammatory actions in animals, suggesting that it offers a promising treatment substitute for inflammatory disorders. However, SJ that was used in this study have not yet been scientifically evaluated for its efficacy as an anti-inflammatory agent *in vitro* and the possible mechanisms of action. The anti-inflammatory activities of the ethyl acetate leaves extract of SJ were, therefore, determined in this study.

1.2 Statement of the problem

Inflammation-related diseases are a leading cause of death in the world today and has been an economic concern for many societies globally. Chronic diseases includes atherosclerosis, cardiovascular disorders, as well as cancers have been reported to be associated with inflammation (Khansari et al., 2009; Vaziri and Rodriguez-Iturbe, 2006). It is well established that excessive release of pro-inflammatory cytokines and reactive oxygen species aggravate inflammatory injury which ultimately leads to serious cell and tissue damage in chronic inflammatory states (Hold and El-Omar, 2008).

Current treatment approach for the treatment of chronic inflammatory conditions is mainly from NSAIDs, for example aspirin, ibuprofen and diclofenac (Gøtzsche, 2000). Although these drugs provide effective therapy in most conditions, NSAIDs have been hindered by adverse side effects (e.g. asthma, cardiovascular risks and gastrointestinal damage). In addition, long-term consumption of NSAIDs caused hepatoxicity which resulted in liver failure (Bessone, 2010). In fact, their use is restricted. Thus, it is crucial to search for an alternative that can possess optimum anti-inflammatory effects with little side effects.

1.3 Justification of the study

The justification of participatory research is based on the fact that although conventional medicines (NSAIDs) have consistently asserted that its treatments are scientifically proven to have therapeutic or curative effects, they are often to be extravagant or at times inaccessible, as well as have been reported to elicit many adverse effects associated with conventional drug therapies (Houghton,

1995). The use of traditional herbal remedies have been established as alternative treatment modalities which claimed to be safe and possessed great effectiveness (C Recio et al., 2012). Beyond these widespread and expanding use of herbal medicines, however, a major drawback of these medicinal systems is that lacking of scientific evidences to support its claims of efficacy and safety. Research into plants with alleged folkloric use an anti-inflammatory agents is therefore a logical undertaking in the search of new anti-inflammatory drugs as has been clearly demonstrated in the foregoing discussion.

1.4 Objectives

1.4.1 Main objective

The main aim of the present study is to scientifically investigate the anti-inflammatory properties of ethyl acetate leaves extract of *Stachytarpheta jamaicensis* (L.) Vahl (EASJ) plant on *in vitro* and *in vivo* models of inflammation, and to explore the possible molecular mechanisms responsible for its actions.

1.4.2 Specific objectives

The specific objectives of the study are to:

1) Determine the effect of EASJ on nitric oxide (NO) production in lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophage.
2) Determine the effect of EASJ on the expression of soluble cellular adhesion molecules (sCAMs) on LPS-induced HUVECS.
3) Investigate the anti-inflammatory effect of EASJ on LPS-challenged vascular permeability in animal models.
4) Determine the effect of EASJ on H_2O_2-mediated endothelial hypermeability in HUVECs.
5) Investigate the effect of EASJ on the morphological changes of actin cytoskeleton and adherens junction on HUVECs in response to H_2O_2 challenge.
6) Determine the effect of EASJ on the ROS scavenging activity in H_2O_2-induced HUVECs
7) Explore the mechanism of action of EASJ by measuring cAMP signalling activity in HUVECs triggered by H_2O_2.

1.5 Hypothesis

1. EASJ will attenuate the increased production of NO stimulated by LPS in RAW 264.7 cells.
2. EASJ will inhibit the upregulated expression of sCAMs in LPS-mediated HUVECs.
3. EASJ will restrict the LPS-induced vascular hyperpermeability *in vivo*
4. EASJ will suppress the *in vitro* endothelial permeability activated by H_2O_2 in HUVECs.
5. EASJ will inhibit the actin cytoskeletal remodelling and disintegration of adherens junction in H_2O_2-challenged HUVECs.
6. EASJ will inhibit the excessive production of ROS in HUVECs stimulated by H_2O_2.
7. EASJ will enhance the production of endothelial barrier protective mediator, cAMP in HUVECs.

1.6 Overview of the study (Framework)

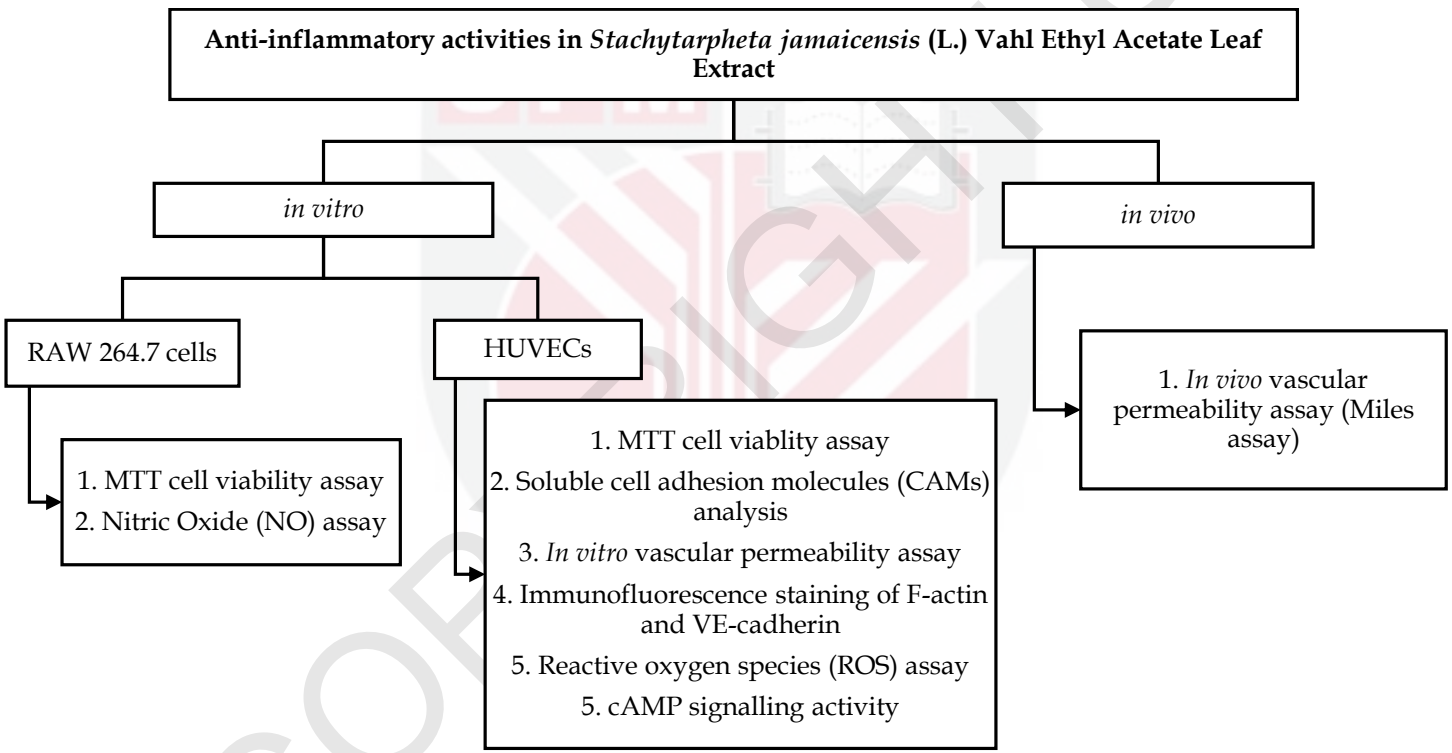

Figure 1.1: Conceptual Framework of the Study

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