CONTROLLED TRIAL OF ORAL *CHANNA STRIATUS* EXTRACT AND GLUCOSAMINE SULPHATE AMONG PRIMARY KNEE OSTEOARTHRITIS PATIENTS

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A thesis submitted for the
Degree of Master of Family Medicine

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Abbreviations

ACR	American College of Rheumatology
AEs	Adverse events
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CONSORT	Consolidated Standard of Reporting Trials
COPCORD	Community Oriented Program for Control of Rheumatic Disorder
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
KRK	Klinik Rawatan Keluarga
LOCF	Last observation carry forward
NSAIDs	Non-steroidal anti-inflammatory agents
OARSI	Osteoarthritis Research Society International
SAEs	Serious adverse events
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster University Osteoarthritis

ABSTRAK

Latar Belakang

Osteoarthritis lutut adalah penyakit arthritis utama di seluruh dunia yang mempunyai kesan ketara ke atas kualiti hidup berkaitan dengan kesihatan. Penggunaan perubatan alternatif untuk osteoarthritis semakin popular. *Channa striatus*, ikan air tawar asli di Malaysia adalah terkenal dengan nilai pemakanan dan perubatan dalam rawatan tradisional. Bukti-bukti tersedia ada menyokong potensinya dalam rawatan pesakit osteoarthritis lutut primer.

Objektif

Tujuan kajian ini adalah untuk membandingkan keberkesanan oral ekstrak *Channa striatus* dan Glucosamine sulphate dalam menambahbaikan gejala lutut dan fungsi fizikal, serta dalam penggunaan analgesik penyelamat di kalangan pesakit osteoarthritis lutut primer.

Kaedah

Tujuh puluh lapan pesakit dengan osteoarthritis lutut primer telah didaftar ke dalam ‘double-blind randomized controlled trial’ ini dan diberikan sama ada Channa striatus 500 mg / hari (n = 39) atau Glucosamine sulphate 1500 mg / hari (n = 39) selama enam bulan. Kaedah penentuan keberkesanan adalah Western Ontario dan indeks ‘Mc Master Osteoarthritis Indeks’ (WOMAC) untuk kesakitan, kekakuan dan fungsi fizikal, skala analog visual untuk sakit semasa pergerakan dan skor analgesik untuk

kegunaan analgesia penyelamat. Keputusan dari kaedah penentuan keberkesanan ini adalah dinilai dengan analisis niat untuk merawat. Semua pesakit telah dinilai pada garis permulaan, 3 dan 6 bulan selepas rawatan diberikan.

Keputusan

Semua ciri-ciri asas adalah setanding antara kumpulan *Channa striatus* dan Glucosamine sulphate. Antara 78 pesakit yang menerima rawatan, 73 telah menamatkan kajian 6 bulan (*Channa striatus* , n = 36 dan Glucosamine sulphate , n = 37). Tiada perbezaan yang signifikan dari segi statistik antara kedua-dua kumpulan dalam indeks WOMAC, skala analog visual dan skor analgesik selepas rawatan selama 6 bulan. Walau bagaimanapun, terdapat penambahbaikan yang signifikan dari segi statistik dalam semua domain indeks WOMAC berdasarkan masa untuk kumpulan Channa striatus dari garis permulaan ke 3 bulan sehingga 6 bulan. Walaupun terdapat penambahbaikan dari 3 hingga 6 bulan, ianya tidak signifikan dari segi statistik. Semua parameter profil keselamatan adalah normal bagi kedua-dua kumpulan sebelum dan selepas rawatan.

Kesimpulan

Penggunaan Channa striatus 500 mg / hari adalah setanding dengan Glucosamine sulphate 1500 mg / hari dalam menambahbaikan kesakitan, kekakuan dan fungsi fizikal pesakit osteoarthritis lutut primer. Ia boleh menjadi rawatan alternatif baru dengan profil keselamatan yang baik untuk rawatan jangka panjang osteoarthritis lutut.

ABSTRACT

Background

Knee osteoarthritis is the commonest form of arthritis worldwide with significant impact on the health-related quality of life. Complementary and alternative medicine use in osteoarthritis is gaining popularity. *Channa striatus,* an indigenous fresh water fish in Malaysia is well-known for its nutritional and medicinal value in traditional medicine. The current evidences support its therapeutic potential in treating primary knee osteoarthritis patients.

Objectives

The aim of the study was to compare the effectiveness of oral *Channa striatus* extract and Glucosamine sulphate in improving knee symptoms and physical function, as well as in rescue analgesic consumption among primary knee osteoarthritis patients.

Methods

Seventy eight patients with primary knee osteoarthritis were enrolled into this double-blind randomized controlled trial and assigned to receive either *Channa striatus* 500 mg/day (n = 39) or Glucosamine sulphate 1500 mg/ day (n = 39) for six months. The efficacy outcome measures were Western Ontario and Mc Master Osteoarthritis Index WOMAC index for pain, stiffness and physical function, Visual Analogue Scale

for pain during movement and Analgesic score for rescue analgesia consumption. These outcomes measures were assessed using an intention-to-treat analysis. All patients were evaluated at baseline, 3 and 6 months post randomization.

Results

All the baseline characteristics were comparable between *Channa striatus* and Glucosamine sulphate group. Of 78 patients randomized, 73 completed the study (*Channa striatus*, n = 36 and Glucosamine sulphate, n = 37). There were no statistically significant difference between these two groups in WOMAC index, Visual Analogue scale and Analgesic score after 6 months of intervention. However, there were statistically significant improvement in all the domains of WOMAC index based on time for *Channa striatus* group from baseline to 3 months up to 6 months. Although there were improvement observed from 3 to 6 months of treatment, they were not statistically significant. All the safety profile parameters were normal for both groups before and after the intervention.

Conclusions

Channa striatus 500 mg/ day is comparable to Glucosamine sulphate 1500 mg/ day in improving pain, stiffness and physical function in patients with primary knee osteoarthritis. It could be a new alternative treatment with good safety profile for medium to long term management of knee osteoarthritis.

CHAPTER 1

INTRODUCTION

1.1 KNEE OSTEOARTHRITIS AND COMPLEMENTARY AND ALTERNATIVE MEDICINE

Osteoarthritis is a progressive degenerative joint disease, characterized by articular cartilage disruption with new bone formation (1). The knee is the commonest joint involved in osteoarthritis (2). The primary knee osteoarthritis implies an idiopathic cause or no known prior event or disease leading to osteoarthritis. In order to diagnose knee osteoarthritis, there should be knee pain PLUS at least 1 of 3 criteria: age > 50 years old, knee stiffness < 30 minutes and/ or crepitus on active movement PLUS radiographic osteophytes, as endorsed by American College of Rheumatology (ACR) (3).

Knee osteoarthritis is the one of the commonest form of arthritis worldwide. Based on the Global Burden of Disease 2010 study, the prevalence of knee osteoarthritis was increasing with age with global prevalence of 3.8% in 2010 (4). The Community Oriented Program for Control of Rheumatic Disorder (COPCORD) survey for musculoskeletal pain in Malaysia had revealed that knee osteoarthritis is the most frequently diagnosed condition in knee pain (5). Above all, the burden of

osteoarthritis on individual, socioeconomic and health care system is anticipated to increase substantially over coming decades with the rising trend of aging population worldwide (4).

Various guidelines are developed and constantly updated to effectively manage knee osteoarthritis according to evidence-based recommendation. The combination of non-pharmacological and pharmacological treatment modalities are crucial for the optimal management of knee osteoarthritis. However, the pharmacological treatment is mainly as symptom-modifying agents. The first line of symptom-modifying agent has been the acetaminophen. Non-steroidal anti-inflammatory agents (NSAIDs) is considered in those non-responsive to acetaminophen (6-9). Nevertheless, NSAIDs in general were associated with increased risk of serious gastrointestinal, cardiovascular and renal harms (10).

Hence, the use of complementary and alternative medicine is gaining popularity among individuals with osteoarthritis (11, 12). Those commonly use in osteoarthritis include herbals, cod liver oil, vitamins, mineral, glucosamine and chondroitin (12, 13). Glucosamine is the most persistently used complementary and alternative medicine modality among older adults with radiographic knee osteoarthritis (14). Studies on Glucosamine sulphate in osteoarthritis have collectively demonstrated a superiority to placebo for improvement in pain and physical function (15, 16). Moreover, the consumption of rescue pain analgesia (NSAIDs) has significantly reduced with continuous use of glucosamine sulphate (17).

Apart from glucosamine sulphate, interest has been directed towards the use of *Channa striatus* in treating knee osteoarthritis (18). *Channa striatus,* an indigenous fresh water fish, is well-known as Haruan among Malaysian. It is widely consumed as a nutritious food and used as a remedy in traditional medicine. Its therapeutic potentials include antimicrobial, antifungal, anti-inflammatory, induction of platelet aggregation, promoting cell proliferation as well as anti-nociceptive properties (19).

The evidences on beneficial effects of *Channa striatus* in treating osteoarthritis had been reported in animal studies (20, 21). Thereafter, study conducted on patients with knee osteoarthritis had demonstrated a significant improvement in pain, symptoms and quality of life following treatment with oral *Channa striatus* extract for 3 months (18). Nevertheless, clinical evidence available for effectiveness of *Channa striatus* in treating patient with knee osteoarthritis remained scarce.

Therefore, it would be beneficial to assess the therapeutic effectiveness of *Channa striatus* in knee osteoarthritis over a longer duration of administration, in comparison with another well-studied modality of treatment, Glucosamine sulphate.

1.2 JUSTIFICATION/ RATIONALE

With the initial evidence of *Channa striatus* on patient with osteoarthritis, it would be beneficial to assess its therapeutic effectiveness over a longer duration of administration, in comparison with another well-studied modality of treatment, Glucosamine sulphate. The finding from the present study would further consolidate the current evidence on *Channa striatus* in clinical effectiveness and safety over a longer term. Moreover, *Channa striatus* might prove to be a better and yet free of side effect complementary alternative medicine than glucosamine sulphate. Above all, limit the use of conventional treatment, non-steroidal anti-inflammatory drugs in the treatment of knee osteoarthritis.

The cost-effectiveness of treatment and impact on healthcare budget are also increasingly important. *Channa striatus* is an indigenous species in Malaysia. All the necessities for farming *Channa striatus* are well in placed. The *Channa striatus* products farmed and manufactured locally would be cheaper than the imported complementary alternative medicine. Thereby mitigate the clinical and socioeconomic burden of osteoarthritis in Malaysia. In addition, this would create revenue and work opportunities to Malaysians.

1.3 OBJECTIVES

General Objectives

To compare the effectiveness of oral *Channa striatus* (Haruan) extract 500mg/day and Glucosamine sulphate 1500mg/day on the symptoms, physical function and analgesic consumption among primary knee osteoarthritis patients.

Specific Objectives

1. To compare the mean of pain, stiffness, physical function score and global score using Western Ontario and Mc Master Osteoarthritis Index (WOMAC) between *Channa striatus* and Glucosamine sulphate group

2. To compare the mean of pain on movement using visual analogue scale (VAS) between *Channa striatus* and Glucosamine sulphate group

3. To compare the mean of analgesic score between *Channa striatus* and Glucosamine sulphate group

1.4 RESEARCH HYPOTHESIS

1. There is a significant difference of pain, stiffness, physical function score and global score using Western Ontario and Mc Master Osteoarthritis Index (WOMAC) between *Channa striatus* and Glucosamine sulphate group

2. There is a significant difference of pain on movement using visual analogue scale (VAS) between *Channa striatus* and Glucosamine sulphate group

3. There is a significant difference of analgesic score between *Channa striatus* and Glucosamine sulphate group

1.5 OPERATIONAL DEFINITION

1. Pain – As measured by pain domain of WOMAC Index and Visual analogue scale

2. Joint stiffness – As measured by stiffness domain of WOMAC Index

3. Physical function – As measured by physical function domain of WOMAC Index

4. Compliance – More than 80% of medication was consumed as prescribed (4 capsules per day) within 6 month period

CHAPTER 2

LITERATURE REVIEW

2.1 Knee Osteoarthritis

Osteoarthritis is a progressive degenerative joint disease. It is characterized by non-inflammatory disruption of the articular cartilage with reactive new bone formation at the joint surface and margins (1). Although defects in the poorly innervated articular cartilage are not, in themselves, symptomatic, a clinical syndrome of symptoms, often includes pain, may evolve from such defects (3). The process may involve one or multiple joints. However, the knee is the commonest site of involvement in osteoarthritis (2).

Various classifications exist for subsets of osteoarthritis. It can be classified according to site of joint involvement or etiology. The etiological classification subdivided the osteoarthritis into primary (idiopathic or no known prior event or disease related to osteoarthritis) and secondary (presence of known event or disease associated with osteoarthritis) (3).

2.2 Diagnosis of Knee Osteoarthritis

To diagnose primary knee osteoarthritis, three different sets of classification criteria could be utilized under different circumstances as endorsed by American College of

Rheumatology (ACR). These diagnostic criteria sets are grouped under either clinical only, clinical and laboratory or clinical and radiographic criteria, with each set yielded different diagnostic sensitivity and specificity. For diagnostic criteria set involving clinical examination only, there should be knee pain PLUS at least 3 of the following 6 features: age > 50 years old, knee stiffness < 30 minutes, crepitus on active movement, bony tenderness over the knee joint, bony enlargement and no palpable warmth. This combination set demonstrated 95% sensitivity and 69% specificity for primary knee osteoarthritis (3).

As for the clinical and laboratory criteria set, knee pain PLUS at least 5 of the following 9 clinical or laboratory findings should be present (must have at least 1 laboratory test performed): age > 50 years old, knee stiffness < 30 minutes, crepitus on active movement, bony tenderness over the knee joint, bony enlargement, no palpable warmth, erythrocyte sedimentation rate (ESR) < 40 mm/ hour, rheumatoid factor (RF) < 1:40 and synovial fluid findings suggestive of osteoarthritis (viscous, clear, and/or white blood cell count < 2000 cells/mm^3). This criteria set is 92% sensitive and 75% specific in diagnosing primary knee osteoarthritis (3).

The clinical and radiographic criteria set is the most commonly used diagnostic criteria in the clinical trials. This criteria set has the comparable sensitivity of 91% and highest specificity of 86% among the three. It consists of knee pain PLUS at least 1 of 3 criteria: age > 50 years old, knee stiffness < 30 minutes and/ or crepitus on active movement PLUS radiographic osteophytes (3). The radiographic evidence of knee osteoarthritis based on Kellgren and Lawrence system has defined the

osteoarthritis severity into 5 grades using a combination of osteophyte, degree of joint space narrowing, sclerosis and bony deformity as follows (22, 23):

- Grade 0 - No changes
- Grade 1 - Possible osteophyte and doubtful joint space narrowing
- Grade 2 - Definite osteophyte and possible joint space narrowing
- Grade 3 - Moderate multiple osteophytes, definite joint space narrowing, some sclerosis and possible deformity of bone ends
- Grade 4 - Large osteophytes, marked joint space narrowing, severe sclerosis and deformity of bone ends

2.3 Prevalence of Knee Osteoarthritis

Knee osteoarthritis is the one of the commonest form of arthritis worldwide. The Global Burden of Disease 2010 study had estimated the global prevalence of radiographically confirmed symptomatic knee osteoarthritis in 2010 was 3.8%. The prevalence was rising with age and peaked at around 50 years old with higher percentage in female than in male. In Southeast Asia countries, the prevalence was 2.2% compared with the highest prevalence of 4.4% in high income Asia Pacific countries (4).

The Community Oriented Program for Control of Rheumatic Disorder (COPCORD) established in the late 1970s had initiated the effort of assembling data on the burden of rheumatic disease in resource constraints developing countries including Malaysia. The knee was the commonest site of musculoskeletal pain with knee

osteoarthritis being possibly the commonest of all specific rheumatic diseases in most of the communities under COPCORD studies. The prevalence of knee osteoarthritis had been ranged from 1.4% in urban Filipino to 19.3% in rural communities in Iran with the prevalence increases with age (2).

Based on the COPCORD survey for musculoskeletal pain in Malaysia, the prevalence of joint and/or musculoskeletal pain was 14.4% in the study population with the higher prevalence rate in older age group. The knee pain constituted 64.8% of all complaint pertaining to the joints. More than half of those with knee pain had clinical evidence of osteoarthritis making it the most frequently diagnosed condition (5).

2.4 Impact of Knee Osteoarthritis

Evidences from various studies either globally or regionally have consistently showed that the prevalence of knee osteoarthritis is increasing steeply with age (2, 4, 5). Although the current level of population aging vary widely by geographical region, but all nations are facing with an accelerating numbers of aging population. The world's older population had increased another 10.4 million since 2007 to a total of 506 million in 2008 representing a shocking growth of an average of 870,000 people each month during the year. Many countries in Asia are indeed aging rapidly. The population aged 65 years and over in Asia is estimated to increase more than double in the next two decades from 6.8% in 2008 to 16.2% in 2040. It is estimated that the proportion of people aged 65 years over in Malaysia will increase by 269% from 2008 to 2040 (24).

With the aging of the world population, the tremendous burden of osteoarthritis on individual and socioeconomic (25) is anticipated to pose a major challenge in health systems globally. According to the Global Burden of Disease 2010 study on 291 health conditions, knee and hip osteoarthritis ranked the 11th highest contributor to global disability and 38th highest in disability-adjusted life years. The years of life lived with disability for hip and knee osteoarthritis had increased to 17.1 million in 2010 (0.69% of total disability-adjusted life years) compared to 10.5 million in 1990 (0.42% of total disability-adjusted life years) (4). The major disabilities reported are the usual daily activities necessary to maintain independence including inability to squat, lifting, climbing, carrying, walking, difficulty in dressing, bathing, combing and feeding (5). These pose a significant negative impact on health-related quality of life in people with knee osteoarthritis (26).

Moreover, the socioeconomic burden of osteoarthritis has been enormous, typically measured in direct and indirect costs. The direct costs are attributed to health care provision including non-pharmacological and pharmacological treatment as well as long term care (25). Based on a US population-based study of health care utilization in individuals with knee osteoarthritis, there was an average of six more physician visits and 3.8 more non-physician visits every year than the osteoarthritis-free cohort (27). Similarly, the indirect costs incurred are substantial. These are attributed to productivity loss from workforce absenteeism, presenteeism (due to effect on functional ability) as well as forced early retirement with consequent income loss and reduced taxation revenue (28).

The burden of osteoarthritis on individual, socioeconomic and health care system is anticipated to increase substantially over coming decades particularly in low-income and middle-income countries with the rising trend of aging population worldwide. Given the magnitude of the disease burden, strategies to reduce knee osteoarthritis burden through primary & secondary prevention programs have become increasingly important and demanded greater attention (4).

2.5 Management of Knee Osteoarthritis

Various guidelines are developed and constantly updated to effectively manage knee osteoarthritis according to evidence-based recommendation. These guidelines include European League Against Rheumatism (EULAR) recommendation (2003), American College of Rheumatology (ACR) recommendations (2012), Osteoarthritis Research Society International (OARSI) guideline (2014) as well as the local Malaysia clinical practice guideline (2013). All these guidelines (6-9) in general have the recommendation for management of knee osteoarthritis divided into three main categories: non-pharmacological, pharmacological and surgical. The combination of non-pharmacological and pharmacological treatment modalities are important for optimal management of knee osteoarthritis.

The non-pharmacological treatment includes exercise, weight management, strength training, self-management, education, physiotherapy and occupational therapy. In contrast, the pharmacological treatment is mainly symptom-modifying agents. None is recognized as structure (disease) modifying agent by any guidelines or the regulatory agencies (29). The first line of symptom-modifying agent has been

acetaminophen with NSAIDS to be considered in those non-responsive to acetaminophen (6-8).

A meta-analysis of randomized controlled trials assessing the best evidence for efficacy of acetaminophen in the treatment of osteoarthritis had confirmed the effectiveness of acetaminophen for relieving pain in osteoarthritis. The effect size of 0.21 was small, but was statistically significant and acetaminophen had a higher clinical response rate than placebo (30).

In fact, acetaminophen is well tolerated with good bioavailability after oral administration at recommended therapeutic doses (maximum 4 g/ day). No serious side effects have been observed although rarer side effects may emerge with higher doses or prolonged utilization such as renal dysfunction, higher blood pressure and hepatotoxicity. Nevertheless, acetaminophen is safe as a long term treatment up to 6 – 12 months. The mechanism of action of acetaminophen is complex. Generally, it suppresses prostaglandin production but does not possess any anti-inflammatory properties (31, 32).

Non-steroidal anti-inflammatory agents (NSAIDs) have better efficacy and higher patient preferences compared to acetaminophen in treatment of osteoarthritis (33). The effect size of pain relief for NSAIDs was 0.29 (95% CI: 0.22 – 0.35), that was greater than acetaminophen with an effect size of 0.14 (95% CI: 0.05 – 0.22) (34). Based on a systematic review and network meta-analysis assessing the comparative effectiveness of pharmacologic treatment for primary knee osteoarthritis, the

ibuprofen, naproxen, diclofenac and celecoxib were significantly superior to acetaminophen in pain, stiffness and physical function-related outcomes (35). Moreover, Ibuprofen is commonly used in clinical trials of Glucosamine sulphate in knee osteoarthritis either for direct comparison (36, 37) or as rescue analgesia during the trials (15, 38).

Ibuprofen is a non-steroidal compound with analgesic activity linked to its anti-inflammatory effects and is related to reduction in cyclo-oxygenase (COX)-1 and COX-2 derived prostanoids production (39). It has been used for treatment of rheumatic and other more severe musculoskeletal conditions. It has comparable therapeutic benefits with coxibs and other NSAIDS (40). In fact, Ibuprofen at a dose of 1800 – 2400 mg per day had a good safety profile for treatment of inflammatory pain conditions including osteoarthritis, spondylo-arthropathies and other rheumatic conditions. The risk for gastrointestinal, hepatorenal and other rarer adverse drug reactions is relatively lower compared to other NSAIDS. The pharmacokinetic properties of Ibuprofen, particularly the short plasma half-life of elimination and lack of pathologically related metabolites production are responsible for its low toxic potential (41).

As mentioned, the better efficacy of NSAIDs has to deal with the expense of greater side effects. NSAIDs in general were associated with increased risk of serious gastrointestinal, cardiovascular and renal harms compared with placebo. Comparing both non-selective NSAIDs and selective COX-2 inhibitors, the latter were better or comparably tolerated. However, the serious adverse events were similar (10).

Hence, cautious use of NSAIDs with conservative dosing and treatment duration is mandatory particularly in those with moderate to high co-morbidity risk (7-9).

2.6 Complementary Alternative Medicine

In order to prevent and avoid potential adverse effects from conventional pharmacological treatment, attention has been directed towards complementary and alternative medicine (42, 43). Indeed, the use of complementary and alternative medicine is gaining popularity among individuals with osteoarthritis (11, 12). According to the World Health Organization, complementary and alternative medicine is the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses (44). The trend of complementary and alternative medicine use is varied between countries around the world (45).

In Malaysia, the complementary and alternative medicine is termed “Traditional and complementary medicine”. It comprises a form of health-related practices designed to prevent, treat and / or manage illnesses and / or preserve the mental and physical well-being of individuals and includes practices such as traditional Malay medicine, traditional Chinese medicine, traditional Indian medicine, homeopathy and complementary therapies and excludes medical or dental practices utilized by registered medical or dental practitioners. Traditional medicine has a remarkable role in the present health care system in Malaysia. It has been recognized by Ministry of

Health Malaysia as an integral part of national healthcare systems with its own National Policy on Traditional and Complementary Medicine established in 1999 (46).

Based on a study conducted among patients with chronic disease including osteoarthritis in Malaysia, the utilization of traditional and complementary medicine was common (63.9%) with varying types of modalities reported (42). Majority of the elderly in Malaysia perceived traditional and complementary medicine as much more effective (55.1%) with minimum side effects (69.5%) compared to the conventional medicine (47). Dietary supplements are among the dominant complementary and alternative medicine modalities consumed widely (45). Those commonly use in osteoarthritis include herbals, cod liver oil, vitamins, mineral, glucosamine and chondroitin (12, 13).

2.7 Glucosamine in Knee Osteoarthritis

Glucosamine use is common among individual with knee osteoarthritis. It is the most persistently used complementary and alternative medicine modality based on a 4 years study among older adults with radiographic knee osteoarthritis (14). Glucosamine is a natural aminosaccharide forming the constituent of glycosaminoglycan in the cartilage matrix and synovial fluid. The potential of glucosamine in suppression of numerous inflammatory and degenerative mediators have contributed to attenuation of articular cartilage degeneration, thus delaying the osteoarthritic disease progression. All these highlighted the role of exogenous

glucosamine administration for its symptomatic relief as well as disease-modifying effects in osteoarthritis (48, 49).

Numerous studies conducted to determine the effect of glucosamine sulphate on osteoarthritis symptoms have collectively demonstrated a superiority to placebo for improvement in pain and physical function (15, 16). The need for rescue pain analgesia (NSAIDs) has significantly reduced with continuous use of glucosamine sulphate (17). Moreover, there are evidences supporting the disease modifying effects of long term glucosamine sulphate. Two studies over 3 years period had shown a significant retardation of the joint space narrowing in osteoarthritis (50, 51). Above all, treatment with glucosamine sulphate for at least 12 months and up to 3 years may delay the need for total joint replacement for at least 5 years following treatment discontinuation (52). Long term treatment with glucosamine sulphate is also well-tolerated and safe with a comparable adverse event rate to placebo. In fact, the adverse events (i.e. headache, abdominal pain, dyspepsia, diarrhea) reported were generally transient and of mild to moderate severity (51, 53, 54).

Consequently, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for management of knee osteoarthritis has made recommendation for chronic use of symptomatic slow-acting drugs for osteoarthritis, in particular prescription glucosamine sulphate and chondroitin sulphate, as the first line pharmacological treatment for slow onset medium to long term control of symptoms (55). In addition, the guidelines from European League Against Rheumatism (EULAR) has graded both glucosamine sulphate and chondroitin sulphate with high level of evidence for symptomatic

treatment of osteoarthritis (6). Based on Malaysia clinical practice guideline, glucosamine sulphate is also recommended as part of treatment consideration at any time in managing osteoarthritis (8).

2.8 *Channa striatus* in Knee Osteoarthritis

In Malaysia, there are various types of complementary and alternative medicine use for treatment of chronic diseases including osteoarthritis (42). Apart from glucosamine sulphate, interest has been growing towards the use of *Channa striatus* as a local traditional remedy in treating knee osteoarthritis (18). *Channa striatus* is well-known as Haruan among Malaysian. It is an indigenous fresh water fish species belonging to the family of Channidae and widely distributed in several Asian countries including Malaysia. Other than consumed as a nutritious food, it is also popular as a remedy in traditional medicine, especially in post-operative wound healing (19).

Studies had been done on different components of *Channa striatus* including the fillets, roe (gonad of the fish in the pre-spawning season) and the mucous covering of the fish to analyze its biochemical compositions. It has a very good composition of amino acids and fatty acids as well as mineral compounds that contributed to its highly valued medicinal properties (56, 57). The important amino acids are glycine, lysine and arginine, whereas the fatty acids are arachidonic acid, palmitic acid and docosahexaenoic acid (38). The therapeutic potential of *Channa striatus* including

antimicrobial, antifungal, anti-inflammatory, induction of platelet aggregation, promoting cell proliferation as well as anti-nociceptive properties (19).

The wound healing properties of *Channa striatus* was explored by Baie *et al.* in a study that focused on the effects of *Channa striatus* on different constituents of extracellular matrix of healing wounds in rats. The *Channa striatus* treated wounds had an increase in uronic acid content suggesting an enhanced glycosaminoglycan synthesis in the healing wounds (58). The glycosaminoglycan has been an important first component of extracellular matrix synthesized during wound healing process (59). In addition, there was an increased hyaluronic acid, dermatan, keratin and chondroitin sulphate in the *Channa striatus* treated wounds that all together increased the rate of wound contraction and formed a stable scar, accelerating the process of wound healing (58).

The effectiveness of *Channa striatus* in wound healing was further substantiated by the observation of its ability to increase the tensile strength of the wounds. It promotes the collagen remodeling through synthesis of inter-and intra-molecular protein that cross-linked to form fibrous scar, the end process of wound healing (60). On these basis, *Channa striatus* is gaining its role in wound healing with more convincing scientific explanation for its potential therapeutic effects.

Apart from wound healing properties, the anti-nociceptive effect of *Channa* striatus is another interesting focus in the research. The anti-nociceptive activity of whole fillet and mucous extracts of *Channa striatus* was first studied on mouse by Mat Jais *et al.* in 1977 to establish the scientific basis for the well-known pain-relieving effects of the