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COMPARATIVE EFFECTIVENESS OF *Channa striatus* EXTRACT VERSUS GLUCOSAMINE SULPHATE FOR THE TREATMENT OF PRIMARY KNEE OSTEOARTHRITIS: A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Channa striatus, an indigenous freshwater fish, has been shown to treat knee osteoarthritis, but no study has been done to compare its effectiveness with other oral therapy. This study aimed to compare the effectiveness of oral Channa striatus extract and glucosamine sulphate in knee osteoarthritis symptoms and physical function. This is a double-blind randomised controlled trial, conducted among 78 patients with primary knee osteoarthritis. Patients were assigned to receive either 500 mg/d of Channa striatus or 1,500 mg/d of glucosamine sulphate for 6 months. The main outcome measures were pain, stiffness and physical function, as assessed by the Western Ontario and Mc Master Osteoarthritis Index (WOMAC) at baseline, 3- and 6-months post-randomisation. Seventy-three patients completed the study (Channa striatus, n = 37; glucosamine sulphate, n = 37). There was no significant between-group difference in the WOMAC index. However, the within-group comparison pointed to a significant improvement in all the WOMAC domains in both groups from baseline to 6 months. The effectiveness of Channa striatus shows no difference from that of glucosamine sulphate in reducing the symptoms of knee osteoarthritis. Channa striatus could be a new alternative treatment for the management of knee osteoarthritis.

***Keywords*:** *Channa striatus*, Glucosamine, Knee osteoarthritis, Randomised controlled trial

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INTRODUCTION

Knee osteoarthritis (OA) is one of the commonest forms of arthritis worldwide. The burden of OA on individual, socioeconomic and health care systems is anticipated to increase substantially over the coming decades, with the increased trend of the ageing population worldwide (Cross *et al*. 2014).

The popularity of complementary and alternative medicine for OA is increasing. These commonly include herbals, cod liver oil, vitamins, mineral, glucosamine and chondroitin (Lapane *et al*. 2012; Nik Shafii *et al.* 2018). Glucosamine is the most commonly used complementary and alternative medicine modality to treat OA (Yang *et al*. 2013). Studies of glucosamine sulphate for OA have collectively demonstrated its superiority to placebo for improvement of pain and physical function (Bruyère *et al*. 2016; Kongtharvonskul *et al.* 2015). Research also showed that continuous use of glucosamine sulphate was associated with a significant reduction in the consumption of rescue pain analgesia and nonsteroidal anti-inflammatory drugs (Rovati *et al.* 2016).

Apart from glucosamine sulphate, attention has focused on the use of *Channa striatus* in the treatment of knee OA (Kadir *et al*. 2014). *Channa striatus*, an indigenous freshwater fish known as *haruan* in Malaysia, is widely consumed due to its nutritious properties and it is used as a remedy in traditional medicine. The therapeutic potential of *Channa striatus* is due to its antimicrobial, antifungal, anti-inflammatory and antinociceptive properties, in addition to its role in inducing platelet aggregation and promoting cell proliferation (Mat Jais 2007). Animal studies have provided evidence for the beneficial effects of *Channa striatus* in treating OA (Al-Saffar, Ganabadi and Fakuraz 2011; Michelle, Shanti and Mohamad 2004). A study of patients with knee OA demonstrated a significant improvement in pain, other OA-related symptoms, and quality of life following treatment with oral *Channa striatus* extract for 3 months (Kadir *et al*. 2014). Hence, the present study aimed to explore the therapeutic potential of *Channa striatus* comparing its effectiveness with glucosamine sulphate, a well-studied treatment modality.

MATERIAL AND METHODS

A double-blind randomised controlled trial was conducted among 78 knee OA patients between December 2014 and March 2016 at the Outpatient and Orthopedic Clinic in Hospital Universiti Sains Malaysia, a tertiary teaching hospital in Malaysia. Patients with age more than 40 years old, ability to read Malay language, radiological grade I to III based on Kellgren-Lawrence classification and unilateral or bilateral knee OA diagnosed according to the American College of Rheumatology (knee pain and radiographic osteophytes plus at least one of three symptoms/signs; aged more than 50 years, who experienced morning stiffness of fewer than 30 minutes and crepitus on active motion) were included. Patients with secondary knee OA, with disabling comorbid condition such as renal disease, liver disease, neoplasm and other rheumatic diseases, the patient who is pregnant or nursing, patient with severe knee pain and willing for surgical intervention, patients who had joint lavage, arthroscopy or treatment with hyaluronic acid or glucosamine during the previous 6 months, patients who had been treated with intra-articular corticosteroids during the past 3 months and patients who have an allergy to oral *Channa striatus* and glucosamine sulphate were excluded.

A randomisation list in blocks of eight was done using a computer-generated randomisation method by a statistician who is part of the research team. Patients were randomised in the ratio of 1:1 to receive either oral *Channa striatus* extract or glucosamine

sulphate using the sealed envelope method. The randomisation codes are then put into sealed, opaque envelopes and numbered sequentially. The treatment assignment was done by the research assistant. The research assistant will open the consecutive envelope to randomise eligible patients accordingly. None of the researchers involved in the fieldwork knew the randomisation scheme.

The patients were screened at visit 1. Written informed consent was obtained from all the patients, and those who fulfilled the inclusion and exclusion criteria were called for visit 2. At visit 2, the patients completed a sociodemographic survey, the validated Malay version of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire and pain score based on the visual analogue scale (VAS) 0 mm–100 mm. Baseline renal and liver parameters were measured to determine the safety profiles of the drugs. The patients were allocated into two groups based on the randomisation list; the patient either received oral *Channa striatus* extract 500 mg/day or oral glucosamine sulphate 1,500 mg/day. The capsules were taken orally with water once daily at any time of the day, with or without a meal. The dose of *Channa striatus* 500 mg/day was chosen because a clinical trial that compared multiple doses of *Channa striatus* either 500 mg/day or 1,000 mg/day has similar efficacy on knee OA (Azidah *et al*. 2017). Following randomisation, the patients were followed up at visit 3 (month 3) and visit 4 (month 6). At each visit, they completed the WOMAC questionnaire and provided blood samples to analyse the renal and liver parameters.

Patients were prescribed paracetamol or ibuprofen, as needed to use as rescue analgesia if they experienced knee joint pain during the study. They were required to document the types and number of analgesic tablets taken in a diary and bring it to every visit. Patients were not allowed to change to another type of analgesia without first informing the investigators.

The sample size calculation for comparing two means by using Power and Sample Size Calculation (PS) software was applied. The standard deviation value was adapted from a study conducted by Giordano *et al*. (2009). The detectable mean difference for pain, stiffness, function, visual analogue scale and analgesic score between the *Channa striatus* and glucosamine sulphate group was based on expert opinion. Based on the sample size calculation for each objective, the biggest sample size yielded was 32 per group (from WOMAC stiffness score). After considering the 20% dropout rate, the sample size calculated was 39 per group.

Ethical Approval

This trial was registered at the Australian New Zealand Clinical Trial Registry (ANZCTR) with the registration number ACTRN12615000901505. This study protocol was approved by the Research Ethics Committee (Human), with reference number: 00007718; IRB Reg. No: 00004494 and procedures were following the Helsinki Declaration of 1975. The participants involved in the study had signed the consent form to participate in the study.

***Channa striatus* Extract and Glucosamine Sulphate Preparation**

Channa striatus (whole fish) were procured fresh to the Good Manufacturing Practice (GMP)-certified Major Interest Sdn. Bhd, located in a state in the north of Malaysia. The *Channa striatus* was specially prepared for this study and it was not available as a commercial product. Following the process of cleaning, gutting and autoclave, finally the orally administered freeze-dried *Channa striatus* was ready for packing. Freeze-dried

Channa striatus was packed into an empty halal hard gelatin capsule. Each capsule contained 125 mg of freeze-dried *Channa striatus* extract. Whereas, glucosamine sulphate powder in sachet form (dose of 1,500 mg per sachet) was packed into an empty hard halal gelatin capsule, with 375 mg per capsule. This is to ensure that the same number of capsules were received by the patients. Both were weighed for standard distribution using Sartorius analytical digital balance. Both the glucosamine sulphate and *Channa striatus* extract preparation was identical in appearance, taste and smell. Only one co-researcher involved in the blinding procedure knew the contents in each group of bottles, however, he was not involved in the patient's enrollment, treatment assignment and follow up.

Western Ontario and McMaster University Osteoarthritis Index (WOMAC)

The outcome measure used in this study was the WOMAC. The WOMAC is a self-administered disease-specific questionnaire, which is widely used to assess the symptoms and physical disability of a patient with hip and/or knee OA (Bellamy and Buchanan 1986; Bellamy *et al.* 1988). It has been widely used to evaluate clinical outcome measures following treatment interventions in OA research (Ethgen *et al*. 2004). The WOMAC measures total pain, total stiffness and total physical functioning score. The original questionnaire consists of 24 questions (five questions for pain, two questions for stiffness and 17 questions for physical function) and it has been validated in the Malay language. This questionnaire is available in a Likert version rated on an ordinal scale of one to four and as a VAS (Bellamy *et al.* 1988). This study used the VAS, with a 100-mm linear scale was used to measure pain on movement. On the scale, 0 representing no pain and 100 represented the most unbearable pain. The participants were required to mark on the linear scale based on their experience with pain on movement.

Statistical Analysis

An intention-to-treat analysis approach was used. Analysis of the data was performed using SPSS version 20.0. Baseline differences were compared using an independent *t*-test, Pearson's Chi-squared test, Fisher's exact test and Mann-Whitney U test. Numerical variables were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]). Categorical variables were presented as frequencies and percentages. A repeated measure analysis of covariance (ANCOVA) was used to determine the differences in outcome parameters of the WOMAC. The result is presented as the mean differences, with a 95% confidence interval (CI). A *p*-value of less than 0.05 was considered significant.

RESULTS

In total, 78 patients were randomised to receive 500 mg/day of *Channa striatus* (*n* = 39) or 1,500 mg/day of glucosamine sulphate (*n* = 39) (Figure 1). Four patients dropped-out before the three-month follow-up. Two dropped-outs were due to decreased blood pressure and muscle cramps (*Channa striatus* group) and another two dropped-outs were due to headaches and were lost to follow-up (glucosamine sulphate group). After the three-month follow-up, one patient dropped-out due to a traumatic fall (*Channa striatus* group). Thus, 73 patients completed the 6-month study and 74 patients (response rate, 94.9%) were included in the statistical analysis. Figure 1 showed the study enrollment and conduct.

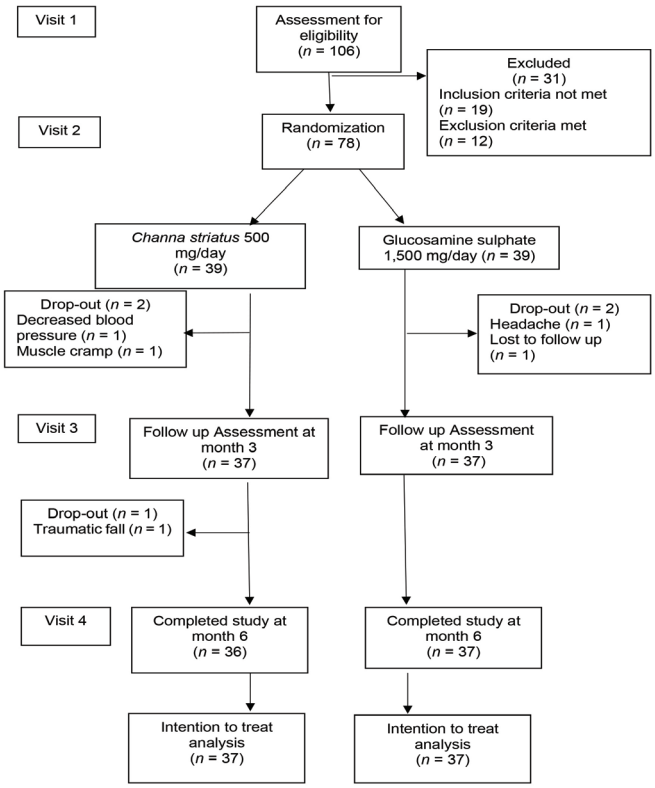

Figure 1: Flow diagram of study enrolment and conduct.

There were no statistically significant differences in the demographics, clinical characteristics and radiographic features of *Channa striatus* and glucosamine sulphate groups at baseline, as shown in Table 1. There were also no statistically significant differences in the scores of the WOMAC domains (i.e. pain, stiffness, physical function and global score) in the *Channa striatus* and glucosamine sulphate groups at baseline, as depicted in Table 1.

Table 1: Baseline characteristics of *Channa striatus* and glucosamine sulphate groups.

Characteristic	***Channa striatus* (*n* = 37)**	**Glucosamine (*n* = 37)**	***p*-value**
Age (years), mean (SD)	52.89 (6.36)	53.35 (7.36)	0.775[a]
Body mass index (kg/m^2), mean (SD)	29.25 (4.79)	27.50 (4.67)	0.116[a]
Duration of knee pain (years), median (IQR)	3.00 (3.00)	3.00 (5.50)	0.608[d]

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Table 1: (*continued*)

Characteristic	*Channa striatus* (*n* = 37)	Glucosamine (*n* = 37)	*p*-value
Gender, *n* (%)			
Male	16 (43.2)	14 (37.8)	0.636[b]
Female	21 (56.8)	23 (62.2)	
Marital status, *n* (%)			
Married	37 (100.0)	35 (94.6)	0.493[c]
Single	0 (0.0)	2 (5.4)	
Education, *n* (%)			
Primary	5 (13.5)	6 (16.2)	0.077[b]
Secondary	29 (78.4)	21 (56.8)	
University	3 (8.1)	10 (27.0)	
Occupation, *n* (%)			
Unemployed/self-employed	7 (18.9)	14 (37.8)	0.071[b]
Government/private sector	30 (81.1)	23 (62.2)	
Knee osteoarthritis grading, mean (SD)			
Grade I	19 (51.4)	21 (56.8)	0.825[b]
Grade II	10 (27.0)	10 (27.0)	
Grade III	8 (21.6)	6 (16.2)	
Medical illness, *n* (%)			
Yes	20 (54.1)	24 (64.9)	0.344[b]
No	17 (45.9)	13 (35.1)	
WOMAC domain			
Pain score	196.99 (112.89)	187.66 (101.00)	0.709[a]
Stiffness score	73.91 (55.74)	89.20 (57.13)	0.248[a]
Physical function score	658.41 (406.07)	656.85 (368.28)	0.986[a]
Global score	929.30 (559.91)	933.72 (503.82)	0.972[a]

Notes: a = determined by independent *t*-test; b = determined by Pearson chi-squared test; c = determined by Fisher's exact test; d = determined by Mann-Whitney test; SD = standard deviation; IQR = interquartile range.

Group Effect: WOMAC score between the *Channa striatus* and glucosamine sulphate groups.

There were no significant mean difference in pain ($p = 0.818$), stiffness ($p = 0.285$), physical function ($p = 0.742$) and global ($p = 0.926$) domains of WOMAC score between *Channa striatus* and glucosamine sulphate groups after 6 months, as depicted in Table 2.

Table 2: Mean difference of WOMAC score between *Channa striatus* and glucosamine sulphate group.

Domain	Comparison	Mean difference (95% CI)	*p*-value
Pain	*Channa striatus*-Glucosamine	-4.09 (-39.36, 31.18)	0.818
Stiffness	*Channa striatus*-Glucosamine	-9.70 (-27.68, 8.27)	0.285
Physical function	*Channa striatus*-Glucosamine	22.32 (-112.62, 157.26)	0.742
Global	*Channa striatus*-Glucosamine	8.53 (-173.17, 190.22)	0.926

Notes: Repeated measures ANCOVA between group analysis regardless of time was applied; Numerical covariate (analgaesic score) was controlled by using repeated measure ANCOVA; Assumption of normality, homogeneity of variance, compound symmetry and homogeneity of regression were checked and fulfilled; Level of significance was set at 0.05 (two-tailed).

Time Effect: WOMAC score of the *Channa striatus* and glucosamine sulphate groups.

As shown by the WOMAC scores, all domains (i.e. pain, stiffness, physical function and global scores) showed a significant improvement in the *Channa striatus* treatment group at the 3-month follow up, as shown in Table 3. However, non-significant improvements were observed from 3 months–6 months. The glucosamine sulphate group showed significant improvements in all the WOMAC domains (i.e. pain, stiffness, physical function and global scores) at the 6-month follow-up. These significant improvements were observed in all the domains from zero month–3 months and 3 months–6 months, except for pain, which showed a non-significant improvement from 3 months–6 months.

Table 3: Comparison of WOMAC score of *Channa striatus* and glucosamine groups.

Domain	Comparison	*Channa striatus*		Glucosamine	
		mean difference (95% CI)	*p*-value	mean difference (95% CI)	*p*-value
Pain	Month 0–3	89.49 (45.59, 133.38)	< 0.001	70.70 (22.11, 119.29)	0.003
	Month 0–6	103.85 (54.73, 152.98)	< 0.001	100.84 (50.62, 151.06)	< 0.001
	Month 3–6	14.37 (-11.68, 40.41)	0.521	30.14 (-9.39, 69.66)	0.190
Stiffness	Month 0–3	31.32 (9.62, 53.03)	0.003	30.49 (9.55, 51.42)	0.002
	Month 0–6	40.78 (23.55, 58.03)	< 0.001	51.97 (28.53, 75.42)	< 0.001
	Month 3–6	9.46 (-7.68, 26.59)	0.520	21.49 (3.95, 39.03)	0.012

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Table 3: (*continued*)

Domain	Comparison	*Channa striatus*		Glucosamine	
		mean difference (95% CI)	*p*-value	mean difference (95% CI)	*p*-value
Physical function	Month 0–3	225.69 (71.53, 379.85)	0.002	246.34 (88.42, 404.26)	0.001
	Month 0–6	309.04 (155.49, 462.60)	< 0.001	369.64 (203.56, 535.71)	< 0.001
	Month 3–6	83.35 (-40.82, 207.53)	0.300	123.30 (9.97, 236.62)	0.029
Global	Month 0–3	346.50 (138.53, 554.47)	0.001	347.53 (130.56, 564.50)	0.001
	Month 0–6	453.68 (247.57, 659.78)	< 0.001	522.45 (293.01, 751.88)	< 0.001
	Month 3–6	107.18 (-44.95, 259.30)	0.255	174.92 (-339.73, -10.11)	0.034

Notes: Repeated measure ANCOVA within group analysis was applied followed by pairwise comparison with confidence interval adjustment; Numerical covariate (analgaesic score) was controlled by using repeated measures ANCOVA; **p*-value is significant; CI = confidence interval.

VAS and Analgaesic Score between *Channa striatus* and glucosamine sulphate group.

There was no statistically significant mean difference in pain on movement evaluated with a visual analogue scale between *Channa striatus* and glucosamine sulphate groups ($p = 0.971$) after 6 months of treatment as shown in Table 4. There was also no statistically significant median difference in analgaesic score between the *Channa striatus* and glucosamine sulphate group at 3 months ($p = 0.200$) and 6 months ($p = 0.725$) of treatment.

Table 4: Mean difference on VAS score between *C. striatus* and glucosamine sulphate group at 6 months.

Domain	Comparison	Mean difference (95% CI)	*p*-value
Pain on movement	*Channa striatus*-glucosamine	-0.14 (-8.17, 7.88)	0.971

Notes: Repeated measures ANCOVA between group analysis regardless of time was applied; Numerical covariate (analgaesic score) was controlled by using repeated measure ANCOVA; Assumption of normality, homogeneity of variance, compound symmetry and homogeneity of regression were checked and fulfilled; Level of significance was set at 0.05 (two-tailed); VAS = visual analog scale; CI = confidence interval.

Safety Profile

In total, four adverse events were reported throughout the 6-month treatment period: three in the *Channa striatus* group (7.8%) and one in the glucosamine sulphate group (2.6%). However, following a clinical assessment, these were considered unrelated to the investigational drugs. No serious adverse events were reported. All the laboratory parameters were within normal ranges.

DISCUSSION

This is the first study to compare the effectiveness of the *Channa striatus* versus glucosamine in treating knee OA. The chondroprotective effect of *Channa striatus* has been postulated due to anti-inflammatory activity and its anabolic activity of the articular cartilage (Abdul Kadir *et al*. 2019). The potential benefit of *Channa striatus* in OA was reported in animal studies, which revealed a marked reduction in inflammation and pathological changes of the articular cartilages and synovial membranes of osteoarthritic joints (Abdul Kadir *et al*. 2019; Al-Saffar Ganabadi and Fakuraz 2011; Michelle, Shanti and Mohamad 2004).

In an OA-induced rabbit model study*, Channa striatus* is superior to glucosamine in reduction of the severity of the articular cartilage structure. In the study, the OA-induced rabbits were divided into three groups and were randomly assigned to control, glucosamine and *Channa striatus* group. The *Channa striatus* group was shown to have a better histopathological score compared to the glucosamine and control groups. However, both *Channa striatus* and glucosamine has similar efficacy based on the OA biomarker test that was serum cartilage oligomeric matrix protein (Abdul Kadir *et al*. 2019). However, this is the first study that reported the comparative study between *Channa striatus* and glucosamine. In this study, it was noted that both groups have a similar effect on the symptoms of knee OA.

Overall, the clinical characteristics of the populations in the present study were similar to those of patients in most clinical trials on glucosamine sulphate (Giordano *et al*. 2009; Herrero-Beaumont *et al*. 2007; Pavelka *et al*. 2002; Reginster *et al*. 2001). The majority of the participants were females (Giordano *et al.* 2009; Pavelka *et al*. 2002; Reginster *et al*. 2001) and the majority of the participants were overweight (Reginster *et al.* 2001) as shown by the mean body mass index (BMI) of 27 kg/m^2. The clinical characteristics of the study population were also similar to those of an earlier study of *Channa striatus*, in which the mean age was 49 years old and the majority (81.8%) of the participants were females, although the mean BMI (25.2 kg/m^2) was lower in that study than in the present one (Kadir *et al*. 2014).

The effectiveness of glucosamine sulphate in the treatment of knee OA is well known, with numerous studies providing evidence of its benefits (Braham, Dawson and Goodman 2003; Bruyère, Altman and Reginster 2016; Cibere *et al*. 2004; Hughes and Carr 2002; Reginster *et al*. 2005). A 6-month study demonstrated a significant improvement in WOMAC pain, physical function and global subscales (Herrero-Beaumont *et al*. 2007). A few long term studies on glucosamine sulphate showed significant retardation of joint space narrowing supporting its disease-modifying potential (Bruyère *et al*. 2004; Reginster *et al*. 2001). Long term studies of glucosamine sulphate also showed significant improvement in WOMAC scores (Bruyère *et al*. 2004; Pavelka *et al*. 2002; Reginster *et al*. 2001).

Similarly, in the current study, significant improvements were observed in the glucosamine sulphate group in all the WOMAC domains from (0 month–3 months) and (3 months–6 months) but not in the pain domain from (3 months–6 months). Although the latter showed an improvement from (3 months–6 months), the improvement failed to reach statistical significance. Thus, the results suggest that the analgesic effects of glucosamine sulphate are greater in the first three months of treatment.

A few studies reported the therapeutic effect of *Channa striatus* in knee OA (Abdul Kadir *et al*. 2019; Azidah *et al*. 2017; Kadir *et al*. 2014; Michelle, Shanti and Mohamad 2004). In the present study, there were significant improvements in pain, stiffness and physical function within the *Channa striatus* group. These significant improvements were evident after 3 months of treatment and were similar to the glucosamine sulphate group (Table 3). The findings of the present study are consistent with those of a 3-month study of *Channa*

striatus extract used to treat primary knee OA that reported a significant improvement in knee pain, other knee OA related symptoms and quality of life in the *Channa striatus* group (Kadir *et al*. 2014). In that study, the clinical effects were evident after 2 months of treatment. However, in the present study, the first assessment was not undertaken until after 3 months of the treatment.

The main symptoms of knee OA are pain, stiffness and altered function. Pain-related symptoms can be due to inflamed synovium and damaged subchondral bone (Felson 2005) There are few mechanisms postulated for its effect in knee OA. This mechanism includes wound healing, anti-inflammatory, analgesic and antioxidant properties (Azidah *et al*. 2017). It is postulated that via multiple mechanisms these *Channa striatus* extracts can reduce the catabolic effect that is degeneration of the cartilage and induced anabolic effect via synthesis of the glycosaminoglycan and hyaluronic acid (Abdul Kadir *et al.* 2019). This would strengthen the structure of the articular cartilage, thereby preventing further degradation and reducing inflammation.

In the current study, there were no differences in the pain, stiffness and physical function of the *Channa striatus,* and glucosamine sulphate treatment groups after 6 months. This finding suggests that *Channa striatus* has therapeutic potential, which is no different to that of glucosamine sulphate in improving knee pain, physical function, and possibly, stiffness in individuals with primary knee OA. In a future study, placebo and non-steroidal anti-inflammatory drugs (NSAIDs) as the control group is recommended.

CONCLUSION

Treatment with *Channa striatus* (500 mg/day) showed no difference to that of glucosamine sulphate (1500 mg/day) in reducing pain and stiffness and improving physical function in patients with primary knee OA. With a good safety profile, *Channa striatus* (500 mg/day) could be a new alternative treatment for medium to long term management of primary knee OA.

Limitations

The use of a composite scoring system (WOMAC) as efficacy outcome measurement rely on patient-reported or subjective assessment. There was no objective evidence on the effects of *Channa striatus* for structural changes in knee OA. Thus, whether *Channa striatus* has the potential as a disease-modifying agent cannot be concluded from the present data.

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