UNIVERSITI PUTRA MALAYSIA

EFFICACY OF CHANNA STRIATUS BLOCH AQUEOUS EXTRACT AND ZERUMBONE IN ALLEVIATING INDUCED KNEE OSTEOARTHRITIS IN RATS

FAYAK JABBAR TAQI AL-SAFFAR

FPV 2011 10

EFFICACY OF *CHANNA STRIATUS* BLOCH AQUEOUS EXTRACT AND ZERUMBONE IN ALLEVIATING INDUCED KNEE OSTEOARTHRITIS IN RATS

By

FAYAK JABBAR TAQI AL-SAFFAR

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

May 2011

DEDICATION

Dedicated with love and gratitude to:

My beloved parents

&

My wife

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Doctor of Philosophy

EFFICACY OF *CHANNA STRIATUS* BLOCH AQUEOUS EXTRACT AND ZERUMBONE IN ALLEVIATING INDUCED KNEE OSTEOARTHRITIS IN RATS

By

FAYAK JABBAR TAQI AL-SAFFAR

May 2011

Chairman: Associate Professor Shanthi Ganabadi, PhD

Faculty: Veterinary Medicine

The aim of this study was to evaluate the chondroprotective effects of two natural remedies, aqueous extract of *Channa striatus* (CS) and crystalline zerumbone purified from the rhizomes of *Zingiber Zerumbet* Smith, on experimentally induced knee osteoarthritis (OA) in Sprague-Dawley rats. Preliminary study was implemented to determine the effective method for the induction of OA in the knee joints of rats prior to the treatment. Accordingly, monosodium iodoacetate (MIA) was selected to achieve the experimental knee osteoarthritis in rats.

Evaluation of OA changes following 4 weeks of treatment was done through macroscopic and microscopic examinations supported with radiography to the knee joints. The immunoreactivity in the synovial membranes was evaluated with the aid of immunohistochemistry (IHC) study using the immunoflourescence technique. The study showed improved density of the following neuropeptide nerve fibers: protein

gene product (PGP) 9.5, calcitonin gene-related peptide (CGRP) and neuropeptide Y (NPY). Anti-inflammatory property of CS extract and zerumbone was assayed through estimation of serum prostaglandins E_2 (PGE_2) and $F_2\alpha$ ($PGF_2\alpha$) concentrations using the enzyme immunoassay kits, to ascertain their positive effect on the OA joints. The concentrations of the prostaglandins were determined during three periods that is before and during OA periods and after 4 weeks of the treatment. For the zerumbone treatment group, some phase I and phase II hepatic metabolizing enzymes (cytochrome P450, glutathione *S*-transferase) and oxidative stress biomarkers (malondialdehyde, glutathione) were determined to explore hepatic status after treatment.

Following 4 weeks of the treatment with 10 ml/kg of the aqueous CS extract and 2ml/kg of zerumbone, histopathological changes of joints articular cartilages decreased and the immunoreactivity in the synovial membranes improved. The OA changes decreased significantly in zerumbone-treated rats. This difference may be due to the dual anti-inflammatory and antioxidant properties of zerumbone, while the CS extract only has the anti-inflammatory property. Assay of hormones in serum of rats revealed an important role of PGE_2 but not $PGF_2\alpha$ during OA induction and following the treatment with both natural remedies. In conclusion, both CS extract and zerumbone have obvious improved effect against experimentally induced knee OA in rats, but with zerumbone producing markedly different effect. The safety profile of zerumbone shown by the absence of oxidative stress suggests an opportunity to study the possibility of using this compound at higher dosage regimen and/or longer duration of for the treatment of OA or other disease.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia Sebagai memenuhi keperluan untuk Doktor Falsafah

EFIKASI EKSTRAK AKEOUS CHANNA STRIATUS BLOCH DAN ZERUMBON BAGI MENGURANGKAN OSTEOARTRITIS LUTUT YANG DIANH PADA TIKUS

Oleh

FAYAK JABBAR TAQI AL-SAFFAR

May 2011

Pengerusi: Profesor madya Shanthi Ganabadi, PhD

Fakulti: Perubatan Veterinar

Tujuan penyelidikan ini adalah untuk menilai kesan kondroperlindung dua remedi semula jadi, iaitu ekstrak akueus *Channa striatus* (CS) dan zerumbon hablur yang ditulenkan daripada rizom *Zingiber zerumbet* Smith, terhadap osteoartritis (OA) lutut teraruh ujikaji tikus Sprague-Dawley. Kajian awal dijalankan untuk menentukan kaedah berkesan untuk pengaruhan OA dalam sendi lutut tikus sebelum rawatan. Dengan demikian, mononatrium iodoasetat (MIA) telah dipilih untuk tujuan menyatakan OA ujkaji pada tikus.

Penilaian perubahan OA 4 minggu selepas rawatan dilakukan secara pemeriksaan makroskopi dan mikroskopi dan disokong dengan radiografi sendi lutut. Keimunreaktifan pada membran sinovium dinilai dengan bantuan kajian immunohistokimia (IHC) mengguna teknik immunopendarfluoran. Kajian ini menunjukkan peningkatan ketumpatan gentian saraf neuropeptida berikut: produk

gen protein (PGP) 9.5, peptida terkait gen kalsitonin (CGRP) dan neuropeptida Y (NPY). Sifat antikeradangan ekstrak CS dan zerumbon telah diassaikan melalui sukatan prostaglandin E_2 dan $F_2\alpha$ serum kit mengguna kit imunoassai enzim untuk untuk memastikan kesan positif pada sendi OA. Kepekatan prostaglandin tersebut ditentukan dalam tiga tempoh, iaitu sebelum, semasa OA dan 4 minggu selepas rawatan. Untuk kumpulan rawatan zerumbon, beberapa enzim metabolisme hepar fasa I dan II (sitokrom P450, glutation *S*-transferase) dan penanda tekanan oksidatif (melondialdehid, glutation) telah ditentukan untuk meninjau status hepar selepas rawatan.

Selepas 4 minggu rawatan dengan 10 ml/kg ekstrak CS akueus dan 2 ml/kg zerumbon, perubahan histopatologi menjadi bertambah kurang dan keimunoreaktifan membran sinovium beransur pulih. Perubahan OA berkurangan secara tererti ($P<0.05$) pada tikus yang dirawat dengan zerumbon. Perbezaan tersebut mungkin disebabkan oleh sifat berkembar antikeradangan dan antipengoksidaan zerumbon, manakala, ekstrak CS hanya mempunyai sifat antikerandangan. Assai hormon pada serum tikus telah mendedahkan peranan penting PGE_2 tetapi bukan $PGF_2\alpha$ semasa pengaruahan OA dan berikutan kedua-dua remedi semula jadi ini. Kesimpulannya kedua-dua ekstrak CS dan zerumbon mempunyai kesan penambahbaikan nyata terhadap OA lutut teraruh ujikaji pada tikus, tetapi dengan zerumbon memberi kesan yang berbeza ketara. Profil keselamatan zerumbon yang ternyata daripada ketiadaan tekanan oksida ini, membuka peluang untuk mengkaji kemungkinan menggunakan sebatian ini pada dos lebih tinggi dan/atau dalam tempoh lebih lama dalam rawatan OA atau penyakit lain.

ACKNOWLEDGEMENTS

This work would not have been possible without the help and encouragement of many people. First, I would like to offer a special thank to my supervisor Assoc. Prof. Dr. Shanthi Ganabadi. She has been unfailingly enthusiastic about this project. Without her encouragement and trust, I surely would not have completed my degree. Most of all, her door is always open, so that I can get guidance and help from her at any time. I would also like to express my heartiest appreciation to my co-supervisors; Assoc. Prof. Dr. Sharida Fakurazi and Assoc. Prof. Dr. Halimatun Yaakub for their guidance and incessant support. I really appreciate the time and effort they put into thinking critically about my experiments and hypotheses. Special thanks to the following staff in the Faculty of Veterinary Medicine for their kind co-operation rendered at the time of this project was carried out: Mr. Othman N. Mior at Radiology Unit; Miss Khatijah Muhamad at Molecular Biology (Ultracentrifuge unit) and Mr. Yap Keng Chee (Hormone lab.).

Special acknowledgement to Universiti Putra Malaysia, as this study was supported by e-Science grant (Project No.: 02-01-04-SF0882) awarded by Malaysian Ministry of Science, Technology and Innovation.

Finally, I would like to express my deepest gratitude to my greatest parents and wife for their endless encouragement, love and emotional support, which had helped me in all undertakings and the completion of this project.

I certify that a Thesis Examination Committee has met on 19 May 2011 to conduct the final examination of FAYAK JABBAR TAQI AL-SAFFAR on his thesis entitled "Efficacy of *Channa striatus* Bloch aqueous extract and zerumbone in alleviating induced knee osteoarthritis 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 a warded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

MOHAMED ALI RAGION, PhD
Professor
Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

DATO' TENGKU AZMI IBRAHIM, PhD
Professor
Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

SABRINA SUKARDI, PhD
Associate Professor
Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

CAMILLE VAILLANT, PhD
Programme Director for the BSc in Bioveterinary Science
Veterinary Science
University of Liverpool
(External Examiner)

NORITAH OMAR, PhD
Associate Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

This thesis was submitted to the senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Shanthi Ganabadi, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Sharida Fakurazi, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Halimatun Yaakub, PhD
Associate Professor
Faculty of Agriculture
Universiti Putra Malaysia
(Member)

_____

HASANAH MOHD GHAZALI, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

DECLARATION

I declare that the thesis is my original work except for quotation and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for my other degree at Universiti Putra Malaysia or at any other institution.

FAYAK JABBAR TAQI AL-SAFFAR

Date: 19 May 2011

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ACUC	Animal care and use committee
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
B	Basal group
BCA	Bicinchoninic acid
BHT	Butylated hydroxytoluene
°C	Degree Celsius
CCL	Cranial cruciate ligament
CDNB	1-chloro-2, 4-dinitrobenzene
CEL	Celecoxib
CGRP	Calcitonin gene related peptide
CO	Corn oil
COL	Collagenase
COX	Cyclooxygenase
CS	*Channa striatus*
CY	Cytochrome
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
Fig.	Figure
FITC	Fluorescein isothiocyanate
g	Gravity force
GSH	Glutathione
GST	Glutathione *S*- transferase

Gt XRb IgG Cy3	Goat Anti-rabbit Immunoglobulin G Cyanine 3
H and E	Hematoxylin and Eosin
HI	First Haruan (*Channa striatus* extract) treated group
HII	Second Haruan (*Channa striatus* extract) treated group
h	hour
IHC	Immunohistochemistry
IL-1β	Interleukin-1beta
IL-1Ra	Interleukin-1Receptor antagonist
KCl	Potassium chloride
L	Liter
M	Mole
µM	Micromole
mg	Milligram
m/sec	Meter/second
µm	Micrometer
MDA	Malondialdehyde
ml/kg	Milliliter/kilogram
MIA	Monosodium iodoacetate
min	Minute
n	Number
NADP	Nicotinamide adenine dinucleotide phosphate
nm	Nanometer
NO·	Nitric oxide
NP	Neuropeptide
NS	Normal saline

NSAIDs	Non-steroidal anti-inflammatory drugs
$O_2^{\cdot -}$	Superoxide
OA	Osteoarthritis
·OH	Hydroxyl
oMSCs	Ovine Mesenchymal Stromal cells
PBS	Phosphate buffer saline
pg	Picogram
PG	Prostaglandin
PGP	Protein gene product
RDO	Rapid Decalcifiant osseous
RO	Alkoxyl
ROO	peroxyl
rpm	Revolute per minute
SCs	Stem Cells
SEM	Standard error of mean
SM	Synovial membrane
SP	Substance P
SPSS	Statistical Package for the Social Sciences
TNF-α	Tumor necrosis factor-alpha
USA	United State of American
WHO	World Health Organization
ZER	Zerumbone
ZI	First zerumbone treated group
ZII	Second zerumbone treated group
w/v	Weight/volume

CHAPTER 1

GENERAL INTRODUCTION

1.1 Definition of osteoarthritis

Osteoarthritis which is also known as degenerative arthritis or degenerative joint disease is derived from the Greek word "*osteo*", meaning "of the bone", "*arthro*", meaning "joint", and "*itis*", meaning inflammation, although many sufferers have little or no inflammation. In fact, "*itis*" in Osteoarthritis is not conspicuous feature of the disease and it is solely to wear and tear mechanism (Gonzales-Penserga, 2009).

Osteoarthritis is defined in many ways and any simple definition is deceptive of its complexity. Osteologists detected characteristic features of osteoarthritis such as bony spicules and erosion on joint surfaces and those skeletal changes may reflect more severe involvement than in the clinical diagnosis (Weiss, 2006). Osteoarthritis can be defined by joint symptoms, by structural pathology or by the combination of the two. Osteoarthritis is an age-related disease and that all tissues of the joint are involved, although the loss of articular cartilage and changes in the adjacent bone remain the most striking features (Arden and Nevitt, 2006). In essence, the protective cushion found in the joints between bones eventually wears down and that the bones rub against other, resulting in inflammation and pain (Arden and Nevitt, 2006).

Osteoarthritis commonly affects the joints that support the weight of the body such as hips, knees, ankles and spine. The real cause of OA is yet unknown but some factors such as aging, obesity, joint injury, joint stress, and heredity seem to play a role in the development and perpetuation (Arden and Nevitt, 2006; Gonzales-Penserga, 2009; Ahmed, 2010). The disease is one of the common disabling chronic joint illness affecting humans and different domestic animals. Osteoarthritis is usually accompanied by subchondral responses (Guzman *et al*., 2003) and synovitis which contributes to its pathogenesis through formation of different catabolic and pro-inflammatory mediators such as nitric oxide, PGE_2, pro-inflammatory cytokines and several neuropeptides (Sutton *et al*., 2009).

1.2 Classification of osteoarthritis

Osteoarthritis is classified as being primary or secondary. Primary or idiopathic OA is wear and tear condition; age related and is the more commonly diagnosed type. Primary OA may be developed in a single joint (knee, hip, and spine) or generalized (three or more joint groups). Secondary OA has a specific cause so that it may appear after the following conditions: metabolic (e.g. calcium crystal deposition), anatomical (e.g. congenital dislocation of the hip), traumatic (e.g. fracture through a joint) and inflammatory (septic arthritis) (Creamer and Hochberg, 1997; Arden and Nevitt, 2006).

1.3 Etiology of osteoarthritis

Many risk factors such as mechanical injuries, obesity, peripheral neuropathy, genetic factors and increased age have been identified and the interaction of these factors is known to initiate this joint disorder, but still the exact etiology is not known yet (Ahmed, 2010; Lin *et al*., 2010). Numerous studies showed a strong association between obesity and radiographic knee OA (Grotle *et al*., 2008). The role of genetic factor was well investigated by several studies. It was postulated that polymorphism or mutations in genes encoding extracellular matrix molecules (type II collagen, aggrecan, bone morphometric protein and vitamin D receptors) can play a role in the establishment of this joint disorder (Spector and MacGregor, 2004; Valdes *et al*., 2006).

1.4 Symptoms and diagnosis of osteoarthritis

The symptoms of OA are often characterized by significant functional impairment associated with pain as well as inflammation, joint stiffness and deformity and loss of mobility. Pain is increased when the joint is loaded and with the progression of the disease, pain can occur at rest (Fernihough *et al*., 2004; Goldring and Goldring, 2006). Diagnostic tools and evaluation of OA includes case history, physical test, x-ray examination and in some cases, laboratory testing. Many different joint scoring have been developed which differ from each other in subjective and objective criteria (Rutgers *et al*., 2010).

1.5 Pathogenesis of osteoarthritis

The pathophysiology of the disease involves not only the breakdown of the articular cartilage but also changes in the subchondral bone and synovium. The cartilage has received the most attention in past decades due to extensive damage evident in histopathological specimens and from imaging studies (Samuels *et al*., 2008). Chondrocytes in the mature articular cartilage are responsible to produce and maintain the extracellular matrix. Therefore, any reduction in chondrocyte density will contribute to the development of OA (Lee *et al*., 2005).

Chondrocytes offer limited assistance to articular cartilage, but are instead essential due to their role in the synthesis and turnover of the extracellular matrix which they accomplish through a constant turnover mechanism (Acosta *et al*., 2006). In turn, the matrix provides an environment for nutrition diffusion for chondrocytes, as well as providing biomechanical competence to the joint surface. Biomechanical reckoning indicating that damage of the surface zone of articular cartilage leads to increased loading of the cartilage matrix, resulting in higher stress on the underlying cartilage and subsequent subchondral response (Stoop *et al*., 2001). Radiographic diagnosis can identify the characteristic features of OA such as osteophyte formation, thickening of the subchondral bone, cyst development, reduced joint space and joint misalignment (Guermazi *et al.,* 2003).

The role and relationship of the following NPs: CGRP, substance P (SP), NPY and PGP 9.5 in OA development and progression had been well identified in the knee joints of human and domestic animals (Heppelmann *et al.*, 1997; Tamura *et al.*, 1998; Tahmasebi-Sarvestani *et al.*, 2001; Michelle *et al*., 2004; Miller *et al*., 2005). Reduction of these fibers in OA may be due to their depletion or necrosis (Buma *et al*., 2000) or indirectly due to the production of oxygen free radicals during OA events and subsequently their necrosis (Konttinen *et al*., 1992).

1.6 Incidence of osteoarthritis

Osteoarthritis is well known to cause major health burden in human and veterinary practice. In human, OA affects a large population with considerable morbidity and disability (Dumond *et al*., 2004). Recent survey of the World Health Organization (WHO) revealed 10% of the world population with the average of age 60 years suffers osteoarthritis pain (McDougall, 2006). In the veterinary field, OA is widely encountered in many animal species. In equine, OA is a naturally occurring degenerative disease which is age related and factors such as stress of racing and training may accelerates its development (Cantley *et al*., 1999). The disease is considered as the primary cause of equine lameness that leads to economic losses in equine industry (Williams, 2007). In dogs, the disease is considered a progressive degenerative condition affecting about 20% of the adult animals (Macphail, 2000). Previous records indicated that once canine OA becomes clinically apparent, the treatment will be directed only to slow down its progression and improving the general mobility and quality of life of the affected dogs (Doig *et al*., 2000).

Osteoarthritic pain in feline species is very difficult to detect or diagnose clinically. However, radiographic evidences showed higher percentages of aged cats affected are due to OA (Taylor and Robertson, 2004) and recent researchers found that patellar luxation is an important cause of this condition (Loughin *et al*., 2006).

1.7 Current regulation of osteoarthritis

Treatment and regulation of osteoarthritis is very complicated due to lack of commercial drugs definitely proven to modify its development and progression. Non steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the treatment of pain due to OA but they are not 100% safe because some complications may occur in their long term use such as suppression of blood platelets, incomplete pain relief and mucosal disruption of gastrointestinal tract (Bove *et al*., 2003; Fernihough *et al*., 2004). Current therapeutic interventions are useful for controlling symptoms, specially the pain. Adverse side effects of OA regulations may be ameliorated by the use of botanical or animal extracts alternatives. *Channa striatus* (common name: Haruan) extract and zerumbone are such candidates. To date there was only one preliminary investigation undertaken to study the effect of *Channa* extract on PGP 9.5 immunoreactivity in surgically-induced OA in rabbit. Therefore this study was undertaken to identify the chondroprotective effect of channa extract and zerumbone and to compare their effect on the densities of nerve fibers of some OA related neuropeptides. Prostaglandins in the serum were assayed to explore their role and relationship during OA and following the treatment with both natural remedies.

1.8 Hypothesis

Anti-inflammatory properties of the *Channa striatus* aqueous extract and the anti-inflammatory as well as antioxidant properties of zerumbone could alleviate osteoarthritic changes in the knee joints of the Sprague Dawley rats with experimentally induced osteoarthritis.

1.9 Objectives of the study

The objectives of this study were to

1. explore the effective method for induction of experimental osteoarthritis by intraarticular injection of chemicals.
2. study the chondroprotective effect of *Channa striatus* extract and zerumbone on experimentally induced knee osteoarthritis in rat.
3. examine immunoreactivity improvement effect of *Channa striatus* extract and zerumbone in the synovial membranes in experimentally induced knee osteoarthritis in rat (Immunohistochemical study).
4. study the role of serum PGE_2 and $PGF_2\alpha$ during osteoarthritis and following the treatment with *Channa striatus* extract and zerumbone against experimentally induced knee osteoarthritis in rat (Hormonal assay study).

5. identify some hepatic metabolizing enzymes and oxidative stress biomarkers in rats administrated zerumbone against experimentally induced knee osteoarthritis in rat (Toxicological study).

REFERENCES

Abdelwahab, S.I., Abdul, A.B., Devi, N., Taha, M.M.E., Al-zubairi, A.S., Mohan, S. & Mariod, A.A. (2010). Regression of cervical intraepithelial neoplasia by zerumbone in female Balb/c mice prenatally exposed to diethylstilboestrol: Involvement of mitochondria-regulated apoptosis. *Experimental and Toxicologic Pathology*. 62(5): 461-469.

Abdul, A.B.H., Al-Zubairi, A.S., Tailan, N.D., Wahab, S.I.A., Zain, Z.N.M., Ruslay, S. & Syam, M.M. (2008). Anticancer activity of natural compound (zerumbone) extracted from *Zingiber zerumbet* in human HeLa cervical cancer cells. *International Journal of Pharmacology*. 4(3): 160-168.

Abraham, S.K. & Singh, S.P. (1999). Anti-genotoxicity and glutathione *S*-transferase activity in mice pretreated with caffeinated and decaffeinated coffee. *Food & Chemical Toxicology*. 37(7): 733-739.

Acosta, C.A., Izal, I., Ripalda, P., Douglas-Price, A.L. & Forriol, F. (2006). Gene expression and proliferation analysis in young, aged, and osteoarthritic sheep chondrocytes effect of growth factor treatment. *Journal of Orthopaedic Research*. 24(11): 2087-2094.

Adams, C.S. & Horton, W.E. (1998). Chondrocyte apoptosis increases with age in the articular cartilage of adult animals. *The Anatomical Record*. 250(4): 418-425.

Ahmed, M., Bergström, J., Lundblad, H., Gillespie, W.J. & Kreicbergs, A. (1998). Sensory nerves in the interface membrane of aspetic loose hip prostheses. *The Journal of Bone & Joint Surgery* [Br] 80-B: 151-155.

Ahmed, R. S., Suke, S. G., Seth, V., Chakraborti, A., Tripathi, A. K. & Banerjee, B. D. (2008). Protective effects of dietary ginger (*Zingiber officinales* Rosc.) on lindane-induced oxidative stress in rats. *Phytotherapy Research*. 22(7): 902-906.

Ahmed, A.S. (2010). Proteasome targeted therapy in arthritis models. Published by Karolinska Institutet, Stockholm, Sweden. Printed by Larserics Digital Print AB, Sweden. ISBN: 978-91-7457-012-0.

Aizawa, T., Kon, T., Einhorn, T.A. & Gerstenfeld, L.C. (2001). Induction of apoptosis in chondrocytes by tumor necrosis factor-alpha. *Journal of Orthopaedic Research*. 19(5): 785-796.

AL-Saffar, F.J., Ganabadi, S., Yaakub, H., & Fakurazi, S. (2009). Collagenase and sodium iodoacetate – induced experimental osteoarthritis model in Sprague Dawley rats. *Asian Journal of Scientific Research*. 2(4): 167-179.

AL-Saffar, F.J., Ganabadi, S, Fakurazi, S., Yaakub, H. & Lip, M. (2010). Chondroprotective effect of zerumbone on monosodium iodoacetate induced osteoarthritis in rats. *Journal of Applied Sciences*. 10(4): 248-260.

Altinkaynak, K., Süleyman, H. & Akçay, F. (2003). Effect of nimesulide, rofecoxib and celecoxib on gastric tissue glutathione level in rats with indomethacin-induced gastric ulcerations. *Polish Journal of Pharmacology*. 55(4): 645-648.

Appleyard, R.C., Burkhardt, D., Ghosh, P., Read, R., Cake, M., Swain, M.V. & Murrell, G.A.C. (2003). Topographical analysis of the structural, biochemical and dynamic biomechanical properties of cartilage in an ovine model of osteoarthritis. *Osteoarthritis & Cartilage*. 11(1): 65-77.

Arden, N. & Nevitt, M.C. (2006). Osteoarthritis: Epidemiology. *Best practice & Research Clinical Rheumatology*. 20(1): 3-25.

Baie, S.H. & Sheikh, K.A. (2000a). The wound healing properties of *Channa striatus*- cetrimide cream – wound contraction and glycosaminoglycan measurement. *Journal of Ethnopharmacology*. 73(1-2): 15-30.

Baie, S.H. & Sheikh, K.A. (2000b). The wound healing properties of *Channa striatus*- cetrimide cream – tensile strength measurement. *Journal of Ethnopharmacology*. 71(1-2): 93-100.

Bains, J.S. & Shaw, C.A. (1997). Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. *Brain Research Reviews*. 25(3): 335-358.

Barry, F.P. & Murphy, J.M. (2004). Mesenchymal stem cells: clinical applications and biological characterization. *The International Journal of Biochemistry & Cell Biology*. 36(4): 568-584.

Bastos-Pereira, A. L., Lugarini, D., Oliveira-Christoff, A., Ávila, T. V., Teixeira, S., Pires, A. R.A., Muscará, M. N., Cadena, S.M.S.C., Donatti, L., Silva de Assis, H.C. & Acco, A. (2010). Celecoxib prevents tumor growth in an animal model by a COX-2 independent mechanism. *Cancer Chemotherapy & Pharmacology*. 65: 267–276.

Beyreuther, B., Callizot, N. & Stöhr, T. (2007). Antinociceptive efficacy of lacosamide in the monosodium iodoacetate rat model for osteoarthritis pain. *Arthritis Research & Therapy*. 9(1): R14.

Blanco, F.J., Ochs, R.L., Schwarz, H. & Lotz, M. (1995). Chondrocyte apoptosis induced by nitric oxide. *American Journal of Pathology*. 146(1): 75-85.

Blom, A.B., Van Lent, P.L.E.M., Holthuysen, A.E.M., Van der kraan, P.M., Roth, J., Van Rooijen, N. & Van den Berg, W.B. (2004). Synovial lining macrophages mediate osteophyte formation during experimental osteoarthritis. *Osteoarthritis & Cartilage*. 12(8): 627-635.

Bobinaca, D., Spanjola, J.,Zoricica, S. & Marica,I. (2003). Changes in articular cartilage and subchondral bone histomorphometry in osteoarthritic knee joints in humans. *Official Journal of the International Bone and Mineral Society*, 32: 284-290.

Bove, S.E., Calcaterra, S.L., Brooker, R.M., Huber, C.M., Guzman, R.E., Juneau, P.L., Schrier, D.J. & Kilgore, K.S. (2003). Weight bearing as a measure of disease progression and efficacy of anti-inflammatory compounds in a model of monosodium iodoacetate-induced osteoarthritis. *Osteoarthritis & Cartilage*. 11(11): 821-830.

Brain, S.D. & Cox, H.M. (2006). Neuropeptides and their receptors: innovative science providing novel therapeutic targets. *British Journal of Pharmacology.* 147(S1): 202-211.

Brodie, M. J., Hensby, C. N., Parke, A. & Gordon, D. (1980). Is prostacyclin the major pro-inflammatory prostanoid in joint fluid? *Life Sciences*. 27(7): 603-608.

Brunner, L.J., Bennett, W.M. & Koop, D.R. (1998). Cyclosporine suppresses rat hepatic cytochrome P450 in a time-dependent manner. *Kidney International.* 54(1): 216-223.

Buettner, G.R. (1993). The pecking order of free radicals and antioxidants: lipid peroxidation, α-tocopherol, and ascorbate. *Archives of Biochemistry and Biophysics.* 300(2): 535-543.

Buma, P., Elmans, L., Van den berg, W.B. & Schrama, L.H. (2000). Neurovascular plasticity in the knee joint of an arthritic mouse model. *The Anatomical Record.* 260(1): 51-61.

Cahue, S., Sharma, L., Dunlop, D., Ionescu, M. Song, J., Lobanok, T., King, L. & Poole, A.R. (2007). The ratio of type II collagen breakdown to synthesis and its relationship with the progression of knee osteoarthritis. *Osteoarthritis & Cartilage.* 15(7): 819-823.

Cantley, C.E.L., Firth, E.C., Delahunt, J.W., Pfeiffer, D.U. & Thompson, K.G. (1999). Naturally occurring osteoarthritis in the metacarpophalangeal joints of wild horses. *Equine Veterinary Journal.* 31(1): 73-81.

Carmona, J.U., Argüelles, D., Climent, F. & Prades, M. (2007). Autologous platelet concentrates as a treatment of horses with osteoarthritis: A preliminary pilot clinical study. *Journal of Equine Veterinary Science.* 27(4): 167-170.

Carpenter, T.A., Everett, J.R., Hall, L.D., Harper, G.P., Hodgson, R.J. & James, M.F. (1995). Visualisation of subchondral erosion in rat monoarticular arthritis by magnetic resonance imaging. *Skeletal Radiology,* 24: 341-349.

Caron, J.P., Bowker, R.M., Abhold, R.H., Toppin, D.S., Sonea, I.M. & Vex, K.B. (1992). Substance P in the synovial membrane and fluid of the equine middle carpal joint. *Equine Veterinary Journal.* 24(5): 364-366.

Carroll, G.L. & Simonson, S.M. (2005). Recent developments in nonsteroidal anti inflammatory drugs in cats. *Journal of the American Animal Hospital Association.* 41(6): 347-354.

Catalá, A. (2006). An overview of lipid peroxidation with emphasis in outer segments of photoreceptors and the chemiluminescence assay. *The International Journal of Biochemistry & Cell Biology.* 38(9): 1482-1495.

Cerinic, M.M., Konttinen, Y., Generini, S. & Cutolo, M. (1998). Neuropeptides and steroid hormones in arthritis. *Current Opinion in Rheumatology.* 10(3): 220-235.

Chakravarthi, S., Jessop, C.E. & Bulleid, N.J. (2006). The role of glutathione in disulphide bond formation and endoplasmic-reticulum-generated oxidative stress. *European Molecular Biology Organization Reports.* 7(3): 271-275.

Chaudhary, D.P., Boparai, R.K. & Bansal, D.D. (2007). Implications of oxidative stress in high sucrose low magnesium diet fed rats. *European Journal of Nutrition.* 46(7): 383-390.

Chen, W., Koenigs, L.L., Thompson, S.J., Peter, R.M., Rettie, A.E., Trager, W.F. & Nelson, S.D. (1998). Oxidation of acetaminophen to its toxic quinone imine and nontoxic catechol metabolites by baculovirus-expressed and purified human cytochromes P450 2E1 and 2A6. *Chemical Research in Toxicology.* 11(4): 295–301.

Chien,T.Y., Chen, L.G., Lee, C.J., Lee, F.Y. & Wang, C.C. (2008). Anti-inflammatory constituents of *Zingiber zerumbet*. *Food Chemistry*. 110(3): 584-589.

Choi, J.H., Choi, J.H., Kim, D.Y., Yoon, J.H., Youn, H.Y., Yi, J.B., Rhee, H.I., Ryu, K.H., Jung, K., Han, C.K., Kwak, W.J. & Cho, Y.B. (2002). Effects of SKI 306X, a new herbal agent, on proteoglycan degradation in cartilage explant culture and collagenase-induced rabbit osteoarthritis model. *Osteoarthritis & Cartilage.* 10(6): 471-478.

Choi, E.Y. & Cho, Y.O. (2009). Effect of vitamin B_6 deficiency on antioxidative status in rats with exercise-induced oxidative stress. *Nutrition Research and Practice.* 3(3): 208-211.

Clarke, S.P. & Bennett, D. (2006). Feline osteoarthritis: a prospective study of 28 cases. *Journal of Small Animal Practice*. 47(8): 439-445.

Cornelis, M.C., Bae, S.C., Kim,I & El-Sohemy, A. (2010). CYP1A2 genotype and rheumatoid arthritis in Koreans. *Rheumatology International.* 30(10): 1349-1354.

Cournil, C., Liagre, B., Grossin, L., Vol, C., Abid, A., Jouzeau, J.Y., Terlain, B., Netter, P. & Gillet, P. (2001). Overexpression and induction of heat shock protein (Hsp) 70 protects *in vitro* and *in vivo* from mono-iodoacetate (MIA)-induced chondrocytes death. *Arthritis Research.* 3 (Suppl. 1): A1-A16, P41.

Creamer, P. & Hochberg, M.C. (1997). Osteoarthritis. *The Lancet.* 350: 503-509.

Crovace, A., Lacitignola, L., Miolo, A. & Fanizzi, F.P. (2006). Surgery plus chondroprotection for canine cranial cruciate ligament (CCL) rupture: a proton-NMR study. *Veterinary and Comparative Orthopaedics and Traumatology.* 19(4): 239-245.

Curry, S.L., Cogar, S.M. & Cook, J.L. (2005). Nonsteroidal antiinflammatory drugs: A Review. *Journal of the American Animal Hospital Association.* 41: 298-309.

Dabhi, J.K., Solanki, J.K. & Mehta, A. (2008). Antiatherosclerotic activity of ibuprofen, a non-selective COX inhibitor-An animal study. *Indian Journal of Experimental Biology.* 46(6): 476-481.

Dambisya, Y.M., Lee, T.L., Sathivulu, V. & Mat Jais, A. M. (1999). Influence of temperature, pH and naloxone on the antinociceptive activity of *Channa striatus* (haruan) extracts in mice. *Journal of Ethnopharmacology.* 66(2): 181-186.

Dieppe, P.A. & Lohmander, L.S. (2005). Pathogenesis and management of pain in osteoarthritis. *The Lancet* 365: 965-973.

Dirmeier, M., Capellino, S., Schubert, T., Angele, P., Anders, S. & Straub, R.H. (2008). Lower density of synovial nerve fibers positive for calcitonin gene-related peptide relative to substance P in rheumatoid arthritis but not in osteoarthritis. *Rheumatology.* 47(1): 36-40.

Doig, P.A., Purbrick, K.A., Hare, J.E. & Mckeown, D.B. (2000). Clinical efficacy and tolerance of meloxicam in dogs with chronic osteoarthritis. *Canadian Veterinary Journal.* 41(4): 296-300.

Donoso, M.V., Brown, N., Carrasco, C., Cortes, V., Fournier, A. & Huidobro-Toro, J.P. (1997). Stimulation of the sympathetic perimesentric arterial nerves releases neuropeptide Y potentiating the vasomotor activity of noradrenaline: involvement of neuropeptide Y-Y1 receptors. *Journal of Neurochemistry.* 69(3): 1048-1059.

Du, Z.X., Zhang, H.Y., Meng, X., Guan, Y. & Wang, H.Q. (2009). Role of oxidative stress and intracellular glutathione in the sensitivity to apoptosis induced by proteasome inhibitor in thyroid cancer cells. *BMC Cancer.* 9: 56.

Dumond, H., Presle, N., Pottie, P., Pacquelet, S., Terlain, B., Netter, P., Gepstein, A., Livne, E. & Jouzeau, J.Y. (2004). Site specific changes in gene expression and cartilage metabolism during early experimental osteoarthritis. *Osteoarthritis & Cartilage.* 12(4): 284-295.

El-Medany, A., Mahgoub, A., Mustafa, A., Arafa, M. & Morsi, M. (2005). The effects of selective cyclooxygenase-2 inhibitors, celecoxib and rofecoxib, on experimental colitis induced by acetic acid in rats. *European Journal of Pharmacology.* 507(1-3): 291-299.

Faizah, S., Somchit, M.N. & Shukriyah, M.H. (2002). *Zingiber zerumbet* (Lempoyang): A potential anti-inflammatory agent. Proceedings of the Regional Symposium on Environment and Natural Resources. 10-11th April, Hotel Renaissance Kula Lumpur, Malaysia .Vol.1: 516-520.

Fakurazi, S., Hairuszah, I., Mohd Lip, J. & Shanthi, G. (2008a). The effect of pretreatment of zerumbone on fatty liver following ethanol induced hepatotoxicity. *Journal of Biological Sciences.* 8(8): 1348-1351.

Fakurazi, S., Hairuszah, I. & Nanthini, U. (2008b). *Moringa oleifera* Lam prevents acetaminophen induced liver injury through restoration of glutathione level. *Food and Chemical Toxicology.* 46(8): 2611-2615.

Fenton, J.I., Chlebek-Brown, K.A., Peters, T.L., Caron, J.P. & Orth, M.W. (2000). Glucosamine HCl reduces equine articular cartilage degradation in explant culture. *Osteoarthritis & Cartilage.* 8(4): 258-265.

Fernihough, J., Gentry, C., Malcangio, M., Fox, A., Rediske, J., Pellas, T., Kidd, B., Bevan, S. & Winter, J. (2004). Pain related behavior in two models of osteoarthritis in the rat knee. *Pain.* 112(1-2): 83-93.

Fernihough, J., Gentry, C., Bevan, S. & Winter, J. (2005). Regulation of calcitonin gene-related peptide and TRPV1 in a rat model of osteoarthritis. *Neuroscience Letters*. 388(2): 75-80.

Fiorito, S., Magrini, L., Adrey, J., Mailhé, D. & Brouty-Boyé, D. (2005). Inflammatory status and cartilage regenerative potential of synovial fibroblasts from patients with osteoarthritis and chondropathy. *Rheumatology.* 44(2): 164-171.

Fleming, B.C., Hulstyn, M.J., Oksendahl, H.L. & Fadale, P.D. (2005). Ligament injury, reconstruction and osteoarthritis. *Current Opinion in Orthopaedics.* 16(5): 354-362.

Fortier, L.A. & Nixon, A.J. (1997). Distributional changes in Substance P nociceptive fiber patterns in naturally osteoarthritic articulations. *Journal of Rheumatology.* 24(3): 524-530.

Foster, B.C., Vandenhoek, S., Li, K.Y., Tang, R., Budzinski, J.W. & Krantis, A. (2002). Effect of several Chinese natural health products of human cytochrome P450 metabolism. *Journal of Pharmacy & Pharmaceutical Sciences.* 5(2): 185-189.

Galois, L., Etienne, S., Grossin, L., Watrin-Pinzano, A., Cournil-Henrionnet, C., Loeuille, D., Netter, P., Mainard, D. & Gillet, P. (2004). Dose-response relationship for exercise on severity of experimental osteoarthritis in rats: a pilot study. *Osteoarthritis & Cartilage.* 12(10): 779-786.

Goldring, S.R. & Goldring, M.B. (2006). Clinical aspects, pathology and pathophysiology of osteoarthritis. *Journal Musculoskeletal & Neuronal Interactions.* 6(4): 376-478.

Goldring, M.B. & Goldring, S.R. (2007). Osteoarthritis. *Journal of Cellular Physiology.* 213:626-634.

Gonzales-Penserga, E.Z. (2009). Disease mechanism in osteoarthritis. *Philippine Journal of Internal Medicine*, 47: 231-235.

Goodrich, L.R. & Nixon, A.J. (2006). Medical treatment of osteoarthritis in the Horse-A review. *The Veterinary Journal.* 171(1): 51-69.

Grosvenor, P.W., Gothard, P.K., McWilliam, N.C., Supriono, A. & Gray, D.O. (1995). Medicinal plants from Riau Province, Sumatra, Indonesia. Part 1: Uses. *Journal of Ehnopharmacology.* 45(2): 75-95.

Grotle, M., Hagen, K.B., Natvig, B., Dahl, F.A. & Kvien, T.K. (2008). Obesity and osteoarthritis in knee, hip and /or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskeletal Disorders.* 9: 132.

Guermazi, A., Zaim, S., Taouli, B., Miaux,Y., Peterfy, C.G. & Genant, H.K. (2003). MR findings in knee osteoarthritis. *European Radiology.* 13(6): 1370-1386.

Guzman, R.E., Evans, M.G., Bove, S., Morenko, B. & Kilgore, K. (2003). Mono-iodoacetate-induced histologic changes in subchondral bone and articular cartilage of rat femorotibial joints: an animal model of osteoarthritis. *Toxicologic Pathology.* 31(6): 619-624.

Habig, W.H., Pabst, M.J. & Jakoby, W.B. (1974). Glutathione *S*-transferases. *The Journal of Biological Chemistry.* 249(22): 7130-7139.

Hanesch, U., Heppelmann, B. & Schmidt, R.F. (1991). Substance P- and calcitonin gene-related peptide immunoreactivity in primary afferent neurons of the cat's knee joint. *Neuroscience.* 45(1): 185-193.

Hattori, K., Ikeuchi, K., Morita, Y. & Takakura, Y. (2005). Quantitative ultrasonic assessment for detecting microscopic cartilage damage in osteoarthritis. *Arthritis Research & Therapy.* 7(1): R38-R46.

Hayes, A. W. (2008). Principles and Methods of Toxicology. 5th ed., Taylor and Francis group, LLC, CRC press. 6000 Broken Sound Parkway, NW, Suite 300, Boca Raton, FL 33487- 2742.

Haynes, M.K., Hume, E.L. & Smith, J.B. (2002). Phenotypic characterization of inflammatory cells from osteoarthritic synovium and synovial fluids. *Clinical Immunology.* 105(3): 315-325.

Heppelmann, B., Shahbazian, Z. & Hanesch, U. (1997). Quantitative examination of calcitonin gene-related peptide immunoreactive nerve fibers in the cat knee joint capsule. *Anatomy and Embryology.* 195(6): 525-530.

Hernanz, A., Medina, S., de Miguel, E. & Martín-Mola, E. (2003). Effect of calcitonin gene-related peptide, neuropeptide Y, substance P, and vasoactive intestinal peptide on interleukin-1 β, interleukin-6 and tumor necrosis factor-alpha production by peripheral whole blood cells from rheumatoid arthritis and osteoarthritis patients. *Regulatory Peptides*. 115(1): 19-24.

Hildebrand, C., Oqvist, G., Brax, L. & Tuisku, F. (1991). Anatomy of the rat knee joint and fiber composition of a major articular nerve. *The Anatomical Record*, 229: 545-555.

Hinchcliff, K.W., Kaneps, A.J. & Geor, R.J. (2008). Equine exercise physiology: the science of exercise in a athletic horse. www.elsevierhealth.com, pp 138.

Hinton, R., Moody, R.L., Davis, A.W. & Thomas, S.F. (2002). Osteoarthritis: diagnosis and therapeutic considerations. *American Family Physician.* 65(5): 841-848.

Huang, G.C., Chien, T.Y., Chen, L.G. & Wang, C.C. (2005). Antitumor effects of zerumbone from Zingiber zerumbet in P-388D1 cells in vitro and in vivo. *Planta Medica.* 71(3): 219-224.

Hukkanen, M., Konttinen,Y.T., Rees, R.G., Santavirta, S., Terenghi,G. & Polak, J.M. (1992). Distribution of nerve endings and sensory neuropeptides in rat synovium, meniscus and bone. *International Journal of Tissue Reaction.* 14(1): 1-10.

Huttunen, K.M., Mähönen, N., Leppänen, J., Vepsäläinen, J., Juvonen, R.O., Raunio, H., Kumpulainen, H., Järvinen, T. & Rautio, J. (2007). Novel cyclic phosphate prodrug approach for cytochrome P450-activated drugs containing an alcohol functionality. *Pharmaceutical Research*. 24(4): 679-687.

Hyc, A., Osiecka-Iwan, A., Dziunyez, P. & Moskalewski, S. (2007). Preparation of rat synovial membrane for studies of cytokines secretion. *Folia Histochemica Et Cytobiologica*, 45: 57-60.

Ibrahim, M.Y., Abdul, A.B., Abdel Wahab, S.I., Elhassan, M.M., Alzubairi, A.S. & Syam, M.M. (2009). Attenuation of cisplatin-induced hepatotoxicity in rats using zerumbone. *Research Journal of Biological Sciences*. 4(7): 777-784.

Ikeda, N., Nozawa-Inoue, K, Takagi, R. & Maeda, T. (2004). Development of the synovial membrane in the rat temporomandibular joint as demonstrated by immunocytochemistry for heat shock protein 25. *The Anatomical Record*, part A 2797: 623-635.

Inoue, H., Shimoyama,Y., Hirabayashi, K., Kajigaya, H., Yamamoto, S., Oda, H. & Koshihara,Y. (2001). Production of neuropeptide substance P by synovial fibroblasts from patients with rheumatoid arthritis and osteoarthritis. *Neuroscience Letters.* 303(3): 149-152.

Jang, S.I., Kim, H.J., Hwang, K.M., Jekal, S.J., Pae, H.O., Choi, B.M., Yun, Y.G., Kwon, T.O., Chung, H.T. & Kim, Y.C. (2003). Hepatoprotective effect of baicalin, a major flavone from *Scutellaria radix*, on acetaminophen-induced liver injury in mice. *Immunopharmacology and Immunotoxicology.* 25(4): 585-594.

Janusz, M.J., Bendele, A.M., Brown, K.K, Taiwo, Y.O., Hsieh, L. & Heitmeyer, S.A. (2002). Induction of osteoarthritis in the rat by surgical tear of the meniscus: Inhibition of joint damage by a matrix metalloproteinase inhibitor. *Osteoarthritis & Cartilage.* 10(10): 785-791.

Jerram, R.M., Walker, A.M. & Warman, C.G.A. (2005). Proximal tibial intraarticular ostectomy for treatment of canine cranial cruciate ligament injury. *Veterinary Surgery.* 34(3): 196-205.

Johnston, S.A. (1997). Osteoarthritis. Joint anatomy, physiology and pathobiology. *Veterinary Clinical North America of Small Animal Practice.* 27(4): 699–723.

Jouglin, M., Robert, C., Valette, J.P., Gavard, F., Quintin-Colonna, F. & Denoix, J.M. (2000). Metalloproteinases and tumor necrosis factor-alpha activities in synovial fluids of horses: correlation with articular cartilage alterations. *Veterinary Research.* 31(5): 507-515.

Jusman, S.W.A. & Abdul Halim, S. (2009). Oxidative stress in liver tissue of rat induced by chronic systemic hypoxia. *MAKARA, KESEHATAN* 13: 34-38.

Karatopuk, D.U. & GöKçimen, A. (2010). Effect of tenoxicam on rat liver tissue. *Turkish Journal of Gastroenterology.* 21(2): 146-152.

Kataria, N., Kataria, A.K., Maan, R. & Gahlot, A.K. (2010). Evaluation of oxidative stress in brucella infected cows. *Journal of Stress Physiology & Biochemistry.* 6(2): 19-25.

Kerksick, C. & Willoughby, D. (2005). The antioxidant role of glutathione and N-acetyl-cysteine supplements and exercise-induced oxidative stress. *Journal of the International Society of Sports Nutrition.* 2(2): 38-44.

Kerwin, S.C. (2007). Feline osteoarthritis. *79th Western Veterinary Conference*. V215. Texas A&M University, USA.

Kikuchi, T., Sakuta, T. & Yamaguchi, T. (1998). Intra-articular injection of collagenase induces experimental osteoarthritis in mature rabbits. *Osteoarthritis & Cartilage.* 6(3): 177-186.

Kilty, C., Doyle, S., Hassett, B. & Manning, F. (1998). Glutathione *S*-transferases as biomarkers of organ damage: applications of rodent and canine GST enzyme immunoassays. *Chemico-Biological Interactions* 111-112: 123-135.

Kobayashi, K., Mishima, H., Harwood, F., Hashimoto, S., Toyoguchi, T., Goomer, R., Moriya, H. & Amiel, D. (2002). The suppressive effect of hyaluronan on nitric oxide production and cell apoptosis in the central region of meniscus following partial meniscectomy. *The Iowa Orthopaedic Journal.* 22: 39–41.

Kobayashi, K., Imaizumi, R., Sumichika, H., Tanaka, H., Goda, M., Fukunari, A. & Komatsu, H. (2003). Sodium iodoacetate-induced experimental osteoarthritis and associated pain model in rats. *The Journal of Veterinary Medical Science.* 65(11): 1195-1199.

Konttinen, Y.T, Hukkanen, M., Segerberg, M, Rees, R, Kemppinen, P., Sorsa, T., Saari, H., Polak, J.M. & Santavirta, S. (1992). Relationship between neuropeptide immunoreactive nerves and inflammatory cells in adjuvant arthritic rats. *Scandinavian Journal of Rheumatology* 21(2): 55–59.

Koul, A., Tanwar, L. & Arora, N. (2009). Celecoxib administration exhibits tissue specific effect on ^{3}H-benzo (a) pyrene-DNA adduct formation in cigarette smoke inhaling mice. *Indian Journal of experimental Biology.* 47(2): 83-90.

Lampe, W.J., King, I.B., Li, S., Grate, M.T., Barale, K.V., Chen, C., Feng, Z. & Potter, J.D. (2000). Brassica vegetables increase and apiaceous vegetables decrease cytochrome P450 1A2 activity in humans: changes in caffeine metabolite ratios in response to controlled vegetable diets. *Carcinogenesis.* 21(6): 1157-1162.

Lascelles, B.D., Court, M.H., Hardie, E.M. & Robertson, S.A. (2007). Nonsteroidal anti-inflammatory drugs in cats: a review. *Veterinary Anaesthesia & Analgesia.* 34(4): 228-250.

Lascelles, B.D. (2010). Feline degenerative joint disease. *Veterinary Surgery*. 39(1): 2-13.

Lee, S.W., Chung, W.T., Choi, S.M., Kim, K.T., Yoo, K.S. & Yoo, Y.H. (2005). Clematis mandshurica protected to apoptosis of rat chondrocytes. *Journal of Ethnopharmacology.* 101(1-3): 294-298.

Lefèvre, G., Beljean-Leymarie, M., Beyerle, F., Bonnefont-Rousselot, D., Cristol, J.P.,Thérond, P. & torreilles, J. (1998). Evaluation of lipid peroxidation by assaying the thiobarbituric acid-reactive substances. *Annles de Biologie Clinique.* 56(3): 305-319.

Levine, J.D., Dardick, S.J., Roizen, M.F., Helms, C. & Basbaum, A.I. (1986). Contribution of sensory afferents and sympathetic efferents to joint injury in experimental arthritis. *The Journal of Neuroscience.* 6(12): 3423-3429.

Lin, J., Li, R., Kang, X. & Li, H. (2010). Risk factors for radiographic tibiofemoral knee osteoarthritis: The wuchuan osteoarthritis study. *International Journal of Rheumatology.* 2010: ID 385826, 6 pages.

Liu, P.T., Ioannides, C., Shavila, J., Symons, A.M. & Parke, D.V. (1993). Effects of ether anaesthesia and fasting on various cytochromes P450 of rat liver and kidney. *Biochemical Pharmacology* 45(4): 871-877.

Loughin, C.A., Kerwin, S.C., Hosgood, G., Ringwood, P.B., Williams, J., Stefanacci, J.D. & McCarthy, R.J. (2006). Clinical signs and results of treatment in cats with patellar luxation: 42 cases (1992-2002). *Journal of the American Veterinary Medical Association.* 228(9): 1370-1375.

Loughlin, J. (2005). Polymorphism in signal transduction is a major route through which osteoarthritis susceptibility is acting. *Current Opinion in Rheumatology.* 17(5): 629-633.

Mach, D.B., Rogers, S.D., Sabino, M.C., Luger, N.M., Schwei, M.J., Pomonis, J.D., Keyser, C.P., Clohisy, D.R., Adams, D.J., O'Leary, P. & Mantyh, P.W. (2002). Origins of skeletal pain: Sensory and sympathetic innervation of the mouse femur. *Neuroscience.* 113(1):155-166.

Macphail, C.M. (2000). Treatment of canine osteoarthritis. *WALTHAM Focus* 10(2): 25-31.

Mahmoudabad, A.B.Z., Saberi, M. & Pirzad, J. (2008). Critical role of GSH in sulfur mustard-induced oxidative stress and cytotoxicity in human skin fibroblast cell line. *Iranian Journal of Pharmaceutical Research.* 7(1): 35-41.

Mapp, P.I., Walsh, D.A., Garrett, N.E., Kidd, B.L., Cruwys, S.C., Polak, J.M. & Blake, D.R. (1994). Effect of three animal models of inflammation on nerve fibers in the synovium. *Annals of the Rheumatic Diseases.* 53(4): 240-246.

Marshall, K.W., Theriault, E. & Homonko, D.A. (1994). Distribution of substance P and calcitonin gene related peptide immunoreactivity in the normal feline knee. *Journal of Rheumatology.* 21(5): 883-889.

Martel-Pelletier, J., Boilean, C., Pelletier, J-P and Roughley, P.J. (2008). Cartilage in normal and osteoarthritis conditions. *Best Practice & Research Clinical Rheumatology*, 22:351-384.

Mat Jais, A.M., McCullock, R. & Croft, K. (1994). Fatty acid and amino acid composition in haruan as a potential role in wound healing. *General Pharmacology.* 25(5): 947-950.

Mat Jais, A.M., Dambisya, Y.M. & Lee, T.L. (1997). Antinociceptive activity of *Channa striatus* (haruan) extracts in mice. *Journal of Ethnopharmacology.* 57(2): 125-130.

Mat Jais, A.M., Matori, M.F., Kittakoop, P. & Sowanborirux, K. (1998). Fatty acid compositions in Mucus and Roe of Haruan, *Channa striatus*, for wound healing. *General Pharmacology.* 30(4): 561-563.

Mat Jais, A.M. (2007). Molecular size of the bio-active components from Haruan *Channa striatus* extract. *Journal of applied Sciences.* 7(15): 2198-2199.

Mateos, R., Lecumberri, E., Ramos, S., Goya, L. & Bravo, L. (2005). Determination of malondialdehyde (MDA) by high-performance liquid chromatography in serum and liver as a biomarker for oxidative stress application to a rat model for hypercholesterolemia and evaluation of the effect of diets rich in phenolic antioxidants from fruits. *Journal of Chromatography.* B 827: 76-82.

Matsui, H., Shimizu, M. & Tsuji, H. (1997). Cartilage and subchondral bone interaction in osteoarthrosis of human knee joint: A histological and histomorphometric study. *Microscopy Research and Technique*, 37: 333-342.

McDougall, J. J. (2006). Pain and OA. *Journal Musculoskeletal & Neuronal Interactions.* 6(4): 385-386.

McDougall, J.J.,Watkins, L. & Li, Z. (2006). Vasoactive intestinal peptide (VIP) is a modulator of joint pain in a rat model of osteoarthritis. *Pain.* 123(1-2): 98-105.

Medina, S., Del Río, M., Hernanz, A. & De la Fuente, M. (2000). Age-related changes in the neuropeptide Y effects on murine lymphoproliferation and interleukin-2 production. *Peptides*. 21(9): 1403-1409.

Meister, A. (1994). Glutathione – Ascorbic acid antioxidant system in animals. *The Journal of Biological Chemistry*, 296: 9397-9400.

Michelle, N.Y.T., Shanthi, G. & Loqman, M.Y. (2004). Effect of orally Administered *Channa striatus* extract against experimentally-induced osteoarthritis in rabbits. *The International Journal of Applied Research in Veterinary Medicine.* 2(3): 171-175.

Miller, D., Forrester, K., Leonard, C., Salo, P. & Bray, R.C. (2005). ACL deficiency impairs the vasoconstrictive efficacy of neuropeptide Y and phenylephrine in articular tissues: a laser speckle perfusion imaging study. *Journal of Applied Physiology.* 98: 329-333.

Modi, M., Mittal, M. & Flora, S.J.S. (2007). Combined administration of selenium and *meso*-2, 3-dimercaptosuccinic acid on arsenic mobilization and tissue oxidative stress in chronic arsenic-exposed male rats. *Indian Journal of Pharmacology.* 39(2): 107-114.

Moore, E.E., Bendele, A.M., Thompson, D.L., Littau, A., Waggie, K.S., Reardon, B. & Ellsworth, J.L. (2005). Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. *Osteoarthritis & Cartilage.* 13(7): 623-631.

Moreland, L.W. (2003). Intra-articular hyaluroanan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Research & Therapy.* 5(2): 54-67.

Mrugala, D., Bony, C., Neves, N., Caillot, L., Fabre, S., Moukoko, D., Jorgensen, C. & Noël, D. (2008). Phenotypic and functional characterisation of ovine mesenchymal stem cells: application to a cartilage defect model. *Annals of the Rheumatic Diseases*. 67(3): 288-295.

Murakami, A., Takahashi, M., Jiwajinda, S., Koshimizu, K. & Ohigashi, H. (1999). Identification of zerumbone in *Zingiber zerumbet* smith as a potent inhibitor of 12-*O*-Tetradecanoylphorbol-13-acetate-induced Epstien-Barr Virus activation. *Bioscience, Biotechnology & Biochemistry*. 63(10): 1811-1812.

Murakami, A., Takahashi, D., Kinoshita, T., Koshimizu, K., Kim, H.W., Yoshihiro, A., Nakamura,Y., Jiwajinda, S., Terao, J. & Ohigashi, H. (2002). Zerumbone, a Southeast Asian ginger sesquiterpene, markedly suppresses free radical generation, proinflammatory protein production, and cancer cell proliferation accompanied by apoptosis: the α, β-unsaturated carbonyl group is a prerequisite. *Carcinogenesis.* 23(5): 795-802.

Murakami, A., Hayashi, R., Takana, T., Kwon, K.H., Ohigashi, H. & Safitri, R. (2003). Suppression of dextran sodium sulfate-induced colitis in mice by zerumbone, a subtropical ginger sesquiterpene, and nimesulide: separately and in combination. *Biochemical Pharmacology*. 66(7): 1253-1261.

Murakami, A., Tanaka, T., Lee, J.Y., Surh,Y.J., Kim, H.W., Kawabata, K., Nakamura,Y., Jiwajinda, S. & Ohigashi, H. (2004). Zerumbone, a sesquiterpene in subtropical ginger, suppresses skin tumor initiation and promotion stages in ICR mice. *International Journal of Cancer* 110(4): 481-490.

Murphy, J.M., Fink, D.J., Hunziker, E.B. & Barry, F.P. (2003). Stem cell therapy in a caprine model of osteoarthritis. *Arthritis & Rheumatism*. 48(12): 3464-3474.

Nakamura, Y., Ohigashi, H., Masuda, S., Murakami, A., Morimitsu, Y., Kawamoto, Y., Osawa, T., Imagawa, M. & Uchida, K. (2000). Redox regulation of glutathione *S*-transferase induction by benzyl isothiocyanate: correlation of enzyme induction with the formation of reactive oxygen intermediates. *Cancer Research.* 60(2): 219-225.

Nakamura, Y., Yoshida C., Murakami, A., Ohigashi, H., Osawa, T. & Uchida, K. (2004). Zerumbone, a tropical ginger sesquiterpene, activates phase II drug metabolizing enzymes. *FEBS Letters.* 572(1-3): 245-250.

Nelson, D.R., Koymans, L., Kamataki, T., Stegeman, J.J., Feyereisen, R., Waxman, D.J., Waterman, M.R., Gotoh, O., Coon, M.J., Estabrook, R.W., Gunsalus, I.C., & Nebert, D.W. (1996). P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. *Pharmacogenetics*. 6(1): 1-42.

Nigam, S. & Schewe, T. (2000). Phospholipase A_2s and lipid peroxidation. *Biochimica et Biophysica Acta.* 1488(1): 167-181.

Nickell, R., Schummer, A., Seiferle, E., Wilkens, H., Wille, K-H & Frewein, J. (1986). The Anatomy of Domestic Animals. Volume 1: The Locomotor System of the Domestic Mammals, Paul Parley, Berlin.

Nissalo, S., Hukkanen, M., Imai, S., Törnwall, J. & Konttinen, Y.T. (2002). Neuropeptides in experimental and degenerative arthritis. *Annales of New York Academy of Sciences.* 966: 384-399.

North American Veterinary Conference, Orlando, Florida, January, 13, 1998. Canine skeletal development and soundness. Copyright© 1998 Veterinary Learning Systems, a division of MediMedia, *pp*: 26-27.

Oakley, S.P., Lassere, M.N., Portek, I., Szomor, Z., Ghosh, P., Kirkham, B.W., Murrell, G.A.C., Wulf, S. & Appleyard, R.C. (2004). Biomechanical, histologic and macroscopic assessment of articular cartilage in a sheep model of osteoarthritis. *Osteoarthritis & Cartilage.* 12(8): 667-679.

Ohkawa, H., Ohishi, N. & Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical Biochemistry.* 95(2): 351-358.

Oliva, F., Tarantino, U. & Maffulli, N. (2005). Immunohistochemical localization of calcitonin gene related peptide and substance P in the rat knee cartilage at birth. *Physiological Research.* 54(5): 549-556.

Omura, T. & Sato, R. (1964). The carbone monoxide-binding pigment of liver microsomes. *The Journal of Biological Chemistry.* 239(7): 2370-2378.

Orthopaedic Research Center. Number 13, (Fall 2007). Equine osteoarthritis: Three studies show promise. Collage of Veterinary Medicine and Biomedical sciences. www. csuequineortho.com.

Park, k., Yang, J.H., Choi, Y., Lee, C., Kim, S.Y. & Byun, Y. (2005). Chemoprevention of 4-NQO-induced oral carcinogenesis by co-administration of all-*trans* retinoic acid loaded microspheres and celecoxib. *Journal of Controlled Release.* 104(1): 167-179.

Pearle, A.D., Scanzello, C.R., George, S., Mandl, L.A., DiCarlo, E.F., Peterson, M., Sculco, T.P. & Crow, M.K. (2007). Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis & Cartilage.* 15(5): 516-523.

Pelletier, J.P., Martel-Pelletier, J., Altman, R.D., Ghandur-Mnaymneh, L., Howell, D.S. & Woessner Jr, J.F. (1983). Collagenolytic activity and collagen matrix breakdown of the articular cartilage in the Pond-Nuki dog model of osteoarthritis. *Arthritis & Rheumatism.* 26(7): 866-874.

Pelletier, J.P., DiBattista, J.A., Raynauld, J.P., Wilhelm, S. & Martel-Pelletier, J. (1995). The in vivo effects of intraarticular corticosteroid injections on cartilage lesions, stromelysin, interleukin-1, and oncogene protein synthesis in experimental osteoarthritis. *Laboratory Investigation*. 72(5): 578-586.

Pelletier, J.P., Caron, J.P., Evans, C., Robbins, P.D., Georgescu, H.I., Jovanovic, D., Fernandes, J.C. & Martel-Pelletier J. (1997). In vivo suppression of early experimental osteoarthritis by interleukin-1 receptor antagonist using gene therapy. *Arthritis & Rheumatism*. 40(6): 1012-1019.

Pomonis, J.D., Boulet, J.M., Gottshall, S.L., Phillips, S., Sellers, R., Bunton, T. & Walker, K. (2005). Development and pharmacological characterization of a rat model of osteoarthritis pain. *Pain*. 114(3): 339-346.

Pompella, A., Visvikis, A., Paolicchi, A., De Tata, V. & Casini, A. F. (2003).The changing faces of glutathione, a cellular protagonist. *Biochemical Pharmacology.* 66(8): 1499–1503.

Pool, C.A. (1997). Articular cartilage chondrons: form, function and failure. *Journal of Anatomy*, 191: 1-13.

Rainis, T., Maor, I., Lanir, A., Shnizer, S. & Lavy, A. (2007). Enhanced oxidative stress & leucocyte activation in neoplastic tissues of the colon. *Digestive Diseases & Sciences*. 52(2): 526-530.

Ray, S.D., Parikh, H., Hickey, E., Bagchi, M. & Bagchi, D. (2001). Differential effects of IH636 grape seed proanthocyanidin extract and DNA repair modulator 4-aminobenzamide on liver microsomal cytochrome 450 2E1-dependent aniline hydroxylation. *Molecular & Cellular Biochem*istry. 218: 27-33.

Raza, H., John, A., Lakhani, M.S., Ahmed, I. & Montague,W. (1998). Multiplicity and tissue specific expression of camel cytochrome P450(s)[1]. *Comparative Biochemistry and Physiology Part C*. 121(1-3): 205-211.

Roy, S. & Ghadially, F.N. (1967). Ultrastructure of rat synovial membrane. *Annals of the Rheumatic Diseases*, 26: 26-38.

Ruslay, S., Abas, F., Shaari, K., Zainal, Z., Maulidiani, Sirat, H., Israf, D.A. & Lajis, N.H. (2007). Characterization of the components present in the active fractions of health gingers (*Curcuma Xanthorrhiza* and *Zingiber zerumbet*) by HPLC-DAD-ESIMS. *Food Chemistry.* 104(3): 1183-1191.

Rutgers, M., van Pelt, M.J.P, Dhert, W.J.A., Creemers, L.B. & Saris, D.B.F. (2010). Evaluation of histological scoring systems for tissue-engineered, repaired and osteoarthritic cartilage. *Osteoarthritis & Cartilage*. 18(1): 12-23.

Sakinah, S.A.S., Handayani, S.T. & Hawariah, L.P.A. (2007). Zerumbone induced apoptosis in liver cancer cells via modulation of Bax/Bcl-2 ratio. *Cancer Cell International.* 7: 4.

Salo, P.T. & Theriault, E. (1997). Number, distribution and neuropeptide content of rat knee joint afferents. *Journal of Anatomy*. 190(Pt 4): 515-522.

Samuels, J., Krasnokutsky, S. & Abramson, S.B. (2008). Osteoarthritis: a tale of three tissues. *Bulletin of the NYU Hospital for joint diseases*. 66(3): 244-250.

Sandberg, M., Yasar, Ü., Strömberg, P., Höög, J.O. & Eliasson, E. (2002). Oxidation of celecoxib by polymorphic cytochrome P450 2C9 and alcohol dehydrogenase. *British Journal of Clinical Pharmacology*. 54(4): 423-429.

Sau, A., Tregno, F.P., Valentino, F., Federici, G. & Caccuri, A.M. (2010). Glutathione transferases and development of new principles to overcome drug resistance. *Archives of Biochemistry and Biophysics*. 500(2): 116-122.

Saxler, G., Löer, F., Skumavc, M., Pförtner, J. & Hanesch, U. (2007). Localization of SP^- and $CGRP^-$ immunopostive nerve fibers in the hip joint of patients with painful osteoarthritis and of patients with painless failed total hip arthroplasties. *European Journal of Pain*. 11(1): 67-74.

Sedlak, J. & Lindsay, R.H. (1968). Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. *Analytical Biochemistry*. 25(10): 192-205.

Senior Care Guidelines. (2009). American Association of Feline Practitioners. *Journal of Feline Medicine and Surgery*. 11(9): 763-778.

Shakibaei, M, John.T, Tanzil, G.S, Lehmann, I. & Mobasheri, A. (2007). Suppression of NF-κB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. *Biochemical Pharmacology*. 73(9): 1434-1445.

Sheikh, K.A., Baie, S.H. & Khan, G.M. (2005). Haruan (*Channa striatus*) incorporated palm- oil creams: Formulation and stability studies. *Pakistan Journal of Pharmaceutical Sciences*. 18(1): 1-5.

Sido, B., Hack, V., Hochlehnert, A., Lipps, H., Herfarth, C. & Dröge, W. (1998). Impairment of intestinal glutathione synthesis in patients with inflammatory bowel disease. *Gut*. 42(4): 485-492.

Smith, G.N., Mickler, E.A., Albrecht, M.E., Myers, S.L. & Brandt, K.D. (2002). Severity of medial meniscus damage in the canine knee after anterior cruciate ligament transection. *Osteoarthritis & Cartilage*. 10(4): 321-326.

Smith, C., Marks, A. & Lieberman, M. (2005). Basic Medical Biochemistry. A Clinical Approach. *2nd ed. Maryland: Lippincott Williams & Wilkins*, 842-861.

Somchit, M.N. & Nur Shukriyah, M.H. (2003). Anti-inflammatory property of ethanol and water extracts of Zingiber zerumbet. *Indian Journal of Pharmacology.* 35(3): 181-182.

Somchit, M.N., Solihah, M.H., Israf, D.A., Zuraini,A., Arifah, A.K. & Mat Jais, A.M. (2004). Effect of three local Malaysian channa spp. fish on chronic inflammation. *Oriental Pharmacy and Experimental Medicine*. 4(2): 91-94.

Somparn, N., Kukongviriyapan, U., Tassaneeyakul, W., Jetsrisuparb, A. & Kukongviriyapan, V. (2007). Modification of CYP2E1 and CYP3A4 activities in haemoglobin E-beta thalassemia patients. *European Journal of Clinical Pharmacology*. 63(1): 43-50.

Spector,T.D. & MacGregor, A.J. (2004). Risk factors for osteoarthritis: genetics[1]. *Osteoarthritis & Cartilage*. 12(S1): 39-44.

Stoop, R., Buma, P., van der Kraan, P.M., Hollander, A.P., Billinghurst, R.C., Meijers, T.H.M., Poole, A.R. & van den Berg, W.B. (2001). Type II collagen degradation in articular cartilage fibrillation after anterior cruciate ligament transection in rats. *Osteoarthritis & Cartilage*. 9(4): 308-315.

Sutton, S, Clutterbuck, A., Harris, P., Gent, T., Freeman, S., Foster, N., Barrett-Jolley, R. & Mobasheri A. (2009). The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis. *The Veterinary Journal.* 179(1): 10-24.

Swarnakar, S., Ganguly, K., Kundu, P., Banerjee, A., Maity, P. & Sharma, A.V. (2005). Curcumin regulates expression and activity of matrix metalloproteinases 9 and 2 during prevention and healing of indomethacin-induced gastric ulcer. *The journal of Biological Chemistry*. 280(10): 9409-9415.

Szabolcs, A., Tiszlavicz, L., Kaszaki, J., Pósa, A., Berkó, A., Varga, I.S., Boros, I., Szüts, V., Lonovics, J. & Takàcs, T. (2007). Zerumbone exerts a beneficial effect on inflammatory parameters of cholecystokinin octapeptide – induced experimental pancreatitis but fails to improve histology. *Pancreas*. 35(3): 249-255.

Tahmasebi-Sarvestani, A., Tedman, R. & Goss, A.N. (2001). The influence of experimentally induced osteoarthritis on articular nerve fibers of the sheep temporomandibular joint. *Journal of Orofacial Pain*. 15(3): 206-217.

Tamura, R., Hanesch, U., Schmidt, R.F., Kumazawa,T. & Mizumura, K. (1998). Examination of colocalization of calcitonin gene-related peptide- and substance P- like immunoreactivity in the knee joint of the dog. *Neuroscience Letters*. 254(1): 53-56.

Tanaka, T., Shimizu, M., Kohno, H., Yoshitani, S., Tsukio, Y., Murakami, A., Safitri, R., Takahashi, D.,Yamamoto, K., Koshimizu, K., Ohigashi, H. & Mori, H. (2001). Chemoprevention of azoxymethane-induced rat aberrant crypt foci by dietary zerumbone isolated from *Zingiber zerumbet*. *Life Sciences*. 69(16): 1935-1945.

Taylor, P.M. & Robertson, S.A. (2004). Pain management in cats-past, present and future. Part 1. The cat is unique. *Journal of Feline Medicine and Surgery.* 6(5): 313-320.

Tewtrakul, S., Sardsaengjun, C. & Itchayapruk, J. (1997). Studies on volatile oil components in Zingiber zerumbet Smith rhizomes by gas chromatography. *Songklanakarin Journal of Science and Technology*, 19: 197-202.

Tramèr, M.R., Moore, R.A., Reynolds, D.J.M. & McQuay, H.J. (2000). Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain*. 85: 169-182.

Valdes, A.M., Van Oene, M., Hart, D.J., Surdulescu, G.L., Loughlin, J., Doherty, M. & Spector, T.D. (2006). Reproducible genetic associations between candidate genes and clinical knee osteoarthritis in men and women. *Arthritis & Rheumatism*. 54(2): 533-539.

Van der Kraan, P.M., Vitters, E.L., Van Beuningen, H.M., Van de Putte, L.B. & van den Berg, W.B. (1990). Degenerative knee joint lesions in mice after a single intra-articular collagenase injection. A new model of osteoarthritis. *Journal of Experimental Pathology*. 71(1): 19-31.

Vander, A., Sherman, J. & Luciano, D. (2001). *Human physiology, the mechanisms of body function*. McGrow-Hill Higher Education, *pp*: 207.

Verbruggen, G. (2006). Chondroprotective drugs in degenerative joint diseases. *Rheumatology*. 45(2): 129-138.

Visco, D.M., Hill, M.A., Widmer,W.R., Johnstone, B. & Myers, S.L. (1996). Experimental osteoarthritis in dogs: a comparison of Pond-Nuki and medial arthrotomy methods. *Osteoarthritis & Cartilage*. 4(1): 9-22.

Vitcheva, V. & Mitcheva, M. (2007). Changes in liver and brain cytochrome P450 after multiple cocaine administration, alone and in combination with nifedipine. *Arhiv za Higijenu Rada I Toksikologiju*. 58(3): 287-291.

Wei, OY, Xavier, R. & Marimuthu, K. (2010). Screening of antibacterial activity of mucus extract of snakehead fish, Channa striatus (Bloch). *European Review for Medical and Pharmacological Sciences*, 14: 675-681.

Weiss, E. (2006). Osteoarthritis and body mass. *Journal of Archaeological Science.* 33(5): 690-695.

Williams, V.S. (2007). Intraarticular hyaluronic acid supplementation in the horse: The role of molecular weight. *Journal of Equine Veterinary Science*. 27(7): 298-303.

Witter, J. & Dionne, R.A. (2004). What can chronic arthritis pain teach about developing new analgesic drugs? *Arthritis Research & Ther*apy. 6(6): 279-281.

Yang, Y., Cheng, J.Z., Singhal, S.S., Saini, M., Pandya, U., Awasthi, S. & Awasthi, Y.C. (2001). Role of Glutathione *S*-transferases in protection against lipid peroxidation. *The Journal of Biological Chemistry*. 276(22): 19220-19230.

Yee, H.C., Said, Z., Hussien, N., Bustaman, A. & Abdullah, N.H. (2006). Screening of chemically synthesized analogues of zerumbone for anti-cancer properties and in vivo investigation of zerumbone in female Balb/C mice with cervical intraepithelial neoplasm (CIN). BSc, Thesis Abstract. MAKNA – UPM, Cancer Research Laboratory (Match), institute Bioscience (IBS), Universiti Putra Malaysia.

Young, A.A., Smith, M.M., Smith, S.M., Cake, M.A., Ghosh, P., Read, R.A., Melrose, J., Sonnabend, D.H., Roughley, P.J. & Little, C.B. (2005). Regional assessment of articular cartilage gene expression and small proteoglycan metabolism in an animal model of osteoarthritis. *Arthritis Research & Therapy*. 7(4): R852-R861.

Zakaria, Z.A., Somchit, M.N., Sulaiman, M.R. & Mat Jais, A.M. (2004). Preliminary investigation on the antinociceptive properties of Haruan (*Channa striatus*) fillet extracted with various solvent systems. *Pakistan Journal of Biological Sciences*. 7(10): 1706 –1710.

Zhu, H.Z., Zhang, X.L. and Chen, Y.S. (1998). Expression of glutathione *S*-transferase placental mRNA in hepatic preneoplastic lesions in rats. *World Journal of Gastroentrology.* 4(1): 38-40.

Zuraini, A., Somchit, M.N., Solihah, M.H., Goh, Y.M., Arifah, A.K., Zakaria, M.S., Somchit, N., Rajion, M.A., Zakaria, Z.A. & Mat Jais, A.M. (2006). Fatty acid and amino acid composition of three local Malaysian *Channa spp*. fish. *Food Chemistry*. 97(4): 674-678.