UNIVERSITI PUTRA MALAYSIA

EFFECTS OF Morinda citrifolia L. AND Morinda elliptica L. LEAF ETHANOLIC EXTRACTS ON FATIGUE AND OSTEOARTHRITIS

WAN NURFARAHIN BINTI WAN OSMAN

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By

WAN NURFARAHIN BINTI WAN OSMAN

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I dedicated this thesis to the society.

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

EFFECTS OF *Morinda citrifolia* L. and *Morinda elliptica* L. LEAF ETHANOLIC EXTRACTS ON FATIGUE AND OSTEOARTHRITIS

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WAN NURFARAHIN BINTI WAN OSMAN

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Chair: Prof. Suhaila Mohamed, PhD
Faculty: Institute of Bioscience

Morinda citrifolia (MC) has been used in folk remedies by Polynesians for over 2000 years and have a broad range of therapeutic effects. *Morinda elliptica* (ME) or locally known as 'Mengkudu kecil' used by Malaysian as medicinal plants for treatment of several health problems. This study investigated the effect of *M. citrifolia* and *M. elliptica* ethanolic leaf extracts on fatigue in mice and joint cartilage degradation in bovine explants culture and in monosodium iodoacetate (MIA)-induced osteoarthritis (OA) rats model.

Exercise-induced fatigue was used to examine the anti-fatigue effects of *M. citrifolia* and *M. elliptica* leaf ethanolic extract. Balb/C female mice were divided into six groups (n=10): Control; Green tea (200 mg/kg); MCL (200 mg/kg); MCH (400 mg/kg); MEL (200 mg/kg) and MEH (400 mg/kg). The force-swim test study was assessed after six weeks of treatments. The mice were evaluated for endurance test via swimming time to exhaustion, biochemical and gene expression analyses. The swimming time was quadrupled after being treated with a high dose 400mg/kg BW of *M. citrifolia* compared to the control group. *M. citrifolia* and *M. elliptica* leaf extract increased liver and muscle glycogen contents and reduced blood lactic acid and blood urea nitrogen level. The extracts showed improvement in endurance capacity in mice with increased fatty acid and carbohydrate metabolism, increased in the anti-oxidant responses, decreased in substrate depletion in cell and increased in mitochondrial biogenesis.

Osteoarthritis (OA) study was evaluated using monosodium-iodoacetate-induced rat model. Sprague-Dawley male rates were divided into seven groups (n=8): Healthy; non-treated OA; OA+Diclofenac (5 mg/kg); OA+MCL (200 mg/kg); OA+MCH (400 mg/kg); OA+MEL (200 mg/kg); and OA+MEH (400 mg/kg). All rats were osteoarthritis-induced by intra-articular injection of 3 mg of monosodium iodoacetate into right knee joints. After six weeks of treatments, the rats were evaluated for knee

osteoarthritis via physical (radiology and histology observations), biochemical, ELISA and gene expression analyses. The rats treated with extracts showed reduction of cartilage erosion and smooth articular cartilage structure compared to the untreated rats. *M. citrifolia* and *M. elliptica* leaf extracts significantly decreased serum level of MMP1, MMP3, MMP13, PIINP, PIICP, CTXII, TNFα, IL-1β, NO and increased serum PINP compared to the non-treated group. The extracts reduced osteoarthritis progression by inhibiting the articular cartilage and collagen degradation and suppressing the inflammation responses. The extracts also improved the structure of subchondral bone which was affected in progressive osteoarthritis.

It can be concluded in this study that both *M. citrifolia* and *M. elliptica* leaf extracts helped in fatigue elimination by enhancing the energy regulation and production that benefit physical activities. The extracts also protected the articular cartilage in arthritis joints by reducing the cartilage degradation and enhancing proteoglycan and collagen synthesis, providing a natural alternative treatment for osteoarthritis.

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

KESAN ESKTRAK ETANOL DAUN *Morinda citrifolia* L. dan *Morinda elliptica* L. TERHADAP KELETIHAN DAN OSTEOARTHRITIS

Oleh

WAN NURFARAHIN BINTI WAN OSMAN

Disember 2016

Pengerusi: Prof. Suhaila Mohamed, PhD
Fakulti: Institut Biosains

Morinda citrifolia (MC) telah digunakan sebagai rawatan tradisional oleh penduduk Polinesia selama lebih 2000 tahun dan mempunyai pelbagai kesan terapeutik. *Morinda elliptica* (ME) atau mengkudu kecil telah digunakan oleh rakyat Malaysia sebagai pokok ubatan untuk beberapa masalah kesihatan. Kajian ini akan melaporkan kesan esktrak etanol daun *M. citrifolia* dan *M. elliptica* untuk menghilangkan keletihan dan degradasi rawan pada sendi dalam kultur bovin eksplant dan model tikus osteoarthritis yang diransang oleh monosodium-iodoacete (MIA).

Tikus betina Balb/c telah dibahagikan kepada enam kumpulan (n=10): Kumpulan kawalan; the hijau (200 mg/kg); MCL (200 mg/kg); MCH (400 mg/kg); MEL (200 mg/kg) dan MEH (400 mg/kg). Ujian senaman dengan berenang di akses selepas enam minggu rawatan diberikan. Tikus di ukur kadar daya ketahanan melalui tempoh masa berenang sehingga keletihan, analisis biokimia dan analisi keekspresian gen. Dos tinggi tumbuhan *M. citrifolia* (400mg/kg BW) menunjukkan tempoh berenang paling lama sebanyak empat kali ganda berbanding kumpulan kawalan. Ekstrak daun *M. citrifolia* and *M. elliptica* meningkatkan tahap glicogen dalam hati dan otot, dan menurunkan tahap asid laktik dan urea nitrogen dalam darah. Kedua-dua ekstrak daun menunjukkan peningkatan di dalam kapasiti ketahanan dengan penambahan metabolisma asid lemak dan karbohidrat, meningkatkan aktiviti anti-oksida, dan juga mengurangkan penurunan substrak di dalam sel dan memantapkan biogenesis mitokondria

Kajian osteoarthritis (OA) telah dinilai menggunakan model haiwan yang diransang dengan monosodium-iodoasetat. Tikus jantan Sprague-Dawley telah dibahagikan kepada tujuh kumpulan (n=8): Kumpulan kawalan; kumpulan yang tidak dirawat; OA+Diclofenac (5 mg/kg); OA+MCL (200 mg/kg); OA+MCH (400 mg/kg); OA+MEL (200 mg/kg); dan OA+MEH (400 mg/kg). Semua tikus di cucuk dengan 3 mg monosodium-iodoasetat ke lutut kaki kanan untuk mencetuskan osteoarthritis. Selepas enam minggu rawatan, tikus di ukur kadar perkembangan osteoarthtritis melalui kaedah fizikal (radiologi dan histologi), biokimia, ELISA dan analisis

keekspresian gen. Tikus yang menerima rawatan menunjukkan penambah-baikan pada kartilag berbanding dengan kumpulan kawalan. Daun ekstrak *M. citrifolia* dan *M. elliptica* meningkatkan tahap serum MMP1, MMP3, MMP13, PIINP, PIICP, CTXII, TNFα, IL-1β, NO dan menurunkan tahap serum PINP berbanding kumpulan yang tidak menerima rawatan. Rawatan ini telah mengurangkan perkembangan osteoarthritis dengan menghalang degradasi rawan artikular dan kolagen dan juga melalui penindasan respon inflamasi. Ekstrak itu juga menambah-baik struktur tulang subkondral yang dijejaskan oleh perkembangan osteoarthritis.

Dengan ini dapat disimpulkan, kedua-dua *M. citrifolia* dan *M. elliptica* membantu dalam melawan keletihan dengan menambah-baik kawalan dan pengeluaran tenaga, yang secara tidak lansungnya memberi manfaat untuk aktiviti fizikal dan penyembuhan penyakit. Ekstrak ini juga melindungi rawan articular dalam sendi arthritis, di mana ia merupakan salah satu daripada rawatan semulajadi alternatif untuk osteoarthritis.

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I certify that a Thesis Examination Committee has met on 1st of December 2016 to conduct the final examination of Wan Nurfarahin binti Wan Osman on her thesis entitled ("Effects of *Morinda citrifolia L. and Morinda elliptica L.* Leaf Ethanolic Extracts on Fatigue and Osteoarthritis 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.

Members of the Thesis Examination Committee were as follows:

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Professor,
Institute of Bioscience,
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Rasedee @ Mat bin Abdullah, PhD
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Faculty of Veterinary Medicine,
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Abbas Ali Mahdi, PhD
Professor,
King George's Medical University,
India
(External Examiner)

……...
NOR AINI AB. SHUKOR, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 28 February 2017

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:

Suhaila Mohamed, PhD
Professor
Institute of Bioscience
Universiti Putra Malaysia
(Chairman)

Noordin Mohamed Mustapha, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Md. Zuki Abu Bakar @ Zakaria, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

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Name of
Chairman of
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Committee: _____

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LIST OF ABBREVIATIONS

ACADM	Acyl-CoA dehydrogenase
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
AMPK	Protein kinase, AMP-activated, alpha 1 catalytic subunit 1
ATP	Adenosine triphosphate
OX2	Cyclooxygenase 2
CTXII	C telopeptide type II collagen
COX4I2	cytochrome C oxidase subunit 4I2
ECM	Extracellular matrix
FAT/CD36	Fatty acid translocase
FDA	Food and Drug Administration
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GTP	Green tea polyphenols
IL	IL Interleukin
IL-1β	IL-1β Interleukin 1beta
INFγ	Interferon-gamma
MC	*Morinda citrifolia*
ME	*Morinda elliptica*
MCL	*Morinda citrifolia* low dose
MCH	*Morinda citrifolia* high dose
MEL	*Morinda elliptica* low dose
MEH	*Morinda elliptica* high dose
MIA	Mono-iodoacetate
MMP	Matrix metalloproteinase
NRF1	Nuclear respiratory factor 1
NRF2	Nuclear factor (erythroid-derived 2)-like 2
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PCr	Phosphocreatinine
PDK4	Pyruvate dehydrogenase kinase 4
PGC1α/PPARGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PGE2	Prostaglandin E2
PINP	Procollagen Type I N-terminal propeptides
PIINP/PIICP	Pro-collagen type II N and C terminal
RA	Rheumatoid arthritis
ROS	Reactive oxygen species
SOD2	superoxide dismutase 2, mitochondrial
TFAM	mitochondrial transcription factor A
TIMP	Tissue inhibitors of metalloproteinases
TNFα	Tumor necrosis factor alpha
UCP	Uncoupling protein
WHO	World health organization

CHAPTER 1

INTRODUCTION

1.1 Research background

Fatigue (physical, mental or both) can be described as the lack of motivation and energy, which not to be confused with drowsiness (the need to sleep). Usual terms used are exhausted, lethargic and tired. Chronic fatigue syndrome occurs in various neurological, psychiatric and systemic diseases (Binu et al., 2005). The available modern medicine for curing chronic fatigue is still limited, thus potential alternatives from traditional medicine to combat fatigue is worth investigating. Ergogenic functional foods help improve physical performance or suppress fatigue by enhancing energy production, regulation or efficiency. It is not only useful in sports but also to combat illnesses.

Osteoarthritis (OA) is the most common type of degenerative disease and it is the fourth leading cause of disability worldwide. The disease usually develops in the elderly and is more common in women than in men. In 2010, WHO estimated that 524 million people were aged 65 or older and this number is expected to triple which represents 16% of the world's population by 2050 (Malaysia Health Technology Assessment Section, 2013). Osteoarthritis affects daily life of patients especially in movement. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common treatment for OA throughout the world. Given that the high cost and risk for negative side effects of drug pharmacotherapy including the NSAIDs, there is urgent need for new treatment options for patients suffering from OA.

Morinda citrifolia L. has been used in folk remedies by Polynesians for over 2000 years (Tabrah and Eveleth, 1966). It is an edible and medicinal tropical plant and is the second out of 12 most popular plants used in herbal remedies to treat various diseases (Krauss, 1993). Two clinical studies involving post-menopausal women and athletes demonstrated the *M. citrifolia* fruit juice property to improve endurance (Langford et al., 2004; Palu et al., 2008). Another *in vivo* study on aged mice with Tahitian Noni Juice (TNJ) given orally showed significantly longer swimming and rotarod time when compared with young and aged control mice (Ma et al., 2007). Fruit TNJ also showed potential therapeutic effect for osteoarthritis patients as well as improved their quality of life and symptoms (Wang et al., 2011). *Morinda elliptica* L. or locally known as 'Mengkudu kecil' used by Malaysian as medicinal plants for treatment of several health problems. The leaves are used for headache, cholera, diarrhea, fever, loss of appetite and wounds (Burkill et al., 1966). The natural pigment extracted from *M. elliptica*, anthraquinones have been used traditionally as dyes (Burkill, 1935) and have shown antimicrobial, antiviral, cytotoxic, antileukemic, anti-cancer and antioxidant activities (Ali et al., 2000; Jasril et al., 2003). There is no report on anti-fatigue and anti-osteoarthritis study of *M. citrifolia* and *M. elliptica* leaf.

The present study investigates the effect and mechanism of *M. citrifolia* and *M. elliptica* leaf ethanolic extract on fatigue elimination by using swimming test model and osteoarthritis treatment using monosodium iodoacetate-induced animal model.

1.2 Hypothesis

The *M. citrifolia* and *M. elliptica* (either one or both) leaf alcohol extract enhance performances and endurance of exercised mice through the regulation of complexes of proteins and expression of genes involved in fatigue mechanism. Either one or both *M. citrifolia* or *M. elliptica* leaf alcohol extract mitigate the progression of monosodium-iodoacetate-induced osteoarthritis by suppressing proteins and genes involved in cartilage degradation and stimulating the expression of proteins and genes involved in proteoglycan and chondrocytes synthesis.

1.3 General objective

To determine the potential of *M. citrifolia* and *M. elliptica* leaf alcoholic extract as fatigue and osteoarthritis alternative treatment.

1.4 Specific objectives

1. To determine the anti-fatigue effects of *M. citrifolia* and *M. elliptica* leaf extract
2. To determine the protective effect of *M. citrifolia* and *M. elliptica* leaf extract on cartilage degradation in IL-1β-induced bovine cartilage explants culture
3. To determine the effect of *M. citrifolia* and *M. elliptica* leaf extract in enhancing repair of articular cartilage in osteoarthritis animal models induced with monosodium iodoacetate (MIA)
4. To determine the articular cartilage and subchondral bone changes in MIA-induced osteoarthritis rats treated with *M. citrifolia* and *M. elliptica* leaf extract by using micro-CT evaluation.

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BIODATA OF STUDENT

Wan Nurfarahin binti Wan Osman was born in Kuala Terengganu, Terengganu on 3rd of November 1989. She received her primary education at SK Pusat Chabang Tiga, and secondary education at SMK (A) Sheikh Abdul Malek in Kuala Terengganu. She continues her tertiary education at Matriculation of Kolej Perak, Gopeng, Perak. She graduated with Bachelor of Health Science (Hons) (Biomedicine) from Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan in 2011. She worked as research assistant with Prof. Dr. Suhaila Mohamed for six months, and then registered as her master's student on February 2012, in Medical Biotechnology at Institute of Bioscience, Universiti Putra Malaysia. After completed all her master's research objectives, she passed a conversion exam and continue as a PhD student on February 2014. Throughout her study, her research team led by Prof. Dr. Suhaila Mohamed has filed two patents.

LIST OF PUBLICATIONS

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