



Efficacy of snakehead fish (*Channa striatus*) in subjects with allergic rhinitis: a randomized controlled trial

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Abstract

Allergic rhinitis is a prevailing chronic inflammatory respiratory disorder that affects 10–30% of the population globally. *Channa striatus* (Channa) is a snakehead, freshwater fish that has been used traditionally to enhance wound healing and relief post-operative pain. This study evaluates the efficacy of oral Channa extract on allergic rhinitis subjects on total nasal symptom score and serum immunoglobulin E (Ig E). A randomized, double-blind, placebo-controlled trial was conducted by comparing the oral Channa extract 500 mg/day and placebo among allergic rhinitis subjects for a 6-week intervention period. Subjects aged 18–50 years old, diagnosed with allergic rhinitis based on total symptoms score, naso-endoscopy findings, and positive skin prick test were included in this trial. All subjects were treated with antihistamine (levocetirizine) and local corticosteroid nasal spray (fluticasone furoate nasal spray). Laboratory-based blood tests were used as safety measures. A total of 70 subjects were randomized. Channa group showed significant improvement in nasal blockage ($p < 0.05$), nasal itchiness ($p < 0.05$), eye itchiness ($p < 0.05$) and general symptoms ($p < 0.05$) compared to the placebo groups. Serum Ig E were significantly lowered in Channa group compared to placebo ($p < 0.001$). No significant differences were found between the groups in terms of nasal discharge, sneezing, palate itchiness, and smell score. No serious adverse events were reported. In conclusion, Channa has a beneficial role in improving nasal symptoms and reduction in serum Ig E in allergic rhinitis subjects.

Keywords Allergic rhinitis · *Channa striatus* · Immunoglobulin E · Nasal symptoms score

Introduction

Allergic rhinitis (AR) is one of the most prevalent chronic inflammatory disorder of the nasal mucous membrane, characterized by nasal obstruction, watery nasal discharge, sneezing and pruritus (Blaiss et al. 2018). Globally, the prevalence is estimated to be between 10 and 30% and leading to reduced quality of life and substantial public health problem (Zheng et al. 2015). Recently there has been dramatic

increase of its prevalent worldwide (Scadding et al. 2017). Allergic rhinitis is a typical Th2 immune disorder characterized by a high level of antigen specific immunoglobulin E (Ig E) production (Frew 2018; Khan 2014; Yamamoto et al. 2006). Allergic rhinitis can be divided roughly into seasonal and perennial rhinitis (Matsumoto et al. 2018).

Pharmacotherapy used to control symptoms of AR are intranasal or oral antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, and/or decongestants (Scadding et al. 2017). The managements also include avoidance of allergens and immunotherapy. However, every of them has its own disadvantage (Ganesh et al. 2017; Rajakulasingam et al. 2018). Antigen avoidance is not feasible for those who stay in antigen prone environments, while immunotherapy has adherence difficulty due to efficacy concerns among sufferers. Pharmacological agents like antihistamines and topical steroids might cause sedation and nasal irritation (Ganesh et al. 2017). Recently, there was an increased practice of using complementary and alternative medicine for allergic rhinitis (Bielory 2018). This interest is due to

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limitations of conventional medicine and the influence of cultural diversity (Kern and Bielory 2014).

Channa striatus (Channa) is a freshwater striped murrel commonly known as snakehead fish. This fish is widely consumed as food in Southeast Asia and is famous for its medicinal properties, especially in inducing wound healing in post-natal and post-operative recoveries (Haniffa et al. 2014). The fish extract is rich in proteins, amino acids and fatty acids (Haniffa et al. 2014). This snakehead fish exhibits high levels of amino acids such as aspartic acid, glycine and glutamic acid which have key role in the wound healing process (Rahayu et al. 2016). CS extract also has both n-3 eicosanoids such as eicosapentaenoic acid (EPA), docosahexanoic acid (DHA) and n-6 eicosanoids such as arachidonic acid (Mohamed et al. 2014; Rahayu et al. 2016).

A few data have reported the CS anti-inflammatory, chondroprotective, wound healing, anti-nociceptive and anti-oxidant activities (Ab Wahab et al. 2015; Abu Bakar et al. 2015; Al-Saffar et al. 2011; Azidah et al. 2017; Baie and Sheikh 2000; Radzak et al. 2014). In rats with monosodium iodoacetate induced OA, it was shown that animals treated with CS had reduced levels of PGE₂, comparable with animals treated with celecoxib which is a group of COX-2 inhibitor (Al-Saffar et al. 2011). It is postulated that CS extract works through the inhibition of cyclooxygenase expression (Al-Saffar et al. 2011). A randomized, placebo-controlled, double-blind study was conducted to assess the effects of CS extract supplementation for 12 weeks among pulmonary TB patients who received standard tuberculosis treatment. There were significant reductions of [Tumour Necrosis Factor- α , Interferon (IFN)- γ , and Interleukin (IL)-10] at week 12 compared to baseline in the CS group (Paliliewu et al. 2013). Based on its anti-inflammatory activity, it is postulated that this fish can decrease the anti-inflammatory agents responsible for allergic rhinitis manifestations.

Immunoglobulin E constitutes the typical TH2 immunoglobulin and elevated concentrations of Ig E which are described in allergic diseases (Curin et al. 2018). Significant elevated concentrations of IL-5 and Ig E, in nasal secretion with consistently-elevated concentrations of Ig E in serum has been reported in AR (Kramer et al. 2000; Yu et al. 2018). Positive serum specific Ig E has been reported to have strong correlation association with nasal symptoms in response to allergen exposure (Hamilton 2018; Paloma et al. 2018). Serum Ig E has been used as one of the tool to diagnose AR other than clinical symptoms and skin prick test (Bousquet et al. 2008; Seidman et al. 2015). In comparison to skin prick test, serum Ig E can be performed on patients with skin lesion and are taking antihistamines (Jiang et al. 2010; Seidman et al. 2015).

In view of its anti-inflammatory properties, its use in amelioration of AR was explored. Therefore, this study aims to evaluate the potential efficacy of Channa extract as an adjunct to treatment in AR subjects on symptoms score and serum Ig E.

Materials and methods

Study design and setting

A double-blinded, placebo controlled study was conducted among AR patients at the Otorhinolaryngology Clinic, Universiti Sains Malaysia from January 2013 until February 2014. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Human Research Ethics Committee (Reference Number: 00007718, IRB No: 00004494), Universiti Sains Malaysia and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all individual participants in the study.

Study population

The inclusion criteria were as follows: age between 18 and 50 years old, diagnosed AR based on total nasal symptom score, nasoendoscopy findings, and a positive skin prick test. The exclusion criteria were patients with concurrent rhinosinusitis or other nasal pathology, disabling co-morbid condition such as severe hematologic disorders, renal disease, liver disease, neoplasms, pregnancy or nursing mothers, history of allergy to Channa, history of surgical intervention for conditions related to AR, currently taking traditional medication.

Data collection procedure

The subjects meeting the criteria were randomized into 500 mg/day oral Channa or a placebo group. A randomization list was generated by a co-investigator (not involved in the field) by using a computer-generated table in blocks of four and subject numbers were allocated based on 1:1 ratio. Prediction of allocation sequence by researchers in the field was minimized by labelling the bottle containing the investigational product with the randomization numbers and the subjects were prescribed investigational product sequentially, following time of participation in the study. Randomization was executed, following the predetermined protocol with no adaptation. Blinding of participants and attending physicians were achieved by using placebo in the capsule which is physically identical to capsule with active

supplement. Only one co-investigator who prepared the product knew of the randomization scheme, and the blinding was maintained throughout the study until the last patient follow-up.

Eligibility was determined at the screening visit, during which history, physical examination, nasoendoscopy and skin prick test were performed. Laboratory investigation such as full blood count (FBC), renal profile (RP), liver function test (LFT) and immunoglobulin E (Ig E) levels were taken at this visit and the subjects was also assessed with AR symptoms score at this visit. During the study, all subjects were prescribed with antihistamine (levocetirizine) and topical corticosteroid nasal spray (fluticasone furoate). At the final visit (week 6), the subjects were assessed in terms of compliance and AR symptoms score. A second laboratory investigation including Ig E, FBC, RP and LFT were done.

Skin prick test

Skin prick test for *Dermatophagoides pteronyssinus* (house dust mite), *Dermatophagoides farina* (house dust mite), *Blomia tropicalis* (house dust mite), *Felis domesticus* (cat) and shrimp was performed on each patient's arm at the screening visit. Isotonic saline and 10 mg/ml histamine dihydrochloride were used as negative and positive controls, respectively. The presence of a wheel with a diameter of 3 mm or more, at 15 min after the prick was interpreted as a positive reaction.

Outcome measures

The primary outcome is the change of the AR symptoms score and serum Ig E from baseline to week 6. The AR symptoms score is a visual analogue scale (VAS) of 0–10 used to evaluate the severity of AR symptoms which includes nasal symptoms: sneezing, itching, rhinorrhea and nasal blockage; non-nasal symptoms: smell function, eye itchiness, palate itchiness and general symptoms experienced during the last 4 weeks (Qi et al. 2016). 0 is equal to no symptoms, and 10 is equal to very severe symptoms. This scale have been used to rate the presence of AR symptoms in trial (Qi et al. 2016).

Serum Ig E was measured with ImmunoCAP specific IgE test (Phadia AB, Uppsala, Sweden). The sensitivity and specificity of this measurement were reported to be 0.819, and 0.872, respectively (Jiang et al. 2010).

Assessment of safety

The assessment of safety was based on adverse events and biochemical parameters [urea, creatinine, aspartate transaminase (AST), and alanine transaminase (ALT)] tests.

CS extract dose determination and preparation

The dose for this study was determined based on previous clinical trials using Channa (Ab Wahab et al. 2015; Abu Bakar et al. 2015; Azidah et al. 2017; Kadir et al. 2014). In all the trials, oral CS extract of 500 mg/day was found to be effective and safe. The Channa extract preparation is based on previous literature (Kadir et al. 2014). The orally administered freeze dry CS extract, and the placebo (maltodextrin) was provided by the late Professor Saringat bin Baie from School of Pharmacy, Universiti Sains Malaysia. The CS extract and the placebo were available as 250-mg capsules. All the investigational products were identical to ensure proper blinding procedure. Each patient was instructed to take orally, once daily 2 capsules/day irrespective of their groups. It can be taken at any time with or without a meal.

Statistical analysis

The sample size calculation was based on Power and Sample Size Calculation software (Type I error of 5% and Type II error of 20%) (Dupont and Plummer 1997). The sample size was calculated for comparing two means in the change in AR symptoms score at week 6. A sample size of 32 in each group was needed to detect the decrease of 10 with a standard deviation of 16 (Yang et al. 2010). Thirty-five patients in each group were enrolled to allow for a 10% drop out rate.

Analyses were performed using SPSS for Windows version 22.0. For outcome analyses, the Independent T test was used to assess changes from baseline to week 6 by treatment groups in primary outcomes. A *p* value < 0.05 was regarded as statistically significant difference.

Results

A total of 70 participants was equally randomized to treatment and placebo groups. There was no drop-out. The demographic characteristics were comparable between the two groups (Table 1). Skin prick test revealed that 48% of the

Table 1 Demographics and clinical history of study subjects

Variables	Placebo Mean SD or N (%)	CS 500 mg Mean SD or N (%)
Age (years)	33.2 (9.1)	35.3 (10.7)
Gender		
Male	16 (47.7)	15 (42.9)
Female	18 (51.4)	20 (57.1)
Family history of allergic rhinitis	23 (65.4)	19 (53.8)
Family history of asthma	3 (11.5)	5 (19.2)

Table 2 Mean difference of the outcomes of the study from baseline to week-6 between the treatment groups

Mean difference	Placebo Mean (SD)	CS 500 mg	<i>p</i> value
Nasal symptoms score			
Blockage	− 1.65 (1.60)	− 2.69 (1.81)	0.033
Nasal discharge	− 1.96 (1.87)	− 1.88 (1.68)	0.876
Nasal itchiness	− 1.54 (1.50)	− 2.28 (1.39)	0.022
Sneezing	− 1.62 (1.88)	− 2.15 (1.38)	0.285
Non nasal symptoms score			
Smell	− 0.65 (1.96)	− 1.42 (1.42)	0.111
Eye itchiness	− 1.62 (1.60)	− 2.60 (1.80)	0.032
Palate itchiness	− 0.81 (1.13)	− 0.46 (1.07)	0.262
General symptoms	− 1.49 (1.42)	− 2.58 (1.76)	0.026
Serum Ig E (kUA/l)	− 13.69 (97.33)	− 34.41 (40.41)	0.010

Data presented as mean difference from baseline to week-6 for the outcomes of the study among the treatment groups. Results from one way ANOVA analysis

subjects were tested positive to *Dermatophagoides Pteronyssinus*, followed by *Blomia tropicalis* at 46% and shrimp at 6%.

Table 2 showed the comparison of mean difference of nasal symptoms score between the treatment groups. Subjects of the Channa group showed significant reduction of blockage and itchiness symptoms compared to subjects of placebo group ($p < 0.05$). There was also more reduction of sneezing symptoms in the Channa group than the placebo group, but it was not statistically significant. Subjects of the Channa group also had significant improvement of non-nasal symptoms score (Table 2) in terms of eye itchiness and general symptoms compared to the subjects of the placebo group ($p < 0.05$). Greater reduction of serum Ig E was also observed in the Channa group [− 34.41 (40.41)] compared to the placebo group ($p < 0.05$). There was no serious adverse event reported in this trial. No significant differences in the laboratory parameters (LFT, RP, and FBC) were observed between the groups over time, and all parameters were within normal limits.

Discussion

The present study reports the first randomized, double-blind, placebo controlled trial on the efficacy of Channa extract in AR subjects. The results highlighted that Channa extract was effective in alleviating AR symptoms and reduction of serum Ig E. The improvement of nasal symptoms such as nasal blockage and nasal itchiness results in improvement of AR patients' quality of life. Nasal blockage the most disturbing symptom of allergic rhinitis, impairs the human natural nasal breath and is often associated with poor sleep quality.

The inflammatory response in the nasal mucosa in patients with allergic rhinitis is characterized by typical symptoms of allergic rhinitis for example rhinorrhoea and nasal congestion after exposure to allergen. These initial symptoms are caused by an immediate Ig E-mediated mast cell response that is by influx of mediators into the nasal mucosa with eosinophils, basophils and T cells expressing Th2 cytokines including IL-4, a switch factor for Ig E synthesis, and IL-5 and eosinophil growth factor (Broide 2010). It is postulated that the immunomodulatory effect of the Ig E by Channa has caused improvement in the AR symptom in general. The success of decreasing the Ig E levels has managed to down regulate the chemokines and histamine that has been released into the nasal mucosa and thereby improving the itchiness and improving the symptoms in general.

The beneficial effects of CS extract on AR is postulated through its anti-inflammatory property. The result of current study is parallel to the study done by Abedi et al. (2012). In the study, the Channa cream was found to block migration of polymorphonuclear leucocytes to the dermis as potent as 1% hydrocortisone cream using croton oil induced ear edema model in mice (Abedi et al. 2012). Abedi et al. (2012) also reiterates that the anti-inflammatory effects of Channa was evidence by inhibition of myeloperoxidase (MPO) activity. MPO is a pro-inflammatory enzyme that is released by activated neutrophils and macrophages.

The exact mechanism on how CS extract works as anti-inflammatory agent is still not clear. However, there are probably a few mechanisms which can be postulated. Channa supplementation has been reported to cause reduction of TNF- α , IFN- γ , and IL-10 among pulmonary tuberculosis patients and PGE₂ in osteoarthritis animal model (Al-Saffar et al. 2011; Paliliewu et al. 2013). The results of this study reiterate the facts that anti-inflammatory effect of CS is attributed to the reduction of Ig E levels. The Ig E molecule is an important immunoglobulin responsible for the cascade of mediating an allergic immune response. It binds to the mast cells and basophils through the heterotrimeric link, which has high affinity for Ig E receptor, FcεR1. Allergens initiate a cascade of events by cross-linking Ig E molecules bound to the FcεR1 receptor. These events lead to immediate hypersensitivity allergic response and are characterized by cellular degranulation and release of mediators such as histamine and synthesis of pro inflammatory mediators, cytokines and chemokines. It is postulated that Channa is able to reduce certain chemokines, in which it plays a key role in the regulation of eosinophil and the activation of neutrophil. By reducing chemokines such as IL-5 and IL-8, it could result in the improvement of the nasal symptom score.

Recently there has been a considerable interest in the use of omega 3 fatty acids for the prevention and treatment of symptoms of eczema, rhinitis and asthma (Anandan et al. 2009). Studies have shown that high levels of

omega 3 fatty acids in the diet was found to be associated with a decreased risk of allergic sensitization and allergic rhinitis (Hibbeln et al. 2007). *Channa* extracts are rich in omega 3 fatty acids such as eicosapentaenoic acid (EPA), docosahexanoic acid (DHA) (Zuraini et al. 2006). These fatty acids are able to inhibit some of the inflammatory reactions including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, production of inflammatory cytokines and T cell reactivity (Calder 2013). Therefore, both of these fatty acids potentially reduce airway inflammation and bronchoconstriction (Thien et al. 2011). Fish oil supplementation in allergic pregnant mothers' diet has been reported to attenuate the cytokine responses to allergen by cord blood lymphocytes (Dunstan et al. 2003). Dunstan et al. (2003) found that all neonatal cytokines (IL-5, IL-13, IL-10 and interferon γ) responses (to all allergens) were lower for the omega 3 group compared to the control group.

Recently, there have been considerable interest in studying dietary marine omega-3 fatty acid supplements during pregnancy as a prevention of the allergic conditions in offspring, particularly for those with a genetic predisposition to the allergy disease (Gunaratne et al. 2015). However, the systemic review which was carried out stated that, there was limited current evidence to support maternal n-3 fatty acid supplementation during pregnancy and/or lactation in reducing allergic disease among children. Few differences in childhood allergic disease were seen between women who were supplemented with and those who were not (Gunaratne et al. 2015).

Another possible mechanism of *Channa* action in AR is through its anti-oxidant properties (Radzak et al. 2014). Speculation has been raised regarding the role of antioxidant and allergic disease (Allan et al. 2010). It has been reported that the recent increase in allergic disease is a consequence of declining dietary antioxidant intake (Allan et al. 2010). In vivo studies have proclaimed that antioxidant supplementation at the time of primary and subsequent allergen exposure attenuates allergic inflammatory responses (Allan et al. 2010). *Channa* extract possesses essential amino acid such as glycine, serine, threonine, cysteine, asparagine, glutamine, and glutamic acid which has antioxidant properties as synergists or primary antioxidant (Dahlan-Daud et al. 2010; Radzak et al. 2014). A study conducted in Wistar rats with induced gastric ulcers reported an increase of catalase and superoxide dismutase; decreased of malondialdehyde, an end product of lipid peroxidation in rats treated with *Channa* extract (Ali Khan et al. 2014).

The limitations of this study were comparatively short in duration with a small number of subjects. We also did not measure other immunological markers for AR such as IL-4 or eosinophil count. It is recommended that a long-term study which may involve more subjects, can be performed to assess *Channa* therapeutic potential in AR.

Conclusion

The results of this study suggest that adjunctive supplementation of *Channa* accelerates the therapeutic effects of routine pharmacotherapy in AR subjects by reducing AR related symptoms and serum Ig E. This study can be made as a benchmark to pioneer the role of *Channa* as an adjunct, towards allergic rhinitis treatment, in future.

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Compliance with ethical standards

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the Human Research Ethics Committee (Reference Number: 00007718, IRB No: 00004494), Universiti Sains Malaysia and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest This manuscript described has not been published before; not under consideration for publication anywhere else; and has been approved by all co-authors.

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