UNIVERSITI PUTRA MALAYSIA

EFFECTS OF Morinda citrifolia L. LEAF AQUEOUS EXTRACT ON FATIGUE AND BONE HEALTH

NOR AIJRATUL ASIKIN BT MOHAMAD SHALAN

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By

NOR AIJRATUL ASIKIN BT MOHAMAD SHALAN

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

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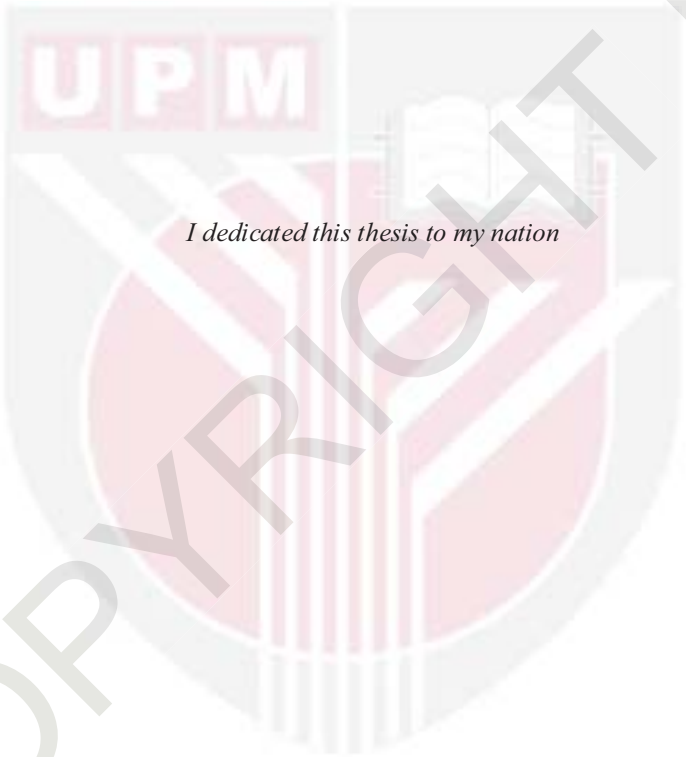

I dedicated this thesis to my nation

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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NOR AIJRATUL ASIKIN BT MOHAMAD SHALAN

December 2015

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

Morinda citrifolia, locally known as Mengkudu, has been used for thousands of years in folk medicine. Traditionally, *M. citrifolia* fruit has been consumed to combat fatigue and help restore vigor to the body while its leaf crude extract has been used for patients with bone fractures or dislocation. Yet, the explorasion is too little to understand the cellular mechanisms behind these effects. Therefore, we aimed to evaluate the anti-fatigue and bone protective potential beneficial effects of *M. citrifolia* using *in vivo* model.

Since the rising numbers of hepatotoxicity case reports on *M. citrifolia* fruit, a chronic toxicity study was conducted *in vivo*, using both *M. citrifolia* fruit and leaf aqueous extract. The six months study showed the *M. citrifolia* fruit extract at a dose of 2 mg /ml drinking aqueous, produced chronic toxicity effects apparent through deteriorated liver histological observations (hepatocyte necrosis), reduced liver length, serum ALP and albumin reduction, injury symptoms (hypoactivity, excessive grooming, sunken eyes and hunched posture) and 8% mortality within three months. This hepatotoxicity observations support the six liver injury reports in humans which was linked to *M. citrifolia* fruit juice consumption. However both doses of *M. citrifolia* leaf extracts and the low dose of fruit extract (1mg/ml drinking aqueous) demonstrated no detectable toxicity.

Exercised-induced fatigue was used to examine the ergogenic effects of *M. citrifolia* leaf aqueous extract. The four weeks study repeatedly showed the *M. citrifolia* leaf extract (containing 6 mg/g scopoletin) progressively prolonged the time to exhaustion by three-fold longer than the group of control and tea extract. The *M. citrifolia* leaf extract improved antioxidant activities, regulated stress hormone and neurotransmitters expressions, enhanced fatty acid metabolism and mitochondrial biogenesis, augmented skeletal muscle angiogenesis and increased the anti-inflammatory responses.

Bone protective ability of *M. citrifolia* leaf aqueous extract was evaluated using ovariectomy-induced osteoporosis model. The four months study showed the *M. citrifolia* leaf extract dose-dependently favours bone regeneration and suppressed bone resorption through improving the bone size and structure, bone mechanical properties (strength and flexibility), and bone mineralization and density. As was suggested from gene expression study outcomes, *M. citrifolia* leaf bone protective mechanisms might involved the enhancement of bone formation cells generation and survival, and inhibition of bone resorption cells growth and activities. The expression of estrogen receptor marker also suggests that bone loss prevention by *M. citrifolia* might be due to phytoestrogenic activities.

It can be concluded from this study that the consumption of *M. citrifolia* leaf will not lead to hepatotoxicity, however the hepatotoxicity effects of the *M. citrifolia* fruit extract (at 2mg/ml dose) may be caused by the anthraquinones present in the seeds and skin. The *M. citrifolia* leaf extract helped delay fatigue by enhancing energy production, regulation and efficiency, which suggests benefits for physical activities and disease recovery. *M. citrifolia* leaf extract also protected bone from deterioration under condition of estrogen deficiency, indicating benefits for the aged and menopausal women.

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

KESAN ESKTRAK AIR DAUN *Morinda citrifolia* L. TERHADAP KEPENATAN DAN KESIHATAN TULANG

Oleh

NOR AIJRATUL ASIKIN BT MOHAMAD SHALAN

Disember 2015

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Morinda citrifolia, secara tempatan dikenali sebagai Mengkudu, telah digunakan ribuan tahun dalam perubatan lama. Secara tradisional, buah *M. citrifolia* dimakan untuk memerangi keletihan dan membantu memulihkan tenaga kepada badan, sementara ekstrak mentah daunnya digunakan untuk pesakit yang patah tulang atau terseliuh. Namun, eksplorasi adalah terlalu kecil untuk memahami mekanisme selular di sebalik kesan-kesan ini. Oleh itu, kami bertujuan untuk menilai kesan anti-keletihan dan perlindungan tulang *M. citrifolia* menggunakan model *in vivo*.

Sejak peningkatan angka laporan kes hepatoksisiti terhadap buah *M. citrifolia*, kajian kronik toksisiti telah dijalankan *in vivo*, menggunakan estrak akueus kedua-dua daun dan buah *M. citrifolia*. Kajian selama enam bulan menunjukkan ekstrak buah *M. citrifolia* pada dos 2mg/ml air minuman, menghasilkan kesan ketoksikan kronik jelas hati yang telah merosot melalui pemerhatian histologi (hepatosit nekrosis), pengurangan panjang hati, pengurangan serum ALP dan albumin, tanda-tanda kecederaan (hipoaktiviti, berlebihan dandanan, mata cengkung dan postur membongkok) dan 8% kematian dalam tempoh tiga bulan. Pemerhatian hepatoksisiti ini menyokong enam laporan kecederaan hati pada manusia yang dikaitkan dengan penggunaan jus buah *M. citrifolia*. Walau bagaimanapun kedua-dua dos estrak daun *M. citrifolia* dan estrak buah dos rendah (1mg/ml air minuman) menunjukkan tiada kesan keracunan.

Keletihan yang disebabkan oleh senaman telah digunakan untuk mengkaji kesan ergogenik ekstrak akueus daun *M. citrifolia*. Kajian empat minggu berulang kali menunjukkan ekstrak daun *M. citrifolia* (mengandungi 6 mg/g scopoletin) secara progresif memanjangkan masa untuk keletihan dengan tiga kali ganda lebih lama daripada kumpulan kawalan dan ekstrak teh. Ekstrak daun *M. citrifolia* telah meningkatkan aktiviti antioksidan, pengawalan hormon tekanan dan ekspresi neurotransmitter, meningkatkan metabolisme asid lemak dan biogenesis mitokondria, menambahkan angiogenesis otot rangka dan meningkatkan tindak balas anti-radang.

Keupayaan melindungi tulang estrak akueus daun *M. citrifolia* dinilai menggunakan model osteoporosis yang disebabkan oleh ovariektomi. Kajian empat bulan menunjukkan ekstrak daun *M. citrifolia* kebergantungan dos mendorong pertumbuhan tulang dan menindas penyerapan tulang melalui peningkatan saiz tulang dan struktur, sifat-sifat mekanikal tulang (kekuatan dan fleksibiliti), dan mineral tulang dan kepadatan. Seperti yang dicadangkan dari hasil kajian ekspresi gen, mekanisme perlindungan tulang daun *M. citrifolia* mungkin melibatkan peningkatan penjanaan dan ketahanan sel-sel pembentukan tulang dan mengelakkan pertumbuhan dan aktiviti sel-sel penyerapan tulang. Ekspresi penanda reseptor estrogen juga mencadangkan bahawa pencegahan kehilangan tulang oleh *M. citrifolia* mungkin disebabkan oleh aktiviti fitoestrogenik.

Boleh disimpulkan dari kajian ini bahawa pengambilan daun *M. citrifolia* tidak akan mendorong kepada hepatoksisiti, walau bagaimanapun kesan hepatoksisiti estrak buah *M. citrifolia* (pada dos 2mg/ml) mungkin disebabkan oleh kehadiran anthraquinones di dalam biji benih dan kulit. Estrak daun *M. citrifolia* dapat membantu melengahkan keletihan dengan meningkatkan penghasilan, pengawalan dan kecekapan tenaga, yang mencadangkan kebaikan untuk aktiviti fizikal dan pemulihan penyakit. Estrak daun *M. citrifolia* juga melindungi tulang dari kemerosotan dibawah kondisi kekurangan estrogen, yang menunjukkan manfaat kepada perempuan tua dan menopaus.

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I certify that a Thesis Examination Committee has met on 9 December 2015 to conduct the final examination of Nor Aijratul Asikin bt Mohamad Shalan on her thesis entitled "Effects of Morinda citrifolia L. Leaf Aqueous Extract on Fatigue and Bone Health" 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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5-HIAA	5-hydroxyindole acetic acid
5-HT	5-hydroxytryptamine
Ach	Acetylcholine
ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMPK/PRKAA 1	Protein kinase, AMP-activated, alpha 1 catalytic subunit
AST	Aspartate aminotranferase
ATF2	Activating transcription factor 2
ATP	Adenosine triphosphate
b3-AR	b3-adrenergic receptors
BCAAs	Branched-chain amino acids
BMD	Bone mineral density
CaMKIV	Ca2+/calmodulin-dependent protein kinase IV
CnA	Calcineurin A
CNS	Central nervous system
COL1A1	Collagen, type I, alpha 1A
CREB	cAMP response element–binding protein
CRH	Corticotropin-releasing hormone
DRD2	Dopamine receptor D2
ERKs	Signal-regulated kinases
ERRα	Estrogen receptor–related α
ESR1	Estrogen receptor 1
FA	Fatty acid
FoxO1	Forkhead box protein O1
f-TRP	Free tryptophan
H6PD	Hexose-6-phosphate dehydrogenase
HNF4α	Hepatocyte nuclear factor 4α
HPA	Hypothalamic-pituitary-adrenocortical axis
HSC	Haemopoietic stem cells
IFN	Interferon
IL	Interleukin
JNK	c-Jun N-terminal kinases
M-CSF	Macrophage colony stimulating factor
MEF2C	Myocyte enhancer factor 2C
MHC	Histocompatibility complex
MnSOD	Manganese superoxide dismutase
MSC	Mesenchymal stem cells
NFATC1	Nuclear factors of activated T cell 1
NFE2L2	Nuclear factor, erythroid derived 2, like 2
NR3C	Nuclear receptor subfamily 3, group C, member 1
NRF1	Nuclear respiratory factor 1
OPG	Osteoprotegerin
OVX	Ovariectomy
p38 MAPK	p38 mitogen-activated protein kinase
PCr	Phosphocreatine

PGC-1α	Peroxisome proliferator-activated receptor c coactivator 1α
PGE2	Prostaglandin E2
PPAR	Peroxisome proliferator-activated receptor
PTH	Parathyroid hormone
RANKL	Receptor activator of NF-kappa B ligand
RCE	Ratings of percieved exertion
ROS	Reactive oxygen species
RUNX2	Runt-related transcription factor 2
SLC6A2	Solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2
SLC6A4	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4
SOD2	Superoxide dismutase 2
TFAM	Mitochondrial transcription factor A
TNF-α	Tumor necrosis factor alpha
TRP	Tryptophan
UCP3	Uncoupling protein 3
VEGFA	Vascular endothelial growth factor A

CHAPTER 1

INTRODUCTION

1.1 Research Background

Fatigue is a complex phenomenon that can be described as an overwhelming feeling of exhaustion at rest and with activity, deficiency of energy that precludes regular tasks, inertia or lack of endurance, and loss of vigor (Noakes, 2012; Silverman, 2005). Fatigue may be influenced or caused by excessive accumulation of reactive oxygen species (ROS) in the contracting muscles, that inhibit force production (Reid, 2001a), muscle contraction-associated pro-inflammatory cytokines increase (Radak et al., 2012), energy source depletion and excess metabolite accumulation (You et al., 2011), de-regulation of neuro-immune-endocrine dysfunction or alteration of hypothalamic–pituitary–adrenal (HPA) axis activity (Gupta et al., 2007; Rajeevan et al., 2007; Watanabe et al., 2008).

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. Compounds with ergogenic potential include vitamins, protein, amino acid, sodium bicarbonate (Shelton & Kumar, 2010), caffeine, creatine monohydrate and herbs (Chen et al., 2012). However, some of the ergogenic compounds are associated with undesirable effects. Ephedrine and pseudoephedrine for example have detrimental cardiovascular effects, erythropoietin increases the risk of thromboembolic events, and antioxidants, proteins and amino acids does not increase endurance or strength (Juhn, 2003).

Bone strength and integrity rely on sustaining a subtle balance between bone resorption by osteoclasts and bone formation by osteoblasts. With age, diseases or sedentary life style this balance tends to favor osteoclasts linked bone resorption rather than bone formation, making bones brittle and increases fracture risk (Martin & Sims, 2005). Dietary compounds that suppress osteoclasts activities help prevent and treat osteoporosis, Paget's disease, and bone associated inflammation such as in rheumatoid arthritis or periodontal disease. Dietary compounds that can promote bone formation will be a good complementary therapy for patients with bone resorption disorders.

Osteoporosis is a condition whereby the bone mineral density (BMD) or mass is significantly below (over 2.5 standard deviations) the mean for normal young woman. Osteoporosis causes over 8.9 million fractures annually, (Johnell & Kanis, 2006), and affecting over 200 million women worldwide; approximately 10% aged 60, 20% aged 70, 40% aged 80 and 70% aged 90 (World Health Organization, 2007).

Osteoporosis increases fracture risks and physically debilitating injuries occurrence that affect physical and mental health. Physical activity and healthy diet (that includes

calcium and vitamins) help ameliorate osteoporosis. Medicines that treat osteoporosis and other bone related disorders may have side effects. These medicines include: (i) bisphosphonates that suppress osteoclast activities, (ii) Human parathyroid hormone (not recommended over 2 years use), (iii) RANK ligand (RANKL) inhibitors, (iv) Estrogen agonist or antagonist (or selective estrogen receptor modulator - SERM) that have estrogen-like effects on some tissues and estrogen-blocking effects on other tissues, (v) Calcitonin, the hormone for calcium regulation and bone metabolism (for women over 5 years after menopause), (vi) Estrogen and hormone therapy may increase hormone related cancer and cardiovascular event risks (Manson et al. 2013), (vii) Denosumab (a human monoclonal antibody), and (viii) anabolic agents such as Strontium and Teriparatide (Tella & Gallagher, 2014).

Morinda citrifolia fruit, (called noni in USA, Mengkudu in Malaysia) has been traditionally consumed by Polynesians to maintain health and vigor besides combating fatigue or diseases (Thaman, 1990). Two clinical studies on athletes and post-menopausal women 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, given increasing doses of Tahitian Noni Juice orally showed significantly longer average time in both the swim test and the rotarod test when compared with young and aged control (Ma et al., 2007). However, *M. citrifolia* fruit have been associated with liver toxicity (Millonig, Stadlmann, & Vogel, 2005a). *M. citrifolia* leaf reportedly have antioxidant, liver-protective and wound healing properties without any acute, sub-acute and sub-chronic oral toxicity (B. West, Tani, Palu, Tolson, & Jensen, 2007). The *M. citrifolia* leaves extract oral no observed-adverse-effect level (NOAEL) is 1000 mg/kg (Lagarto, Bueno, & Merino, 2013). There is no report on anti fatigue effect of *M. citrifolia* leaf.

M. citrifolia leaf is traditionally used as a poultice for broken bones and sprains, deep cuts, bruises, sores and wounds (Bushnell, Fukuda, & Makinodan, 1950). *M. citrifolia* leaf aqueous extract promoted osteogenic differentiation and matrix mineralization in human periodontal ligament cells (Boonanantanasarn et al. 2012) thus indicating its general potential in enhancing bone formation.

The present study investigates the efficacy and mechanisms of *M. citrifolia* leaf aqueous extract on fatigue elimination by using exercise-induced fatigue model and protection of bone quality in osteoporosis induced by estrogen deficiency.

1.2 Hypothesis

The *M. citrifolia* leaf aqueous extract enhances performance of exercised mice through the regulation of proteins and genes involved in fatigue central and peripheral mechanism. *M. citrifolia* aqueous extract prevents bone loss associated with estrogen deficiency after ovariectomy by suppressing proteins and genes involved in bone resorption, and stimulating the expression of protein and genes involved in bone formation.

1.3 General objective

To investigate the potential of *Morinda citrifolia* leaf aqueous extract as ergogenic and osteoporosis alternative treatment.

1.4 Specific objectives

1. To determine the toxic effect of *M. citrifolia* fruit and leaf aqueous extract.
2. To determine the ergogenic effect of *M. citrifolia* leaf aqueous extract using on exercise-induced fatigue mice model.
3. To determine the anti-osteoporotic effect of *M. citrifolia* leaf aqueous extract using on ovariectomized-induced osteoporosis rat model.

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