Snakehead Fish (*Channa Striatus*) in the Management of Osteoarthritis: Clinical Research and Possible Mechanism of Action

Azidah Abdul Kadir

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

**Corresponding Author:** Azidah Abdul Kadir, Associate Professor, Department of Family Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan, Malaysia, Email: azidahkb@usm.my

**Abstract**

Knee Osteoarthritis (OA) is the most prevalent degenerative arthritis, and this is a matter of concern given the growth in the number of aging and obese individuals. Research on disease modifying drugs (DMOADs) to treat OA is important since currently there is no effective treatment available to prevent disease progression. *Channa striatus* (CS), an indigenous fish known as Haruan in Malaysia, is part of the Malaysian diet and also used in traditional medicine. The extract of CS, a freshwater fish, has been evaluated for use as DMOADs in the treatment of knee OA. The chondroprotective potential of CS has been evaluated in in-vivo studies and randomized controlled trials. The possible mechanism of CS extract in OA can be attributed to its anti-inflammatory activity, improvement of extracellular matrix homeostasis, reduction of chondrocyte apoptosis, reduced oxidative activity, and analgesic properties. Thus, literature review suggest that CS demonstrate a possible DMOADs in the management of OA.

**Keywords:** Knee Osteoarthritis, Channa Striatus (Cs), Apoptosis, Anti-inflammatory activity

**Introduction**

Knee OA is the most prevalent degenerative arthritis, and this is a matter of concern given the growth in the number of aging and obese individuals; causing disability and substantial economic costs [1]. Research on disease modifying drugs (DMOADs) to treat OA is important since currently there is no effective treatment available in preventing disease progression [2].

The exact pathophysiology of OA is still unknown. However, recently, the understanding of the physiopathology of OA is improving owing to the accumulation of evidence. It is proposed that in OA, there is a disproportion between production [3,4] and degradation of the extracellular matrix [5]. Reduced production and increased degradation of the matrix couple with chondrocytes apoptosis leads to cartilage destruction. The destruction of the matrix is induced by a few inflammatory cytokines such as IL-1β, matrix metalloproteinase, cyclooxygenase 2 (COX)-2; prostaglandins such as PGE_2_, a disintegrin and metalloproteinase with thrombospondin motifs and proteases [6-8]. The inflammatory mediators (such as interleukins IL-1b, IL-6, IL-8 and tumor necrosis factor a (TNF-a), mechanical and oxidative stress further compromise the function and viability of chondrocytes [9].

**Channa Striatus**

*Channa striatus* (CS) is an indigenous fresh water snakehead fish, native to tropical regions such as Asia and Southern China [10]. This murrels belongs to the family Channidae and usually inhabits rice fields, rivers, and lakes [11]. The communities in Southeast Asian countries, China, India, and Bangladesh not only consumed this fish as food, but, it is more popular as medicine to treat various conditions [10,11]. This fish is cooked in various dishes like soup, roasted, steamed, curried, and fried [12]. This murrels has been considered as a very good source of health food among Asians due to its good quality of nutrients, taste, and medicinal values. Thus, this fish is cultured commercially in India, Thailand, Taiwan, and Philippines due to its high demand and high market value [13,14].

In Southeast Asian, countries like Malaysia and Indonesia, this fish is believed to promote wound healing, reduce post-operative pain, and boost energy for the sick people [15,16]. It is widely...
consumed by postpartum women and post-circumcision boys in these countries [10]. In Bangladesh, this fish is believed to boost energy and to provide ‘sex power’ in male. In Andhra Pradesh, India this fish is taken raw to treat asthma.

**Fatty Acids and Amino Acids Components of CS**

A few studies had been conducted to assess the fatty acids and amino acids of CS [16-20]. The crude protein content and the total lipid content of the snakehead fillet was 23.0% and 11.9% respectively (all in% dry weight) [20]. The fatty acids in the CS extracts can be grouped to saturated (SFA), monounsaturated (MUFA), and polyunsaturated fatty acids (PUFA) [17]. The SFA in the extracts are trideconoic, pentadecanoic, myristic, palmitic, heptadecanoic, and stearic acids. While MUFA consists of myristoleic, palmitoleic, and oleic acids, and last but not least, PUFA acid linoleic, linolenic and arachidonic acids [17]. The major component of the fatty acids is the polyunsaturated fatty acid (PUFA) which is good for health [17]. The ability of CS to produce unsaturated fatty acids such as eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA) in high amounts partly explains the efficiency of the fish as a wound healing agent [21].

**Biomedical Research in CS**

Scientific research carried out, have unraveled the biomedical potential of the fish [11]. Numerous studies demonstrated its therapeutic potential and medicinal value, including wound healing, anti-inflammatory, anti-nociceptive, and anti-depressant properties [22-25,10,12].

Many studies have been conducted to assess the wound healing properties of this fish. In the study of malnourished rats using laparotomy wound model, both oral and topical CS extract groups had higher tensile strength, epithelial, and fibroblast cell counts than the control group [26]. The synthesis of glycosaminoglycans during the wound healing process was found to be enhanced in an animal study using topical CS cream [27,28]. In Wistar rats with experimentally induced gastric ulcers, orally administered extract of CS was found to have reduction of gastric juice and increase levels of catalase compared to the control group [29]. The wound healing properties of CS are attributed to its fatty acid and amino acid composition, especially glycine and Arachidonic acid, which may be involved in promoting wound healing by increasing the collagen production, growth of epithelial cells, and contraction of tissue surrounding the wound [27,28,11].

A clinical study involving post-caesarean women showed that oral CS extract lead to improved wound cosmetic appearance and rapid uterus involution compared to the placebo group [22,24]. In a recent trial conducted among post coronary bypass grafting patients, this fish extract also has been shown to hasten recovery and improved the quality of life of the treated patients [30].

Some studies have reported the anti-inflammatory activity of CS extract [23,31-33]. The anti-inflammatory effect of CS extract-based cream was found to be as potent as 1% hydrocortisone cream in reducing acute inflammation in mouse model using croton oil-induced ear oedema [23]. CS extract cream is able to block the migration of polymorphonuclear leucocytes to the dermis [23].

CS extracts have shown antinociceptive properties in many animal model studies [34,35]. An in vivo study showed that CS extract enhanced the activity of other antinociceptive agents such as morphine, suggesting its interaction with opioid receptors [18,33]. Zakaria et al. proposed that CS extract is capable of mediating peripherally induced nociception.

The effect of CS extract supplementation on immune level and healing of pulmonary tuberculosis infection was assessed in a trial that was conducted in a randomised, double-blind method for 12 weeks duration [36]. They reported significant reduction of serum TNF-α, IFN-γ, and IL-10 at week 12 compared to baseline in the CS extract group but did not reach statistically different value in comparison with placebo groups [36].

In view of CS anti-inflammatory properties, a study was conducted to investigate its therapeutic potential and immune-modulatory effect in allergic rhinitis patients. The study was conducted in a randomized method using placebo as controlled group among 70 allergic rhinitis subjects for a 6-week intervention period [37]. In the study, there were improvement of nasal symptoms and reduction of serum Immunoglobulin E in CS treated group compared to placebo [37]. These studies further supported the role of CS in the treatment of diseases with clear inflammatory component.

CS extracts have shown antinociceptive properties in many animal model studies [34,35]. An in vivo study showed that CS extract enhanced
the activity of other antinociceptive agents such as morphine, suggesting its interaction with opioid receptors [35,33]. Zakaria et al. proposed that CS extract is capable of mediating peripherally induced nociception. The presence of amino acids such as glycine, glutamate, and aspartic acid could contribute to this effect [33]. These amino acids have been found to be involved in endogenous pain inhibition [38].

Two studies showed that CS extract had antidepressant-like effect in the mouse model of depression [39, 25]. It is postulated that CS extract produced antidepressant activity through serotonergic receptor and alpha adrenoceptors system [35,39].

### Anti-Arthritic Effect of CS

The potential of CS in the treatment of osteoarthritis has been evaluated in animal and human studies (Table 1) [41-44,31]. To date, four animal studies and two clinical trials have been reported in the literature that tested the efficacy of CS in the treatment of OA. In an anterior cruciate ligament transection induced arthritic rabbit, Michelle et al. in 2004 showed that CS extracts improved soft tissue swelling and density of protein gene product (PGP 9.5) immunoreactive nerve fibers in the synovial membrane of treated animals compared with that of controls [33]. Ganabadi et al. 2009, As-Saffar et al. 2011a and As-Saffar et al. 2011b reported similar findings.

It showed that PGP 9.5 was reduced in the arthritic joints in experimental animals and humans [43,31,45]. The reduction of these fibers may be due to the production of oxygen free radicals during the OA events that may enhance NPs excretion leading to their exhaustion and subsequent necrosis of these fibers [45,46]. The improvement of the nerve fibers showed that CS works through reduced inflammation in the joint structures including synovial membrane.

In rats with monosodium iodoacetate induced OA, it showed that animals treated with CS extract had reduced levels of PGE2 comparable with animals treated with celecoxib which is a group of COX-2 inhibitor. It is postulated that CS extract works through inhibition of the cyclooxygenase expression [40]. The CS extract-treated group also showed better histopathological scores and immunohistochemistry findings than the control [40].

A randomised, controlled, double-blind trial assessed the efficacy of CS extract at 500 mg/day compared with placebo in primary knee OA subjects for a 3-month intervention period had been conducted. The results of the study showed that CS improved knee OA symptoms including pain based on Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaires. The study also reported that the quality of life (QOL) is higher in those treated with CS than those subjects in the control group [44].

A three-arm trial conducted recently comparing oral CS extract 1000 mg/day or 500 mg/day and placebo among knee OA patients for a 6-months intervention period. The main outcome measures were Western Ontario and McMaster University Osteoarthritis Index (WOMAC), analgesic scores and serum cartilage oligomeric matrix protein (COMP). They noted significant reductions in WOMAC stiffness and function scores at month 6 in CS 1000 mg/day and CS 500 mg/day compared to placebo groups. However, no significant differences were found in terms of pain, analgesic scores, and serum COMP (osteoarthritis biomarker).

<table>
<thead>
<tr>
<th>Studies</th>
<th>Experiment design and treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelle et al. 2004 [31]</td>
<td>ACLT induced OA rabbits Two groups; CS and control. The outcomes measured: • Radiographic and innervations of the synovial membrane • Density of PGP 9.5-immunoreactive nerve fibers in the synovial membrane</td>
<td>• Reduction in soft tissue swelling observed in radiograph • Improvement in the density of PGP 9.5-immunoreactive nerve fibers in the synovial membrane</td>
</tr>
<tr>
<td>Ganabadi et al. 2009 [43]</td>
<td>Collagenase induced arthritis in rats. Three groups; CS, Zingiber officinale (ZO), normal saline.</td>
<td>• Improvement in the density of PGP 9.5-immunoreactive nerve fibers in the synovial membrane more in CS and ZO</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Kadir AA                      |                                                                              | The outcomes measured:  
- PGP 9.5 in synovial membrane group compared to control. However, huge reduction in CS compared to ZO.                                                                                                                                                                                                                                                                                                                                                           |
| As-Saffar et al. 2011a [40]   | Monosodium iodoacetate induced arthritis in rats. Four groups; two groups were given CS extract, Celecoxib and control (normal saline). The outcomes measured:  
- PGE$_2$  
- PGE$_{2\alpha}$  
- PGP 9.5, anti-calcitonin gene related peptide (CGRP) and neuropeptides Y (NPY) in synovial membrane  
- Histopathology score of the articular cartilage and synovial membrane | Significant reduction in PGE$_2$ level, improved immunoreactivity in synovium and reduced histopathological scores in CS groups compared to control.                                                                                                                                                                                                                                                                                                                                                                 |
| Kadir et al. 2014 [44]        | A randomized, double-blind, placebo-controlled trial comparing the effects of oral CS extract 500 mg/day with placebo given for 3-month intervention period (n = 84) | Significant improvement of pain, symptom scores and quality of life (QOL) domain score (<0.05) in CS compared to placebo group.                                                                                                                                                                                                                                                                                                                                                                                  |
| Kadir et al. 2017 [47]        | 3-arm randomized, double-blind, placebo-controlled trial comparing oral CS extract 1000 mg/day or 500 mg/day and placebo for a 6-month intervention | Significant reductions in stiffness and function scores were achieved in CS 1000 mg/day and CS 500 mg/day compared to placebo groups (p < 0.05).                                                                                                                                                                                                                                                                                                                                                                       |

**Potential Channa Striatus Mechanism of Action in OA**

The effect of CS extract on osteoarthritis is postulated through its anti-inflammatory, wound healing, antioxidant and analgesics properties [22,24,40,27,48,33]. The anti-inflammatory effects play a big role in the CS mechanism of actions in OA. It reduces catabolic breakdown of ECM, cell apoptosis and pain. CS demonstrated anti-inflammatory action via inhibiting the activity of inflammatory mediator PGE$_2$ [40,41], TNF-α [49,36], IL-10 [36] and interferon [36].

EPA, DHA and AA [50,21] are present in CS extract. It is postulated that EPA and DHA contribute to the anti-inflammatory action of CS extract [49]. EPA and DHA had been shown to decrease the production of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and COX-2 [51,52]. EPA also can inhibit AA metabolism competitively and suppress production of the n-6 eicosanoid inflammatory mediators [51]. CS extract also had palmitic acid, stearic acid, and linoleic acid which have been demonstrated to catalyze COX-2- prostaglandin biosynthesis [53]. Oleic and linoleic acid supplementation had been shown to suppress the activity of cyclooxygenase synthase among 30 healthy volunteers [54].

This fish had wound healing properties which can result in increased synthesis of...
Glycosaminoglycan (GAG) and hyaluronic acid, these actions can result in increased production of ECM, thus strengthen the articular cartilage. Improvement of the matrix component in OA by CS extract also has been shown by improvement of Safranin O fast green staining in histology assessment of articular cartilages in an animal study.

Glycine is one of the amino acids detected in CS extract. Glycine has been found to help in the formation of collagen. It also acts synergistically with other amino acid like alanine, arginine, proline, isoleucine, phenylalanine, and serine to form a polypeptide that promotes tissue repair and healing. CS extract also had high amount of arginine. Arginine supplementation has been observed to enhance the amount of collagen deposited into a standardised wound.

CS extracts has been found to exhibit antinociceptive activity and also enhance morphine-induced anti-nociception. This fish extract possessed peripheral antinociceptive activity through muscarinic, GABA, a- and b-adrenergic systems. PGF2 and TNF-α are two of the inflammatory mediators that contribute to the nociceptive pathway in the progression of OA. PGF2 exert its effects via a variety of E prostanoid (EP) receptors (EP1, EP2, EP3, EP4), and direct TNF-α application in the periphery induces neuropathic pain. Thus the antinociceptive activity of CS extract is possible through the blockade of PGF2 and TNF-α production.

A body of evidence suggests that the progression of OA in patients may be primarily driven by an increase in oxidative stress. Nitric oxide (NO) and its redox derivatives have been shown to be involved in cartilage damage, and the reactive oxygen species (ROS) scavenger superoxide dismutase is reduced in the cartilage of humans and animal models of OA.

Among freshwater fishes, CS appears to have a medium level of anti-oxidant activities. This property is possibly contributed by some of the major amino acids and fatty acids in CS extract. CS extract exhibit significant antioxidant activities such as 2,2-diphenyl-picyrylhydrazyl (DPPH) radical scavenging, ferric ion reduction and azin-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS) indicating its possible anti-oxidative interference both in onset and downstream consequences of osteoarthritis.

The activity of reactive oxygen species is balanced by CS antioxidants activity that act by inhibiting oxidative enzymes, scavenging free radicals or chelating ion metals.

**Conclusion**

The current review indicates that CS has considerable therapeutic effect in the treatment of OA. The CS extract acts through its anti-inflammatory, wound healing, antioxidant and analgesics properties. Currently it is still unknown which (bioactive) compound of CS involved in these mechanism of actions. Studies into the identification of the bioactive compound and its exact mechanism of action should be conducted as CS is a promising candidate for future neutrauthecal and pharmaceutical products.

**References**

osteoathritis: identifying molecular targets. PM&R, 3(6), S3-S11.


tropical anguillid eel Anguilla marmorata from peninsular Malaysia. ZooKeys, (695), 103–110. Advance online publication. http://doi.org/10.3897/zookeys.695.13298


