



UNIVERSITI PUTRA MALAYSIA

***EVALUATION OF CLINACANTHUS NUTANS(BURM. F.) LINDAU AND
FICUS DELTOIDEA LEAF EXTRACTS FOR CARTILAGE AND BONE
MARROW HEALTH IN EXPERIMENTAL RAT OSTEOARTHRITIS***

NUR ADEELAH CHE AHMAD TANTOWI

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**EVALUATION OF *Clinacanthus nutans* AND *Ficus deltoidea* LEAF EXTRACTS
FOR CARTILAGE AND BONE MARROW HEALTH IN
EXPERIMENTAL RAT OSTEOARTHRITIS**

By

NUR ADEELAH BINTI CHE AHMAD TANTOWI

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

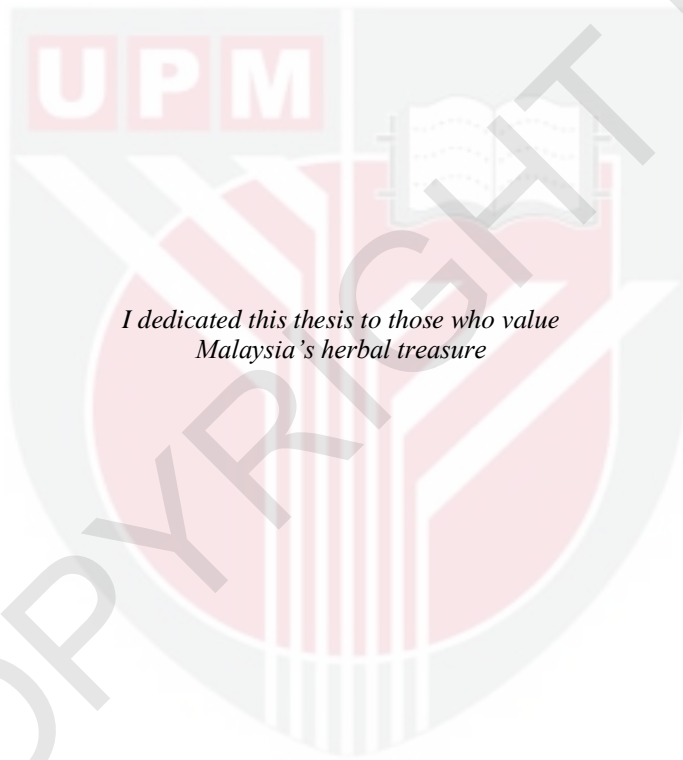
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*I dedicated this thesis to those who value
Malaysia's herbal treasure*

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

EVALUATION OF *Clinacanthus nutans* AND *Ficus deltoidea* LEAF EXTRACTS FOR CARTILAGE AND BONE MARROW HEALTH IN EXPERIMENTAL RAT OSTEOARTHRITIS

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September 2016

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

Medicinal plants have been used to treat various ailments including in osteoarthritis (OA) for decades. Currently, the existing drugs for treating OA only alleviate symptoms and improve the joint function, but cannot treat cartilage and bone damage. Developing therapeutics from plant-derived sources may exert less negative side effects, compared to the use of common non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis. Hereby, the present study investigated the effect of *Clinacanthus nutans* (belalai gajah) and *Ficus deltoidea* (mas cotek), compared with diclofenac, on cartilage and bone marrow health on experimental OA model.

In preliminary *in vitro* bovine cartilage explant culture, the recombinant bovine IL-1 β of 10 ng/mL was added to the cartilage explants in DMEM/F12 media to induce OA condition. CN or FD leaf extracts at 20, 40, and 80 μ g/mL, or diclofenac at 5 μ g/mL, were simultaneously added into the medium after IL-1 β induction. The amount of proteoglycan loss, reactive oxygen species (ROS) produced, and chondrocytes morphology were evaluated. In *in vivo* experiment, 42 12-week-old Sprague Dawley female rats were randomized into seven groups (n=7). The rats were subjected to bilateral ovariectomy (OVX) and OA was induced by intra-articular injection of monosodium iodoacetate (MIA) at 60 mg/mL into right knee joints, excluding healthy group. Healthy and OA non-treated groups were given deionized water while treatment groups were orally treated with 200 or 400 mg/kg body weight of CN or FD leaf extracts or 5 mg/kg body weight of diclofenac once a day for 28 days. Serum levels of inflammation including interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), and prostaglandin E₂ (PGE₂); cartilage catabolic including matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 13 (MMP-13), C-terminal cross-linked telopeptide of type II collagen (CTX-II), and N-terminal propeptide of collagen type II (PIINP); and bone turnover markers including osteoprotegerin, osteocalcin, receptor activator of nuclear kappa-beta ligand (RANKL), and C-terminal crosslinked telopeptide type I collagen (CTX-I) were assessed by enzyme-linked immunosorbent assay (ELISA).

Articular cartilage changes were determined by radiological, macroscopic, and histological observations. Gene expressions of inflammatory including nuclear factor kappa beta (NF- κ), interleukin 1 beta (IL-1 β), tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), cyclooxygenase 2 (COX-2), and prostaglandin E₂ (PGE₂); and cartilage catabolic mediators including matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 13 (MMP-13), A disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4), and A disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) were determined to study the mechanisms involved. Bone turnover regulations were evaluated via bone mass density, dimension, biomechanics, and microarchitecture.

Flavones of apigenin derivatives including vitexin, isovitexin, schaftoside, and isoschaftoside were identified in both CN and FD leaf extracts. Preliminary *in vitro* study showed chondroprotective effects of CN and FD leaf extracts and diclofenac by significantly inhibiting proteoglycan loss, ROS production, and preventing chondrocytes apoptosis. In *in vivo* study, CN and FD leaf extracts possessed cartilage and bone protecting nature by significantly suppressing the augmented activities of inflammatory (IL-1 β , IL-6, and PGE₂), and cartilage catabolic (MMP-1 and MMP-13) serum levels comparable to diclofenac. The osteoarthritic rats treated with the extracts and diclofenac showed significant reduction of cartilage erosion via radiological, macroscopic and histological images, compared to untreated osteoarthritic rats. The extracts significantly down-regulated NF- κ , IL-1 β , TNF- α , IL-6, PGE₂, MMP-1, and MMP-13 expressions in the osteoarthritic cartilage similar to diclofenac. Furthermore, CN and FD leaf extracts administration protected bone marrow by significantly increased bone volume ratio, decreased trabecular separation, and decreased total porosity of the bone marrow. These findings were supported by bone turnover markers; which the extracts significantly increased bone formation (osteoprotegerin and osteocalcin) and reduced bone resorption (CTX-I and RANKL) markers, comparable to diclofenac.

Overall, CN and FD leaf extracts were demonstrated to be a potent agent mitigating cartilage and bone loss in OA. The results achieved were at least as good than those with diclofenac, a widely used NSAID and a benchmark pharmacological treatment for OA. The main bioactive compounds are probably responsible for anti-inflammatory and antioxidant properties in the protection of cartilage and bone marrow in OA.

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

EVALUASI KESAN *Clinacanthus nutans* DAN *Ficus deltoidea* TERHADAP KESIHATAN TULANG RAWAN DAN TULANG SUMSUM MENGGUNAKAN MODEL EKSPERIMEN TIKUS OSTEOARTRITIS

Oleh

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Tumbuhan perubatan telah digunakan untuk mengubati berbagai penyakit selama puluhan tahun termasuk osteoarthritis (OA). Dewasa ini, ubat yang ada untuk OA hanya mengurangkan gejala dan meningkatkan fungsi sendi, tetapi tidak dapat mencegah kerosakan tulang rawan dan tulang sumsum. Mengembangkan terapi dari sumber tanaman dapat mengurangkan kesan sampingan negatif berbanding penggunaan ubat konvensional untuk osteoarthritis iaitu ubat anti-radang bukan steroid (NSAIDs). Dengan ini, kami bertujuan mengkaji kesan *Clinacanthus nutans* (belalai gajah) dan *Ficus deltoidea* (mas cotek), dibandingkan dengan *diclofenac*, terhadap kesihatan tulang rawan dan tulang sumsum menggunakan model OA.

Dalam kajian *in vitro* kultur tulang rawan lembu, IL-1 β rekombinan dari lembu sebanyak 10 ng/mL ditambahkan ke dalam kultur tulang rawan dalam media DMEM/F12 untuk mencetus kondisi OA. Daun ekstrak CN atau FD pada 20, 40, dan 80 mg/mL atau *diclofenac* pada 5 mg/mL kemudiannya ditambah ke dalam media setelah induksi IL-1 β . Jumlah penguraian proteoglikan, spesies oksigen reaktif (ROS) yang dihasilkan, dan morfologi kondrosit telah dicatatkan. Dalam kajian *in vivo*, 42 ekor tikus betina *Sprague Dawley* berusia 12 minggu dibahagi 7 kumpulan secara rawak (n=7). Tikus menjalani ovariektomi (OVX) secara bilateral dan OA dicetuskan dengan suntikan intrasendi bahan kimia *monosodium iodoacetate* (MIA) pada 60 mg/mL ke dalam sendi lutut kanan, tidak termasuk kumpulan yang sihat. Kumpulan yang sihat dan OA kawalan negatif diberi air deionisasi sementara kumpulan lain diberikan ekstrak daun CN atau FD pada 200 dan 400 mg/kg berat badan atau *diclofenac* pada 5 mg/kg berat badan sekali sehari selama 28 hari. Kadar serum darah untuk tanda terjadi radang termasuk interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), dan prostaglandin E₂ (PGE₂); katabolik tulang rawan termasuk *matrix metalloproteinase 1* (MMP-1), *matrix metalloproteinase 13* (MMP-13), *C-terminal cross-linked telopeptide of type II collagen* (CTX-II), dan *N-terminal propeptide of collagen type II* (PIINP); dan perubahan metabolisme tulang termasuk osteoprotegerin, *osteocalcin*, *receptor activator of nuclear kappa-beta ligand* (RANKL), dan *C-terminal crosslinked telopeptide type I collagen* (CTX-I), dinilai oleh *enzyme-linked immunosorbent assay* (ELISA).

Perubahan tulang rawan ditentukan daripada ujian radiologi, makroskopik, dan histologi. Ekspresi gen dari tulang rawan oleh faktor inflamasi termasuk *nuclear factor kappa beta* (NF- κ), interleukin 1 beta (IL-1 β), *tumor necrosis factor alpha* (TNF- α), interleukin 6 (IL-6), *cyclooxygenase 2* (COX-2), dan prostaglandin E₂ (PGE₂); dan factor katabolik tulang rawan termasuk *matrix metalloproteinase 1* (MMP-1), *matrix metalloproteinase 13* (MMP-13), *A disintegrin and metalloproteinase with thrombospondin motifs 4* (ADAMTS-4), dan *A disintegrin and metalloproteinase with thrombospondin motifs 5* (ADAMTS-5). Keadaan kesihatan tulang ditentukan oleh kepadatan, dimensi, kekuatan biomekanik, dan binaan mikro tulang.

Flavon derivatif daripada kompaun apigenin termasuk vitexin, isovitexin, *schaftoside*, dan *isoschaftoside* ditemukan dalam daun ekstrak CN dan FD. Kajian *in vitro* menunjukkan efek kondroprotektif oleh daun ekstrak CN dan FD dan *diclofenac* dengan mengurangkan penguraian proteoglikan, produksi ROS, dan mencegah apoptosis oleh kondrosit. Dalam kajian *in vivo*, daun ekstrak CN dan FD melindungi tulang rawan dengan menghalang aktiviti inflamasi (IL-1 β , IL-6, and PGE₂), dan katabolisme oleh tulang rawan (MMP-1 and MMP-13) setara dengan *diclofenac*. Ekstrak juga mengurangkan penguraian tulang rawan seperti yang ditunjukkan oleh gambar radiologi, makroskopik, histologi. Ekstrak juga menurunkan kadar ekspresi gen termasuk NF- κ , IL-1 β , TNF- α , IL-6, PGE₂, MMP-1, dan MMP-13, setara dengan *diclofenac*. Selanjutnya, daun ekstrak CN dan FD melindungi tulang sumsum dengan meningkatkan nisbah jumlah tulang, mengurangkan jarak tulang trabekular, dan mengurangkan jumlah keporosan tulang. Penemuan ini disokong oleh penanda kadar metabolisme tulang; yang mana ekstrak meningkatkan aktiviti penambahan tulang (*osteoprotegerin* dan *osteocalcin*) dan mengurangkan aktiviti penguraian tulang (CTX-I dan RANKL), sama banding dengan *diclofenac*.

Secara keseluruhan, daun ekstrak CN dan FD ditunjukkan sebagai agen berguna dalam mengurangkan kerosakan tulang rawan dan tulang sumsum dalam OA, setara dengan ubat *diclofenac*, ubat konvensional dalam rawatan OA. Bahan bioaktif utama mungkin menjadi bahan aktif anti-inflamasi dan antioksidan untuk melindungi tulang rawan dan tulang sumsum dalam model OA.

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I certify that a Thesis Examination Committee has met on (24th January 2017) to conduct the final examination of Nur Adeelah binti Che Ahmad Tantowi on her thesis entitled "Evaluation of *Clinacanthus nutans* and *Ficus deltoidea* Leaf Extracts for Cartilage and Bone Marrow Health in Experimental Rat 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.

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LIST OF ABBREVIATIONS

ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
BALP	Bone-specific alkaline phosphatase
BMD	Bone mass/mineral density
BMP-2	Bone morphogenetic protein 2
CN	<i>Clinacanthus nutans</i>
COX-2	Cyclooxygenase 2
CTX-I	C-terminal crosslinked telopeptide type I collagen
CTX-II	C-terminal crosslinked telopeptide type II collagen
DIC	Diclofenac
ELISA	Enzyme-linked immunosorbent assay
FD	<i>Ficus deltoidea</i>
FTIR	Fourier transform infrared
H&E	Hematoxylin and eosin
HIF2- α	Hypoxia inducible factor 2 alpha
HPLC	High performance liquid chromatography
ICTP	Pyridinoline C-telopeptide of type I collagen
IL	Interleukin
iNOS	Inducible nitric oxide synthase
MIA	Monosodium iodoacetate
MMP	Matrix metalloproteinase
NO	Nitric oxide
NTX-I	N-terminal crosslinked telopeptide type I collagen
OA	Osteoarthritis
OP	Osteoporosis
OPG	Osteoprotegerin
OVX	Ovariectomy
PCR	Polymerase chain reaction
PGE ₂	Prostaglandin E ₂
PICP	Procollagen type I C-terminal propeptide
PIINP	Procollagen type II N-terminal propeptide
PINP	Procollagen type I N-terminal propeptide
RANKL	Receptor activator of nuclear kappa-beta ligand
ROS	Reactive oxygen species
RUNX-2	Runt related transcription factor 2
TB	Toluidine blue
TNF- α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

CHAPTER 1

INTRODUCTION

1.1 Background

Osteoarthritis (OA) is one of the common musculoskeletal diseases and the major causes of disability worldwide. The disease usually develops in the elderly, notably more common in postmenopausal women. World Health Organization (WHO) has reported that OA affects 9.6% of men and 18% of women aged over 60 years (World Health Organization, 2016). In Malaysia, it is reported that the prevalence of OA is 10% to 20% of the adult population (Arthritis Foundation Malaysia, 2016). According to the United Nations, the adult population over 60 is reported to increase more than 20% of the world's population by 2050 (United Nations, 2004).

At present, there is no known cure for OA. Despite the efficacy of the commonly used drug for relieving pain symptom of OA, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), the long term used of the drug pharmacotherapy is associated with substantial gastrointestinal and cardiovascular adverse events (Patrignani et al., 2011; McGettigan and Henry, 2013). More invasive treatments including intra-articular injections and surgery are intrusive and costly. Furthermore, intra-articular treatments such as hyaluronic acid and glucocorticoid injections may provide pain relief; however, recent observations show that these treatments may further drive cartilage breakdown (Gonzalez-Fuentes et al., 2010).

The exact pathological mechanism of OA is still unclear. Although OA is not considered as immunological disorders, current research indicates that pro-inflammatory mediators play a central role in the pathogenesis of OA. Among the mediators, TNF- α and IL-1 β play a major role in OA pathogenesis, as these cytokines can stimulate the production of various inflammatory and catabolic factors implicated in OA. For instance, TNF- α and IL-1 β induce release of other pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS-4 and -5) that cleave the collagen and proteoglycan networks, as well as diminishing anabolism of extracellular matrix components (Rai et al., 2008; Kapoor et al., 2011). In addition, TNF- α and IL-1 β also drive chondrocytes to up-regulate the expression of gene encoding iNOS and COX-2 and stimulate release of PGE₂ and NO, which contribute to inflammation and cartilage destruction (Rai et al., 2008). As the process continues, catabolic activity of the cartilage matrix is increased and followed by fibrillation of the cartilage surface. After this degeneration is established, it starts to cause loss of more cartilage at a diarthrodial joint (Sellam and Berenbaum, 2010).

1.2 Hypothesis and Research Objectives

The main objectives of OA therapy are to counteract the local inflammation and delay joint degradation. Two of Malaysian herbs, *Clinacanthus nutans* (CN) and *Ficus deltoidea* (FD) have been reported to exhibit anti-inflammatory and antioxidant properties (Wanikiat et al., 2008; Zunoliza et al., 2009; Misbah et al., 2013; Arullappan et al., 2014), which are hypothesized to interfere with the inflammation and oxidative stress cascades in OA, and reduce cartilage degradation and bone marrow loss in OA progression. In general, the objective of this study is to evaluate the effect of CN and FD leaf extracts on cartilage and bone marrow in rat osteoarthritis model, compared with a commonly used non-steroidal anti-inflammatory drug (NSAID), diclofenac. Specifically, this study aims to assess the efficacy of CN and FD in OA disease in the following manners:

- a) To identify the active compounds of CN and FD leaf extracts.
- b) To assess chondroprotective effects of CN and FD leaf extracts on IL-1 β -induced cartilage degradation on bovine cartilage explant culture.
- c) To evaluate CN and FD leaf extracts on the repair of articular cartilage in rat osteoarthritis model induced by monosodium iodoacetate (MIA).
- d) To determine CN and FD effects on regulating bone turnover in rat osteoarthritis rat model induced by monosodium iodoacetate (MIA).

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LIST OF PUBLICATIONS

Patent:

1. Suhaila Mohamed, **Nur Adeelah Che Ahmad Tantowi**, Wan Nurfarahin Wan Osman, Nor Aijratul Asikin Mohamad Shalan, and Rubiatul Adawiyah Bokhari. Composition for enhancing bone growth, preventing bone resorption disorders and joint health. UPM Patent Filing No. PI2015703814.

Book chapter:

1. **Nur Adeelah Che Ahmad Tantowi**, Rubiatul Adawiyah binti Bokhari, and Suhaila Mohamed. (2016). Chapter Three - Therapeutic Dietary Compounds for Arthritis and Joint Ailments. Occurrences, Structure, Biosynthesis, and Health Benefits Based on Their Evidences of Medicinal Phytochemicals in Vegetables and Fruits. Volume 5. ISBN: 978-1-63485-273-9.

Proceeding:

1. **Che Ahmad Tantowi, N. A.**, Mohamed, S., & Hussin, P. (2016). Effect of ficus deltoidea, a medicinal plant, on cartilage protection in cartilage explant and postmenopausal rat models of osteoarthritis. *Osteoarthritis and Cartilage*, 24, S353-S354. (World Congress on Osteoarthritis 2016).
2. **Che Ahmad Tantowi, N.A.**, Mohamed, S., & Lau, S. F. (2017). Relationship between osteoarthritis and osteoporosis in ovariectomized osteoarthritis rat model treated with mistletoe fig leaf extract. *Osteoporosis International*, 28 (1), P454. (World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases 2017).

Publication:

1. **Che Ahmad Tantowi, N. A.**, Hussin, P., Lau, S. F., Mohamed, S. (2017). Mistletoe fig (*Ficus deltoidea* Jack) leaf extract prevented postmenopausal osteoarthritis by attenuating inflammation and cartilage degradation in rat model. *Menopause*, 24.9.