UNIVERSITI PUTRA MALAYSIA

EFFICACY OF Labisia pumila Benth. & Hook. f. AND Vernonia amygdalina delile LEAF EXTRACTS IN ALLEVIATING POSTMENOPAUSAL OSTEOARTHRITIS IN RATS

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By

IFFAH NADHIRA MADZUKI

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

September 2018

I dedicated this thesis to those who value
Malaysia`s herbal treasure

Abstract of thesis presented to the senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

EFFICACY OF L*abisia pumila* Benth. & Hook. f. AND *Vernonia amygdalina* delile LEAF EXTRACTS IN ALLEVIATING POSTMENOPAUSAL OSTEOARTHRITIS IN RATS

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IFFAH NADHIRA BINTI MADZUKI

September 2018

Chair : Prof. Suhaila Mohamed, PhD
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Osteoarthritis (OA) is a degenerative condition that causes pain and joint stiffness, predominantly in women aged over 60 years. Development of inflammation in OA joint can trigger chondrocytes to produce proteolytic enzymes that cause cartilage degeneration. Therefore, non-steroidal anti-inflammatory drugs (NSAIDs) is the most common medication prescribed for OA to control inflammation and reduce pain. However, NSAIDs eventually exert adverse side effects. Developing alternative medicines for OA from herbal plant that naturally contains anti-inflammatory and antioxidant properties may offer safer treatment. Hereby, the current study was conducted to investigate the efficacy of *Labisia pumila* and *Vernonia amygdalina* leaf extracts in alleviating postmenopausal OA.

In the preliminary study, the *ex vivo* explant culture was used to determine the effect of the several plant extracts on inhibition of cartilage degradation under inflammatory conditions induced by interleukin 1 beta (IL-1β). IL-1β plays a major role in OA by stimulating production of inflammatory and catabolic factors. Therefore, the amount of proteoglycan release and nitric oxide (NO) production by the cartilage and chondrocyte morphology were evaluated. Among the extracts, *L. pumila* and *V. amygdalina* leaves show the best chondroprotective potential. Hence, *L. pumila* and *V. amygdalina* were selected to test on animal for their efficacy. In *in vivo* study, female Sprague Dawley rats were grouped into (n=8): sham-treated healthy (SHAM), non-treated ovariectomised OA, positive control (diclofenac-treated), treated *L. pumila* and *V. amygdalina* leaf extracts at 150 and 300 mg/kg body wt, and combination of extracts, each at 150 mg/kg body wt. The rats were subjected to bilateral ovariectomy and OA was induced by intra-articular injection of monosodium iodoacetate (MIA) (3 mg in 50 µl saline). The SHAM rats received sham-operated and saline solution intra-articular injection. SHAM and non-treated OA rats were administered with deionised water while treatment groups received leaf extracts or diclofenac by oral gavage once daily for 8 weeks. After 8 weeks of treatment, the collected tibiofemoral joint, serum and urine samples were examined for

macroscopic, biochemical, joint histological and bone turnover changes. Then, the efficacy of bioactive compounds that present in the extracts; quercetin, caffeic acid, gallic acid, apigenin, kaempferol, kaempferol-3-o-glucoside, myricetin, rutin, and naringin in the exertion of chondroprotective effect was determined in IL-1β pre-treated cartilage.

The preliminary study showed the extracts significantly reduced proteoglycan release and NO production by the cartilage. In the animal model, the extracts significantly reduced collagenase activity, inflammation and cartilage catabolism biomarkers and increased expression of cartilage synthesis and bone formation biomarkers. The extracts also mitigated cartilage fibrillation and erosion, subchondral bone lesions, osteophyte formation and epiphyseal/metaphyseal trabecular bone loss. The extracts significantly ($p<0.05$) increased volume, density, trabecular thickness and separation, and reduced porosity in epiphyseal/metaphyseal bone trabeculum. The study on chondroprotective effect of the extracts' bioactive compounds by *ex vivo* study showed that, quercetin, caffeic acid, gallic acid, kaempferol, kaempferol-3-O-glucoside, apigenin, myricetin, rutin and naringin significantly ($p<0.05$) reduced nitric oxide production and proteoglycan release compared to non-treated cartilage. Caffeic acid, myricetin, naringin and rutin inhibited collagenase activity and prevented inflammation of the cartilage, comparable to diclofenac.

This study concluded that both *Labisia pumila* and *Vernonia amygdalina* leaf extracts effective in ameliorating cartilage degradation and subchondral bone alteration in the postmenopausal OA, comparable to diclofenac.

Abstrak tesis ini dikemukan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KEBERKESANAN EKSTRAK DAUN L*abisia pumila* Benth. & Hook. f. DAN *Vernonia amygdalina* delile DALAM MEREDAKAN OSTEOARTRITIS PASCAMENOPAUS DI UJIKAJI TIKUS

Oleh

IFFAH NADHIRA BINTI MADZUKI

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Pengerusi : Prof. Suhaila Mohamed, PhD
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Osteoartritis (OA) merupakan keadaan penyahjanaan pada sendi yang menyebabkan kesakitan dan kekakuan, yang kebanyakannya berlaku pada wanita berusia lebih 60 tahun. Perkembangan keradangan di sendi OA boleh mencetus kondrosit menghasilkan enzim proteolitik yang menyebabkan degenerasi rawan. Oleh itu, drug anti-radang bukan steroid (NSAID) adalah ubat yang paling biasa dipreskripsikan untuk merawat OA bagi mengawal keradangan dan mengurangkan kesakitan. Bagaimanapun, NSAID akan membawa kesan sampingan buruk. Penghasilan alternative ubat untuk OA dari tumbuhan herba yang semulajadinya mengandungi anti radang dan antioksida mungkin boleh menawarkan rawatan yang lebih selamat. Justeru itu, kajian ini dijalankan untuk mengkaji keberkesanan ekstrak daun *Labisia pumila* dan *Vernonia amygdalina* dalam meredakan OA pascamenopaus di ujikaji tikus.

Dalam kajian awal, kultur eksplan rawan *ex vivo* telah diguna untuk menentukan kesan beberapa ekstrak tumbuhan dalam perencatan degradasi rawan dibawah pengaruh radang interleukin 1 beta (IL-1β). IL-1β memainkan peranan besar dalam menghasilkan radang dan katabolic factor. Oleh itu, jumlah pembebasan proteoglikan and penghasilan nitrik oksida (NO) daripada rawan dan morfologi kondrosit di nilai. Diantara ekstrak-ekstrak, *L. pumila* and *V. amygdalina* menunjukkan potensi kondropelindungan yang terbaik. Oleh itu, *L. pumila* and *V. amygdalina* dipilih untuk diuji keberkesanannya ke atas haiwan. Dalam kajian *in vivo*, tikus Sprague-Dawley betina di bahagikan kepada 8 kumpulan (n=8); sihat diperlaku palsu (SHAM), OA tidak diperlaku, kawalan positif (diperlaku diklofenak), diperlaku ekstrak daun pokok *L. pumila* and *V. amygdalina* pada kadar 150 dan 300 mg/kg berat badan dan gabungan kedua-dua ekstrak yang setiap satu pada kadar 150 mg/kg berat badan. Ovariektomi bilateral dan suntikan mononatrium iodoasetat (MIA) (3 mg dalam 50 µl larutan garam) pencetus OA secara intraartikular dijalankan pada tikus. Tikus SHAM menerima pembedahan palsu dan disuntik larutan salin secara intraartikular. Tikus SHAM and OA tidak dipelaku menerima air dinyah-ion sementara, kumpulan diperlaku menerima ekstrak dan diklofenak secara gavaj oral sekali setiap hari selama 8 minggu. Selepas 8 minggu rawatan, sempel sendi tibiofemur, serum dan urin diperiksa bagi perubahan mikroskopi, biokimia, histologi sendi dan pusing ganti tulang. Keberkesanan sebatian biokatif yang terkandung dalam ekstrak, iaitu kuersetin,

asid kafeik, acid galik, apigenin, kampferol, kampferol-3-o-glukosida, mirisetin, rutin, dan naringin, dalam pemberian kesan kondroperlindungan ditentukan dalam rawan pralaku IL-1β.

Kajian awal menunjukkan ekstrak secara tererti ($p<0.05$) mengurangkan pembebasan proteoglikan dan penghasilan NO daripada rawan. Dalam haiwan model, ekstrak ini secara tererti ($p<0.05$) mengurangkan aktiviti kolagenase, biopenanda keradangan, dan katabolisme rawan dan meningkatkan penyataan biopenanda pembentukan tulang dan sintesis rawan. Ekstrak ini juga mengurangkan pemfibrilan and hakisan rawan, lesion tulang subkondral, pembentukan osteofit, dan kehilangan tulang trabekular epifiseal/metafiseal. Ekstrak secara tererti ($p<0.05$) meningkatkan isipadu dan ketumpatan, ketebalan dan pengasingan trabekular, dan mengurangkan keronggaan trabekulum tulang epifiseal/metafiseal. Kajian terhadap kesan kondroperlindungan sebatian bioaktif milik ekstrak oleh *ex vivo* menunjukkan kuersetin, acid kafeik, asid galik, keampferol, kaepmferol-3-O-glukosida, apigenin, mirisetin, rutin, and naringin secara tererti ($p<0.05$) mengurangkan penghasilan NO dan pembebasan proteoglikan berbanding rawan yang tidak dirawat. Asid kafeik, mirisetin, naringin, dan rutin merencat aktiviti kolagenase and menghalang berlakunya keradangan pada rawan, standing dengan diklofenak.

Kajian in menyimpulkan ekstrak daun *Labisia pumila* and *Vernonia amygdalina* berkesan dalam mengurangkan degradasi rawan dan ubah suai tulang subkondral OA pasca-menopaus, setanding dengan diklofenak.

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I certify that a Thesis Examination Committee has met on (data of viva voce) to conduct the final examination of Iffah Nadhira Binti Madzuki on her thesis entitled "Efficacy of *Labisia Pumila* And *Vernonia Amygdalina* Leaf Extracts in Alleviating Postmenopausal Osteoarthrtitis in Rats" 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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ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
AGE	Advanced glycation end products
BMD	bone mineral density
BV/TV	Bone volume fraction
CASP3	Caspase 3
COX-2	Cyclooxygenase-2
CTX-II	C-terminal crosslinked telopeptide type II collagen
ECM	Extracellular matrix
ELISA	Enzyme-linked immunosorbent assay
ESR1	Estrogen receptor alpha
FTIR	Fourier transform infrared
GAG	glycosaminoglycan
H&E	Haematoxylin and eosin
HGF	Hepatocyte growth factor
HIF	Hypoxia inducible factor
HPLC	High performance liquid chromatography
IL	Interleukin
IL-1β	Interleukin-1 beta
iNOS	Inducible nitric oxide synthase
KL	Kellgren-Lawrence
LP	*Labisia pumila*
LP+VA	*Labisia pumila* and *Vernonia amygdalina*
MAPK	Mitogen activated protein kinase
MIA	Monosodium iodoacetate
MMP	Matrix metalloproteinase
NF-ƙB	Nuclear factor kappa B
NO	Nitric oxide
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International scoring
OPG	Osteoprotegerin
PGE_2	And prostaglandin E2
PIINP	Procollagen type II N-terminal propeptide
PINP	Procollagen type 1 N-terminal propeptide
RANKL	Receptor activator of nuclear kappa-beta ligand
ROS	Reactive oxygen species
RUNX2	Runt-related transcription factor 2
SERM	Selective estrogen receptor modulator
SO	With Safranin O
SOD	Superoxide dismutase
TB	Toluidine blue
Tb. Sp	trabecular separation
Tb. Th	trabecular thickness and
TGF-β1	Transforming growth factor beta 1
TIMP	Tissue inhibitor metalloproteinases
TNF-α	And tumour necrosis factor-alpha
VA	*Vernonia amygdalina*

VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1 Background and hypothesis

Osteoarthritis (OA) is a joint degeneration disease causing pain in joint especially knee and hip and commonly due to aging and majorly affect those at age of 65 years. According to the World Health Organisation (WHO), 9.6% of men and 18% of women aged over 60 years are affected with OA (World Health Organisation, 2018). In Malaysia, it is estimated that 23% of the elderly at the age of over 55 years and 33% at the age of over 65 years suffered from knee pain (Ismail, 2008).

The symptoms of OA include pain, inflammation, morning stiffness and decrease physical function which then impair quality of life. The OA is characterised by cartilage damage, formation of osteophyte and sclerosis, subchondral bone changes, and tendon and synovium tissue inflammation. Although OA has been considered as cartilage disorder, however the recent findings show OA also involved subchondral bone deterioration (Burr & Gallant, 2012; Goldring & Goldring, 2016). The articular cartilage degradation involved overexpression of matrix degrading enzymes, inflammation markers and oxidative stress, and loss of proteoglycan and collagen matrix network. Meanwhile, OA subchondral bone had sclerosis, osteophyte formation, trabecular plate perforation, trabecular bone loss and bone cysts (Li et al., 2013 and Burr & Gallant, 2012).

Although the exact pathological mechanism of OA is still unclear, the current evidences indicates that pro-inflammatory mediators including interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α) play a major role in OA pathogenesis. These pro-inflammatory cytokines induce the release of other pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and aggrecanses (a disintegrin and metalloproteinase with thrombospondin motifs, ADAMTS) that break down the cartilage network (Roy et al., 2015; Loeser et al., 2012). In addition, IL-1β and TNF-α stimulate chondrocytes to elevate the expressions of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE_2), which contribute to pain (Rai et al., 2008).

Generally, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are prescribed to OA patients to alleviate pain. These treatments have been proven effective in reducing symptomatic OA (da Costa et al., 2017) but the adverse effects of these current prescriptions have raised concern among consumers. The long term usage of NSAIDs was reported to cause urticaria, angioedema and/or anaphylaxis (Kowalski et al., 2013), cardiovascular health issues (Trelle et al., 2011), and gastroduodenal lesion (Traversa et al., 1995).

Counteracting inflammation pathway by plant-derived sources may exert less adverse effects and offer safer alternative treatment for OA. The Malaysian herbs, *Labisia pumila* (known as Kacip Fatimah) and *Vernonia Amygdalina* (known as Bitter leaves or Bismillah) have been reported to exhibit anti-inflammatory and anti-oxidative properties (Karimi et al., 2013; Rodrigues et al., 2016). *Labisia pumila* is known traditionally to facilitate childbirth (Burkill, 1935) and protects bone against osteoporosis (Fathilah et al., 2012). Meanwhile, *Vernonia amygdalina* used to treat malaria (Iwalokun, 2001) and diabetes (Atangwho et al., 2013). Therefore, these herbs are hypothesized to interfere with inflammation cascade in OA, and reduce pain, cartilage degradation and subchondral bone alteration.

1.2 General objective

To investigate the efficacy of *Labisia pumila* and *Vernonia amygdalina* leaf extracts in alleviating postmenopausal OA in rats.

1.3 Specific objectives

1) To investigate the cartilage protective effects of *L. pumila* and *V. amygdalina* leaf extracts in OA-induced ovariectomised rat model.
2) To study subchondral bone protective effects of of *L. pumila* and *V. amygdalina* leaf extracts in OA-induced ovariectomised rat model.
3) To understand the effects of the extracts on cartilage and subchondral bone via mRNA expressions.
4) To identify the compounds present in the of *L. pumila* and *V. amygdalina* leaf extracts
5) To verify the chondroprotective effects of bioactive compounds in *L. pumila* and *V. amygdalina* leaf extracts in *ex vivo* bovine cartilage explant model.

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