ABSTRACT

THE EFFECT OF *CHANNA STRIATUS* AS AN ADJUVANT THERAPY IN TREATMENT OF ALLERGIC RHINITIS

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Introduction: Allergic rhinitis is a Type 1 mediated hypersensitivity reaction which is characterized by one or more of the following symptoms which is sneezing, rhinorrhea, nasal congestion and nasal itchiness. Management of allergic rhinitis includes patient education and counseling, pharmacotherapy, and allergen-specific immunotherapy. In this study, we were determining the role of *channa straitus* as a adjuvant therapy in treatment of allergic rhinitis

Objectives: To detemine the therapeutic efect of *channa striatus* and to compare the total nasal symptom score and levels of IgE between *channa straitus* and placebo group.

Methodology: There were 70 patients aged 18 to 50 years old, diagnosed allergic rhinitis based on total symptoms score, nasoendoscopy findings, and positive skin prick test were involved in this prospective, randomized, double blinded, comparative clinical trial. They were divided equally into 2 groups which is *channa* and placebo group. The patients were screened with detailed history, physical examination and nasoendosopy.Baseline FBC, BUSE, LFT, and IgE levels were obtained prior to commencement of treatment. Both groups were treated with the same conventional treatment, antihistamine (levocetrizine 5mg) with local corticosteroid nasal spray (*Avamys* nasal spray). Assessment of compliance, drug diary, adverse effects, symptoms score and nasendoscopy were made at Week 0, 2^{th}, and $6^{th.}$. Serum IgE levels were measured at week 0 and 6^{th}.

Results: Channa group showed significant improvement in nasal symptoms such as nasal blockage (p=0.034) and nasal itchiness (p=0.022), non-nasal symptoms such as eye itchiness (p=0.032) and symptoms in general (p=0.026). IgE levels were significantly lower in *Channa* group compared to placebo (p-value <0.001).There were no statistical significant in term of nasal discharge, sneezing, palate itchiness, and smell score. There were no serious adverse reactions reported in the *channa* group.

Conclusions: *Channa striatus* has a beneficial role in improving nasal and non-nasal symptoms with reduction in IgE levels in patients suffering from allergic rhinitis.

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PREFACE

Allergic rhinitis is a chronic allergic inflammation of the nasal airways. Its occurs when an allergen, such as dust, pollen, is inhaled by individual with a sensitized immune system. It is an IgE mediated inflammatory reaction presenting with nasal obstruction, watery nasal discharge, sneezing, itchy nose and eyes. All these symptoms would significantly have a physical, physiological, and social impact to the patients. . The objective of this study was to determine the effects of *Channa Striatus* as an adjuvant and its therapeutic effect in the management of allergic rhinitis. We hope that this study can be made as a benchmark to further explore the role of *Channa Striatus* as a adjunct in treatment of Allergic Rhinitis and further improve patients quality of life

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ABBREVIATIONS

AR	Allergic Rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
IgE	Immunoglobulin E
Th	T Helper
MHC	Major Histocompatibility Complex
IL	Interleukin
ICAM	Intercellular Adhesion Molecule
GMCSF	Granulocyte Macrophage Colony Stimulating Factor
RANTES	Regulated on activation, normal T expressed and secreted
TNF-α	Tumour Necrosis Factor alpha
FBC	Full Blood Count
BUSE	Blood Urea, serum Electrolytes
LFT	Liver function test
RAST	Radioallergosorbent test
ORL-HNS	Otorhinolaryngology, Head & Neck Surgery
HUSM	Hospital Universiti Sains Malaysia

ABSTRAK

Tajuk

Kerberkesanan *Channa Striatus* sebagai terapi tambahan dalam rawatan alahan radang hidung.

Pengenalan

Alahan radang hidung adalah penyakit jenis 1 tindak balas hipersensitif serta merta, yang dicirikan oleh satu atau lebih daripada gejala berikut seperti bersin, hidung berair,hidung tersumbat dan hidung gatal. Pengurusan alahan radang hidung tewrmasuk pendidikan dan kaunselling pesakit, farmakoterapi, dan imunoterapi alergen tertentu.

Objektif

Untuk menentukan kesan terapeutik *channa striatus* dan membandingkan keseleruhan skor gejala hidung dan paras IgE dengan kumpulan *channa striatus* dan placebo.

Metodologi

Seramai 70 pesakit alahan radang hidung yang berumur 18 hingga 50 tahun telah mengambil bahagian dalam kajian prospektif ini. Kesemua pesakit ini telah dibahagikan secara rawak kepada dua kumpulan dalam kuantiti yang sama iaitu kumpulan *channa* dan placebo. Sejarah pesakit, pemeriksaan fizikal and endoskopi hidung disaring terlebih dahulu. Paras FBC, BUSE, LFT dan IgE telah diambil sebelum memulakan rawatan. Kedua-dua kumpulan diberikan rawatan yang konvesional iaitu antihistamin

(levocetrizine 5mg) with spray hidung corticosteroid setempat (*Avamys* nasal spray). Pemenuhan ubat, diari ubat, kesan sampingan, skor gejala, dan endoskopi hidung dinilai pada minggu 0, ke-2, dan ke-6. Paras serum IgE diambil pada minggu 0 dan ke-6.

Keputusan

Kumpulan *channa* menunjukan pengurangan yang signifikan bagi gejala hidung seperti hidung tersumbat (p=0.034) dan hidung gatal (p=0.022), gejala bukan dari hidung seperti kegatalan mata (p=0.032) and gejala keseleruhan (p=0.026). Paras IgE menunjukan pengurangan yang signifikan dalam kumpulan *Channa* berbanding dengan kumpulan placebo (p-value <0.001). Tiada perbezaan yang signifikan dalam skor gejala hidung berair, bersin, mulut gatal, and pembauan. Tiada kesan sampingan yang dilaporkan dalam kumpulan *channa.*

Kesimpulan

Channa striatus memainkan peranan yang baik sebagai terapi tambahan dalam mengurangkan gejala hidung dan bukan hidung disamping mengurangkan paras IgE bagi pesakit alahan radang hidung.

Kata-kata penting: Alahan radang hidung, *Channa Striatus*, IgE

ABSTRACT

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The Effects of *Channa Striatus* as an Adjuvant Therapy in Treatment of Allergic Rhinitis

Introduction

Allergic rhinitis is a Type 1 mediated hypersensitivity reaction which is characterized by one or more of the following symptoms which is sneezing, rhinorrhea, nasal congestion and nasal itchiness. Management of allergic rhinitis includes patient education and counseling, pharmacotherapy, and allergen-specific immunotherapy. In this study, we were determining the role of *channa straitus* as a adjuvant therapy in treatment of allergic rhinitis

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There were 70 patients aged 18 to 50 years old, diagnosed allergic rhinitis based on total symptoms score, nasoendoscopy findings, and positive skin prick test were involved in this prospective, randomized, double blinded, comparative clinical trial. They were

divided equally into 2 groups which is *channa* and placebo group. The patients were screened with detailed history, physical examination and nasoendosopy.

Baseline FBC, BUSE, LFT, and IgE levels were obtained prior to commencement of treatment. Both groups were treated with the same conventional treatment, antihistamine (levocetrizine 5mg) with local corticosteroid nasal spray (*Avamys* nasal spray). Assessment of compliance, drug diary, adverse effects, symptoms score and nasendoscopy were made at Week 0, 2^{th}, and $6^{th.}$. Serum IgE levels were measured at week 0 and 6^{th}.

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Channa group showed significant improvement in nasal symptoms such as nasal blockage (p=0.034) and nasal itchiness (p=0.022), non-nasal symptoms such as eye itchiness (p=0.032) and symptoms in general (p=0.026). IgE levels were significantly lower in *Channa* group compared to placebo (p-value <0.001).There were no statistical significant in term of nasal discharge, sneezing, palate itchiness, and smell score. There were no serious adverse reactions reported in the *channa* group.

Conclusions

Channa striatus has a beneficial role in improving nasal and non-nasal symptoms with reduction in IgE levels in patients suffering from allergic rhinitis.

Key words: Allergic rhinitis, *Channa Striatus*, IgE

CHAPTER 1

INTRODUCTION

1.1 Epidemiology

Allergic rhinitis is an inflammation of the nasal mucous membrane, an IgE mediated reaction, presenting with nasal obstruction, watery nasal discharge, sneezing and itchy nose and eyes (Howarth, 1997). Allergic rhinitis is still one of the most widespread chronic inflammatory diseases in the world. It represents a global health issue affecting between 10% to 25% of the world population with increasing prevalence over the last decade (Strachan et al., 1997). It is the most common chronic condition in children and it is estimated to affect up to 40% of all children (Benedikt LM. et al, 2006). There is a wide variation among Asian countries. The prevalence of asthma in Japan had increased from 3.5% in 1982 to 4.6% in 1999 to 9.1% in 2006 and it was accompanied by an increase in allergic rhinitis of up to 32% (Arbes et al., 2009). Similarly,2 surveys performed in Taiwan using an identical method showed that the prevalence of childhood asthma had increased from 1.3% in 1974 to 5.07% in 1985 (Holm et al,1995). The percentage of children in Singapore who had experienced asthma at least once increased from 5.5% in 1967 to 13.7% in 1987 and to 20.7% in 1996.In Singaporean pre-schoolers aged 4 to 6 years, the cumulative and previous 12-month prevalence of wheezing were 27.5% and 16.0% respectively. Asthma was reported by 11.7% of this group of children, and the current prevalence of rhinitis was 25.3%.

Although allergic rhinitis occurs frequently which affects both adults and children, however it remains largely undiagnosed. The condition maybe frequently trivialized (by the patient) and/or unrecognized (by the doctor), resulting in inadequate control of symptoms (Sibbald, 1991). In the United Kingdom, only 18% of subjects with rhinitis had visited their general practitioner over the preceding 2 years concerning their allergic rhinitis (James, 2002). A later study in France showed that 19% of 230 patients with typical symptoms of allergic rhinitis had never consulted a doctor for their nasal problem (Horak et al., 2002). However, allergic rhinitis has been identified as one of the top ten reasons for visits to primary care clinic (Enerback et al., 1986).

1.2 Mortality & Morbidity

Although the prevalence of allergic rhinitis is increasing worldwide and considered as a major health problem, it is not associated with mortality unless if accompanied by severe asthma or anaphylaxis. However it carries a significant morbidity. Morbidity is manifested in several ways. Annually, an estimated 824,000 school days are missed, and an estimated 4,230,00 days of reduced quality of life functions are reported (Mariana et al.,2000). Allergic rhinitis often coexist with other disorders, such as asthma and maybe associated with asthma exacerbations (McMenamin 1994, Mariana 1996, Mediaty, A., NeuberK.2005).These co-exist morbidities suggesting the concept of “one airway, one disease” (Gordon et al ., 1997). Evidence now suggests that uncontrolled allergic rhinitis can actually worsen the

inflammation associated with asthma (Valero et al., 2007). This could lead to further morbidity and even mortality.

Patients with asthma and allergic rhinitis have a reduced quality of life, and the burden of asthma, as assessed by disability adjusted life years, ranks 22nd among all diseases worldwide (Allergic rhinitis and its Impact on Asthma (ARIA) 2008). Allergic rhinitis is also associated with otitis media, Eustachian tube dysfunction, sinusitis, nasal polyps, allergic conjunctivitis, and atopic dermatitis (Knani et al., 1992). Individuals with allergic rhinitis have a higher frequency of these conditions than individuals without allergic rhinitis. Allergic rhinitis can frequently lead to insignificant impairment of quality of life. Symptoms such as fatigue, drowsiness (due to the disease or other medications) and malaise can lead to impaired work and school performance, learning difficulties, missed school or work days, sleep disorders and traffic accidents (Leurs et al.,2002,Leynaert et al.,2000). It can affect the physical, physiological and social aspects of the patients life and also can impact their functions at work. These aspects or "quality of life" issues provide information that cannot be obtained using conventional clinical and functional measures and they provide a focus on patient's own perception of disease. Recent studies suggest that allergic rhinitis adversely affects sleep related quality of living of patients (Jonathan C,2000). The sleep related quality of life impairment in patients with AR is however assessed by means of questionnaires (Pratt E.L, et al., 2007). The annual costs of treating asthma and allergic rhinitis and associated diseases, both direct costs (hospitalization, medications) and indirect costs (time lost from work, premature death) are substantial and represent an even heavier burden in societies with emerging economies. The Asthma Insights and Reality in Asia-Pacific region showed that the annual per-patient direct costs ranged from US $108 in Malaysia to US $ 1010 in Hong Kong (Zamzil et al., 2010). The overall costs (direct and indirect) of allergic rhinitis were recently estimated to be ranging from $5.3 to $20

billion per year (Togias, 2000). These include the costs associated with medications, lost work productivity, and physician consultations. Approximately US $3 billion are spent annually in Germany alone (Novak, 2003). Employees with untreated allergies are reportedly 10% less productive than coworkers without allergies, whereas those using allergy medications to treat allergic rhinitis were only 3% less productive (Laslet M.V, et al, 2000). This suggest that effective medications may reduce the overall cost of decreased productivity. As a consequence, its impact on quality of life, the association with multiple co-morbidities and the considerable socio-economic burden, allergic rhinitis is considered a major respiratory disorder (Van Cauwenberge, 2000, Van Hoecke, 2006).

1.3 Pathophysiology

Allergic rhinitis involves inflammation of the mucous membranes of the nose, eyes, Eustachian tubes, middle ear, sinuses and pharynx. The nose is undoubtly involved while the other organs are affected only in certain individuals. The inflammation of mucous membranes is characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulin E (IgE)-mediated response to an extrinsic protein or polysaccharides which is called allergen. Allergy represents an exaggerated immunologic response to an otherwise innocuous agent, which causes harm to the host.

Allergic rhinitis is clinically defined as a symptomatic disorder of nose, which occurs following exposure to allergen that causes IgE- mediated inflammation of nasal mucosa. The cardinal symptoms of allergic rhinitis as mentioned above and characteristically one or more

of above symptoms should be present (Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update).The process by which symptoms of allergic rhinitis is produced is complex, involving cells, mediators, cytokines and adhesion molecules and it can be divided into 4 steps:

1. Sensitization
2. Early phase reaction
3. Late phase reaction
4. Systemic activation

1.3.1 Sensitization

Allergens in the environment such as house dust mite, pollen act as the first step in this process. They may be harmless to the non-atopic individuals but in atopics, they might trigger cascades of events. These allergens will adhere to antigen presenting cells in the nose, are the dendritic cells called Langerhans cells which is a CDI-positive cells containing Birbeck granules. These cells are increased after allergen challenge in allergic rhinitis patients. The Langerhans cells will form a network in human respiratory mucosa at its largest amount in the epithelial surface of upper airways. The dendritic cells will present the allergen to the T lymphocytes in the local lymph nodes (Varga et al., 1999)

Antigen presentation by dendritic cells needs T cell receptor recognition of peptide fragment associated with Major Histocompatibility Complex (MHC) molecule and co-stimulatory for example CD 28 and B7 or CD40 and CD40 ligand. Resting Langerhans cells are well equipped for antigen binding and processing. However, in order for the dendritic cells to stimulate T cells effectively, they need maturation signal for instance viruses, or adjuvant such as diesel exhaust particles. Without these signal, Tcells response will not happen. Airway mucosal dendritic cells play an important part in determining primary sensitization or tolerance to antigens. In atopic individuals, the two cells predominates at the site of allergic response. There is some evidence said that antigen presentation airway dendritic cells (Langerhans cells) leads to the preferential development of a Th2 response. In secondary immune response, any cells expressing surface MHC class 2 may serve as an antigen presenting cell, include the activated nasal epithelium.

Antigen presentation by dendritic cells will lead to Th2 response, and Th2 cells will secrete cytokines, mainly IL-4,IL-3 and IL-5. They also stimulate B lymphocytes to proliferate, migrate to nasal lining and produce antibody of immunoglobulin E (IgE) class.B cells are found in epithelium and lamina propria of nasal mucosa, comprising approximately 20 percent of the total lymphocyte population in perennial allergic rhinitis patients (Weiner at al., 1998).

Once IgE is produced, they will adhere to FcER1 of the mast cells, and this mast cell complex will respond to subsequent allergen exposure. The patient is thus sensitized. Skin prick test reveals approximately 30 percent of the population are sensitized in this way with positive responses towards allergens, for instance house dust mites. Nevertheless, not all this

responders response clinically to house dust mites with hay fever, although nonresponders do have a 50 percent chance of developing hay fever in the future.

1.3.2 Early Phase Response

Allergic rhinitis manifest as recurrent bouts of sneezing, rhinorrhoea and nasal itchiness. Mediators such as histamine, leukotriene C4 and prostaglandin D2 are responsible for the production of symptoms in allergic rhinitis (Passali, D., 1999, Pawankar et al., 2009). These mediators released from the mast cells after it degranulates once their cell bound – IgE has been cross linked by allergen. Some of them are preformed in the mast cells cytoplasmic granules, others like leukotriene and prostaglandins are formed from cell membrane arachidonic acid which then undergo metabolic pathways to prostaglandins(via cyclooxygenase pathway) and leukotrienes (via lipooxygenase pathway) (Sampson,A.P.1996)

Histamine will increase ipsilateral glandular secretion by its action on mucus cells and vessels, while secretion on the contralateral side mediated through neural reflexes (Wagenmann et al., 1997).Its action on sensory nerves will induces itching and sneezing (Quah et al., 1997). Histamine mainly causes rhinorrhoea, sneezing and itchiness with less marked effect on nasal obstruction.Its effect on nasal obstruction requires relatively high concentrations. The response is of short duration. Its action on endothelial cells and blood vessels result in vasodilatation, plasma exudation and edema (Proud et al., 1983, Pullers et al., 1999 and Ricca V et al., 1986).

Histamine also possesses proinflammatory and immunomodulatory properties (Noval et al.,1997).These includes upregulation of adhesion molecules on vascular endothelial cells, increased production of cytokine IL-6 and IL-8 by endothelial cells and activation of epithelial cells with consequent ICAM 1 expression and cytokine production.

Prostaglandin D2 release will cause sustained nasal obstruction and it is ten times more potent than histamine (Howarth et al., 1997).Prostaglandin D2 is predominantly released following mast cell degranulation. Leukotriene will increase vascular permeability and oedema and is involved in eosinophil recruitment (Sampson et al, 1984, James, 2002). Leukotrienes belong to the family of eicosanoids. It is generated by the lipooxygenase pathway. The suphidopeptide or cysteinyl leukotrienes previously known as slow reacting substance of anaphylaxis (SRS-A).It plays an important role in asthma and rhinitis. Leukotriene B4 induces neutrophil recruitment (Szucs et al., 2002).

The other cytokines that were released following mast cells degranulation are TH2 cytokines such as IL-4, IL-5, IL-3 and pro-inflammatory cytokines such as IL-6, IL-8, IL-10 and TNF-alpha (Johnson, D.A., Hricik J.G., 1993). Th2 cytokines release following mast cells degranulation which is important in regulation of IgE response (Okuda M et al., 1997)

1.3.3 Late phase response

During late phase response it is more inflammatory in nature and involves ingress of eosinophil, mast cells, T lymphocytes and macrophages into local reaction site (Bascom et al., 1988).the symptoms that were produced during this phase are mainly nasal obstruction and hyperactivity. A late phase response may progress in up to half of the individual tested especially if high doses of allergen are used (Arbes et al., 2005).

Eosinophils first described by Ehrlich in 1879, are associated with asthma, skin and parasitic diseases. They represent less than 1% of the circulating cells in the peripheral blood. The eosinophils migrates into the tissue upon appropriate signal by mechanism which involves chemokines, cytokines, and adhesion molecules. Granulocyte macrophage colony-stimulating factor (GMCSF) and IL-5 enhance eosinophil recruitment, terminal maturation and expression of their adhesion molecules. Exotoxin and chemokines for instance regulated on activation, normal T expressed and secreted (RANTES) also act on eosinophil recruitment and possibly activation. Once the eosinophil enter the tissue, eosinophil gets mature and remain alive for days and weeks, depending on survival signals from their local environment mature eosinophils, which can be found in nasal mucosa and secretions containing eosinophil cationic protein(ECP), eosinophil – derived neurotoxin (EDN), major basic protein (MBP), eosinophil peroxidase and beta glucuronidase (Szucs et al.,2002).

Eosinophils are able to synthesize and release cytokines, for instance IL-3,IL-5,GMCSF, proinflammatory cytokines and as well as chemokines, transforming growth factor (TGF) beta-1,reactive oxygen intermediate, lipid mediators, thromboxane B2 and prostaglandin E1 (Szucs et al.,2002).

An increased T lymphocytes (CD 4^{+} and CD 25^{+}) are also found in the epithelium and submucosa of the individuals with allergic rhinitis (Varney et al., 1992). Increased expression of IL-4, IL-5, GMCSF at mRNA level was noted. In perennial rhinitis, there was an increase in $CD4^{+}$ T cells and B cells in the nasal mucosa, again with a Th2 cytokine pattern (Varga et al., 1999). Besides, macrophages also were found to be increased in nasal mucosa in both seasonal and perennial rhinitis (Holm et al., 1995).

In patients with asthma and rhinitis, epithelial cells are activated and they result in increased production of adhesion molecules, inflammatory mediators such as IL-6, IL-8 and GMCSF (Canonica et al., 1995). Epithelial cells are more sensitive to air pollutants for instance diesel exhaust particles in allergic as compared to normal individuals (Devalia et al., 1999).

1.3.4 Systemic activation

Allergic rhinitis is well known as localized allergic reaction. However, there is evidence in the literature that production of eosinophil and basophil precursors from bone marrow do happen following exposure of nasal mucosa and lung to allergen. These precursor cells will adhere to the reaction site mediated by selectins and adhesion molecules where they infiltrate and mature (Denburg et al., 1999).

Allergic responses as described above can happen via non IgE mediated mechanisms. Some allergen, for instance house dust mites are able to elicit those response through their enzymatic proteolytic activity which activates the cells directly. They can also induce chemokines and cytokines release from epithelial cells and induce airway inflammation

without medication by IgE. Mast cells degranulation can occur due to certain drugs for instance aspirin, morphine and codeine which act directly on mast cells (Roche et al., 1997)

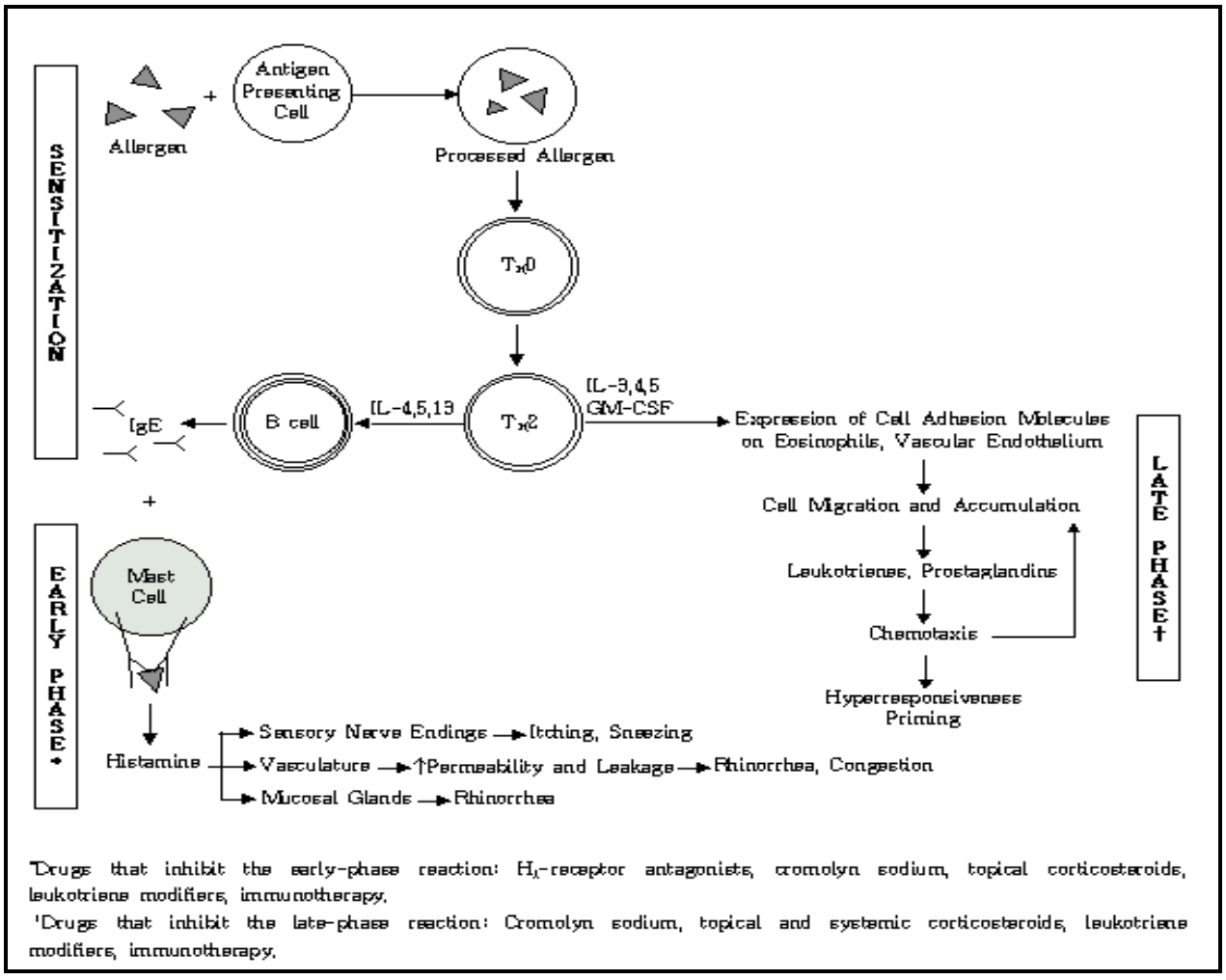

Fig. 1: Pathophysiology of Allergic Rhinitis (*Source: Encyclopedia Britannica,Inc 1994*)

1.4 Classification of Allergic Rhinitis

Recently WHO has classified allergic rhinitis, entitled as “Allergic Rhinitis and its Impact on Asthma” (ARIA), as in part, modified this classification. The old terms of perennial and seasonal allergic rhinitis is replaced by intermittent and persistent based on symptoms duration (Demoly et al., 1998, Bauchau V et al., 2004). According to the document, the patients who are symptomatic less than 4 days a week or less than 4 weeks is termed as Intermittent Allergic Rhinitis (IAR). Symptoms more than 4 days a week or more than 4 weeks is termed as Persistent allergic rhinitis (PAR).

The ARIA classification also introduced a system for assessing allergic rhinitis severity on the presence or absence of impairment in any 4 health related quality of life namely, sleep, daily activities, work/school, and troublesome symptoms. According to ARIA workshop group, allergic rhinitis was defined as mild when there was no impairment in 1 or more areas. Classification of AR-based on duration (Adapted from ARIA, Allergic rhinitis and its impact on Asthma Workshop report, Allergy, *2002*)

Table1: Classification of Allergic Rhinitis based on duration of symptoms

Intermittent Allergic Rhinitis (IAR)	Persistent Allergic Rhinitis(PAR)
< 4 days per week OR < 4 weeks per year	>4 days per week and >4 weeks per year

1.5 Diagnosis

The diagnosis of IgE mediated allergic diseases is routinely based on 4 types of evidence. Three types are part of the clinical work up for allergy, which involves a detailed patient history and physical examination, skin testing, and in certain cases, challenge testing with a suspected allergen. The fourth type is a laboratory procedure, most commonly in vitro determination of circulating serum IgE antibodies specific for allergens.

1.5.1 Skin Prick Test

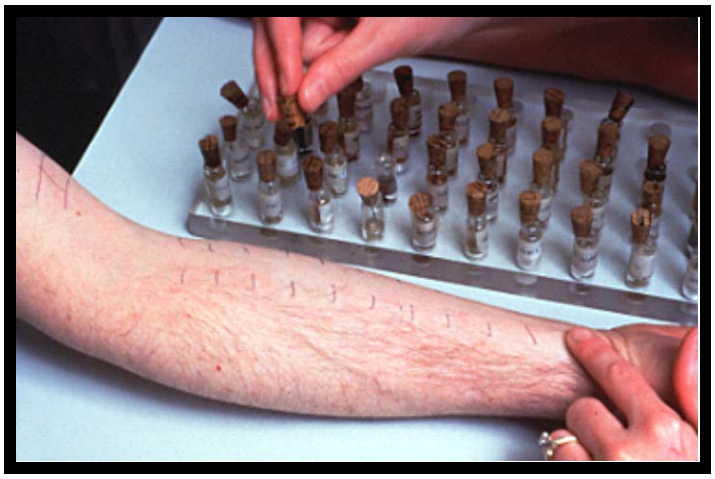

Fig.2 : Skin prick test (Source:GLORIA,Module 1 ,World Allergy Association,2011)

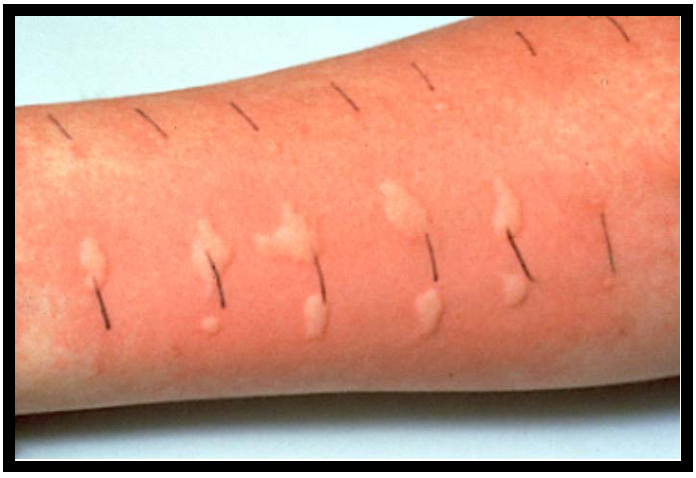

Fig.3: Positive skin prick test (Source: GLORIA, Module 1, World Allergy Association, 2011)

It is considered as the conventional way to test for the presence of allergen-specific IgE and to detect IgE bound to the surface of mast cells in the skin. Allergen in solution is applied to the skin, generally the volar surface of the forearm. When the skin is pricked with a lancet the allergen comes into contact with specific IgE, bound to the surface of cutaneous mast cells. The binding of the allergen leads to activation and the immediate release of mediators including histamine. The release of mediators' results in a wheal and flare type reaction and the test is generally reported as the maximal wheal diameter after 15-20 minutes. The test is considered as positive if the size or diameter of wheal is 3 mm or more. These tests are simple, quick and the most sensitive method of detecting specific IgE. Skin prick tests are particularly helpful in excluding potential allergens as a cause of symptoms as false negatives are uncommon.

1.5.2 Serum specific IgE

In this study we are using ImmunoCAP 100 as the diagnostic method to measure allergen serum specific IgE. The ImmunoCAP 100 is designed as a sandwich immunoassay, has an extremely high total binding capacity, provides high sensitivity and very low concentrations of IgE antibodies can be detected. ImmunoCAP has an extremely high total binding capacity, achieved through a high binding capacity per mg cellulose in combination with an optimal amount of cellulose in each solid phase. This ensures binding of all relevant antibodies, regardless of antibody affinity, still giving low non-specific binding

1.6 Management of allergic rhinitis

Management of allergic rhinitis includes patient education and counselling, medications and allergen specific immunotherapy. Surgery only reserved in selected patients. (Bousquet et al., 2001). Environmental control is more controversial (Schmidt et al., 2005). Medications for allergic rhinitis can be given intranasally or orally .The ARIA guidelines recommend that treatment be prescribed according to severity and duration of disease (Bousquet et al., 2001).

1.6.1 Antihistamines

Antihistamines help to reduce symptoms of running nose, itching, and sneezing and have little or no effect on nasal obstruction (Campbell A et al., 1992) although there are recent expectation e.g. desloratidine and levocetrizine (Horak et al., 2002). Chlorpheniramine is a first generation antihistamine, if possible need to be avoided as this group of antihistamine has effects of sedation, psychomotor retardation and mental impairment. This is probably due to its capability of crossing blood brain barrier (Timmerman et al., 1992). Antihistamine seems to be effective given regularly rather than intermittently and can reduce allergic progression in pediatric age group (Ciprandi et al., 1997) .

1.6.2 Topical Glucocorticoids

These medications are the most effective medicine, provided start earlier before allergen exposure for treatment of rhinitis (Weiner et al., 1998). Topical glucocorticoid helps to reduce inflammation and consequent hyperactivity, improves sense of smell, and reduce nasal and eye symptoms. The onset of action is slow and some improvement can be seen after 6-12hours, with maximum effects after several days. Steroid bioavailability is lowest with fluticasone and mometasone, but in terms of efficacy there is no difference between various preparations (Scadding et al., 2002). Topical corticosteroid helps to reduce the relative risks of exacerbation of asthma by 50 percent or more if is combined with antihistamine (Adam et al., 2002 and Crystal et al., 2002).

1.6.3 Sodium Cromoglycate

This sodium cromoglycate spray is used three to four times daily. It is weakly effective against all rhinitis symptoms. This spray is useful for small children less than four years old for whom topical corticosteroid is not available (Engstrom et al., 1971)

1.6.4 Nasal decongestants

This medication are used topically and helps to lessens nasal obstruction, but causes rhinorrhoea. It is recommended for short term usage, and for instance prior to flying out in otitis media effusion and rhinosinusitis. Prolonged use might cause rhinitis medicamentosa (Scadding et al.,1995).Systemic decongestants is not really effective and has more side effects for instance insomnia and hyperactivity in children, and hypertension in adults (Johnson et al.,1993 and Thomas et al.,1991)

1.6.5 Ipratropium Bromide

This nasal spray is useful against watery rhinorrhoea and maybe curative if used regularly (Kaiser at al., 1995).Sometimes it is beneficial for allergic rhinitis patient who does not respond to corticosteroid alone (Dockhorn et al., 1999).This medication has side effects, for instance dry mouth and eyes and worsening of glaucoma and prostatism (Groth et al., 1983).

1.7 *Channa Striatus*

Fig. 4: *Channa Striatus* (Source: Online Journal of Animal and Feed Research Volume 2: Issue 2, 2012)

In a study by Somchit et al, (2008), it is reported that all three *channa* spp fish possess anti-inflammatory properties. The nutritive quality of three channa spp fish is a source of protein and fatty acid was investigated. All three species were rich in amino acid. All three *channa* spp fish contained archidonic acid which is a precursor for prostaglandin and thromboxane synthesis. This will interfere with the blood clotting process and its attachment to endothelial cells during wound healing (Mohsin, 1983). The levels of DHA in the fish would explain the use of *Channa* spp especially *channa striatus* for decreasing inflammation process (Mat Jais et al., 1998). Therefore, this fish have been suggested as a key component for healthy diets in humans.

Furthermore it is mentioned that *channa striatus* has potent anti-inflammatory and analgesic effects (Zakaria et al, 2005). Thus, we believe that *channa striatus* can strongly decrease the anti-inflammatory agents responsible for allergic rhinitis manifestations. In allergic rhinitis besides confirmation with positive relevant history, serum specific IgE to detect specific allergens are the standard method of investigation today (Quah et al., 1997). Positive serum specific IgE shows close association with nasal symptoms in response to allergen exposure in a general population. *Channa striatus* or referred as "Haruan" in Malay language, is usually consumed to promote healing in surgical wound but no study has been done on its anti-inflammatory effect in allergic rhinitis. There are no extensive studies on the benefit of *channa striatus* biomedical properties which can helps in the treatment of allergic rhinitis such as reduce inflammatory process in manifestation of their symptoms and improve the quality of life. So, this study was proposed to evaluate the potential effect of *channa striatus* as an adjunct to treatment in allergic rhinitis patient. *Channa striatus* extract would be one of the alternative therapy used as combination with the proper treatment modalities. This study will offer new insight, generated new ideas of using our own natural remedies as one of the alternatives therapy in allergic rhinitis and can promote *channa striatus* product. Thus, it will help the agricultural sector to develop and increase our economic activities to a higher level in the future.

CHAPTER 2

OBJECTIVES OF STUDY

2.1 General Objective

1. To determine the therapeutic effect of *channa striatus* in allergic rhinitis patient

2.2 Specific Objective

1. To compare the total nasal symptom score between *channa striatus* and placebo group
2. To compare the levels of specific IgE between *channa striatus* and placebo group

2.3 Research hypothesis

There is difference in terms of using *channa striatus* as therapeutic treatment in improving patients total nasal symptom score, and reduction in IgE levels

2.4 Null hypothesis

There is no difference in outcome in giving *channa striatus* as a therapeutic treatment of allergic rhinitis

CHAPTER 3

METHODOLOGY

Study design : Prospective, randomized, double blinded, comparative clinical trial

Study setting : Otorhinolaryngology – Head & Neck Surgery (ORL-HNS), general outpatient clinic, Hospital Universiti Sains Malaysia (HUSM)

Study population : Patients with allergic rhinitis

Time Frame : January 2013 until February 2014

Inclusion criteria:

-Patients age between 18-50 years old

-Allergic rhinitis diagnosis based on total nasal symptom score, nasoendoscopy findings, and a positive skin prick test

Exclusion criteria:

-Patients with concurrent rhinosinusitis or other nasal pathology

-Patients with disabling co-morbid condition such as severe hematologic disorders, renal disease, liver disease, neoplasms

-Pregnancy or nursing mothers

-Patients with history of allergy to ikan haruan (*channa striatus)* or ikan haruan product

-Patients who has undergone surgical intervention for factors contributing to allergic rhinitis

-Patients on any form of traditional medication

3.1 Sample size determination

Sample size calculation was formulated using PS software.

Sample size based on previous literature by *Yang et al, 2010*, comparing usage of traditional chinese medicine, Xin-yi-san, reducing nasal symptoms of patients with allergic rhinitis by its diverse immunomodulatory effects.

Using PS software:-

$\alpha = 0.05$

Power=0.8

$\sigma = 16$

$\delta = 10$

n=32 per arm

2n= 64

Expected 10% drop-out;

Sample size = 64 x 1.1

= **70**

3.2 Details of Methodology

1. This study was approved by ethics committee.
2. Written consent were obtained from selected patients.
3. Consented patients were randomized into the treatment and placebo groups.
4. Treatment group patients received oral *channa striatus* extract (500mg). Placebo group patients received corn starch (200mg).
5. Both groups of patients continued their nasal spray and loratidine.
6. Subject eligibility were determined before treatment randomization. Subject numbers were allocated strictly sequentially, as subjects are eligible for randomization. Investigators were blinded in the randomization.
7. A randomization list generated using computer provided allocation of subject numbers in a ratio of 1:1 to treatment and placebo group.
8. This is double blind study and once a subject has been randomized, the study treatment that they will receive will not be known to the subject and the investigator.
9. Patients with symptoms of allergic rhinitis were screened with detailed history, physical examination and nasoendoscopy.
10. Patients with positive symptom score, positive nasoendoscopy findings and positive skin prick test was recruited in this study.
11. Baseline blood investigation such as full blood count (FBC), Renal profile (RP), Liver function test (LFT) and Immunoglobulin E (IgE) levels were taken prior commencement of treatment.