UNIVERSITI PUTRA MALAYSIA

EFFICACY OF ORAL INTAKE OF HARUAN [*CHANNA STRIATUS* (BLOCH, 1793)] EXTRACT VERSUS GLUCOSAMINE SULFATE ON KNEE OSTEOARTHRITIS

AZIDAH ABDUL KADIR

FPV 2019 17

EFFICACY OF ORAL INTAKE OF HARUAN [*CHANNA STRIATUS* (BLOCH, 1793)] EXTRACT VERSUS GLUCOSAMINE SULFATE ON KNEE OSTEOARTHRITIS

By

AZIDAH ABDUL KADIR

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

March 2019

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

EFFICACY OF ORAL INTAKE OF HARUAN [CHANNA STRIATUS (BLOCH, 1793)] EXTRACT VERSUS GLUCOSAMINE SULFATE ON KNEE OSTEOARTHRITIS

By

AZIDAH ABDUL KADIR

March 2019

Chairman : Arifah binti Abdul Kadir, PhD
Faculty : Veterinary Medicine

Knee osteoarthritis (OA) is the most prevalent degenerative arthritis and currently there are no pharmacological agents that able to retard the disease progressions. *Channa striatus* (CS) is a freshwater fish and its potential for treating knee OA has been explored but no comparison study has been done with glucosamine (GlcN), which has been widely used to treat osteoarthritis. *In vivo* study was conducted to evaluate the efficacy of CS extract versus GlcN on histomorphometric examinations in experimental OA rabbit model and a clinical trial was done to assess the efficacy of different doses of CS extract versus GlcN on primary knee osteoarthritis patients in terms of knee OA symptoms based on Western Ontario and McMaster University Osteoarthritis Index (WOMAC), analgesic drug consumption, serum cartilage oligomeric matric protein (COMP), cyclooxygenase 2 (COX-2) enzyme and serum Prostaglandin E_2 (PGE_2). OA was induced using Anterior Cruciate Ligament transection in thirty three rabbits and were divided into three groups namely: CS, GlcN and control group. The CS and GlcN groups were orally administered with 51.4 mg/kg of CS extract and 77.5 mg/kg of GlcN sulphate respectively based on the dosage used for human study for eight weeks. The articular cartilage was evaluated macroscopically and histologically using semi-quantitative and quantitative methods. One-way analysis of variance (ANOVA) was used to analyse the histologic assessment and Kruskall Wallis test was used to analyse the macroscopic grading. A randomized, double-blind, placebo-controlled trial comparing the effects of oral CS extract at the dose rate of 1000mg/day or 500mg/day, 1500mg/day of glucosamine sulphate and placebo among knee OA patients for 6-month intervention period was conducted. Repeated measures analysis of covariance and variance was used to analyse the WOMAC index. One-way ANOVA was used to analyse the analgesic score, COMP, COX-2 and PGE_2 level. The results revealed that the severity of macroscopic score was significantly less in CS as compared to GlcN ($p<0.05$) group. CS exhibit less severity of semi-quantitative

histology score compared to control ($p<0.05$) in more compartments of the joints compared to GlcN. Both CS ($p<0.05$) and GlcN ($p<0.05$) groups demonstrated higher cartilage thickness and area; lower roughness than control group. Moreover, less cartilage roughness was expressed in CS group compared to the GlcN group ($p<0.05$). In the clinical trial, 153 patients were analysed. Both CS ($p<0.05$) and GlcN ($p<0.05$) groups demonstrated significant improvement of WOMAC stiffness and physical function compared to placebo. CS (1000mg/day) ($p<0.05$), CS (500mg/day) ($p<0.05$) and GlcN ($p<0.05$) groups reduced serum COX-2 level compared to placebo. Serum PGE_2 was reduced in CS (1000mg/day) ($p<0.05$) compared to placebo. In conclusion, it was found that based on macroscopic, semi-quantitative and quantitative histological examination, CS extract was superior to GlcN in maintaining the structure of the cartilage degeneration on an ACLT OA-induced rabbit model. In the clinical trial, both doses of CS extract had similar efficacy with GlcN in alleviating the symptoms of knee OA and had an anti-inflammatory effect through the reduction of serum COX-2. CS administered at the dose rate of 1000mg/day was effective in reducing PGE_2 level compared to GlcN.

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

KEBERKESANAN EKSTRAK ORAL HARUAN [CHANNA STRIATUS (BLOCH, 1793)] BERBANDING GLUCOSAMINE SULPHATE PADA OSTEOARTHRITIS LUTUT

Oleh

AZIDAH ABDUL KADIR

Mac 2019

Pengerusi : Arifah binti Abdul Kadir, PhD
Fakulti : Perubatan Veterinar

Osteoarthritis (OA) lutut adalah penyakit artritis degeneratif yang paling prevalen dan sehingga kini tiada lagi agen farmakologikal yang mampu untuk melambatkan perkembangan penyakit ini. *Channa striatus* (CS) adalah sejenis ikan air tawar dan potensi CS untuk merawat penyakit ini untuk telah dicadangkan namun tiada kajian perbandingan dijalankan lagi dengan glucosamine (GlcN) yang telah digunakan dengan meluas untuk merawat OA. Kajian *in vivo* telah dijalankan untuk menilai keberkesanan ekstrak CS versus GlcN pada pemeriksaan *histomorphometric* dalam eksperimen model arnab OA dan kajian klinikal dilakukan untuk menilai keberkesanan pelbagai dos ekstrak CS berbanding GlcN dikalangan pesakit lutut OA primer berdasarkan soalselidik *Western Ontario and McMaster University Osteoarthritis Index* (*WOMAC*), kegunaan ubat analgesik , serum *cartilage oligomeric matric protein* (*COMP*), serum *cyclooxygenase 2* (*COX-2*) *enzyme* and serum *Prostaglandin* E_2 (PGE_2). OA telah diaruhkan melalui transeksi pada *ligament* Anterior *Cruciate* (*ACLT*) pada 33 ekor arnab dan secara rawak telah dibahagikan kepada tiga kumpulan iaitu: CS, GlcN dan kumpulan kawalan. Kumpulan CS diberikan 51.4mg/kg ekstrak CS dan kumpulan GlcN diberikan 77.5 mg/kg GlcN sulfat secara berturut berdasarkan dos yang diberikan dalam kajian manusia secara oral melalui air minuman selama lapan minggu sebelum mereka dikorbankan. Rawan articukular telah dinilai secara makroskopik dan histologi menggunakan teknik semi-kuantitatif dan kuantitatif. Analisis *One-way analysis of variance (ANOVA)* telah digunakan bagi penilaian histologi and analisis *Kruskall Wallis telah dijalan untuk* penilaian makroskopik. Sebuah kajian rawak, *double-blind*, *placebo-controlled* telah dijalankan untuk membandingkan keberkesanan ekstrak oral CS yang diberikan pada kadar dos 1000mg/hari atau 500mg/hari, GlcN sulfat 1500mg/hari dan placebo selama enam bulan. Analisis *repeated measures analysis of covariance and variance* digunakan bagi *WOMAC index*. Analisis

One-way ANOVA digunakan bagi aras *COMP, COX-2 and* PGE_2. Keputusan menunjukkan bahawa keterukan skor makroskopik adalah kurang didalam kumpulan CS berbanding kumpulan GlcN ($p<0.05$). CS mempunyai skor semi-kuantitatif histologi kurang teruk berbanding kumpulan kawalan ($p<0.05$) pada kebanyakkan kawasan sendi lutut berbanding kumpulan GlcN. Kumpulan CS ($p<0.05$) dan GlcN ($P<0.05$) mempunyai lebih ketebalan, dan luas kawasan; serta kurang kekasaran permukaan rawan berbanding kumpulan kawalan. Kumpulan yang dirawat dengan CS juga menunjukkan kurang kekasaran permukaan rawan berbanding kumpulan yang dirawat dengan menggunakan GlcN ($p<0.05$). Di dalam kajian klinikal, 153 pesakit telah terlibat. Terdapat penurunan daripada segi kekakuan dan fungsi fizikal WOMAC secara statistik didalam kumpulan CS ($p<0.05$) dan GlcN ($p<0.05$) berbanding kumpulan plasebo. CS (1000mg/hari) ($p<0.05$), CS (500mg/hari) ($p<0.05$) dan GlcN ($p<0.05$) menurunkan serum COX-2 berbanding placebo. Terdapat penurunan serum PGE_2 di dalam kumpulan CS (1000mg/hari) berbanding kumpulan placebo ($p<0.05$). Secara kesimpulannya, berdasarkan keputusan makroskopik dan histologi menggunakan teknik semi-kuantitatif dan kuantitatif, rawatan oral ekstrak CS lebih baik berbanding GlcN di dalam model arnab ACLT OA-teraruh. Di dalam kajian klinikal, kedua-dua dos CS mempunyai efikasi yang sama dengan GlcN untuk mengurangkan gejala penyakit lutut OA dan radang *cytokine* COX 2. CS pada dos kadar 1000mg/hari lebih berkesan berbanding GlcN untuk mengurangkan tahap PGE_2.

ACKNOWLEDGEMENTS

"In The name of Allah S.W.T., The Most Benevolent and Most Merciful. All praise and thanks is due to Allah, the One that has blessed me with guidance and ability to complete this work."

I would like to express my heartfelt appreciation and sincere gratitude to the chairman my supervisory committee, Associate Professor Dr. Arifah binti Abdul Kadir, for her guidance, support and comment that has help me to complete my Phd.

My utmost gratitude and appreciation to other supervisory committee members, Associate Professor Dr. Roslida Abdul Hamid @ Abdul Razak, Associate Professor Dr. Julia Omar and Associate Professor Dr. Abdul Nawfar bin Sadagatullah for their guidance encouragement and support.

I am also indebted and wish to express my special appreciation to my mentor and my former chairman of the supervisory committee, Professor Abdul Manan bin Mat Jais, for his interest, supports and invaluable suggestions that enable me to carry on my project successfully.

My special thanks, thought and gratitude to the late Professor Dr. Saringat bin Bae @ Bai and Associate Professor Dr. Zuraini binti Ahmad who has given me their guidance, support and advice. I would like to acknowledge the late Professor Dr. Saringat bin Bae @ Bai for his assistance in obtaining the *Channa striatus* extract and glucosamine product.

I also would like to express my appreciation to Dr. Thin Win @ Safiyya, Dr. Annas Salleh, Mr. Tan Say Koon, Puan Jamaliah binti Lin, Encik Ismail bin Abdul Manan, Professor Dr. K.N.S. Sirajudeen, Puan Asiah Abu Bakar for their advice, kindness, assistance and cooperation regarding the laboratory work.

Special thanks and gratitude also goes to the staffs of Central Research Laboratory, School of Dental Sciences, Central Research Laboratory, School of Medical Sciences and Animal Research and Service Centre, Health Campus, Universiti Sains Malaysia.

I also like to thank my friends and colleague, Dr Azlina Ishak and Dr Salziyan Badrin who has given me support, assistance and co-operation for my research. I also would like to acknowledge Universiti Sains Malaysia for providing grants to support this study.

Last but not least, my gratitude to my beloved husband (Nik Mohamed Hazli bin Nik Hussain), my sons (Nik Mohammad Hafizullah, Nik Muhammad Aiman, Nik Muhammad Amir, Nik Muhammad Hanif and Nik Muhammad Harriz) and all of my family members for their love and prayers during the course of my study.

I certify that a Thesis Examination Committee has met on 22 March 2019 to conduct the final examination of Azidah binti Abdul Kadir on her thesis entitled "Efficacy of Oral Intake of Haruan [*Channa striatus* (Bloch, 1793)] Extract Versus Glucosamine Sulfate on Knee Osteoarthritis" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

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

Goh Yong Meng, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Internal Examiner)

Norhaizan bt Mohd Esa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Saima Naveed, PhD
Professor
University of Veterinary and Animal Sciences
Pakistan
(External Examiner)

RUSLI HAJI ABDULLAH, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 23 May 2019

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:

Arifah Binti Abdul Kadir, PhD
Associate Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Roslida Abdul Hamid @ Abdul Razak, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Julia Omar, M.Med
Associate Professor
School of Medical Sciences
Universiti Sains Malaysia
(Member)

Abdul Nawfar Sadagatullah, M.Med
Associate Professor
School of Medical Sciences
Universiti Sains Malaysia
(Member)

Zuraini Hj. Ahmad
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
Profesor dan Dekan
Sekolah Pengajian Siswazah
Universiti Putra Malaysia

Date:

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software

Signature: _____ Date: _____

Name and Matric No.: Azidah binti Abdul Kadir, GS 42381

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

Signature:
Name of Chairman of Supervisory Committee: Associate Professor Dr. Arifah Binti Abdul Kadir

PROF. MADYA DR. ARIFAH ABDUL KADIR
Jabatan Sains Praklinikal Veterinar
Fakulti Perubatan Veterinar
Universiti Putra Malaysia
43400 UPM, Serdang, Selangor.

Signature:
Name of Member of Supervisory Committee: Associate Professor Dr. Roslida Abdul Hamid @ Abdul Razak

PROF. MADYA DR ROSLIDA BINTI ABD HAMID
Pensyarah
Jabatan Sains Bioperubatan
Fakulti Perubatan & Sains Kesihatan
Universiti Putra Malaysia
43400 Serdang, Selangor.

Signature:
Name of Member of Supervisory Committee: Associate Professor Dr. Julia Omar

PROF. MADYA (DR) JULIA OMAR
Ketua Jabatan Patologi Kimia
Pusat Pengajian Sains Perubatan
Kampus Kesihatan
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan

Signature:
Name of Member of Supervisory Committee: Associate Professor Dr. Abdul Nawfar Sadagatullah

PROF. MADYA (DR) ABDUL NAWFAR SADAGATULLAH
MD (USM) M.Med Ortho (USM)
No. MPM : 32816, No. NSR : 126530
Pensyarah Kanan & Pakar Perunding Ortopedik
Jabatan Ortopedik
Pusat Pengajian Sains Perubatan
Kampus Kesihatan
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABTS	azino-bis (3 ethylbenzothiazoline-6-sulphonic acid
ACE	angiotensin converting enzyme
ACLT	Anterior cruciate ligament transection
ACR	American College of Rheumatology
ADL	activity of daily living
ALT	alanine transaminase
ARASC	Animal Research and Service Centre
AST	aspartate transaminase
COMP	Serum Cartilage Oligomeric Matrix Protein
COX 2	Cyclooxygenase 2
CS	Channa striatus
DMOADs	disease modifying OA drugs
DPPH	diphenyl-picrylhydrazyl
ECM	extracellular matrix
GAG	glycosaminoglycans
GlcN	Glucosamine
H&E	Hematoxylin and Eosin
IFN	interferon
IL	Interleukin
IQR	Interquartile range
ITT	intend-to-treat
KL	Kellgren and Lawrence

KOOS	Knee Injury and Osteoarthritis Outcome Score
KRK	Klinik Rawatan Keluarga
LF	Lateral Femur
LT	Lateral Tibia
MetS	Metabolic syndrome
MF	Medial Femur
MMP-3	matrix metalloproteinase
MT	Medial Tibia
NACLAR	National Advisory Committee for Laboratory Animal Research Guidelines of Singapore
NO	Nitric oxide
NPs	neuropeptides
NSAIDS	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PCM	paracetamol
PGE_2	Prostaglandin 2
QOL	Quality of Life
RA	Rheumatoid arthritis
RCT	randomized controlled trial
RM ANCOVA	repeated measures analysis of covariance
RM ANOVA	repeated measures analysis of variance
ROS	reactive oxygen species

SD	Standard deviation
SF-36	Short Form General Health Survey
SO_4	sulphate
TNF	Tumour Necrosis Factor
USM	Universiti Sains Malaysia
VAS	Visual Analogue Score
WOMAC	Western Ontario and McMaster University Osteoarthritis index

CHAPTER 1

INTRODUCTION

1.1 Problem statement and justifications of the study

Knee osteoarthritis is a progressive joint disorder, prevalent among the elderly, attribute by cartilage degeneration, bone remodelling and inflammation (Buttgereit *et al.*, 2015). It leads to reduced quality of life owing to pain and disability (Cross *et al.*, 2014). It is anticipated that the incidence of this joint disorder will increase, given the increment in the elderly population and the number of obese patients (Cross *et al.*, 2014). The prevalence of knee OA in Malaysia range from 10% to 20% (Ministry of Health Malaysia *et al.*, 2013). A study by the Community Oriented Program for the Control of Rheumatic Diseases in Malaysia disclosed that 64.8% of subjects' complaint of knee pain and more than half had clinical symptoms of OA (Veerapen *et al.*, 2007). Research on pharmacological agents to treat OA is important since currently there is no effective treatment available to prevent disease progression (Buttgereit *et al.*, 2015).

In view of the above situation, there are many research conducting for chondroprotective agents. Substances that protect articular cartilage during the course of OA have been termed chondroprotective agents (Verbruggen, 2005). Chondroprotective agents is define as a compound that delays progressive joint space narrowing with characteristic of arthritis and improves the biomechanics of articular joints by protecting chondrocytes (Felson and Kim, 2007). These include functions such as: stimulating chondrocyte synthesis of collagen and proteoglycans, enhancing synoviocyte production of hyaluronan, inhibiting cartilage degradation and preventing fibrin formation in the vasculature (Felson and Kim, 2007).

Present pharmacotherapy treatments for knee OA are mainly palliative, as none of these halts the progression of OA or function as disease modifying agents (Cheng and Visco, 2012). Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDS) are mostly used for symptom relief of osteoarthritis (Ausiello and Stafford, 2002). Acetaminophen is used as a first line treatment but it is reported to be less effective than NSAIDs for reducing the symptoms (Verkleij *et al.*, 2011). Thus, many patients resort to NSAIDs for symptom relieved making NSAIDs as the predominant agent for the treatment of OA. Acetaminophen is reported to have a better safety profile in terms of gastrointestinal (GI) and cardiovascular (CVS) disease than NSAIDs (Zhang *et al.*, 2007). NSAIDs post significant risks of peptic ulcer disease and renal failure (Cheng and Visco, 2012). COX-2 inhibitors also have been used for symptoms relieved in OA and have been found to reduce the risk of GI side effects, but concerns have been

raised regarding adverse CVS events (Ausiello and Stafford, 2002). On the other hand, surgical management is not widely used because of factors, such as patient willingness for surgery, economic factors, and health policy. Due to these reasons, the investigation of disease-modifying treatment options for OA has become an important aspect of orthopaedic care (Abadie *et al.*, 2004).

Channa striatus (CS) is a fish from the family of Channidae that lives in fresh water such as river and paddy field. It is acknowledge as food that provide protein and use as traditional medicine in Southeast Asian countries (Mat Jais, 2007). Biomedical research has shown that CS extract has wound-healing, antinociceptive, and anti-inflammatory properties (Ab Wahab *et al.*, 2015; Abedi *et al.*, 2012; Baie and Sheikh, 2000a; Mohamad Isa *et al.*, 2016; Zakaria *et al.*, 2008). Therefore, its use in treating OA has been explored (Al-Saffar *et al.*, 2011a; Kadir *et al.*, 2014; Michelle *et al.*, 2004). Several *in vivo* studies and a clinical trial have shown that CS has chondroprotective activities (Al-Saffar *et al.*, 2011a; Kadir *et al.*, 2014; Michelle *et al.*, 2004). In an anterior cruciate ligament transection-induced arthritic rabbit model, animals treated with CS extract had improved immunoreactivity in the synovium, as measured by protein gene product (PGP 9.5) immunoreactivity in nerve fibres. The treated group also had less soft tissue swelling surrounding the arthritic joint compared to the control group (Michelle *et al.*, 2004). Al-Saffar *et al*. (2011) studied the effects of oral CS extract in chemically induced OA rats. The findings from the *in vivo* study showed that CS extract can regulate the synthesis of the inflammatory hormone prostaglandin E_2 (PGE_2) (Al-Saffar *et al.*, 2011a). The CS-treated group also had better histopathological scores and immunohistochemistry findings than the control group (Al-Saffar *et al.*, 2011a).

The research for treatment alternatives for OA has turned into an imperative part of orthopaedic care inferable from the constraints of current medications and adverse effect of common treatment use to relief symptoms (Abadie *et al.*, 2004). Therefore, this study will offer new evidence of CS as an alternative pharmacotherapy for knee OA. Its usage can reduce the usage of NSAIDS and the secondary adverse effects such as GI and renal complications. It is also beneficial to compare the effect of CS extract with that of glucosamine (GlcN) sulphate, which is one of the frequently used oral medication worldwide to reduce the pain and stiffness due to OA (Kongtharvonskul *et al.*, 2015). GlcN has been recognized globally as a supplement for knee OA (Kongtharvonskul *et al.*, 2015). Literature reviews have showed that GlcN is efficacious for symptoms relieved (Kongtharvonskul *et al.*, 2015). GlcN is known as Symptomatic Slow Acting Drugs for OA (SYSADOA) and has been recommended as first line pharmacological treatment for knee OA by ESCEO (Bruyère *et al.*, 2014). In this study, CS is regarded as SYSADOA such as GlcN since the time window for intervention using nutraceuticals like CS is longer as compared to standard analgesic like NSAIDs which have rapid onset of action. Therefore, GlcN was chosen as an active comparator in view of its action on symptoms control and also because it is available as oral medication. This is also in line with the recommendations of European administrative guidelines on trial of

pharmacotherapy for OA. The guideline recommended a three-arm study which include placebo and active drug (Reginster *et al.*, 2015a).

In this regard, the studies highlighted the fact that CS extract could be one of the therapeutic options for knee OA. Nevertheless, the anti-arthritic properties of CS extract remain to be elucidated. It is postulated that CS extract works by inhibiting cyclooxygenase expression, which is an important enzyme in the formation of prostaglandins (Al-Saffar *et al.*, 2011b). Substantial progress has been made over the past years on the anti-arthritic effect of CS, however, evidence is lacking on the efficacy of CS in treating knee OA symptoms, its mechanism of action and dose determination in human. Since CS at a dose of 500mg/day was found to be effective in knee OA (Kadir *et al.*, 2014), thus the current trial aim to determine whether higher dose of CS is more effective in treatment of knee OA symptoms so that optimal dose for treatment can be administered with sound evidence. Based on Fibonacci sequence for dose increment (Penel and Kramar, 2012), CS dose of 1000mg/day was chosen. It is postulated that a higher dose of CS administered for six months is beneficial for knee OA patients. Additionally, this study can provide evidence on whether the oral administration of CS has an articular cartilage modifying in a rabbit ACLT model of OA and at our knowledge, this is the first animal model study that use the dose of CS based on the dose used in clinical trials, i.e. 1000 mg/day for a human weighing 70 kg.

A dependable and substantial biomarker that can be utilized as a part of clinical preliminaries is needed to evaluate the adequacy of pharmacological medications for knee OA (Lotz *et al.*, 2013). The biomarkers that have been explored include biomarker for cartilage degradation such as Cartilage oligomeric matrix protein (COMP) (Das *et al.*, 2015; Tseng *et al.*, 2009) and inflammatory markers like PGE_2 or COX-2 (Yan *et al.*, 2015). As of now, there is not much confirmation on the utilization of these biomarkers in clinical studies for knee OA (Chua *et al.*, 2008).

The current study do not elucidate the exact mechanism of CS in knee OA but provides evidence regarding the efficacy of CS extract in comparison with glucosamine, a SYSADOA that had been approved as first line pharmacological management in Europe, the recommended dosage and the evidence of its anti-inflammatory activity in clinical trial. This also will be the first clinical trial to determine whether CS has anti-inflammatory mechanism through COX-2 and PGE_2 inhibitions. The *in vivo* study conducted also intended to determine the effect of CS extract based on the dose use in human study and improve the histopathological method that had been used (Al-Saffar *et al.*, 2011a) by using the method recommended by the international guidelines such as Osteoarthritis Research Society International (OARSI) guideline and more objective assessment by using quantitative histological assessment.

Research hypotheses

There are significant differences in terms of histopathological examinations between oral CS extract versus GlcN sulphate in experimentally induced knee OA rabbits and in terms of clinical symptoms and biomarkers between oral 1000mg/day or 500mg/day CS extract, GlcN sulphate and placebo in knee OA patients.

1.2 Objective(s) of the research

The general objective of this study is to determine the efficacy of oral *Channa striatus* extract versus Glucosamine sulphate on knee OA in animal and human models.

The specific objectives of this study are:

a. to evaluate the chondroprotective effect of oral *Channa striatus* extract versus Glucosamine sulphate in experimentally induced knee OA in rabbits by using macroscopic, semi-quantitative and quantitative histologic grading of the articular cartilage.

b. To compare the efficacy and safety of oral 1000mg/day or 500mg/day *Channa striatus* extract, 1500mg/day of glucosamine sulphate and placebo in knee OA patients by determining

c. i. the level of pain, stiffness and physical function score using Western Ontario and McMaster University Osteoarthritis index (WOMAC) among the treatment groups.

ii. the consumption of NSAIDs or Paracetamol by using analgesic score among the treatment groups.

iii. the level of serum Cartilage Oligomeric Matrix Protein (COMP) among the treatment groups.

iv. the level of serum Prostaglandin E_2 (PGE_2) and Cyclooxygenase 2 (COX-2) enzyme among the treatment groups.

REFERENCES

Ab Wahab, S. Z., Abdul Kadir, A., Nik Hussain, N. H., Omar, J., Yunus, R., Baie, S., Mohd Noor, N., Hassan, II, Wan Mahmood, W. H., Abd Razak, A. & Wan Yusoff, W. Z. (2015). The Effect of Channa striatus (Haruan) Extract on Pain and Wound Healing of Post-Lower Segment Caesarean Section Women. *Evid Based Complement Alternat Med,* **2015**, 849647. doi: 10.1155/2015/849647

Abadie, E., Ethgen, D., Avouac, B., Bouvenot, G., Branco, J., Bruyere, O., Calvo, G., Devogelaer, J. P., Dreiser, R. L., Herrero-Beaumont, G., Kahan, A., Kreutz, G., Laslop, A., Lemmel, E. M., Nuki, G., Van De Putte, L., Vanhaelst, L. & Reginster, J. Y. (2004). Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. *Osteoarthritis Cartilage,* **12(4)**, 263-268. doi: 10.1016/j.joca.2004.01.006

Abedi, S., Far, F. E., Hussain, M. K., Ahmad, Z. & Jais, A. M. M. (2012). Effects of Haruan (Channa striatus) Based Cream on Acute Inflammation in Croton Oil Induced Mice Ear Edema Model. *Research Journal of Biological Sciences,* **7(4)**, 181-187.

Abramson, S. B., Attur, M., Amin, A. R. & Clancy, R. (2001). Nitric oxide and inflammatory mediators in the perpetuation of osteoarthritis. *Current rheumatology reports,* **3(6)**, 535-541.

Abu Bakar, M. R., Abdul Kadir, A., Abdul Wahab, S. Z., Abdul Karim, A. H., Nik Hussain, N. H., Mohd Noor, N., Omar, J., Bin Bai @ Bae, S., Wan Mahmood, W. H., Abdul Razak, A. & Yunus, R. (2015). Randomized Controlled Trial on the Effect of Channa striatus Extract on Measurement of the Uterus, Pulsatility Index, Resistive Index of Uterine Artery and Superficial Skin Wound Artery in Post Lower Segment Caesarean Section Women. *PLoS ONE,* **10(7)**, e0133514. doi: 10.1371/journal.pone.0133514

Aigner, T. & McKenna, L. (2002). Molecular pathology and pathobiology of osteoarthritic cartilage. *Cellular and molecular life sciences,* **59(1)**, 5-18.

Al-Saffar, F. J., Ganabadi, S. & Fakurazi, S. (2011a). Response of Channa striatus Extract Against Monosodium Iodoacetate Induced Osteoarthritis in Rats. *Journal of Animal and Veterinary Advances,* **10(4)**, 460-469.

Al-Saffar, F. J., Ganabadi, S., Fakurazi, S. & Yaakub, S. (2011b). Zerumbone significantly improved immunoreactivity in the synovium compared to *Channa striatus* extract in monosodium iodoacetate (MIA)- induced knee ostearthritis in rat. *Journal of Medicinal Plants Research,* **5(9)**, 1701-1710.

Ali Khan, M. S., Mat Jais, A. M., Hussain, J., Siddiqua, F., Gopala Reddy, A., Shivakumar, P. & Madhuri, D. (2014). Gastroprotective Effect of Freeze Dried Stripped Snakehead Fish (Channa striata Bloch.) Aqueous Extract against Aspirin Induced Ulcerogenesis in Pylorus Ligated Rats. *ISRN pharmacology,* **2014**.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., Christy, W., Cooke, T. D., Greenwald, R., Hochberg, M. & et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum,* **29(8)**, 1039-1049.

Altman, R. D. (1991). Criteria for classification of clinical osteoarthritis. *J Rheumatol,* **18**.

Altman, R. D., Abramson, S., Bruyere, O., Clegg, D., Herrero-Beaumont, G., Maheu, E., Moskowitz, R., Pavelka, K. & Reginster, J. Y. (2006). Commentary: osteoarthritis of the knee and glucosamine. *Osteoarthritis Cartilage,* **14(10)**, 963-966. doi: S1063-4584(06)00189-0 [pii] 10.1016/j.joca.2006.06.010 [doi]

Álvarez-Soria, M. A., Largo, R., Santillana, J., Sánchez-Pernaute, O., Calvo, E., Hernandez, M., Egido, J. & Herrero-Beaumont, G. (2006). Long term NSAID treatment inhibits COX-2 synthesis in the knee synovial membrane of patients with osteoarthritis: differential proinflammatory cytokine profile between celecoxib and aceclofenac. *Annals of the rheumatic diseases,* **65(8)**, 998-1005.

Alvarez-Soria MA, L. R., Calvo E, Egido J, Herrer- & G., B. (2005). P309 Differential anticatabolic profile of glucosamine sulfate versus other anti-osteoarthritic drugs on human osteoarthritic chondrocytes and synovial fibroblast in culture. *Osteoarthritis and Cartilage,* **13**, S153. doi: 10.1016/S1063-4584(05)80653-3

Ameye, L. G. & Chee, W. S. (2006). Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. *Arthritis research & therapy,* **8(4)**, R127.

Amiel, D., Toyoguchi, T., Kobayashi, K., Bowden, K., Amiel, M. E. & Healey, R. M. (2003). Long-term effect of sodium hyaluronate (Hyalgan) on osteoarthritis progression in a rabbit model. *Osteoarthritis Cartilage,* **11(9)**, 636-643.

Amin, A. R., Attur, M., Patel, R. N., Thakker, G. D., Marshall, P. J., Rediske, J., Stuchin, S. A., Patel, I. R. & Abramson, S. B. (1997). Superinduction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. Influence of nitric oxide. *Journal of Clinical Investigation,* **99(6)**, 1231.

Anderson, J., Nicolosi, R. & Borzelleca, J. (2005). Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food and Chemical Toxicology,* **43(2)**, 187-201.

Andersson, M. L., Thorstensson, C. A., Roos, E. M., Petersson, I. F., Heinegård, D. & Saxne, T. (2006). Serum levels of cartilage oligomeric matrix protein (COMP) increase temporarily after physical exercise in patients with knee osteoarthritis. *BMC Musculoskeletal disorders,* **7(1)**, 98.

Archer, C. W. & Francis-West, P. (2003). The chondrocyte. *The international journal of biochemistry & cell biology,* **35(4)**, 401-404.

Arendt-Nielsen, L., Egsgaard, L. L. & Petersen, K. K. (2016). Evidence for a central mode of action for etoricoxib (COX-2 inhibitor) in patients with painful knee osteoarthritis. *PAIN,* **157(8)**, 1634-1644. doi: 10.1097/j.pain.0000000000000562

Attur, M., Al-Mussawir, H. E., Patel, J., Kitay, A., Dave, M., Palmer, G., Pillinger, M. H. & Abramson, S. B. (2008). Prostaglandin E2 exerts catabolic effects in osteoarthritis cartilage: evidence for signaling via the EP4 receptor. *The Journal of Immunology,* **181(7)**, 5082-5088.

Ausiello, J. C. & Stafford, R. S. (2002). Trends in medication use for osteoarthritis treatment. *J Rheumatol,* **29(5)**, 999-1005.

Aydın, E. & Turan, Y. (2016). Biochemical Markers for Osteoarthritis: Is There any Promising Candidate? *Meandros Med Dent J,* **17**, 27-34.

Badlani, N., Inoue, A., Healey, R., Coutts, R. & Amiel, D. (2008). The protective effect of OP-1 on articular cartilage in the development of osteoarthritis. *Osteoarthritis Cartilage,* **16(5)**, 600-606. doi: 10.1016/j.joca.2007.09.009

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. doi: http://dx.doi.org/10.1016/S0378-8741(00)00253-1

Baie, S. H. & Sheikh, K. A. (2000b). The wound healing properties of Channa striatus-cetrimide cream — tensile strength measurement. *Journal of Ethnopharmacology,* **71(1)**, 93-100. doi: https://doi.org/10.1016/S0378-8741(99)00184-1

Bannuru, R. R., Schmid, C. H., Kent, D. M., Vaysbrot, E. E., Wong, J. B. & McAlindon, T. E. (2015). Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysisPharmacologic Interventions for Knee OA. *Annals of Internal Medicine,* **162(1)**, 46-54. doi: 10.7326/m14-1231

Bar-Or, D., Rael, L. T., Thomas, G. W. & Brody, E. N. (2015). Inflammatory Pathways in Knee Osteoarthritis: Potential Targets for Treatment. *Current rheumatology reviews,* **11(1)**, 50-58. doi: 10.2174/1573397111666150522094131

Barbul, A., Lazarou, S. A., Efron, D. T., Wasserkrug, H. L. & Efron, G. (1990). Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery,* **108(2)**, 331-337.

Bellamy, N. (2008). *WOMAC osteoarthritis index: user guide IX*: Nicholas Bellamy.

Bendele, A. (2001). Animal models of osteoarthritis. *J Musculoskelet Neuronal Interact,* **1(4)**, 363-376.

Bertrand, J., Cromme, C., Umlauf, D., Frank, S. & Pap, T. (2010). Molecular mechanisms of cartilage remodelling in osteoarthritis. *The international journal of biochemistry & cell biology,* **42(10)**, 1594-1601.

Bi, X. (2018). Correlation of serum cartilage oligomeric matrix protein with knee osteoarthritis diagnosis: a meta-analysis. *Journal of Orthopaedic Surgery and Research,* **13(1)**, 262. doi: 10.1186/s13018-018-0959-y

Bitton, R. (2009). The economic burden of osteoarthritis. *Am J Manag Care,* **15(8 Suppl)**, S230-235.

Black, C., Clar, C., Henderson, R., MacEachern, C., McNamee, P., Quayyum, Z., Royle, P. & Thomas, S. (2009). The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation.

Braza-Boïls, A., Alcaraz, M. J. & Ferrándiz, M. L. (2011). Regulation of the inflammatory response by tin protoporphyrin IX in the rat anterior cruciate ligament transection model of osteoarthritis. *Journal of Orthopaedic Research,* **29(9)**, 1375-1382.

Bruyère, O., Altman, R. D. & Reginster, J.-Y. (2016). Efficacy and safety of glucosamine sulfate in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Seminars in Arthritis and Rheumatism,* **45(4, Supplement)**, S12-S17. doi:https://doi.org/10.1016/j.semarthrit.2015.11.011

Bruyere, O., Burlet, N., Delmas, P., Rizzoli, R., Cooper, C. & Reginster, J. (2008). Evaluation of symptomatic slow-acting drugs in osteoarthritis using the GRADE system. *BMC Musculoskelet Disord,* **9**, 165.

Bruyere, O., Collette, J. H., Ethgen, O., Rovati, L. C., Giacovelli, G., Henrotin, Y. E., Seidel, L. & Reginster, J.-Y. L. (2003). Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee osteoarthritis. *The Journal of rheumatology,* **30(5)**, 1043-1050.

Bruyère, O., Cooper, C., Pelletier, J.-P., Branco, J., Luisa Brandi, M., Guillemin, F., Hochberg, M. C., Kanis, J. A., Kvien, T. K., Martel-Pelletier, J., Rizzoli, R., Silverman, S. & Reginster, J.-Y. (2014). An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Seminars in Arthritis and Rheumatism,* **44(3)**, 253-263. doi: https://doi.org/10.1016/j.semarthrit.2014.05.014

Buckwalter, J. A., Mankin, H. J. & Grodzinsky, A. J. (2005). Articular cartilage and osteoarthritis. *Instructional Course Lectures-American Academy of Orthopaedic Surgeons,* **54**, 465.

Buttgereit, F., Burmester, G. R. & Bijlsma, J. W. (2015). Non-surgical management of knee osteoarthritis: where are we now and where do we need to go? *RMD Open,* **1(1)**, e000027. doi: 10.1136/rmdopen-2014-000027

Calder, P. C. (2013). Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? *British Journal of Clinical Pharmacology,* **75(3)**, 645-662. doi: 10.1111/j.1365-2125.2012.04374.x

Chan, K. O. W. & Ng, G. Y. F. (2011). A review on the effects of glucosamine for knee osteoarthritis based on human and animal studies. *Hong Kong Physiotherapy Journal,* **29(2)**, 42-52. doi: http://dx.doi.org/10.1016/j.hkpj.2011.06.004

Chan, P., Caron, J., Rosa, G. & Orth, M. (2005). Glucosamine and chondroitin sulfate regulate gene expression and synthesis of nitric oxide and prostaglandin E(2) in articular cartilage explants. *Osteoarthritis Cartilage,* **13**, 387 - 394.

Chang, D. G., Iverson, E. P., Schinagl, R. M., Sonoda, M., Amiel, D., Coutts, R. D. & Sah, R. L. (1997). Quantitation and localization of cartilage degeneration following the induction of osteoarthritis in the rabbit knee. *Osteoarthritis Cartilage,* **5(5)**, 357-372.

Charlier, E., Relic, B., Deroyer, C., Malaise, O., Neuville, S., Collée, J., Malaise, M. G. & De Seny, D. (2016). Insights on Molecular Mechanisms of Chondrocytes Death in Osteoarthritis. *International Journal of Molecular Sciences,* **17(12)**, 2146.

Cheng, D. S. & Visco, C. J. (2012). Pharmaceutical therapy for osteoarthritis. *PM R,* **4(5 Suppl)**, S82-88. doi: S1934-1482(12)00074-3

Chevrier, A., Nelea, M., Hurtig, M. B., Hoemann, C. D. & Buschmann, M. D. (2009). Meniscus structure in human, sheep, and rabbit for animal models of meniscus repair. *Journal of Orthopaedic Research,* **27(9)**, 1197-1203.

Chiusaroli, R., Piepoli, T., Zanelli, T., Ballanti, P., Lanza, M., Rovati, L. C. & Caselli, G. (2011). Experimental Pharmacology of Glucosamine Sulfate. *International Journal of Rheumatology,* **2011**, 8. doi: 10.1155/2011/939265

Cho, H., Walker, A., Williams, J. & Hasty, K. A. (2015). Study of osteoarthritis treatment with anti-inflammatory drugs: cyclooxygenase-2 inhibitor and steroids. *BioMed research international,* **2015**.

Cho, H. J., Chang, C. B., Kim, K. W., Park, J. H., Yoo, J. H., Koh, I. J. & Kim, T. K. (2011). Gender and prevalence of knee osteoarthritis types in elderly Koreans. *The Journal of arthroplasty,* **26(7)**, 994-999.

Chua, S., Messier, S. P., Legault, C., Lenz, M. E., Thonar, E.-M. & Loeser, R. F. (2008). Effect of an exercise and dietary intervention on serum biomarkers in overweight and obese adults with osteoarthritis of the knee. *Osteoarthritis and Cartilage,* **16(9)**, 1047-1053.

Cibere, J., Kopec, J. A., Thorne, A., Singer, J., Canvin, J., Robinson, D. B., Pope, J., Hong, P., Grant, E. & Esdaile, J. M. (2004). Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. *Arthritis Care & Research,* **51(5)**, 738-745.

Clària, J. (2003). Cyclooxygenase-2 biology. *Current pharmaceutical design,* **9(27)**, 2177-2190.

Clark, A. G., Jordan, J. M., Vilim, V., Renner, J. B., Dragomir, A. D., Luta, G. & Kraus, V. B. (1999). Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity. *Arthritis Rheum,* **42(11)**, 2356e2364.

Clegg, D., Reda, D., Harris, C., Klein, M., O'Dell, J., Hooper, M., Bradley, J., Bingham CO, r., Weisman, M., Jackson, C., Lane, N., Cush, J., Moreland, L., Schumacher, H., Oddis, C., Wolfe, F., Molitor, J., Yocum, D., Schnitzer, T., Furst, D., Sawitzke, A., Shi, H., Brandt, K., Moskowitz, R. & Williams, H. (2006). Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med,* **354**, 795 - 808.

Cohen-Solal, M., Funck-Brentano, T. & Hay, E. (2013). Animal models of osteoarthritis for the understanding of the bone contribution. *BoneKey reports,* **2**.

Courtney, P. & Doherty, M. (2009). Joint aspiration and injection and synovial fluid analysis. *Best Practice & Research Clinical Rheumatology,* **27(2)**, 137-169. doi: 10.1016/j.berh.2013.02.005

Crofford, L. J. (2013). Use of NSAIDs in treating patients with arthritis. *Arthritis research & therapy,* **15 (Suppl 3)**, S2-S2. doi: 10.1186/ar4174

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., Bridgett, L., Williams, S., Guillemin, F., Hill, C. L., Laslett, L. L., Jones, G., Cicuttini, F., Osborne, R., Vos, T., Buchbinder, R., Woolf, A. & March, L. (2014). The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis,* **73(7)**, 1323-1330. doi: 10.1136/annrheumdis-2013-204763

Curtis, C. L., Hughes, C. E., Flannery, C. R., Little, C. B., Harwood, J. L. & Caterson, B. (2000). n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *Journal of Biological Chemistry,* **275(2)**, 721-724.

Curtis, C. L., Rees, S. G., Cramp, J., Flannery, C. R., Hughes, C. E., Little, C. B., Williams, R., Wilson, C., Dent, C. M. & Harwood, J. L. (2002a). Effects of n-3 fatty acids on cartilage metabolism. *Proceedings of the Nutrition Society,* **61(03)**, 381-389.

Curtis, C. L., Rees, S. G., Little, C. B., Flannery, C. R., Hughes, C. E., Wilson, C., Dent, C. M., Otterness, I. G., Harwood, J. L. & Caterson, B. (2002b). Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids. *Arthritis & Rheumatism,* **46(6)**, 1544-1553.

da Costa, B. R., Reichenbach, S., Keller, N., Nartey, L., Wandel, S., Jüni, P. & Trelle, S. (2017). Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *The Lancet,* **390(10090)**, e21-e33. doi: https://doi.org/10.1016/S0140-6736(17)31744-0

Dahlan-Daud, C. K., Jais, A. M., Ahmad, Z., Akim, A. M. & Adam, A. (2010). Amino and fatty acid compositions in Haruan traditional extract (HTE). *Boletin Latinoamericano y del Caribe de Plantas Medicinales y Aromaticas,* **9(5)**, 414-429.

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. doi: http://dx.doi.org/10.1016/S0378-8741(98)00169-X

Darweesh, H., Abbass, D., Kadah, R., Rashad, A., El Basel, M. & Nasr, A. S. (2010). Serum and synovial cartilage oligomeric matrix protein (COMP) in patients with rheumatoid arthritis and osteoarthritis. *Indian Journal of Rheumatology,* **5(3)**, 112-117.

Das, B. R., Roy, A. & Khan, F. R. (2015). Cartilage oligomeric matrix protein in monitoring and prognostication of osteoarthritis and its utility in drug development. *Perspectives in clinical research,* **6(1)**, 4.

Das Gupta, E., Ng, W. R., Wong, S. F., Bhurhanudeen, A. K. & Yeap, S. S. (2017). Correlation of serum cartilage oligomeric matrix protein (COMP) and interleukin-16 (IL-16) levels with disease severity in primary knee osteoarthritis: A pilot study in a Malaysian population. *PloS one,* **12(9)**, e0184802-e0184802. doi: 10.1371/journal.pone.0184802

de Boer, T. N., Huisman, A. M., Polak, A. A., Niehoff, A. G., van Rinsum, A. C., Saris, D., Bijlsma, J. W. J., Lafeber, F. J. P. G. & Mastbergen, S. C. (2009). The chondroprotective effect of selective COX-2 inhibition in osteoarthritis: ex vivo evaluation of human cartilage tissue after in vivo treatment. *Osteoarthritis and Cartilage,* **17(4)**, 482-488. doi:https://doi.org/10.1016/j.joca.2008.09.002

Dieppe, P. A., Cushnaghan, J. & Shepstone, L. (1997). The Bristol 'OA500'study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. *Osteoarthritis and Cartilage,* **5(2)**, 87-97.

Enck, P., Benedetti, F. & Schedlowski, M. (2008). New Insights into the Placebo and Nocebo Responses. *Neuron,* **59(2)**, 195-206. doi: https://doi.org/10.1016/j.neuron.2008.06.030

Endres, S., Ghorbani, R., Kelley, V. E., Georgilis, K., Lonnemann, G., van der Meer, J. W., Cannon, J. G., Rogers, T. S., Klempner, M. S. & Weber, P. C. (1989). The effect of dietary supplementation with n—3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *New England Journal of Medicine,* **320(5)**, 265-271.

European Agency for the Evaluation of Medicinal Products, Committee for Medicinal Products for Human Use, Committee for Proprietary Medicinal Products & Use., C. f. M. P. f. H. (2010) (Ed, Agency, L. E. M.).

Farouk Musa, A., Dillion, J., Mohd Taib, M., Mohd Yunos, A., Baie, S. & Bin Nordin, R. (2018). A study on the effect of Haruan fish extract (Channa striatus) on wound healing and quality of life of coronary artery bypass grafting (CABG) patients: A prospective, double-blind, randomized, controlled trial *F1000 Research,* **7(469)**, 7:469

Felson, D. T. & Kim, Y.-J. (2007). The futility of current approaches to chondroprotection. *Arthritis & Rheumatism,* **56(5)**, 1378-1383. doi: 10.1002/art.22526

Felson, D. T., Naimark, A., Anderson, J., Kazis, L., Castelli, W. & Meenan, R. F. (1987). The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis & Rheumatology,* **30(8)**, 914-918.

Fidelix, T. S., Macedo, C. R., Maxwell, L. J. & Fernandes Moça Trevisani, V. (2014). Diacerein for osteoarthritis. *Cochrane Database of Systematic Reviews***(2)**.
doi: 10.1002/14651858.CD005117.pub3

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.

Fransen, M., Agaliotis, M., Nairn, L., Votrubec, M., Bridgett, L., Su, S., Jan, S., March, L., Edmonds, J., Norton, R., Woodward, M. & Day, R. (2015). Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Annals of the Rheumatic Diseases,* **74(5)**, 851-858.
doi: 10.1136/annrheumdis-2013-203954

Ganabadi, S. (2009). Channa striatus extract supplementation significantly increased protein gene product 9.5-immunoreactive nerve fibres compared to zingiber officinale extract in collagenase induced osteaoarthritis. *Osteoarthritis and Cartilage,* **17, Supplement 1**, S281-S282.
doi: http://dx.doi.org/10.1016/S1063-4584(09)60546-X

Gilroy, D. W., Tomlinson, A. & Willoughby, D. A. (1998). Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation. *European journal of pharmacology,* **355(2)**, 211-217.

Giordano, N., Fioravanti, A., Papakostas, P., Montella, A., Giorgi, G. & Nuti, R. (2009). The efficacy and tolerability of glucosamine sulfate in the treatment of knee osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Current therapeutic research, clinical and experimental,* **70(3)**, 185-196.

Glyn-Jones, S., Palmer, A., Agricola, R., Price, A., Vincent, T., Weinans, H. & Carr, A. (2015). Osteoarthritis. *The Lancet,* **386(9991)**, 376-387.

Goldring, M. B. & Otero, M. (2011). Inflammation in osteoarthritis. *Current opinion in rheumatology,* **23(5)**, 471-478. doi: 10.1097/BOR.0b013e328349c2b1

Goldring, M. B., Otero, M., Plumb, D. A., Dragomir, C., Favero, M., El Hachem, K., Hashimoto, K., Roach, H. I., Olivotto, E. & Borzì, R. M. (2011). Roles of inflammatory and anabolic cytokines in cartilage metabolism: signals and multiple effectors converge upon MMP-13 regulation in osteoarthritis. *European cells & materials,* **21**, 202.

Gregory, M. H., Capito, N., Kuroki, K., Stoker, A. M., Cook, J. L. & Sherman, S. L. (2012a). A Review of Translational Animal Models for Knee Osteoarthritis. *Arthritis,* **2012**, 14. doi: 10.1155/2012/764621

Gregory, M. H., Capito, N., Kuroki, K., Stoker, A. M., Cook, J. L. & Sherman, S. L. (2012b). A review of translational animal models for knee osteoarthritis. *Arthritis,* **2012**.

Hammad, Y. H., Magid, H. R. & Sobhy, M. M. (2015). Clinical and biochemical study of the comparative efficacy of topical versus oral glucosamine/chondroitin sulfate on osteoarthritis of the knee. *The Egyptian Rheumatologist,* **37(2)**, 85-91.

Hanashi, D., Koshino, T., Uesugi, M. & Saito, T. (2002). Effect of femoral nerve resection on progression of cartilage degeneration induced by anterior cruciate ligament transection in rabbits. *Journal of orthopaedic science,* **7(6)**, 672-676.

Haniffa, M. A. K., Sheela, P. A. J., Kavitha, K. & Jais, A. M. M. (2014). Salutary value of haruan, the striped snakehead Channa striatus–a review. *Asian Pacific journal of tropical biomedicine,* **4**, S8-S15.

Hardy, M. M., Seibert, K., Manning, P. T., Currie, M. G., Woerner, B. M., Edwards, D., Koki, A. & Tripp, C. S. (2002). Cyclooxygenase 2-dependent prostaglandin E2 modulates cartilage proteoglycan degradation in human osteoarthritis explants. *Arthritis & Rheumatism,* **46(7)**, 1789-1803.

Hauser, R. A. (2010). The acceleration of articular cartilage degeneration in osteoarthritis by nonsteroidal anti-inflammatory drugs. *Journal of Prolotherapy,* **2(1)**, 305-322.

Haversath, M., Catelas, I., Li, X., Tassemeier, T. & Jäger, M. (2012). PGE2 and BMP-2 in bone and cartilage metabolism: 2 intertwining pathways. *Canadian Journal of Physiology and Pharmacology,* **90(11)**, 1434-1445. doi: 10.1139/y2012-123

Hawker, G., Melfi, C., Paul, J., Green, R. & Bombardier, C. (1995). Comparison of a generic (SF-36) and a disease specific (WOMAC)(Western Ontario and McMaster Universities Osteoarthritis Index) instrument in the measurement of outcomes after knee replacement surgery. *The Journal of rheumatology,* **22(6)**, 1193-1196.

Health, U. D. o., Services, H. & Investigators, G. f. C. (2009) Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological health (CDRH), and the Good CLinical Practice Program (GCPP) at the Food and Drug Administration.

Henrotin, Y. & Kurz, B. (2007). Antioxidant to treat osteoarthritis: dream or reality? *Current drug targets,* **8(2)**, 347-357.

Henrotin, Y., Lambert, C., Couchourel, D., Ripoll, C. & Chiotelli, E. (2011). Nutraceuticals: do they represent a new era in the management of osteoarthritis? – a narrative review from the lessons taken with five products. *Osteoarthritis and Cartilage,* **19(1)**, 1-21. doi: 10.1016/j.joca.2010.10.017

Herrero-Beaumont, G., Ivorra, J., Del Carmen Trabado, M., Blanco, F., Benito, P., Martin-Mola, E., Paulino, J., Marenco, J., Porto, A., Laff on, A., Araujo, D., Figueroa, M. & Branco, J. (2007). Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum,* **56**, 555 - 567.

Herrero-Beaumont, G., Roman-Blas, J. A., Castañeda, S. & Jimenez, S. A. (2009). Primary osteoarthritis no longer primary: three subsets with distinct etiological, clinical, and therapeutic characteristics. Proceedings from *Seminars in arthritis and rheumatism*

Hoch, J. M., Mattacola, C. G., McKeon, J. M., Howard, J. & Lattermann, C. (2011). Serum cartilage oligomeric matrix protein (sCOMP) is elevated in patients with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and cartilage,* **19(12)**, 1396-1404.

Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J., Towheed, T., Welch, V., Wells, G. & Tugwell, P. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res,* **64(4)**, 465-474.

Hofstede, S. N., Vlieland, T. P. V., van den Ende, C. H., Nelissen, R. G., Marang-van de Mheen, P. J. & van Bodegom-Vos, L. (2015). Variation in use of non-surgical treatments among osteoarthritis patients in orthopaedic practice in the Netherlands. *BMJ open,* **5(9)**, e009117.

Horváth, G., Koroknai, G., Ács, B., Than, P., Bellyei, Á. & Illés, T. (2011). Prevalence of radiographic primary hip and knee osteoarthritis in a representative Central European population. *International orthopaedics,* **35(7)**, 971-975.

Huang, S. M., Bisogno, T., Petros, T. J., Chang, S. Y., Zavitsanos, P. A., Zipkin, R. E., Sivakumar, R., Coop, A., Maeda, D. Y. & De Petrocellis, L. (2001). Identification of a new class of molecules, the arachidonyl amino acids, and characterization of one member that inhibits pain. *Journal of Biological Chemistry,* **276(46)**, 42639-42644.

Hughes, R. & Carr, A. (2002). A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology,* **41(3)**, 279-284.

Iniguez, M., Pablos, J., Carreira, P., Cabre, F. & Gomez-Reino, J. (1998). Detection of COX-1 and COX-2 isoforms in synovial fluid cells from inflammatory joint diseases. *Rheumatology,* **37(7)**, 773-778.

Isa, I. I. M., Bakar, S. A., Tohid, S. F. M. & Jais, A. M. M. (2016). Channa striatus cream down-regulates tumour necrosis factor (TNF)-alpha gene expression and alleviates chronic-like dermatitis in mouse model. *Journal of Ethnopharmacology,* **194**, 469-474.

James, M. J., Gibson, R. A. & Cleland, L. G. (2000). Dietary polyunsaturated fatty acids and inflammatory mediator production. *The American journal of clinical nutrition,* **71(1)**, 343s-348s.

Jiang, D., Zou, J., Huang, L., Shi, Q., Zhu, X., Wang, G. & Yang, H. (2010). Efficacy of intra-articular injection of celecoxib in a rabbit model of osteoarthritis. *Int J Mol Sci,* **11(10)**, 4106-4113. doi: 10.3390/ijms11104106

Jo, H., Ahn, H. J., Kim, E. M., Kim, H. J., Seong, S. C., Lee, I. & Lee, M. C. (2004). Effects of dehydroepiandrosterone on articular cartilage during the development of osteoarthritis. *Arthritis & Rheumatism,* **50(8)**, 2531-2538.

Jordan, J. M., Luta, G., Stabler, T., Renner, J. B., Dragomir, A. D., Vilim, V., Hochberg, M. C., Helmick, C. G. & Kraus, V. B. (2003). Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project. *Arthritis & Rheumatism,* **48(3)**, 675-681.

Kadir, A. A., Wahab, S. Z. A., Zulkifli, M. M., Nor, N. M., Bai@Bae, S. & Haron, J. (2014). The therapeutic effect of the oral Channa striatus extract on primary knee osteoarthritis patients. *Agro food Industry Hi Tech,* **25(3)**, 44-48.

Kamarul, T., Ab-Rahim, S., Tumin, M., Selvaratnam, L. & Ahmad, T. S. (2011). A preliminary study of the effects of glucosamine sulphate and chondroitin sulphate on surgically treated and untreated focal cartilage damage. *Eur Cell Mater,* **21**, 259-271; discussion 270-251.

Kapoor, M., Martel-Pelletier, J., Lajeunesse, D., Pelletier, J.-P. & Fahmi, H. (2011). Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nature Reviews Rheumatology,* **7(1)**, 33-42.

Kato, G., Yasaka, T., Katafuchi, T., Furue, H., Mizuno, M., Iwamoto, Y. & Yoshimura, M. (2006). Direct GABAergic and glycinergic inhibition of the substantia gelatinosa from the rostral ventromedial medulla revealed by in vivo patch-clamp analysis in rats. *Journal of Neuroscience,* **26(6)**, 1787-1794.

Kawasaki, T., Kurosawa, H., Ikeda, H., Kim, S.-g., Osawa, A., Takazawa, Y., Kubota, M. & Ishijima, M. (2008). Additive effects of glucosamine or risedronate for the treatment of osteoarthritis of the knee combined with home exercise: a prospective randomized 18-month trial. *Journal of bone and mineral metabolism,* **26(3)**, 279-287.

Keefe, F. J., Lefebvre, J. C., Egert, J. R., Affleck, G., Sullivan, M. J. & Caldwell, D. S. (2000). The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain,* **87(3)**, 325-334.

Kellgren, J. & Lawrence, J. (1957). Radiological assessment of osteo-arthrosis. *Annals of the rheumatic diseases,* **16(4)**, 494.

Kelly, G. S. (1998). The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. *Alternative medicine review: a journal of clinical therapeutic,* **3(1)**, 27-39.

Knott, L., Avery, N. C., Hollander, A. P. & Tarlton, J. F. (2011). Regulation of osteoarthritis by omega-3 (n-3) polyunsaturated fatty acids in a naturally occurring model of disease. *Osteoarthritis and Cartilage,* **19(9)**, 1150-1157. doi: https://doi.org/10.1016/j.joca.2011.06.005

Kongtharvonskul, J., Anothaisintawee, T., McEvoy, M., Attia, J., Woratanarat, P. & Thakkinstian, A. (2015). Efficacy and safety of glucosamine, diacerein, and NSAIDs in osteoarthritis knee: a systematic review and network meta-analysis. *European Journal of Medical Research,* **20(1)**, 24. doi: 10.1186/s40001-015-0115-7

Kotlarz, H., Gunnarsson, C. L., Fang, H. & Rizzo, J. A. (2010). Osteoarthritis and Absenteeism Costs: Evidence From US National Survey Data. *Journal of Occupational and Environmental Medicine,* **52(3)**, 263-268. doi: 10.1097/JOM.0b013e3181cf00aa

Kraus, V. B., Blanco, F. J., Englund, M., Karsdal, M. A. & Lohmander, L. S. (2015). Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis and Cartilage,* **23(8)**, 1233-1241.

Kremer, J. M., Lawrence, D. A., Jubiz, W., Digiacomo, R., Rynes, R., Bartholomew, L. E. & Sherman, M. (1990). Dietary fish oil and olive oil supplementation in patients with Rheumatoid Arthritis clinical and immunologic effects. *Arthritis & Rheumatology,* **33(6)**, 810-820.

Kuyinu, E. L., Narayanan, G., Nair, L. S. & Laurencin, C. T. (2016). Animal models of osteoarthritis: classification, update, and measurement of outcomes. *Journal of orthopaedic surgery and research,* **11(1)**, 19.

Kwan, S. H., Baie, S. & Nazri Ismail, M. (2016). Profiling of Proteins and Post Translational Modifications of Channa striatus Dried Meat. *Current Proteomics,* **13(1)**, 9-19.

Lai, Y., Yu, X. P., Zhang, Y., Tian, Q., Song, H., Mucignat, M. T., Perris, R., Samuels, J., Krasnokutsky, S., Attur, M., Greenberg, J. D., Abramson, S. B., Di Cesare, P. E. & Liu, C. J. (2012). Enhanced COMP catabolism detected in serum of patients with arthritis and animal disease models through a novel capture ELISA. *Osteoarthritis and Cartilage,* **20(8)**, 854-862. doi: https://doi.org/10.1016/j.joca.2012.05.003

Laila, L., Febriyenti, F., Salhimi, S. M. & Baie, S. (2011). Wound healing effect of Haruan (Channa striatus) spray. *International Wound Journal,* **8(5)**, 484-491. doi: 10.1111/j.1742-481X.2011.00820.x

Laine, L., White, W. B., Rostom, A. & Hochberg, M. (2008). COX-2 Selective Inhibitors in the Treatment of Osteoarthritis. *Seminars in Arthritis and Rheumatism,* **38(3)**, 165-187. doi: https://doi.org/10.1016/j.semarthrit.2007.10.004

Largo, R., Alvarez-Soria, M., Dıez-Ortego, I., Calvo, E., Sanchez-Pernaute, O., Egido, J. & Herrero-Beaumont, G. (2003). Glucosamine inhibits IL-1β-induced NFκB activation in human osteoarthritic chondrocytes. *Osteoarthritis and Cartilage,* **11(4)**, 290-298.

Laverty, S., Girard, C. A., Williams, J. M., Hunziker, E. B. & Pritzker, K. P. (2010). The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in the rabbit. *Osteoarthritis Cartilage,* **18 Suppl 3**, S53-65. doi: 10.1016/j.joca.2010.05.029

Lee, A. S., Ellman, M. B., Yan, D., Kroin, J. S., Cole, B. J., van Wijnen, A. J. & Im, H.-J. (2013). A current review of molecular mechanisms regarding osteoarthritis and pain. *Gene,* **527(2)**, 440-447.

Lee, C., Straus, W. L., Balshaw, R., Barlas, S., Vogel, S. & Schnitzer, T. J. (2004). A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: A meta-analysis. *Arthritis Care & Research,* **51(5)**, 746-754.

Lee, Y., Woo, J.-H., Choi, S., Ji, J. & Song, G. (2010). Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int,* **30**, 357 - 363.

Lequesne, M. (1991). Indices of severity and disease activity for osteoarthritis. Proceedings from *Seminars in arthritis and rheumatism*

Li, X., Ellman, M., Muddasani, P., Wang, J. H.-C., Cs-Szabo, G., van Wijnen, A. J. & Im, H.-J. (2009). Prostaglandin E2 and its cognate EP receptors control human adult articular cartilage homeostasis and are linked to the pathophysiology of osteoarthritis. *Arthritis & Rheumatism,* **60(2)**, 513-523. doi: 10.1002/art.24258

Little, C. & Zaki, S. (2012). What constitutes an "animal model of osteoarthritis"–the need for consensus? *Osteoarthritis and Cartilage,* **20(4)**, 261-267.

Liu-Bryan, R. & Terkeltaub, R. (2015). Emerging regulators of the inflammatory process in osteoarthritis. *Nature Reviews Rheumatology,* **11(1)**, 35-44.

Lohmander, L. S., Saxne, T. & Heinegård, D. (1994). Release of cartilage oligomeric matrix protein (COMP) into joint fluid after knee injury and in osteoarthritis. *Annals of the rheumatic diseases,* **53(1)**, 8-13.

Lotz, M., Martel-Pelletier, J., Christiansen, C., Brandi, M., Bruyère, O., Chapurlat, R., Collette, J., Cooper, C., Giacovelli, G. & Kanis, J. (2013). Value of biomarkers in osteoarthritis: current status and perspectives. *Annals of the rheumatic diseases,* **72(11)**, 1756-1763.

Lübbeke, A., Duc, S., Garavaglia, G., Finckh, A. & Hoffmeyer, P. (2009). BMI and severity of clinical and radiographic signs of hip osteoarthritis. *Obesity,* **17(7)**, 1414-1419.

Ma, Z., Wang, Y., Piao, T. & Liu, J. (2016). Echinocystic Acid Inhibits IL-1β-Induced COX-2 and iNOS Expression in Human Osteoarthritis Chondrocytes. *Inflammation,* **39(2)**, 543-549. doi: 10.1007/s10753-015-0278-y

Maetzel, A., Li, L. C., Pencharz, J., Tomlinson, G. & Bombardier, C. (2004). The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. *Annals of the Rheumatic Diseases,* **63(4)**, 395-401. doi: 10.1136/ard.2003.006031

Maneesh, M., Jayalekshmi, H., Suma, T., Chatterjee, S., Chakrabarti, A. & Singh, T. (2005). Evidence for oxidative stress in osteoarthritis. *Indian journal of clinical Biochemistry,* **20(1)**, 129-130.

Martel-Pelletier, J. (1998). Pathophysiology of osteoarthritis. *Osteoarthritis and cartilage,* **6(6)**, 374-376.

Martel-Pelletier, J., Boileau, C., Pelletier, J.-P. & Roughley, P. J. (2008). Cartilage in normal and osteoarthritis conditions. *Best Practice & Research Clinical Rheumatology,* **22(2)**, 351-384.

Masoud, I., Shapiro, F., Kent, R. & Moses, A. (1986). A longitudinal study of the growth of the New Zealand white rabbit: cumulative and biweekly incremental growth rates for body length, body weight, femoral length, and tibial length. *Journal of orthopaedic research,* **4(2)**, 221-231.

Mastbergen, S., Lafeber, F. & Bijlsma, J. (2002). Selective COX-2 inhibition prevents proinflammatory cytokine-induced cartilage damage. *Rheumatology,* **41(7)**, 801-808.

Mat Jais, A. M. (2007). Pharmacognosy and Pharmacology of Haruan (*Channa striatus*), a medicinal fish with wound healing properties. In, *Boletin Latinoamericano y del Caribe de Plantas Medicinales y Aromaticas*, Santiago, Chile: Derechos de Publication, pp 52-60.

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

Mat Jais, A. M., Matori, A. F., Kittakoop, P. & Sowanborirux, K. (1998). Fatty acid composition in mucus and roe of haruan, *Channa striatus*, for wound healing. *General Pharmacology,* **30(4)**, 561-563.

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

McConnell, S., Kolopack, P. & Davis, A. M. (2001). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis care & research,* **45(5)**, 453-461.

McCoy, A. M. (2015). Animal Models of Osteoarthritis: Comparisons and Key Considerations. *Veterinary Pathology,* **52(5)**, 803-818. doi: 10.1177/0300985815588611

Meydani, S. N., Endres, S., Woods, M. M., Goldin, B. R., Soo, C., Morrill-Labrode, A., Dinarello, C. A. & Gorbach, S. L. (1991). Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *J Nutr,* **121(4)**, 547-555.

Michelle, N. Y. T., Shanti, G. & Loqman, M. Y. (2004). Effect of orally administered Channa striatus extract against experimentally-induced osteoarthritis in rabbits. *International Journal of Applied Res. Veterinar,* **2(3)**, 171-175.

Ministry of Health Malaysia, Malaysian Society of Rheumatology & Academy of Medicine Malaysia (2013). *Clinical Practice Guidelines Management of Osteoarthritis (second edition)*.

Mobasheri, A. (2012). Osteoarthritis year 2012 in review: biomarkers. *Osteoarthritis and Cartilage,* **20(12)**, 1451-1464.

Mobasheri, A. & Batt, M. (2016). An update on the pathophysiology of osteoarthritis. *Annals of Physical and Rehabilitation Medicine,* **59(5)**, 333-339.

Mohamad Isa, I. I., Abu Bakar, S., Md Tohid, S. F. & Mat Jais, A. M. (2016). Channa striatus cream down-regulates tumour necrosis factor (TNF)-alpha gene expression and alleviates chronic-like dermatitis in mouse model. *Journal of Ethnopharmacology,* **194**, 469-474. doi: http://dx.doi.org/10.1016/j.jep.2016.10.033

Mohamed, N., Hamdan, M. R., Salleh, S. N. M. & bin Bai, S. (2014). Effect of Freeze Drying and Spray Drying Processes to Amino Acids and Fatty Acids Contents in Haruan (Channa striatus) Extract. *International Journal of Drug Delivery,* **6(3)**, 301-304.

Mohd, S. M. A. & Abdul Manan, M. J. (2012). Therapeutic potential of the haruan (Channa striatus): from food to medicinal uses. *Malaysian Journal Of Nutrition,* **18(1)**, 125-136.

Mohtar, N., Mohamed, N., Hamdan, M. R., Salleh, S. N. M. & bin Bai, S. (2014). Comparison of Freeze Drying and Spray Drying Methods of Haruan Extract. *International Journal of Drug Delivery,* **6(3)**, 286-291.

Mueller, M. B. & Tuan, R. S. (2011). Anabolic/catabolic balance in pathogenesis of osteoarthritis: identifying molecular targets. *PM&R,* **3(6)**, S3-S11.

Mullen, A., Loscher, C. E. & Roche, H. M. (2010). Anti-inflammatory effects of EPA and DHA are dependent upon time and dose-response elements associated with LPS stimulation in THP-1-derived macrophages. *Journal of Nutritional Biochemistry,* **21(5)**, 444-450. doi: 10.1016/j.jnutbio.2009.02.008

Naito, K., Watari, T., Furuhata, A., Yomogida, S., Sakamoto, K., Kurosawa, H., Kaneko, K. & Nagaoka, I. (2010). Evaluation of the effect of glucosamine on an experimental rat osteoarthritis model. *Life Sci,* **86**, 538 - 543.

Nishimura, A., Hasegawa, M., Kato, K., Yamada, T., Uchida, A. & Sudo, A. (2011). Risk factors for the incidence and progression of radiographic osteoarthritis of the knee among Japanese. *International orthopaedics,* **35(6)**, 839-843.

Notoya, K., Jovanovic, D. V., Reboul, P., Martel-Pelletier, J., Mineau, F. & Pelletier, J.-P. (2000). The induction of cell death in human osteoarthritis chondrocytes by nitric oxide is related to the production of prostaglandin E2 via the induction of cyclooxygenase-2. *The Journal of Immunology,* **165(6)**, 3402-3410.

Ogata, T., Ideno, Y., Akai, M., Seichi, A., Hagino, H., Iwaya, T., Doi, T., Yamada, K., Chen, A. Z., Li, Y. & Hayashi, K. (2018). Effects of glucosamine in patients with osteoarthritis of the knee: a systematic review and meta-analysis. *Clin Rheumatol,* **37(9)**, 2479-2487. doi: 10.1007/s10067-018-4106-2

Oxford Biomed. Retrieved 7 April 2019 from https://www.oxfordbiomed.com/pge2-eia-kit.

Paliliewu, N., Datau, E. A., Matheos, J. C. & Surachmanto, E. E. (2013). Channa striatus capsules induces cytokine conversion in pulmonary tuberculosis patients. *J Exp Integr Med,* **3(3)**, 237-242.

Pasha, M., Huin, R. A. & Hassan, S. (2015). The influence of oral and topical Channa striatus on laparotomy wound healing in malnourished Wistar Rats. *International Journal of Pharmaceutical Science Invention,* **4(5)**, 37-41.

Pavelka, K., Gatterova, J., Olejarova, M., Machacek, S., Giacovelli, G. & Rovati, L. (2002). Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med,* **162**, 2113 - 2123.

Peat, G., McCarney, R. & Croft, P. (2001). Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Annals of the rheumatic diseases,* **60(2)**, 91-97.

Pelletier, J. P., Martel-Pelletier, J. & Abramson, S. B. (2001). Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis & Rheumatism,* **44(6)**, 1237-1247.

Penel, N. & Kramar, A. (2012). What does a modified-Fibonacci dose-escalation actually correspond to? *BMC Medical Research Methodology,* **12(1)**, 103. doi: 10.1186/1471-2288-12-103

Persiani, S., Roda, E., Rovati, L. C., Locatelli, M., Giacovelli, G. & Roda, A. (2005). Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage,* **13(12)**, 1041-1049. doi: 10.1016/j.joca.2005.07.009

Petersen, S., Saxne, T., Heinegard, D., Hansen, M., Holm, L., Koskinen, S., Stordal, C., Christensen, H., Aagaard, P. & Kjaer, M. (2010). Glucosamine but not ibuprofen alters cartilage turnover in osteoarthritis patients in response to physical training. *Osteoarthritis Cartilage,* **18**, 34 - 40.

Pischon, T., Hankinson, S. E., Hotamisligil, G. S., Rifai, N., Willett, W. C. & Rimm, E. B. (2003). Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation,* **108(2)**, 155-160.

Piskin, A., Gulbahar, M. Y., Tomak, Y., Gulman, B., Hokelek, M., Kerimoglu, S., Koksal, B., Alic, T. & Kabak, Y. B. (2007). Osteoarthritis models after anterior cruciate ligament resection and medial meniscectomy in rats. A histological and immunohistochemical study. *Saudi medical journal,* **28(12)**, 1796-1802.

Poolsup, N., Suthisisang, C., Channark, P. & Kittikulsuth, W. (2005). Glucosamine long-term treatment and the progression of knee osteoarthritis: systematic review of randomized controlled trials. *Ann Pharmacother,* **39(6)**, 1080-1087. doi: 10.1345/aph.1E576

Pritzker, K. P. H., Gay, S., Jimenez, S. A., Ostergaard, K., Pelletier, J. P., Revell, P. A., Salter, D. & van den Berg, W. B. (2006). Osteoarthritis cartilage histopathology: grading and staging. *Osteoarthritis and Cartilage,* **14(1)**, 13-29. doi: http://dx.doi.org/10.1016/j.joca.2005.07.014

Quraishi, O., Mancini, J. A. & Riendeau, D. (2002). Inhibition of inducible prostaglandin E 2 synthase by 15-deoxy-Δ 12, 14-prostaglandin J 2 and polyunsaturated fatty acids. *Biochemical pharmacology,* **63(6)**, 1183-1189.

Radzak, H. A., Akim, A. M., Sazali, S. S., Baharum, Z., Nata, D. H. M. S., Jalil, A. A., Sharimala, T., Sumasundram, A. M. M. J. & Mokhtaruddin, N. (2014). Total Phenolic Content, Antioxidant, Cytotoxicity and Hepatoprotective Activities of Aqueous Extract of Channa striatus (Haruan). *IOSR Journal of Nursing and Health Science (IOSR-JNHS),* **3(6)**, 52-59.

Rafi, M. M., Yadav, P. N. & Rossi, A. O. (2007). Glucosamine inhibits LPS-induced COX-2 and iNOS expression in mouse macrophage cells (RAW 264.7) by inhibition of p38-MAP kinase and transcription factor NF-κB. *Molecular nutrition & food research,* **51(5)**, 587-593.

Rahayu, P., Marcelline, F., Sulistyaningrum, E., Suhartono, M. T. & Tjandrawinata, R. R. (2016). Potential effect of striatin (DLBS0333), a bioactive protein fraction isolated from Channa striata for wound treatment. *Asian Pacific Journal of Tropical Biomedicine,* **6(12)**, 1001-1007. doi: https://doi.org/10.1016/j.apjtb.2016.10.008

Rai, M. F., Hashimoto, S., Johnson, E. E., Janiszak, K. L., Fitzgerald, J., Heber-Katz, E., Cheverud, J. M. & Sandell, L. J. (2012). Heritability of articular cartilage regeneration and its association with ear wound healing in mice. *Arthritis & Rheumatism,* **64(7)**, 2300-2310. doi: 10.1002/art.34396

Regan, E., Flannelly, J., Bowler, R., Tran, K., Nicks, M., Carbone, B. D., Glueck, D., Heijnen, H., Mason, R. & Crapo, J. (2005). Extracellular superoxide dismutase and oxidant damage in osteoarthritis. *Arthritis & Rheumatism,* **52(11)**, 3479-3491.

Reginster, J.-Y., Reiter-Niesert, S., Bruyère, O., Berenbaum, F., Brandi, M.-L., Branco, J., Devogelaer, J.-P., Herrero-Beaumont, G., Kanis, J. & Maggi, S. (2015a). Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement. *Osteoarthritis and cartilage,* **23(12)**, 2086-2093.

Reginster, J., Deroisy, R., Rovati, L., Lee, R., Lejeune, E., Bruyere, O., Giacovelli, G., Henrotin, Y., Dacre, J. & Gossett, C. (2001). Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet,* **357**, 251 - 256.

Reginster, J. Y., Reiter-Niesert, S., Bruyere, O., Berenbaum, F., Brandi, M. L., Branco, J., Devogelaer, J. P., Herrero-Beaumont, G., Kanis, J., Maggi, S., Maheu, E., Richette, P., Rizzoli, R. & Cooper, C. (2015b). Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement. *Osteoarthritis Cartilage,* **23(12)**, 2086-2093. doi: 10.1016/j.joca.2015.07.001

Richy, F., Bruyere, O., Ethgen, O., Cucherat, M., Henrotin, Y. & Reginster, J. (2003). Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med,* **163**, 1514 - 1522.

Robinson, M. E., Gagnon, C. M., Riley, J. L. & Price, D. D. (2003). Altering gender role expectations: effects on pain tolerance, pain threshold, and pain ratings. *The Journal of Pain,* **4(5)**, 284-288.

Roman-Blas, J. A., Castañeda, S., Sánchez-Pernaute, O., Largo, R., Herrero-Beaumont, G. & the, C. S. G. S. C. T. S. G. (2017). Combined Treatment With Chondroitin Sulfate and Glucosamine Sulfate Shows No Superiority Over Placebo for Reduction of Joint Pain and Functional Impairment in Patients With Knee Osteoarthritis: A Six-Month Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Arthritis & Rheumatology,* **69(1)**, 77-85. doi: 10.1002/art.39819

Roos, E. M., Roos, H. P., Ekdahl, C. & Lohmander, L. S. (1998). Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. *Scand J Med Sci Sports,* **8(6)**, 439-448.

Salaffi, F., Cavalieri, F., Nolli, M. & Ferraccioli, G. (1991). Analysis of disability in knee osteoarthritis. Relationship with age and psychological variables but not with radiographic score. *The journal of rheumatology,* **18(10)**, 1581-1586.

Saleem, A. M., Taufik Hidayat, M., Mat Jais, A. M., Fakurazi, S., Mohamad Moklas, M. A., Sulaiman, M. R. & Amom, Z. (2011). Antidepressant-like effect of aqueous extrat of Channa striatus fillet in mice models of depression. *European Review for Medical and Pharmacological Sciences,* **15**, 795-802.

Sandell, L. J. (2012). Biomarkers in osteoarthritis. *HSS journal,* **8(1)**, 33-34.

Sandell, L. J. & Aigner, T. (2001). Articular cartilage and changes in arthritis: cell biology of osteoarthritis. *Arthritis Research & Therapy,* **3(2)**, 107.

Sawitzke, A., Shi, H., Finco, M., Dunlop, D., Harris, C., Singer, N., Bradley, J., Silver, D., Jackson, C., Lane, N., Oddis, C., Wolfe, F., Lisse, J., Furst, D., Bingham, C., Reda, D., Moskowitz, R., Williams, H. & Clegg, D. (2010). Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Ann Rheum Dis,* **69**, 1459 - 1464.

Scarpignato, C., Lanas, A., Blandizzi, C., Lems, W. F., Hermann, M. & Hunt, R. H. (2015). Safe prescribing of non-steroidal anti-inflammatory drugs in patients with osteoarthritis–an expert consensus addressing benefits as well as gastrointestinal and cardiovascular risks. *BMC medicine,* **13(1)**, 55.

Schmitz, N., Laverty, S., Kraus, V. B. & Aigner, T. (2010). Basic methods in histopathology of joint tissues. *Osteoarthritis and Cartilage,* **18**, S113-S116. doi: 10.1016/j.joca.2010.05.026

Sharif, M., Kirwan, J. R., Elson, C. J., Granell, R. & Clarke, S. (2004). Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years. *Arthritis & Rheumatism,* **50(8)**, 2479-2488.

Shikhman, A., Amiel, D., D'Lima, D., Hwang, S., Hu, C., Xu, A., Hashimoto, S., Kobayashi, K., Sasho, T. & Lotz, M. (2005). Chondroprotective activity of N-acetylglucosamine in rabbits with experimental osteoarthritis. *Annals of the Rheumatic Diseases,* **64(1)**, 89-94. doi: 10.1136/ard.2003.019406

Shimizu, C., Yoshioka, M., Coutts, R. D., Harwood, F. L., Kubo, T., Hirasawa, Y. & Amiel, D. (1998). Long-term effects of hyaluronan on experimental osteoarthritis in the rabbit knee. *Osteoarthritis Cartilage,* **6(1)**, 1-9. doi: 10.1053/joca.1997.0086

Shin, J.-W., Seol, I.-C. & Son, C.-G. (2010). Interpretation of Animal Dose and Human Equivalent
Dose for Drug Development. *The Journal of Korean Oriental Medicine,* **31(3)**, 1-7.

Siracuse, B. L. & Chamberlain, R. S. (2016). A Preoperative Scale for Determining Surgical Readmission Risk After Total Hip ReplacementSurgical Readmission Risk After Total Hip ReplacementSurgical Readmission Risk After Total Hip Replacement. *JAMA Surgery,* **151(8)**, 701-709. doi: 10.1001/jamasurg.2016.0020

Solihah, M. H. (2005). *Anti-inflammatory and Antinociceptive Properties of Three Local Channa species crude extracts.* (Dissertation). Master of Science, Universiti Putra Malaysia

Somchit, M. N., Solihah, M. H., Israf, D. A., Ahmad, Z., Arifah, A. K. & Mat Jais, A. M. (2004). Anti-inflammatiry activity of Channa striatus, Channa micropeltes and Channa lucius extract: Chronic inflammatory modulation. *J Orient Pharma Exp Med,* **4(91-94)**.

Sowers, M., Karvonen-Gutierrez, C. A., Yosef, M., Jannausch, M., Jiang, Y., Garnero, P. & Jacobson, J. (2009). Longitudinal changes of serum COMP and urinary CTX-II predict X-ray defined knee osteoarthritis severity and stiffness in women. *Osteoarthritis and cartilage,* **17(12)**, 1609-1614.

Srikanth, V. K., Fryer, J. L., Zhai, G., Winzenberg, T. M., Hosmer, D. & Jones, G. (2005). A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis and cartilage,* **13(9)**, 769-781.

Stevenson, J. D. & Roach, R. (2012). The benefits and barriers to physical activity and lifestyle interventions for osteoarthritis affecting the adult knee. *Journal of Orthopaedic Surgery and Research,* **7**, 15-15. doi: 10.1186/1749-799X-7-15

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.

Tahmasebi-Sarvestani, A., Tedman, R. & Goss, A. N. (2001). The influence of experimentally induced osteoarthrosis on articular nerve fibers of the sheep temporomandibular joint. *Journal of orofacial pain,* **15(3)**.

Takahashi, K., Hashimoto, S., Kubo, T., Hirasawa, Y., Lotz, M. & Amiel, D. (2000). Effect of hyaluronan on chondrocyte apoptosis and nitric oxide production in experimentally induced osteoarthritis. *The Journal of rheumatology,* **27(7)**, 1713-1720.

Theiler, R., Sangha, O., Schaeren, S., Michel, B., Tyndall, A., Dick, W. & Stucki, G. (1999). Superior responsiveness of the pain and function sections of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as compared to the Lequesne-Algofunctional Index in patients with osteoarthritis of the lower extremities. *Osteoarthritis and cartilage,* **7(6)**, 515-519.

Tiku, M. L., Narla, H., Jain, M. & Yalamanchili, P. (2007). Glucosamine prevents in vitro collagen degradation in chondrocytes by inhibiting advanced lipoxidation reactions and protein oxidation. *Arthritis Research & Therapy,* **9(4)**, R76. doi: 10.1186/ar2274

Tiraloche, G., Girard, C., Chouinard, L., Sampalis, J., Moquin, L., Ionescu, M., Reiner, A., Poole, A. R. & Laverty, S. (2005). Effect of oral glucosamine on cartilage degradation in a rabbit model of osteoarthritis. *Arthritis & Rheumatism,* **52(4)**, 1118-1128. doi: 10.1002/art.20951

Towheed, T., Maxwell, L., Anastassiades, T., Shea, B., Houpt, J., Welch, V., Hochberg, M. & Wells, G. (2005). *Glucosamine therapy for treating osteoarthritis*, Cochrane Database of Systematic Reviews

Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., Borges, G. L. G., Bromet, E. J., De Girolamo, G. & De Graaf, R. (2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The journal of pain,* **9(10)**, 883-891.

Tseng, S., Reddi, A. H. & Di Cesare, P. E. (2009). Cartilage oligomeric matrix protein (COMP): a biomarker of arthritis. *Biomarker insights,* **4**, 33.

Vane, J. R., Mitchell, J. A., Appleton, I., Tomlinson, A., Bishop-Bailey, D., Croxtall, J. & Willoughby, D. A. (1994). Inducible isoforms of cyclooxygenase and nitric-oxide synthase in inflammation. *Proceedings of the National Academy of Sciences,* **91(6)**, 2046-2050.

Veerapen, K., Wigley, R. D. & Valkenburg, H. (2007). Musculoskeletal pain in Malaysia: a COPCORD survey. *The Journal of rheumatology,* **34(1)**, 207-213.

Verbruggen, G. (2005). Chondroprotective drugs in degenerative joint diseases. *Rheumatology,* **45(2)**, 129-138. doi: 10.1093/rheumatology/kei171

Verkleij, S., Luijsterburg, P., Bohnen, A., Koes, B. & Bierma-Zeinstra, S. (2011). NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. *Osteoarthritis and Cartilage,* **19(8)**, 921-929.

Vilím, V., Vytášek, R., Olejarova, M., Macháček, S., Gatterova, J., Prochazka, B., Kraus, V. & Pavelka, K. (2001). Serum cartilage oligomeric matrix protein reflects the presence of clinically diagnosed synovitis in patients with knee osteoarthritis. *Osteoarthritis and Cartilage,* **9(7)**, 612-618.

Wandel, S., Juni, P., Tenda l, B., Nuesch, E., Villiger, P., Welton, N., Reichenbach, S. & Trelle, S. (2010). Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ,* **341**, c4675.

Weiss, E. (2014). Knee osteoarthritis, body mass index and pain: data from the Osteoarthritis Initiative. *Rheumatology*, keu244.

Wen, Z., Tang, C., Chang, Y., Huang, S., Hsieh, S., Lee, C., Huang, G., Ng, H., Neoh, C., Hsieh, C., Chen, W. & Jean, Y. (2010). Glucosamine sulfate reduces experimental osteoarthritis and nociception in rats: association with changes of mitogen-activated protein kinase in chondrocytes. *Osteoarthritis Cartilage,* **18**, 1192 - 1202.

White, A. G., Birnbaum, H. G., Janagap, C., Buteau, S. & Schein, J. (2008). Direct and Indirect Costs of Pain Therapy for Osteoarthritis in an Insured Population in the United States. *Journal of Occupational and Environmental Medicine,* **50(9)**, 998-1005. doi: 10.1097/JOM.0b013e3181715111

Williams, F. M. & Spector, T. D. (2008). Biomarkers in osteoarthritis. *Arthritis research & therapy,* **10(1)**, 101.

Wisłowska, M. & Jabłońska, B. (2005). Serum cartilage oligomeric matrix protein (COMP) in rheumatoid arthritis and knee osteoarthritis. *Clinical rheumatology,* **24(3)**, 278-284.

Witte, M. B. & Barbul, A. (2002). Role of nitric oxide in wound repair. *The American Journal of Surgery,* **183(4)**, 406-412.

Wu, C.-L., Jain, D., McNeill, J. N., Little, D., Anderson, J. A., Huebner, J. L., Kraus, V. B., Rodriguiz, R. M., Wetsel, W. C. & Guilak, F. (2015). Dietary fatty acid content regulates wound repair and the pathogenesis of osteoarthritis following joint injury. *Annals of the Rheumatic Diseases,* **74(11)**, 2076-2083. doi: 10.1136/annrheumdis-2014-205601

Wu, D., Huang, Y., Gu, Y. & Fan, W. (2013). Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials. *Int J Clin Pract,* **67(6)**, 585-594. doi: 10.1111/ijcp.12115

Yan, Z.-w., Dong, J., Qin, C.-h., Zhao, C.-y., Miao, L.-y. & He, C.-y. (2015). Therapeutic effect of chenodeoxycholic acid in an experimental rabbit model of osteoarthritis. *Mediators of inflammation,* **2015**.

Yoshioka, M., Coutts, R. D., Amiel, D. & Hacker, S. A. (1996). Characterization of a model of osteoarthritis in the rabbit knee. *Osteoarthritis Cartilage,* **4(2)**, 87-98.

Yoshioka, M., Shimizu, C., Harwood, F. L., Coutts, R. D. & Amiel, D. (1997). The effects of hyaluronan during the development of osteoarthritis. *Osteoarthritis Cartilage,* **5(4)**, 251-260.

Zakaria, Z. A., Kumar, G. H., Jais, A. M. M., Sulaiman, M. R. & Somchit, M. N. (2008). Antinociceptive, antiinflammatory and antipyretic properties of Channa striatus fillet aqueous and lipid-based extracts in rats. *Methods and Findings in Experimental and Clinical Pharmacology,* **30(5)**, 355-362.

Zakaria, Z. A., Mat Jais, A. M., Goh, Y. M., Sulaiman, M. R. & Somchit, M. N. (2007). Amino acid and fatty acid composition of an aqueous extract of Channa striatus (Haruan) that exhibits antinociceptive activity. *Clinical And Experimental Pharmacology & Physiology,* **34(3)**, 198-204.

Zakaria, Z. A., Sulaiman, M. R., Mat Jais, A. M. & Somchit, M. N. (2005). Effect of various antagonists on the Channa striatus fillet extract antinociception in mice. *Canadian Journal Of Physiology And Pharmacology,* **83(7)**, 635-642.

Zhang, J. (2018). Meta-analysis of serum C-reactive protein and cartilage oligomeric matrix protein levels as biomarkers for clinical knee osteoarthritis. *BMC Musculoskeletal Disorders,* **19(1)**, 22. doi: 10.1186/s12891-018-1932-y

Zhang, W., Jones, A. & Doherty, M. (2004). Does paracetamol (acetaminophen) reduce the pain of osteoarthritis?: a meta-analysis of randomised controlled trials. *Annals of the rheumatic diseases,* **63(8)**, 901-907.

Zhang, W., Moskowitz, R., Nuki, G., Abramson, S., Altman, R., Arden, N., BiermaZeinstra, S., Brandt, K., Croft, P., Doherty, M., Dougados, M., Hochberg, M., Hunter, D., Kwoh, K., Lohmander, L. & Tugwell, P. (2007). OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage,* **15**, 981 - 1000.

Zhang, W., Moskowitz, R., Nuki, G., Abramson, S., Altman, R., Arden, N., BiermaZeinstra, S., Brandt, K., Croft, P., Doherty, M., Dougados, M., Hochberg, M., Hunter, D., Kwoh, K., Lohmander, L. & Tugwell, P. (2008). OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidencebased, expert consensus guidelines. *Osteoarthritis Cartilage,* **16**, 137 - 162.

Zhang, W., Nuki, G., Moskowitz, R., Abramson, S., Altman, R., Arden, N., BiermaZeinstra, S., Brandt, K., Croft, P., Doherty, M., Dougados, M., Hochberg, M., Hunter, D., Kwoh, K., Lohmander, L. & Tugwell, P. (2010). OARSI recommendations for the management of hip and knee osteoarthritis: Part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage,* **18**, 476 - 499.

Zhang, Y., Xu, L., Nevitt, M. C., Aliabadi, P., Yu, W., Qin, M., Lui, L. Y. & Felson, D. T. (2001). Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. *Arthritis & Rheumatism,* **44(9)**, 2065-2071.

Zhou, Z. Y., Liu, Y. K., Chen, H. L. & Liu, F. (2014). Body mass index and knee osteoarthritis risk: A dose-response meta-analysis. *Obesity,* **22(10)**, 2180-2185.

Ziskoven, C., Jäger, M., Kircher, J., Patzer, T., Bloch, W., Brixius, K. & Krauspe, R. (2011). Physiology and pathophysiology of nitrosative and oxidative stress in osteoarthritic joint destruction. *Canadian journal of physiology and pharmacology,* **89(7)**, 455-466.

Živanović, S., Rackov, L. P., Živanović, A., Jevtić, M., Nikolić, S. & Kocić, S. (2011). Cartilage oligomeric matrix protein-inflammation biomarker in knee osteoarthritis. *Bosnian journal of basic medical sciences,* **11(1)**, 27.

Zuraini, A., Somchit, M. N., Solihah, M. H., Arifah, A. K., Zakaria, M. S., Somchit, N., Zakaria, Z. A. & Mat Jais, A. M. (2005). Fatty acid and amino acid composition of three local Malaysian *Channa spp*. fish. *Food Chemistry,* **97**, 674-678.

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. doi: http://dx.doi.org/10.1016/j.foodchem.2005.04.031

BIODATA OF STUDENT

Associate Professor Dr. Azidah Abdul Kadir is a graduate of Universiti Kebangsaan Malaysia Medical School in 1995. She underwent training in Family Medicine, Universiti Sains Malaysia and had master in Family Medicine in 2002. She had done attachment in Community Geriatric in Queen Elizabeth Hospital Australia in 2008. Currently she is pursuing PhD in Clinical Nutrition at Universiti Putra Malaysia, Malaysia. She works as a lecturer in the Family Medicine Department, School of Medical Sciences, Universiti Sains Malaysia and has been actively involved in administrative post in undergraduate and postgraduate program. Previously, she has worked as Head Department of Family Medicine and also have founded the Student Personal and Professional Development Program for the undergraduate medical program Universiti Sains Malaysia. She also was a member of Conjoint Board of Family Medicine, Malaysia for more than 10 years. Her research mainly involved Complementary and alternative medicine, Osteoarthritis, Diabetes, Geriatric and Primary Care. She also enjoyed writing novels. Her novels written in Bahasa Malaysia are Memori Cinta Medik and Penghujung Elergi.

LIST OF PUBLICATIONS

Oral presentation

A double blind randomized controlled study to evaluate the efficacy of different doses of oral *Channa striatu*s extract on primary knee osteoarthritis patients. 30th Scientific Meeting of Malaysian Society of Pharmacology & Physiology, Shangri-La Hotel, Putrajaya, 15-16.8.2016

A double blind randomized controlled study to evaluate the effect of striped snakehead fish (*Channa striatus*) extract versus glucosamine sulphate on knee osteoarthritis. 20th World Congress on Clinical Nutrition, Rama Gardens Hotel, Bangkok, Thailand. 14-16. 12.2016

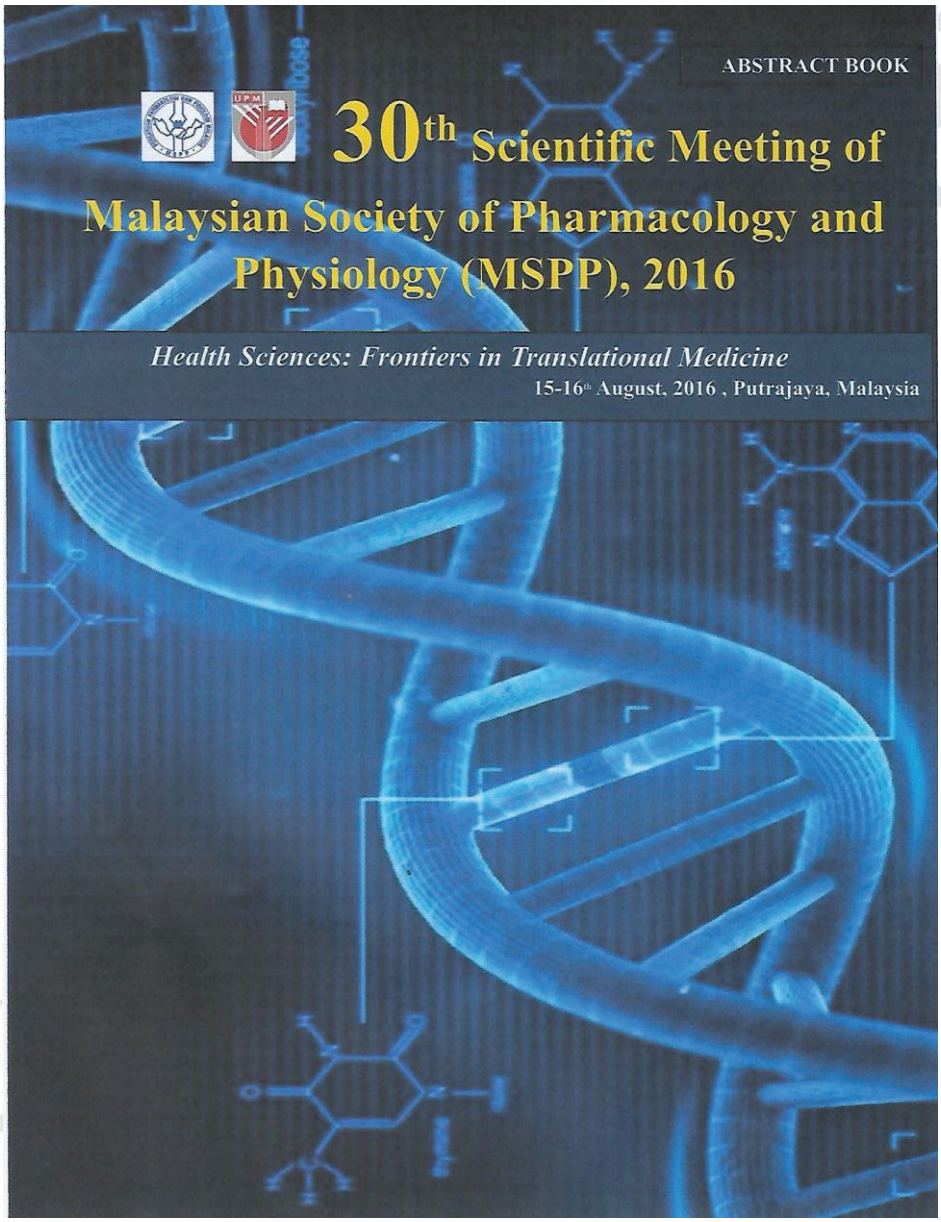
Efficacy of Haruan (*Channa striatus*) extract and glucosamine on an experimental rabbit osteoarthritis model. 31st. Scientific Meeting of Malaysian Society of Pharmacology & Physiology, School of Dental Sciences, Health Campus, USM. 18-19th. August 2017.

Publication

A randomized, double-blind study comparing multiple doses of *Channa striatus* supplementation for knee osteoarthritis. Orient Pharm Exp. Med. Publish online 16 Nov. 2017. DOI 10.1007/s13596-017-0293-7.

Attachment for publications

Oral presentation 1



ORA022

A Double Blind Randomized Controlled Study to Evaluate the Efficacy of Different Doses of Oral *Channa Striatus* Extract among Primary Knee Osteoarthritis Patients

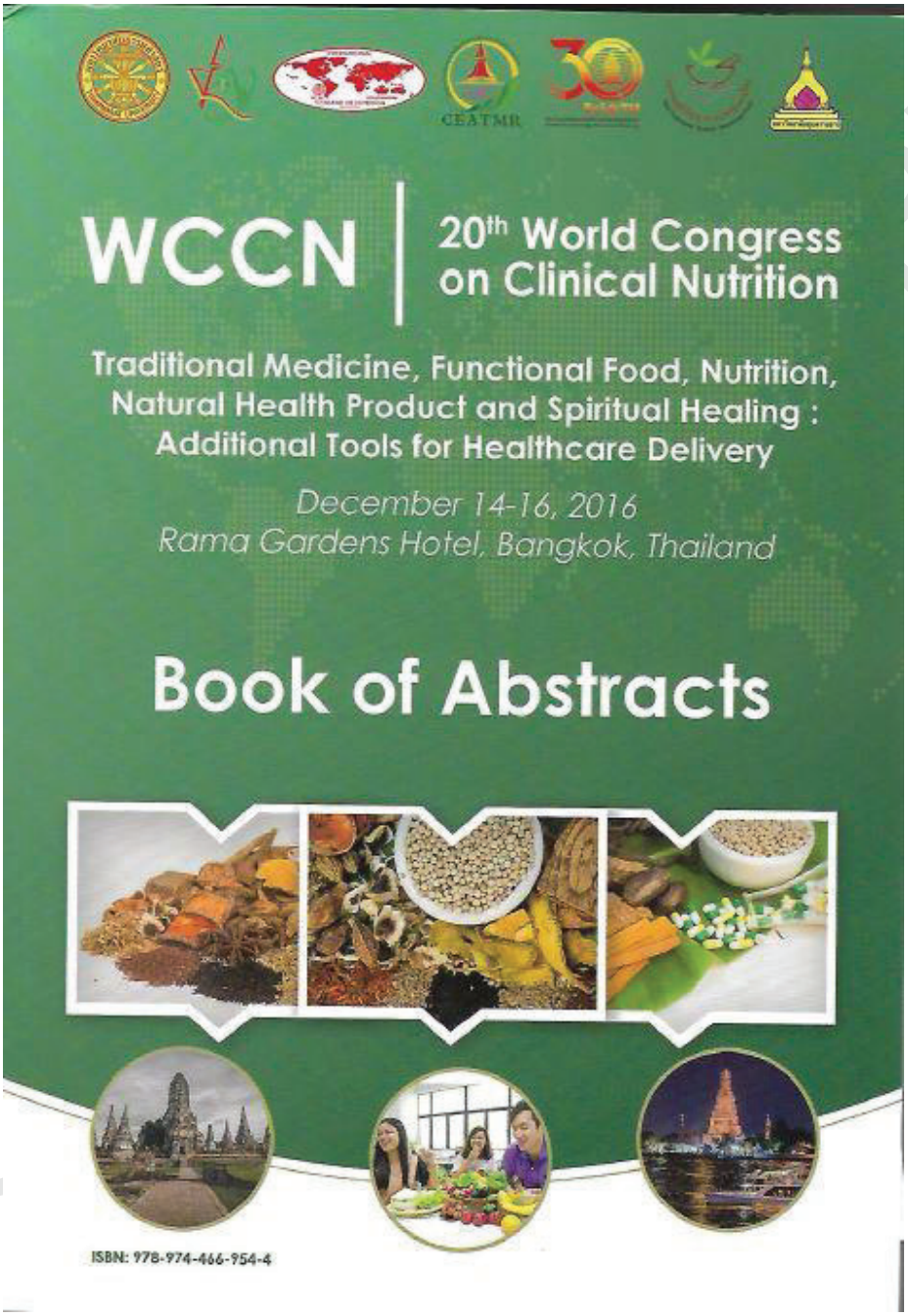
Azidah Abdul Kadir [1,2], Arifah Abdul Kadir[3], Roslida Abd Hamid @ Abd Razak[4], Abdul Manan Mat Jais[5], Zuraini Ahmad[4], Julia Omar[6], Abdul Nawfar Sadagatullah[7], Azlina Ishak[2], Norhayati Mohd Noor[2] , Ahmad Tarmizi Musa[8]

[1] Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Universiti Putra Malaysia, Serdang, Selangor.[2] Department of Family Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan.[3] Department of Veterinary Preclinical Sciences, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400, Selangor. [4] Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor.

Knee osteoarthritis (OA is the leading cause of chronic disability at older age. *Channa striatus* (CS) is a fresh water fish and traditionally known for wound healing. A preliminary clinical trial had shown that CS has beneficial effect in the treatment of knee osteoarthritis (OA).To evaluate the efficacy of different doses of oral *Channa striatus* (Haruan) extract on primary knee osteoarthritis patients.Methodology: A randomized, double-blind, placebo-controlled 3-arm trial comparing oral CS extract 1000mg/day or 500mg/day and placebo among knee OA patients attending outpatient and orthopaedic clinics Universiti Sains Malaysia Hospital for 6-month intervention period was conducted. The main outcome measures were Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and analgesic score. Laboratory based blood tests were used as safety measures. One hundred and twenty patients were randomized and 112 patients were included in the intention-to-treat analysis. There were significant improvement of stiffness and physical function at month 6 between CS 500mg/day vs. placebo ($p<0.005$) and CS 1000mg/day vs. placebo ($p<0.005$) There was no significant difference for analgesic score. The safety profiles were not significant. Both doses of CS showed similar efficacy and more effective than placebo in treating the symptoms of knee OA.

Keywords: Knee osteoarthrits, *Channa striatus*, symptoms, pain

Oral presentation 2



SO4-01

A Double Blind Randomized Controlled Study to Evaluate the Effect of Striped Snakehead Fish (*Channa Striatus*) Extract versus Glucosamine Sulphate on Knee Osteoarthritis

Azidah Abdul Kadir[1,2*], Arifah Abdul Kadir[3], Roslida Abd Hamid Abd Razak[4], Abdul Manan Mat Jais[5], Zuraini Ahmad[4], Julia Omar[6], Abdul Nawfar Sadagatullah[7], Azlina Ishak[2], Norhayati Mohd. Nor[2], Ahmad Tarmizi Musa[8] and Tan Say Koon[6]

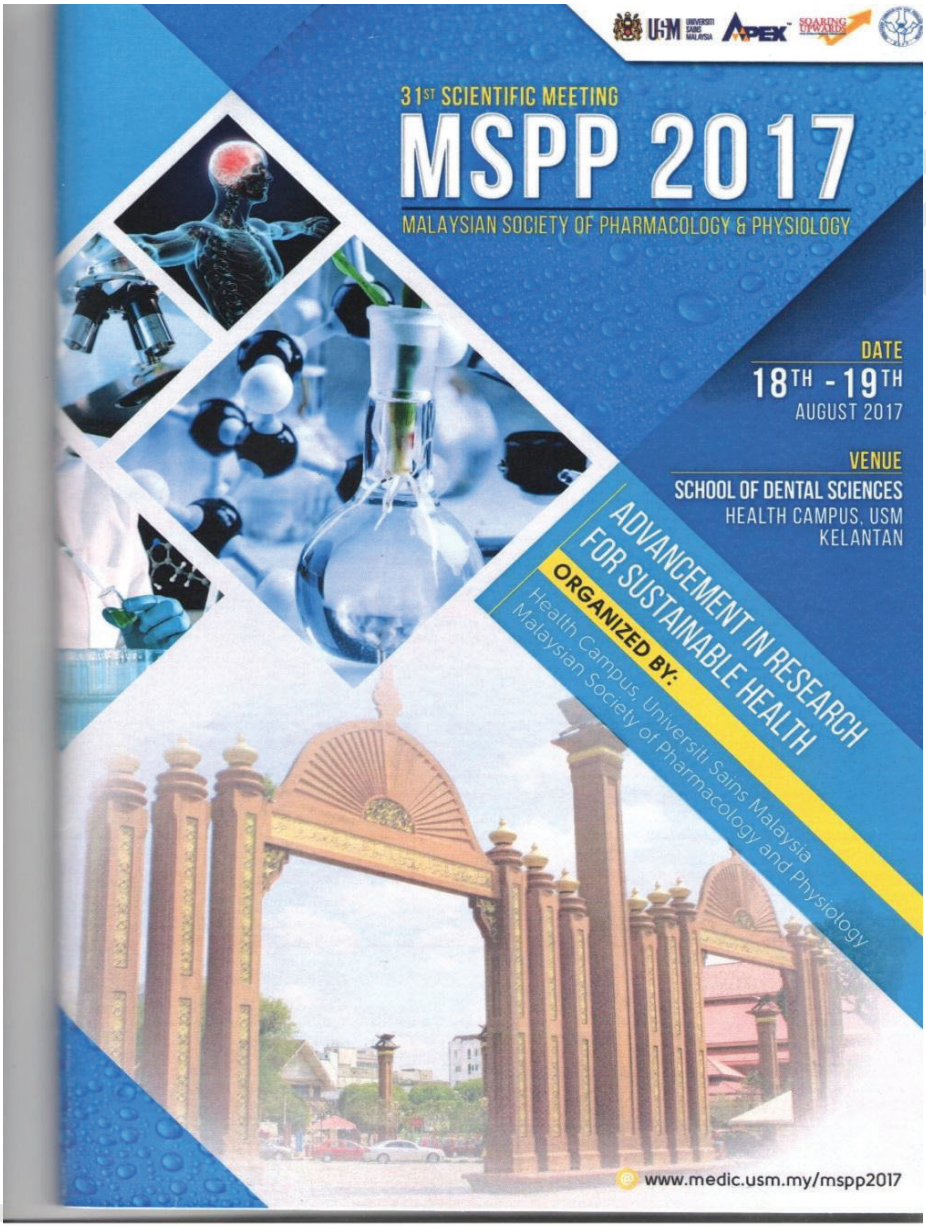
[1]*Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Universiti Putra Malaysia, Serdang, Selangor*
[2]*Department of Family Medicine, School of Medical Sciences, USM Health Campus, 16150 Kubang Kerian, Kelantan*
[3] *Department of Veterinary Preclinical Sciences, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400, Selangor*
[4]*Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Selangor*
[5]*Abmanan Biomedical Sdn Bhd (ABSB), A-G-1, Univ 360 Place, Jalan Raya 2, Taman Serdang Raya, 43300 Seri Serdang, Selangor*
[6]*Department of Chemical Pathology, School of Medical Sciences, USM Health Campus, 16150 Kubang Kerian, Kelantan*
[7]*Department of Orthopaedic, School of Medical Sciences, USM Health Campus, 16150 Kubang Kerian, Kelantan*
[8]*Department of Radiology, School of Medical Sciences, USM Health Campus, 16150 Kubang Kerian, Kelantan*
*Corresponding Author's E-mail: azidahkb@usm.my

Abstract

Knee osteoarthritis is the leading cause of chronic disability at older age. *Channa striatus* (CS) is a snakehaed, fresh water fish and traditionally known for its wound healing properties. Animal studies and a clinical trial had shown that CS has beneficial effect in the treatment of knee osteoarthritis (OA). This study is done to evaluate the efficacy of CS extract versus glucosamine sulphate on knee osteoarthritis. A randomized, double-blind, placebo-controlled trial comparing the effects of oral CS extract 1000mg/day or 500mg/day, placebo and 1500mg/day of glucosamine sulphate among knee OA patients attending outpatient and orthopaedic clinics Universiti Sains Malaysia Hospital for 6-month intervention-period was conducted. The primary outcome measures were to evaluate the difference among the treatment groups based on Western Ontario and McMaster University Osteoarthritis Index (WOMAC), analgesic drug consumption and serum cartilage oligomeric matric protein (COMP). One hundred and sixty patients were randomized into four treatment groups; however, 153 patients were included in the intention-to-treat statistical analysis. There were statistical improvements seen in both CS and glucosamine groups compared to the placebo group at month-6 in terms of WOMAC stiffness ($p<0.05$), physical function ($p<0.05$) and total index score ($p<0.05$). There was no significant difference among the treatment groups for analgesic score and serum COMP. The safety profiles were not significantly different among the groups. In conclusion, both CS and glucosamine sulphate were effective in the treatment of knee OA.

Keywords: Knee osteoarthritis, *Channa striatus*, glucosamine

Oral presentation 3



OB17

EFFICACY OF HARUAN (*CHANNA STRIATUS*) EXTRACT AND GLUCOSAMINE ON AN EXPERIMENTAL RABBIT OSTEOARTHRITIS MODEL

Azidah Abdul Kadir[1,2], Arifah Abdul Kadir [1], Roslida Abd Hamid @ Abd Razak [3], Abdul Manan Mat Jais [3,4], Julia Omar [2], Abdul Nawfar Sadagatullah [2], Salziyan Baldrin [2], Thin Thin Win @Safiya [5], K.N.S Sirajudeen [2], Annas Salleh [1]

[1]Faculty of Veterinary Medicine, [3]Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia, [2]School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia, [4]Abmanan Biomedical Sdn Bhd (ABSB), A-G-1, Univ 360 Place, Jalan Raya 2, Taman Serdang Raya, 43300 Seri Serdang, Selangor, Malaysia, [5]Medical Faculty, International Medical University, No.126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

Objective: To evaluate the efficacy of oral *Channa striatus* (CS) extract versus glucosamine sulphate (GlcN) on histomorphometric examinations of knee osteoarthritis (OA) induced New Zealand White rabbits. **Methodology:** Anterior cruciate ligament transection (ACLT) was performed to induce OAin thirty three maleNew Zealand White rabbits and was randomly divided into three groups: CS, GlcN and control group. The animals were treated orally for eight weeks before they were sacrificed. The articular cartilage was evaluated macroscopically and histologically using semi-quantitative and quantitative methods. **Results:** Macroscopic analysis of cartilage showed that the CS groups have a significantly lower severity grade of total macroscopic score compared to the control ($p < 0.001$) and GlcN ($p < 0.05$) groups. Semi-quantitative histology examination showed that the CS groups and GlcN had lower severity grading in terms of total histology score compared to the control group ($p < 0.001$). No statistical differences was found between CS and GlcN groups. However, CS group significantly had lower degenerative changes compared to the control group in three compartments of the joint (medial femur, medial tibia plateau and lateral tibia plateau) compared to GlcN which had significantly lower severity grading compared to the control group in medial tibia plateau section only. The quantitative histomorphometric analysis showed that cartilage thickness, area, and roughness in the CS ($p < 0.001$) and GlcN ($p < 0.05$) groups were statistically superior compared to the control group. The CS-treated group also demonstrated significantly less cartilage roughness compared to the GlcN -treated group ($p < 0.05$). **Conclusion**: Both oral administration of CS extract and GlcN exhibited chondroprotective action on an ACLT OA-induced rabbit model. However, CS was superior to GlcN in maintaining the structure of the cartilage.

Journal publication:

Orient Pharm Exp Med
https://doi.org/10.1007/s13596-017-0293-7

Online ISSN 221
Print ISSN 1598-2386

RESEARCH ARTICLE

A randomized, double-blind study comparing multiple doses of *Channa striatus* supplementation for knee osteoarthritis

Abdul Kadir Azidah[1,2] · Abdul Kadir Arifah[3] · A. H. Roslida[4] · Abdul Manan Mat Jais[4,5] · Julia Omar[6] · Abdul Nawfar Sadagatullah[7] · Azlina Ishak[2] · Norhayati Mohd. Noor[2] · Ahmad Tarmizi Musa[8]

Received: 3 June 2017 / Accepted: 20 October 2017

Abstract Knee osteoarthritis (OA) is the leading cause of chronic disability at older age. *Channa striatus* (CS) is a freshwater fish that is traditionally valued for its medicinal properties in promoting wound healing and reducing post-operative pain. This study evaluate the efficacy of different doses of oral Channa striatus extract on primary knee osteoarthritis patients. A randomized, double-blind, placebo-controlled 3-arm trial was conducted comparing oral CS extract 1000 mg/day or 500 mg/day and placebo among knee OA patients for a 6-month intervention period. The main outcome measures were Western Ontario and McMaster University Osteoarthritis Index (WOMAC), analgesic scores and serum cartilage oligomeric matric protein (COMP). Laboratory-based blood tests were used as safety measures. A total of 120 patients were randomized, and 112 patients were included in the intention-to-treat analysis. Significant reductions in WOMAC stiffness and function scores were achieved at month 6 in CS 1000 mg/day and CS 500 mg/day compared to placebo groups ($p < 0.05$). No significant differences were found between the groups in terms of analgesic scores, serum COMP and biochemical parameters. No serious adverse events were reported in the study. In conclusion, both doses of CS showed similar efficacy and were more effective than the placebo in treating the symptoms of knee OA.

Keywords Osteoarthritis · Channa Striatus · Arthritis · Complementary · Biomarker

Introduction

Knee osteoarthritis (OA) is a major cause of morbidity and physical disability in older adults worldwide (Zhang et al. 2010). Management of the disease includes non-pharmacological, pharmacological, and surgical therapy (Zhang et al. 2008).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13596-017-0293-7) contains supplementary material, which is available to authorized users.

✉ Abdul Kadir Arifah
arifah@upm.edu.my

[1] Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Universiti Putra Malaysia, Serdang, Selangor, Malaysia

[2] Department of Family Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[3] Department of Veterinary Pre Clinical Sciences, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 Serdang, Selangor Darul Ehsan, Malaysia

[4] Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

[5] Present address: Ahmanan Biomedical Sdn Bhd (ABSB), A-G-1, Univ 360 Place, Jalan Raya 2, Taman Serdang Raya, 43300 Seri Serdang, Selangor, Malaysia

[6] Department of Chemical Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[7] Department of Orthopedic, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[8] Department of Radiology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Published online: 16 November 2017

UNIVERSITI PUTRA MALAYSIA

STATUS CONFIRMATION FOR THESIS / PROJECT REPORT AND COPYRIGHT

ACADEMIC SESSION : Second Semester 2018/2019

TITLE OF THESIS / PROJECT REPORT :

EFFICACY OF ORAL INTAKE OF HARUAN [*Channa striatus* (Bloch, 1793)] EXTRACT VERSUS GLUCOSAMINE SULFATE ON KNEE OSTEOARTHRITIS

NAME OF STUDENT: AZIDAH ABDUL KADIR

I acknowledge that the copyright and other intellectual property in the thesis/project report belonged to Universiti Putra Malaysia and I agree to allow this thesis/project report to be placed at the library under the following terms:

1. This thesis/project report is the property of Universiti Putra Malaysia.
2. The library of Universiti Putra Malaysia has the right to make copies for educational purposes only.
3. The library of Universiti Putra Malaysia is allowed to make copies of this thesis for academic exchange.

I declare that this thesis is classified as :

*Please tick (√)

☐	**CONFIDENTIAL**	(Contain confidential information under Official Secret Act 1972).
☐	**RESTRICTED**	(Contains restricted information as specified by the organization/institution where research was done).
☐	**OPEN ACCESS**	I agree that my thesis/project report to be published as hard copy or online open access.

This thesis is submitted for :

☐ **PATENT** Embargo from _____ (date) until _____ (date)

Approved by:

_____	_____
(Signature of Student)	(Signature of Chairman of Supervisory Committee)
New IC No/ Passport No.:	Name:
Date :	Date :

[Note : If the thesis is CONFIDENTIAL or RESTRICTED, please attach with the letter from the organization/institution with period and reasons for confidentially or restricted.]