Efficacy and safety of Phlai capsule compared to placebo as the treatment in allergic rhinitis patients

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การศึกษาประสิทธิผลและความปลอดภัยสารสกัดไพลแคปซูลเปรียบเทียบกับยาหลอกในผู้ป่วยโรคเยื่อจมูกอักเสบจากภูมิแพ้

นายมิง เฟื้อก หว่าง

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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Field of Study	Clinical Sciences
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มิง เฟื้อก หว่าง : การศึกษาประสิทธิผลและความปลอดภัยสารสกัดไพลแคปซูลเปรียบเทียบกับยาหลอกในผู้ป่วยโรคเยื่อจมูกอักเสบจากภูมิแพ้. (Efficacy and safety of Phlai capsule compared to placebo as the treatment in allergic rhinitis patients) อ.ที่ปรึกษาหลัก : กรเกียรติ์ สนิทวงศ์

ความเกี่ยวข้องทางเภสัชศาสตร์ชาติพันธุ์: มีการศึกษาทางพรีคลินิกแสดงให้เห็นถึงฤทธิ์ต้านการอักเสบของแคปซูลสารสกัดไพลที่มี *Zingiber montanum (J.Koenig) Link ex A.Dietr.* แต่อย่างไรก็ตามผลทางคลินิกของสารดังกล่าวต่อโรคเยื่อจมูกอักเสบจากภูมิแพ้ยังไม่ชัดเจน

วัตถุประสงค์ของการวิจัย: เพื่อประเมินประสิทธิผลและความปลอดภัยของไพล ในการรักษาโรคเยื่อจมูกอักเสบจากภูมิแพ้

วิธีดำเนินการวิจัย: ทำการศึกษาแบบสุ่มตัวอย่างแบบปกปิดทั้งสองด้านและควบคุมด้วยยาหลอก (randomized, double-blind, placebo-controlled study) ผู้ป่วยโรคเยื่อจมูกอักเสบจากภูมิแพ้ได้รับการสุ่มเป็นสามกลุ่ม และได้รับ แคปซูลสารสกัดไพล 100 มิลลิกรัม (สารประกอบ D 4 มิลลิกรัม) หรือ แคปซูลสารสกัดไพล 200 มิลลิกรัม (สารประกอบ D 8 มิลลิกรัม) หรือยาหลอกวันละครั้งเป็นเวลา 4 สัปดาห์ ผลลัพธ์หลัก (Primary outcome) คือการเปลี่ยนแปลงของคะแนน reflective total five symptom score (rT5SS) ผลลัพธ์รอง (Secondary outcomes) คือ การเปลี่ยนแปลงของคะแนน instantaneous total five symptom score (iT5SS), คะแนน reflective individual symptom scores (น้ำมูกไหล, คัดจมูก, จาม, คันจมูก, คันตา), คะแนนแบบสอบถาม Rhinoconjunctivitis Quality of Life-36 Questionnaire (RCQ-36), กระแสหายใจเข้าทางจมูกสูงสุด, และอาการไม่พึงประสงค์

ผลการวิจัย: ผู้ป่วย 262 คนได้รับการลงทะเบียนเข้าร่วมโครงการวิจัย พบว่ากลุ่มที่ได้รับ แคปซูลสารสกัดไพล 100 มิลลิกรัม สามารถทำให้อาการเหล่านี้ดีขึ้นอย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับยาหลอก ได้แก่ rT5SS [adjusted mean difference (aMD) -0.62; 95% CI -1.22, -0.03; p = 0.039], น้ำมูกไหล (aMD -0.19; 95% CI -0.37, 0.002; p = 0.048), คันจมูก (aMD -0.24; 95% CI -0.43, -0.05; p = 0.011), และ คันตา (aMD -0.19; 95% CI -0.36, -0.02; p = 0.033) ที่สัปดาห์ที่ 4 ในขณะที่อาการคัดจมูก, จาม, คะแนน iT5SS, คะแนน RCQ-36 โดยรวม, และกระแสหายใจเข้าทางจมูกสูงสุด ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ และพบว่า แคปซูลสารสกัดไพล 200 มิลลิกรัม ไม่ได้ให้ประโยชน์ใดๆเพิ่มเติมเมื่อเปรียบเทียบกับ 100 มิลลิกรัมนอกจากนี้ อาการไม่พึงประสงค์ยังมีความคล้ายคลึงกันในทั้งสามกลุ่ม

สรุปผลการวิจัย: แคปซูลสารสกัดไพลมีความปลอดภัย และสามารถทำให้คะแนน rT5SS ร่วมกับอาการน้ำมูก

สาขาวิชา เวชศาสตร์คลินิก ลายมือชื่อนิสิต .....

ปีการศึกษา 2564 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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Minh Phuoc Hoang : Efficacy and safety of Phlai capsule compared to placebo as the treatment in allergic rhinitis patients. Advisor: Assoc. Prof. L. KORNKIAT SNIDVONGS, M.D., Ph.D.

: Preclinical studies demonstrated anti-inflammatory effects of Phlai capsule containing *Zingiber montanum* (J.Koenig) Link ex A.Dietr. extract. However, its clinical effect on allergic rhinitis is not evident.

: We sought to assess the efficacy and safety of Phlai for treating allergic rhinitis.

: A randomized, double-blind, placebo-controlled study was conducted. Patients with allergic rhinitis were randomized into three groups and received 100 mg (compound D 4 mg) of Phlai capsule or 200 mg (compound D 8 mg) of Phlai capsule or placebo once a day for 4 weeks. The primary outcome was a change in the reflective total five symptom score (rT5SS). The secondary outcomes were the change in the instantaneous total five symptom score (iT5SS), the reflective individual symptom scores (rhinorrhea, nasal congestion, sneezing, itchy nose, itchy eyes), Rhinoconjunctivitis Quality of Life-36 Questionnaire (RCQ-36) score, peak nasal inspiratory flow, and adverse events.

: Two hundred and sixty-two adult patients were enrolled. Compared with placebo, 100 mg of Phlai capsule improved rT5SS [adjusted mean difference (aMD) -0.62; 95% CI -1.22, -0.03; p = 0.039], rhinorrhea (aMD -0.19; 95% CI -0.37, 0.002; p = 0.048), itchy nose (aMD -0.24; 95% CI -0.43, -0.05; p = 0.011), and itchy eyes (aMD -0.19; 95% CI -0.36, -0.02; p = 0.033) at week 4. Nasal obstruction, sneezing, iT5SS, overall RCQ-36 score, peak nasal inspiratory flow did not reach statistically significance. 200 mg of Phlai capsule did not bring additional benefits compared to 100 mg. Adverse events were similar among groups.

: Phlai was safe. At four weeks, there were small improvements in rT5SS, together with the individual symptoms of rhinorrhea, itchy nose, and itchy eyes. Phlai capsule can be a potential alternative treatment for patients with allergic

Field of Study:	Clinical Sciences	Student's Signature .....
Academic Year:	2021	Advisor's Signature .....

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Minh Phuoc Hoang

TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1 INTRODUCTION

1.1 Introduction

The prevalence of allergic rhinitis (AR) in Thailand is escalating and is reported to be approximately 50% [1, 2]. AR makes a significant impact on quality of life, school, and work performance leading to high medical costs. Oral antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists are the first-line therapies for patients with AR [3]. Apart from standard treatments, the novel therapies have been sought to optimize the management of allergic rhinitis.

Currently, Botulinum toxin (BTX) A has been revealed in both experimental and clinical studies as a potential treatment for chronic rhinitis [4], particularly in the patients with standard treatment failure.

Intralymphatic immunotherapy (ILIT) is a novel form of allergen-specific immunotherapy that can modify the IgE mediated hypersensitivity of AR [5]. ILIT aims to improve the efficacy of AIT by administering specific allergens directly into the lymphoid organs [6] based on the "geographic concept of immunogenicity" that the immune responses can be initiated only in secondary lymphatic organs, including lymph nodes [7, 8].

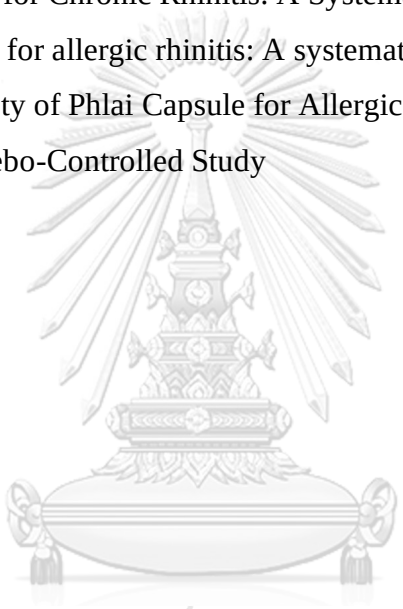
Moreover, a proportion of patients are unsatisfied with standard treatment or willing to use complementary alternative therapies to alleviate the symptoms in the short term, especially herbal medicines. The Zingiberaceae family consists of plants that act as anti-allergic and anti-inflammatory agents and benefit the treatment for allergy and allergic-related diseases such as *Zingiber officinale* [9], *Zingiber zerumbet* [10], and *Zingiber cassumunar* [11, 12]. *Zingiber montanum* (J.König) Link ex A.Dietr. (Synonym: *Zingiber cassumunar* Roxb.) locally known as “Phlai” in Thai has been used as traditional medicine in many diseases, including inflammation, asthma, and respiratory problems [12]. Phlai has a potent bioactive component called compound D [E-4-(3',4'-dimethoxyphenyl) but-3-en-1-ol] in its rhizomes [13]. The active constituent compound D has potential anti-allergic [10, 11, 14] and anti-inflammatory effects [15], suggesting that Phlai could be the novel treatment for AR. Although observed, neither the evidence of efficacy nor safety of Phlai extract in

treating patients with AR is conclusive because it is based on in vitro [16, 17] and animal studies [13, 18] without strong evidence of clinical trials.

First aim is to review the current novel treatments for AR in regard to BTX-A, ILIT, and herbal medicine. Second aim of this study is to assess the clinical effectiveness and safety of Phlai extract for treating patients with AR when compared to placebo.

1.2 Published articles related to the thesis

1. Botulinum Toxin for Chronic Rhinitis: A Systematic Review and Meta-analysis
2. Herbal medicines for allergic rhinitis: A systematic review and meta-analysis
3. Efficacy and Safety of Phlai Capsule for Allergic Rhinitis: A Randomized, Double-Blind, Placebo-Controlled Study



CHAPTER 2 LITERATURE REVIEW

2.1 Botulinum toxin type A

AR is the most common phenotype of chronic rhinitis. AR is caused by an IgE-mediated response after allergen exposure that stimulates the inflammatory mediators and autonomic nervous system [19-21]. Nonallergic rhinitis (NAR) has several subsets with an extensive differential including the most common, non-allergic rhinopathy, also termed “vasomotor rhinitis” or “idiopathic rhinitis,” as well as inflammation related to medications, environmental triggers, hormonal changes, infections, or autoimmune, vasculitis and granulomatous processes. The pathophysiology of NAR may only be partly explained by entopy, neural dysregulation, and/or chemoreceptor activation [22]. Both AR and NAR share the same pathophysiologic mechanism of nasal hyperreactivity associated with increased inflammatory mediators such as neuropeptides, including calcitonin gene related peptide (CGRP) and Substance P (SP) [23]. The mucosal hyperinnervation in both AR and NAR suggests the neuro-inflammatory involvement due to an imbalance between the parasympathetic and sympathetic nervous systems [24].

BTX is a neurotoxic substance generated by Clostridium botulinum and other related Gram-positive species [25]. There are seven neurotoxin serotypes (A-G) of BTX [26]. BTX inactivates muscular and glandular functions by inhibiting acetylcholine release from the presynaptic terminal [4, 27]. The light chain of BTX-A cleaves a specific intracellular protein called SNAP-25 (synaptosome associated protein with a molecular weight of 25 kDa), which leads to the inhibition of neurotransmitter release [25]. Because of its anticholinergic effect at the neuromuscular junction, BTX type A (BTX-A) is a broad-spectrum treatment. There is an extensive use of BTX-A in the treatment of involuntary muscle spasms such as spasmodic torticollis, blepharospasm, cervical dystonia, and spasmodic dysphonia [28]. Acetylcholine is knowns as an essential neurotransmitter in the peripheral parasympathetic nervous system. Thus, BTX-A that can modulate the parasympathetic stimulation is used in treating Frey’s syndrome, hyperhidrosis, epiphora, and sialadenitis [29].

2.1.1 Materials and methods

Randomized controlled trials (RCTs) studying BTX-A in patients with chronic rhinitis at any age were included. Patients with chronic rhinitis were defined as AR, NAR, or mixed population for further subgroup analyses. Diagnostic criteria of AR followed the Allergic Rhinitis and its Impact on Asthma guidelines [21]. Patients who did not meet the AR criteria were defined as NAR. Studies of BTX-A with any type of administration, dosage, and any comparison either with placebo or active treatment for chronic rhinitis were included. The active treatments are acknowledged pharmacotherapies that alleviate chronic rhinitis symptoms. Outcomes measures were not used for excluding the studies. RCTs published in a language other than English were excluded.

The study protocol was registered with PROSPERO, CRD42020203540. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [30]. Electronic systematic searches for RCTs were conducted with no publication year, or publication status restrictions. The date of the last search was August 16, 2020. Literature searches were performed using MEDLINE, Scopus, and EMBASE. References of the included studies and additional sources were manually searched. The search terms were "rhinitis" AND "botulinum neurotoxin" OR "botulinum toxin".

Two review authors (KR and MPH) independently screened the title and abstract of the identified studies based on the predetermined criteria. Full-text of the screened articles were reviewed to select studies for qualitative synthesis. Two authors (KR and KSe) extracted data from the included studies. When there was insufficient information for data extraction or conflicting data, the corresponding author was approached for further information. Disagreements over the study selection or data extraction were solved by consulting the corresponding author (KSn) or discussing among the authors until getting a consensus. Data of AR and NAR were separately extracted from the studies with mixed population where possible. The extracted data included: study design, rhinitis subtype, age, gender, route of BTX-A administration, control arm (placebo and/or active treatment), dose, follow-up period, and outcome measures. Primary outcome was the total nasal symptom score (TNSS). Secondary

outcomes were individual nasal symptoms, disease-specific quality of life, and adverse events. The baseline value, final value, and change score of each outcome were extracted. When a change score could not be extracted, the final value was used for data analysis. Based on a dose-dependent and temporary effect [31], the 12-week time point was set to assess the effects of BTX-A as follows: ≤12-week and >12-week [32].

Data of each route of BTX-A administration were pooled for separate meta-analyses. Subgroup analyses by rhinitis subgroup and injection site were performed. Risk ratio (RR) and 95% confidence interval (CI) were used for dichotomous data. Continuous data were presented as mean difference (MD) or standardized mean difference (SMD), standard deviation (SD) and 95% CI. The standard error, median, range, or 95% CI was imputed if the SD was not reported. Discrepancies in treatment effects among different trials were assessed using a heterogeneity (I^2) statistic. An I^2 of <40%, 40-60% and >60% represented low, moderate and substantial heterogeneity, respectively. When a heterogeneity was low, a fixed-effect model was used. A random-effects model was used if a heterogeneity was high for a more conservative estimate of the differences. All statistical assessments were conducted using Review Manager (RevMan) version 5.4.

Quality of the included studies was evaluated by assessing the risks of bias in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [33]. Risk of bias in each study was assessed in 5 bias domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain was classified as low risk, high risk, or unclear risk. Low risk or high risk of bias was determined if the described methods met the criteria of low risk of bias or high risk of bias of that domain, respectively. Unclear risk of bias was selected when there was either a lack of information or uncertainty over the potential for bias [33].

2.1.2 Results

The electronic and manual systematic searches identified 409 articles. After screening the titles and abstracts, 395 articles were removed. Full text of 14 articles were reviewed for eligibility. Nine studies were included in the qualitative analysis [34-42]. A cross-over RCT by Rohrbach et al. did not report the mean and SD [39].

Thus, the data of this study were not pooled for meta-analysis. Consequently, data from 8 studies were included in the quantitative analysis. Data from the topical BTX studies were not pooled in the meta-analysis of BTX-A injection.

Patients

There were 340 rhinitis patients with a mean age of 39.3 years (age was reported in 8 RCTs [35-42]). One hundred and forty-three participants (42%) were male. All included studies recruited participants above 14 years old. Three RCTs studied AR patients [35, 37, 40], 4 RCTs studied NAR patients [34, 36, 38, 39], and 2 RCTs studied a mixed population [41, 42]. Shemshadi et al. studied chronic AR patients without information regarding allergy tests [41].

Intervention

Two brands of BTX-A were used in the included studies. Six RCTs studied OnabotulinumtoxinA (BOTOX®) [34-39] and the other 3 RCTs used AbobotulinumtoxinA (DYSPORT®) [40-42]. Seven RCTs used BTX-A injection. The injection sites were the nasal septum [42], the inferior turbinates [38], and both the inferior and the middle turbinates [34-37, 40]. Two RCTs used topical BTX-A by inserting the BTX-A-soaked sponges into the nasal cavity [39, 41]. The BTX-A dose ranged from 8 units to 200 units. The follow-up period ranged from 8 weeks to 24 weeks. Placebo was used as the control arm in 8 RCTs [34-39, 41, 42]. Three RCTs had an active treatment as a control arm. The active treatments were triamcinolone injection into the inferior and the middle turbinates [37], ipratropium bromide nasal spray [38], and cetirizine [40].

Total nasal symptom score

The TNSS used in the included studies consisted of 6-point [35, 37, 38], 5-point [34, 36, 39, 42], 4-point [40], and 11-point [41] scale. Four RCTs assessed TNSS between the BTX-A and placebo [35-37, 42]. The effects on TNSS reduction favored BTX-A over placebo for both the ≤12-week effect (SMD -2.22, 95% CI -3.27 to -1.17, 4 RCTs, $p<0.01$) [35-37, 42] (Figure 1) and the >12-week effect (MD -9.69, 95% CI -11.29 to -8.09, 1 RCT, $p<0.01$) [37]. An I^2 of 78% represented substantial

heterogeneity. Two RCTs assessed TNSS between the BTX-A and active comparators (triamcinolone injection [37] and cetirizine [40]). There was no difference in the <12-week effect between both groups (SMD -1.1, 95% CI -4.13 to 1.92, 2 RCTs, p=0.47, I^2=96%) [37, 40]. The >12-week effect favored BTX-A over triamcinolone injection (MD -7.14, 95% CI -8.58 to -5.7, 1 RCT, p<0.01) [37].

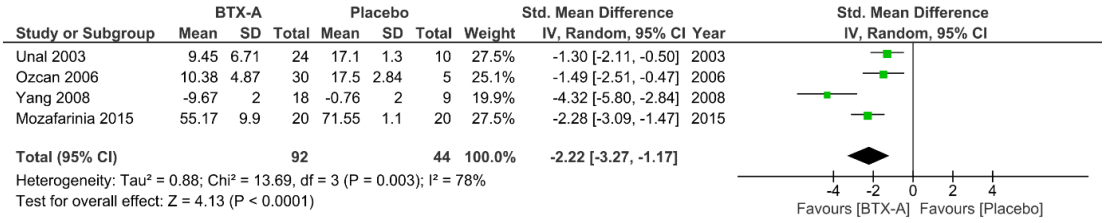


Figure 1. Improvement in total nasal symptom score at ≤12-week time point: Botulinum toxin type A vs placebo. BTX-A = botulinum toxin type A; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference

The results of subgroup analysis by rhinitis subtype were inconclusive because there were only 1-2 studies in each subgroup. However, the data showed that the ≤12-week effects on TNSS favored BTX-A over placebo for NAR (MD -1.49, 95% CI -2.51 to -0.47, 1 RCT, p=0.004) and mixed population subgroups (MD -2.28, 95% CI -3.09 to -1.47, 1 RCT, p<0.001) but there was no difference for AR subgroup (SMD -2.75, 95% CI -5.70 to 0.21, 2 RCTs, p=0.07). Subgroup analyses of the >12-week effects could not be performed due to insufficient data.

The results of subgroup analysis by site of injection were inconclusive because there were only 1-2 studies in each subgroup. However, the data showed that the ≤12-week effects on TNSS were not different between the BTX-A injection into the inferior and the middle turbinates, and the BTX-A injection into the nasal septum (p=0.98). Subgroup analyses of the >12-week effect could not be performed due to insufficient data.

Risk of bias in the included studies

All in all, the included RCTs had poor quality. Unclear risk of biases in random sequence generation, allocation concealment, and incomplete outcome data were found in 67%, 78% and 44% of the included RCTs, respectively. Forty-four percentage had high risk of bias in blinding outcome assessment. Twenty-two percentage had high risk of bias in selective reporting and allocation concealment.

2.1.3 Discussion

To the best of our knowledge, this is the first meta-analysis that evaluated the effectiveness of BTX-A in patients with chronic rhinitis. Our findings support the usage of BTX-A as a treatment for chronic rhinitis for up to 20 weeks. The effects of BTX-A improved the total nasal score, individual nasal symptom scores (rhinorrhea, sneezing, and nasal itching except nasal obstruction), and improved quality of life.

Because AR and NAR share the same pathophysiology of the neurogenic pathway [19], BTX-A is a potential treatment for improving symptoms of chronic rhinitis. BTX-A was reported by Sharri et al. for the first time in 1995 as an inhibitor of autonomic nerves [43]. Recently, five mechanisms of action have been postulated for the effects of BTX-A on the lining of the nasal cavity as follows: (1) inhibition of acetylcholine release from the cholinergic nerve endings in the nasal mucosa [34], (2) inhibition of acetylcholine release from presynaptic terminals of the sphenopalatine ganglion [27, 34], (3) induction of apoptosis in nasal glands [32], (4) suppression of the inflammatory mediators (e.g. SP and vasoactive intestinal peptides) appearance in the nasal mucosa [44], and (5) reduction of eosinophil infiltration and capillary dilatation in the nasal mucosa [45].

According to the innervating patterns of the autonomic nervous system, the cholinergic nerves mainly modulate glandular functions whereas vascular functions are controlled by the adrenergic nerves [34]. Furthermore, the muscarinic acetylcholine receptors on vascular endothelial cells are resistant to atropine, an anticholinergic agent [34]. Therefore, the inhibition of cholinergic activities by BTX-A may play a role only in reducing rhinorrhea (glandular function), not nasal obstruction (vascular function). As demonstrated in this systematic review, the

patients with various subtypes of chronic rhinitis who had experienced failures of standard therapies, such as antihistamines, intranasal steroid sprays, or immunotherapies, received benefits from the BTX-A. Nevertheless, the benefits were demonstrated up to 24 weeks. There is a lack of data regarding the effects after 24 weeks.

There were 2 routes, injection and topical application, of BTX-A administration into the nasal cavity in this systematic review. Three injection sites have been introduced in recent clinical trials, consisting of the nasal turbinates, the nasal septum, and posterior-lateral wall of the nasal cavity [27, 34, 46]. Abahi et al. reported in an open-label RCT that there was no difference in the improvement of nasal symptoms between the nasal turbinates injection and the nasal septum injection [47]. This is in line with the results of subgroup analysis of the present study that showed no difference in reducing TNSS between the BTX-A injection into the nasal turbinates and the nasal septum. Two RCTs that used topical application with nasal sponge showed the benefit of topical BTX-A [39, 41]. In addition, a cohort study that used gelfoam also showed the benefit of topical BTX-A [48]. An advantage of topical administration is that it is non-invasive, which reduces the chance of having side effects such as epistaxis or pain. However, the dosage of topical administration is higher than injection and it is not possible to calculate the amount of topical BTX-A absorbed by the nasal mucosa [4, 27].

The safety of BTX-A was demonstrated by this review. There were no serious local or systemic adverse events reported. Minor adverse events among the 340 patients in these 9 included RCTs were nasal dryness [40], burning sensation [38], and mild epistaxis [40]. However, the severity of epistaxis and the detail of the adverse event were not clearly described in the included studies.

This study had several limitations. The heterogeneity among the included RCTs was substantial when assessing the nasal symptom scores. The effects on individual nasal symptom scores in meta-analyses were mainly based on the study of Shemshadi et al. [41], which had poor methodology descriptions. Allergies were not confirmed by skin or serum specific IgE tests in approximately 40% of participants. The included studies had high risks of bias on blinding outcome assessment and allocation

concealment. All the nine included studies only used subjective outcomes. Thus, further studies by well-designed RCTs with objective outcomes are needed.

Evidence from nine randomized controlled trials demonstrated the beneficial effects of Botulinum toxin type A and it was safe for symptomatic treatment of chronic rhinitis. The effects of BTX-A improved total nasal symptom score, quality of life, and individual nasal symptoms except nasal congestion. These effects were demonstrated up to 20 weeks, except for the quality of life which was ≤12 weeks. The rhinitis subtype (as a favorable group) and the type of administration (as an optimal method) were inconclusive due to a limited number of studies in each subgroup [49].

2.2 Herbal medicine

HM has been used for centuries as a treatment for allergic diseases. It demonstrated the effectiveness in treating allergic conditions such as nasal symptoms called "Bi Qiu" corresponding closely to AR [50]. Consequently, HM is commonly used in Asian countries, especially in East Asia. One Chinese formula called Yu-ping-feng San is modified and used in different trials [51]. To date, there are potential HMs for treating AR worldwide. Thus, the proportion of herbal usage has been escalating for the last three decades [52]. A self-reported survey in Germany revealed 26.5% of participants used alternative medicine for allergy diseases [53]. Since the first human trial was studied in 2002, Butterbur has become one of the most common herbs in Western countries as adjunction treatment for AR patients [54].

A well-written review displayed the diversity of mechanisms of action of HM, including anti-inflammatory, anti-allergic, and immunological effects [55]. To interfere with type 1 hypersensitivity, HM can inhibit the production of inflammatory cells such as mast cells, basophils, eosinophils, and monocytes. Besides, HM shows the ability to impede the histamine, leukotriene, cytokine, and chemokine releases from inflammatory cells. The active compounds in HM modulate the immunological activities of mast cells [55, 56]. Therefore, these effects significantly relieve nasal symptoms of AR, including sneezing, itching, rhinorrhea, nasal obstruction [57]. According to the information we have, the duration of HM treatments to reach the maximum effect is still unknown. Results of recent systematic reviews are

inconsistent, and none of them focused on mechanisms of action [56-58]. During a short period, HM therapy may have a good outcome, but the long-lasting effect may not control AR symptoms. In this review, our primary objective was to systematically assess the effects of treatment based on the duration of given HM. The secondary objective was to evaluate the effect of HM compared with placebo or positive control in the treatment of AR based on their mechanisms of action.

2.2.1 Materials and methods

The study protocol was accessed on PROSPERO with registered ID: CRD42020168367. Electronic searches with PubMed, EMBASE, and Manual additional sources for published and unpublished trials were conducted. The last search was performed on February 9, 2020. Combination of MeSH terms and keywords were "rhinitis, allergic, seasonal", "rhinitis, allergic, perennial", "rhinitis", "*allergic rhinitis", "hay fever", "rhinoconjunctivitis", "pollen allergy", "herbal medicine", "Chinese herb*", "plant extract", "phytomedicine*", "herbaceouse agent", "eastern medicine", "oriental medicine", "alternative medicine". Only human trials and publications in English were selected.

The systematic review was performed under The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format [30]. Randomized controlled trials (RCTs) in AR patients of any age were included. Diagnostic criteria followed the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. Allergies were confirmed by skin prick test (SPT) or serum IgE test [21]. RCTs studied HM compared to placebo or standard treatment were included. Studies had HM plus standard therapy versus standard therapy were included. Standard treatments are antihistamine or intranasal corticosteroids. Interventions of any formulation (decoction, tablet, pill, powder, herbal patch, and nasal spray/drop) with any duration were included. The outcomes were nasal symptoms, ocular symptoms, disease-specific quality of life (QOL), objective measurement for nasal patency, and adverse events. Trials related to homeopathy and immunotherapy were excluded. Studies had experimental extracts containing synthetic chemicals, were also excluded. Conference abstracts were excluded. Cross-over studies with the washout period less than one week were excluded.

Two reviewers (M.P.H. and W.C.) independently screened the titles and abstracts based on pre-agreed eligibility criteria and reviewed the selected articles comprehensively. When provided data in the chosen articles showed insufficient information for completed extraction, contacting corresponding authors was done for further information resources. The third author (K.S.) consulted and resolved disagreements in reviews, if necessary.

Data extracted by reviewers were AR subtypes, disease severity, number of patients received HM and comparators, age, gender, duration of treatment, outcomes, formulation of HM, and effect mechanism. HM has an anti-inflammatory effect if it decreases the migration of inflammatory cells, including mast cells, eosinophils, basophils, monocytes. The anti-allergic effect is defined as it reduces the release of cytokines, chemokine, or mast cell mediators, including histamine, leukotriene, or prostaglandin [55, 59]. HM has an anti-leukotriene effect when it acts as leukotriene biosynthesis inhibitors or leukotriene receptors antagonists [60]. The anti-histaminic effect is defined as it conceals the skin wheal and flare responses in SPT [61]. Moreover, anti-cholinergic and vasoconstrictor effects were also extracted from experimental trials, if available.

Two independent review authors judged the quality of studies following the Cochrane Handbook for Systematic Reviews of Interventions. Five domains were assessed: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each domain was scored as "low risk of bias" if the domain was well-described. It was scored as "high risk of bias" if the method or data of the respective domain has not been mentioned. Unclear risk of bias was selected when the domain data were only mentioned without a clear explanation.

Data were pooled for meta-analysis. Risk ratio (RR) and 95% confidence interval (CI) were used for dichotomous data. Effect treatments of continuous outcomes such as total symptom score were presented as mean difference (MD) or as standardized mean difference (SMD) with standard deviation (SD) and 95% CI. Subgroup analysis by the duration of effect and mechanism effect were conducted. If the change from baseline to endpoint was not available, the final scores were extracted. The standard

error, median, range, and 95% CI were used if the SD was not reported. Discrepancies in treatment effects among different trials were assessed using heterogeneity (I^2) statistic. An I^2 of <40%, 40-60% and >60% represented low, moderate and substantial heterogeneity. As heterogeneity was low, a fixed-effect model was used. On the contrary, a random-effects model was used if heterogeneity was high for a more conservative estimate of the differences. All statistical assessments were conducted using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

2.2.2 Results

A total of 2,032 articles were selected for screening (2,030 from electronic search and two from manual search). The flow diagram of included studies, according to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format is displayed in. Finally, 32 studies were included in qualitative synthesis [62-93] and 29 studies in quantitative synthesis [62, 63, 65-68, 70-86, 88-93].

Patients

There was a total of 2,697 participants with the mean age of 34.57 years in. 51.17% of patients were female. Nineteen studies included patients with perennial allergic rhinitis (PAR) [63, 67, 71, 73, 74, 78-81, 83-90, 92, 93], and thirteen studies had seasonal allergic rhinitis (SAR) population [62, 64-66, 68-70, 72, 76, 77, 82, 91]. One RCT studied patients with seasonally and perennially recurrent symptoms [75].Four of the thirty-two included RCTs recruited the patients under 18 years of age [71, 75, 84, 88].

Intervention

Twenty-seven RCTs used oral HM in various formulations [62-74, 76-83, 86, 88, 90, 92, 93]. Three trials used HM in the form of intranasal spray or oil inhalation [85, 87, 91]. Three RCTs administrated with external herbal patch or moxibustion [75, 84, 89]. The duration of treatments was ranged from 1 to 16 weeks. Different HMs have diverse mechanisms of action in treating AR. Seventeen studies had both anti-inflammatory effect and anti-allergic effect [63, 65, 71, 73-75, 78, 79, 81-83, 85, 86, 88-91, 93]. Five RCTs studied HM having anti-leukotriene effect [64, 67, 68, 70, 77].

The anti-histaminic effect of HM was shown in four RCTs [75, 79, 89, 90]. There were insufficient data to confirm the anti-cholinergic and vasoconstriction effects of HM amongst included trials. Amongst 32 trials, five trials had a control arm with standard treatment [64, 67, 70, 84, 93]. Four used antihistamines [64, 67, 70, 84]. There was one used combination of intranasal corticosteroid spray and antihistamine as control [93]. The other 28 studies used a placebo or inactive comparator.

Total nasal symptom score

Sixteen RCTs compared total nasal symptom score (TNSS) between HM and placebo [65, 67, 68, 70, 72, 76-79, 82, 83, 85, 88-91] and three RCTs compared TNSS between HM and standard treatment [67, 70, 93]. When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo (SMD -0.68; 95%CI -0.98, -0.38; p < 0.01; 11 RCTs) (Figure 2). HM and standard treatment brought similar effects (MD -0.01; 95%CI -0.24, 0.21; p = 0.93; 3 RCTs). When the duration of treatment was 4-12 weeks, the effects still favored HM over placebo (SMD -0.22; 95%CI -0.4, -0.05; p = 0.01; 7 RCTs). Nevertheless, the effects were not statistically different from placebo when the duration of treatment was ≥12 weeks (SMD -0.49; 95%CI -1.13, 0.15; p = 0.13; 5 RCTs).

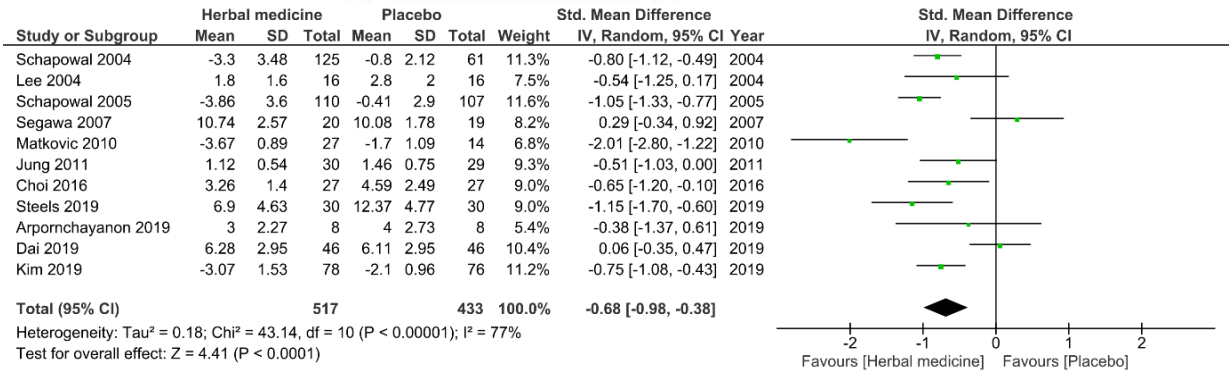


Figure 2. Improvement on total nasal symptom score: herbal medicine versus placebo at ≤ 4-weeks. CI confidence interval; df degrees of freedom; Std. mean difference standardized mean difference

Individual nasal symptom score

Sneezing, rhinorrhea and nasal obstruction scores were assessed by fifteen RCTs [63, 68, 71, 73-75, 80, 81, 83, 85, 88-92] while itching score was assessed by eleven RCTs [63, 68, 74, 75, 80, 85, 88-92]. Data from two studies could not be pooled because the SDs could not be imputed [68, 74].

When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo in sneezing (SMD -0.23; 95%CI -0.44, -0.02; p = 0.03; 12 RCTs), rhinorrhea (SMD -0.32; 95%CI -0.58, -0.06; p = 0.02; 12 RCTs), nasal obstruction (SMD -0.36; 95%CI -0.57, -0.16; p < 0.01; 12 RCTs), and itching (SMD -0.36; 95%CI -0.62, -0.09; p < 0.01; 9 RCTs). When the duration of treatment was > 4 weeks, the effects favored HM over placebo only in nasal obstruction (SMD -0.34; 95%CI -0.66, -0.02; p = 0.04; 3 RCTs), the effects in other individual symptoms were not different from placebo. Two RCTs compared individual nasal symptom score between HM and standard treatment [84, 93]. HM brought similar effects with standard treatment in each symptom.

Total ocular symptom score

Eight RCTs compared the total ocular symptom score (TOSS) between HM and placebo [65, 77, 82, 83, 85, 88, 89, 91]. When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo (SMD -0.32; 95% CI -0.58, -0.05; p = 0.02; 4 RCTs). When the duration of treatment was > 4 weeks, there was no statistically significant difference between the groups.

Disease-specific QOL

Seventeen RCTs compared Rhinoconjunctivitis Quality of life Questionnaire (RQLQ) [64, 66, 74, 75]. Data in five RCTs were not pooled because the SDs could not be imputed [62, 63, 65, 66, 73, 76, 79, 81-86, 89-91, 93]. Data in five trials were not extracted because SD was not imputed [65, 81-84].

When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo (SMD -0.53; 95%CI -0.81, -0.25; p < 0.01; 9 RCTs) (Figure 3) and over standard treatment (SMD -1.89; 95%CI -2.37, -1.41; p < 0.01; 1 RCT) [51]. When the

duration of treatment was 4-12 weeks, the effects still favored HM over placebo (SMD -0.48; 95%CI -0.89, -0.06; p = 0.03; 7 RCTs). Nevertheless, the effects were not statistically different between the groups when the duration of treatment was ≥12 weeks (SMD -0.17; 95%CI -0.47, 0.12; p = 0.24; 3 RCTs). Two RCTs compared RQLQ between HM and standard treatment [84, 93]. SD could not be imputed in one study [84]. The effect favored HM over standard treatment at 4-week time point with SMD -1.89 (95% CI -2.37, -1.41; p < 0.01) [93].

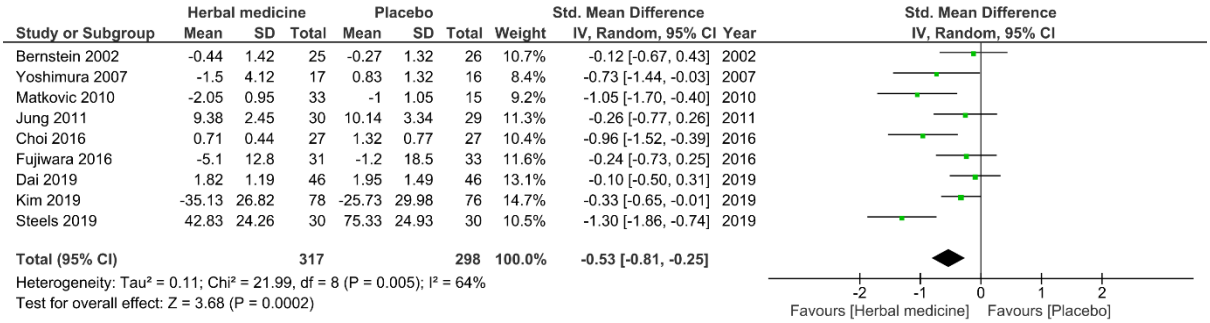


Figure 3. Improvement on Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ): herbal medicine vs placebo at ≤ 4 weeks. CI confidence interval; df degrees of freedom; Std. mean difference standardized mean difference

Objective measurement for nasal patency

Nasal airway resistance (NAR) and peak nasal inspiratory flow (PNIF) were assessed. Four RCTs assessed anterior NAR in the inhalation phase [78, 87, 88, 93]. One study did not show the mean NAR [87]. There were no significant differences between the effects of HM and placebo (MD -0.07; 95%CI -0.19, 0.04; p = 0.22; 2 RCTs) [78, 88] and between the HM and standard treatment (MD -0.01; 95%CI -0.06, 0.04; p = 0.68; 1 RCT) [93]. There was no difference of effect of treatment between groups (MD -0.02; 95% CI -0.06, 0.02; p = 0.4). An I^2 of 0% represented low heterogeneity. Two trials assessed peak nasal inspiratory flow, however, neither of two trials had sufficient data for analysis [67, 92].

The effects of HM on TNSS improvement were better than placebo in all subgroups of mechanism of action: anti-allergic effect (SMD -0.55; 95%CI -0.69, -0.4; p < 0.01, 12 RCTs), anti-inflammatory effect (SMD -0.61; 95%CI -0.88, -0.33; p < 0.01, 13 RCTs), anti-leukotriene effect (SMD -0.67; 95%CI -1.07, -0.27; p < 0.01, 4

RCTs), and anti-histaminic effect (SMD -0.5; 95%CI -0.91, -0.08; p < 0.01, 4 RCTs). The effects of HM on RQLQ improvement were better than placebo in anti-allergic effect (SMD -0.61; 95% CI -1, -0.21; p < 0.01, 9 RCTs) and anti-inflammatory effect (SMD -0.5; 95%CI -0.79, -0.21; p < 0.01, 9 RCTs). There was no difference on RQLQ improvement between HM with anti-histaminic effect and placebo (SMD -0.16; 95% CI -0.40, 0.09; p = 0.2, 3 RCTs).

For the duration of treatment ≤ 4 weeks, the effects of HM on TNSS improvement were better than placebo in both the SAR (SMD -0.92; 95%CI -1.41, -0.43; p < 0.01; 5 RCTs) and PAR subgroups (SMD -0.47; 95%CI -0.77, -0.17; p < 0.01; 6 RCTs). For the duration of 4-12 weeks, the effects on TNSS favored HM only in the SAR subgroup (SMD -0.51; 95%CI -0.87, -0.16; p < 0.01; 3 RCTs), but not in the PAR subgroup (SMD -0.13; 95%CI -0.33, 0.06; p = 0.18; 4 RCTs). For the duration of ≥ 12 weeks, there were no differences between HM and placebo in both the SAR and PAR subgroups. The effects of HM on RQLQ improvement were better than placebo when the duration of treatment was ≤ 4 weeks in both the SAR (SMD -0.82; 95%CI -1.56, -0.08; p < 0.01; 3 RCTs) and PAR (SMD -0.38; 95%CI -0.61, -0.14; p < 0.01; 6 RCTs), but there were no differences after 4 weeks of treatments.

The included studies that had at least one high risk of bias in one domain were defined as “Trials with high risk of bias” where others were defined as “Trials without high risk of bias”. In the trials without high risk of bias subgroup, HM significantly improved TNSS when the duration of treatment was ≤ 4 weeks (SMD -0.89; 95%CI -1.13, -0.65; p < 0.01; 8 RCTs) but there was no difference after 4 weeks. HM significantly improved RQLQ when the duration of treatment was < 12 weeks but there was no difference after this timepoint. In the trials with high risk of bias subgroup, there were no differences between the HM and placebo in both TNSS and RQLQ improvement regardless of the duration of treatment.

Nine RCTs assessed headache, dry mouth/nose, dizziness, somnolence, and gastrointestinal pain/diarrhea events. There were no significant differences in adverse events between the HM and other treatments

2.2.3 Discussion

This systematic review and meta-analysis demonstrated the beneficial effects of HM for treating AR. HM improved total nasal symptoms, individual nasal symptoms, total ocular symptoms, and disease-specific quality of life. These beneficial effects persisted in the high quality RCTs subgroup analysis. In contrast, there were no differences between the HM and placebo in the trials with high risks of bias subgroup. In addition, HMs brought beneficial effects like standard treatments, including antihistamines and intranasal corticosteroids. HMs with anti-inflammatory activities contains plant steroids, of which the structure is close to corticosteroids [93]. Subgroup analyses showed that HMs with anti-allergic effect and anti-inflammatory effect were effective. These effects controlled the early-phase and late-phase symptoms. In addition, anti-histamine and anti-leukotriene effects were also revealed. Jung et al. [79] demonstrated the ability of fermented red ginseng to suppress the wheel and flare response in SPT as a part of the anti-histamine effect. Butterbur and Pycnogenol showed the ability to inhibit leukotriene biosynthesis, similar to zileuton [64, 67, 68, 70, 77]. These effects decrease mucus hypersecretion in the airways and enhance mucociliary [94]. Choosing an appropriate HM should be based on the mechanisms of action of the HM that could improve the prominent symptoms of AR.

The results of this study showed the benefits of HMs up to twelve weeks duration then the benefits decreased. Tachyphylaxis has been known for a long time in other medicines such as antihistamines, intranasal decongestants, and opioids. To the best of our knowledge, this is the first systematic review showing evidence of tachyphylaxis of herbal medicine. There is no evidence regarding whether increasing the dose of HM can restore the original response. Physicians should be aware that the HM response decreases after three months of treatment. The subgroup analyses by AR subtype showed that both the patients with SAR and PAR benefited from the HMs. However, the patients with PAR experienced tachyphylaxis after 4 weeks. To date, the evidence supporting the HM treatments for AR is unclear. The recommendation of HM is controversial [56]. A systematic review utilized a modified Delphi method by Wu et al. [54] showed that butterbur extract was one of the potential alternative treatments for sinusitis and rhinitis. Unlike Western HMs,

Eastern HMs have composite ingredients containing different herbs. Therefore, it is difficult to identify the original or individual component that provides the primary beneficial effects. Lenon et al. [82] studied a new formula that was developed from an existing HM formula, by selecting 7 out of the 18 individual herbal ingredients and found no differences between the HM and placebo. There are four meta-analyses evaluating the effects of Chinese HMs. These meta-analyses included several studies that were published in Chinese. However, those studies were not included in our review. A meta-analysis by Wang et al. [57] showed the benefits of Chinese HM over placebo or inactive comparator in the assessment of TNSS. In contrast, Zhang et al. [58] reported no differences in TNSS or individual nasal symptom scores between the HM and placebo or inactive comparator. Although they found beneficial effects on RQLQ favoring the HM, the heterogeneity was substantial. Another meta-analysis by Zheng et al. [95] assessed pediatric AR from 19 RCTs and showed benefits of Chinese HM over antihistamines. Luo et al. [51] assessed adult patients with AR from 23 RCTs and showed that the Chinese HM formula, Yu ping feng san, was effective for managing adult AR.

Based on the results of this meta-analysis, HM decreased nasal and ocular symptoms related to allergic rhinitis and improved quality of life with no difference from standard treatments. Nevertheless, beneficial effects did not persist after 12 weeks. In addition to the benefits of HM as a sole therapy, its role as an addition to standard treatment also had favorable therapeutic outcomes [61]. Arpornchayanon et al. [88] assessed the effects of cetirizine and HM combination and showed that the combination was superior to cetirizine and placebo. The findings of this study showed that HM was safe and tolerable. This is in agreement with previously published articles which reported no differences in adverse events between the HM and control groups. However, diarrhea or liver toxicity were reported in some cases [54, 56, 92]. In clinical practice, the authors suggest that HM should be considered as a primary treatment only for a short-term treatment. Standard treatments, such as antihistamines and intranasal corticosteroids are the first-line drugs for the long-term treatment while HM can be used as an option or as an adjunct to standard treatment to boost up the treatment effect.

This study had several limitations. The systematic search did not search for articles published in languages other than English. Therefore, our meta-analysis could not cover all current studies. In addition, the included studies had high heterogeneity for outcomes assessment. Subgroup analyses, by mechanism of action of the HM, the AR subtype, and quality of the included studies, were conducted to investigate the heterogeneity. The heterogeneity persisted because different kinds of HM were investigated together.

Evidence from this meta-analysis showed the benefits of HM for treating AR patients. HMs improved nasal symptoms, ocular symptoms, and disease-specific QOL when compared to placebo. Beneficial effects of HMs were similar to standard treatments but only revealed in a short-term treatment, less than 12 weeks. In general, HM is considered safe. In practice, standard treatments such as antihistamines and intranasal corticosteroids should be considered for a long-term treatment [96].

2.3 *Zingiber montanum* (J.König) Link ex A.Dietr.

The Zingiberaceae family consists of plants that act as anti-allergic and anti-inflammatory agents and benefit the treatment for allergy and allergic-related diseases such as *Zingiber officinale* [9], *Zingiber zerumbet* [10], and *Zingiber cassumunar* [11, 12]. *Zingiber cassumunar* Roxb. locally known as “Phlai” in Thai has been used as traditional medicine in many diseases, including inflammation, asthma, and respiratory problems [12]. Phlai has a potent bioactive component called compound D [E-4-(3',4'-dimethoxyphenyl) but-3-en-1-ol] in its rhizomes [13]. The active constituent compound D has potential anti-allergic [10, 11, 14] and anti-inflammatory effects [15], suggesting that Phlai could be the novel treatment for AR. Although observed, neither the evidence of efficacy nor safety of Phlai extract in treating patients with AR is conclusive because it is based on in vitro [16, 17] and animal studies [13, 18] without strong evidence of clinical trials.

CHAPTER 3 RESEARCH OBJECTIVES AND HYPOTHESIS

3.1 Objectives

1. To assess clinical effectiveness of Phlai for treating patients with allergic rhinitis when compared to placebo

2. To assess clinical safety of Phlai

3.2 Hypothesis

Phlai is a Thai herbal medicine which is effective for treating patients with allergic rhinitis with no serious adverse effects

CHAPTER 4 EFFICACY AND SAFETY OF PHLAI CAPSULE COMPARED TO PLACEBO AS THE TREATMENT IN ALLERGIC RHINITIS PATIENTS

4.1 Material and Methods

4.1.1 Study design and participants

We conducted a phase III randomized, double-blind, placebo-controlled trial in the outpatient departments of seven University hospitals in Thailand: (1) Endoscopic Nasal and Sinus Surgery Excellent Center, King Chulalongkorn Memorial Hospital, (2) Siriraj Hospital, (3) Center of Excellence in Otolaryngology-Head & Neck Surgery, Rajavithi Hospital, (4) Phramongkutklao Hospital, (5) Center of Excellence for Allergy, Asthma and Pulmonary Diseases, Thammasat University Hospital, (6) Srinagarind Hospital, and (7) Songklanakarin Hospital. The study was approved by the Central Research Ethics Committee (CREC036/2019) and the Institutional Review Board of all study sites. The study process was explained in detail, including medications and all investigations. All patients had ample time to ask questions which included potential risks and benefits from the study and provided written informed consent; the trial was conducted following the Declaration of Helsinki. This study was funded by the Government Pharmaceutical Organization of Thailand and registered at ClinicalTrials.gov (Study ID: NCT04182919).

4.1.2 Patient population

Adults presented to the outpatient departments with AR symptoms were screened for eligibility. The inclusion criteria were: (1) Age 18-50 years; (2) Allergic rhinitis following diagnostic criteria of ARIA guideline [21]; (3) Not currently using intranasal corticosteroid (including intranasal corticosteroid and intranasal antihistamine combination) for two weeks, systemic corticosteroid for four weeks, oral antihistamine for one week, nasal decongestant for one week, and leukotriene receptor antagonists for one week; (4) Daily reflective total five symptoms score (rT5SS) of 2-10 per day for three consecutive days (total score = 15) and not greater than 10 on any day during the past week. Reflective total five symptoms score (rT5SS) was a sum of individual AR symptoms of rhinorrhea, nasal obstruction, itchy

nose, sneezing, and itchy eyes. All individual AR symptoms were scored on a 4-point scale (0 = no symptom present, 1 = mild symptom that does not interfere with any activities, 2 = moderate symptom that slightly interferes with daily activities or sleep, 3 = severe symptom that significantly bothers daily activities or sleep). Diagnosis of AR was confirmed by skin prick test. Seven common allergens in Thailand were tested for sensitization, comprising *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach, dog hair, cat hair, careless weed, and paragrass (AllerVACtest®10, Greater Pharma, Bangkok, Thailand) [97].

Exclusion criteria were: (1) Underlying severe medical diseases, e.g., COPD, heart disease, chronic renal failure, chronic hepatic failure; (2) Allergic rhinitis and asthma requiring immunotherapy; (3) Receiving antidepressants, sedatives, anxiolytics, opioid or antipsychotics; (4) Uncontrolled asthma requiring inhaled steroids and/or LABA; (5) Previous surgery for nasal polyp or nasal septum deviation; (6) Acute or chronic rhinosinusitis; (7) Pregnancy and lactation; (8) History of allergy to any kind of herb; (9) Refusal to participate.

4.1.3 Randomization and allocation

Randomization, allocation, and blinding were performed by an independent third party who did not involve in clinical practice. A biostatistician generated a central randomization with unequal block sizes with sizes proportional to elements of Pascal's triangle, and a 1:1:1 allocation ratio within each block [98]. A research coordinator performed the patient assignment, concealed and stored the allocation codes. The packages labeled with unique codes were sent to all trial centers.

Intervention

Each standardized *Zingiber montanum* (J.König) Link ex A.Dietr. capsule had 100 mg of Phlai extract equivalent to 4 mg of compound D. Placebo had similar contents with active capsule without compound D: PVP K30, calcium carbonate, dibasic calcium phosphate, sodium starch glycolate, colloidal silicon dioxide, ethanol 96%, purified water, magnesium stearate. Active capsules and placebo appeared identical.

There was a 2-week run-in period of withholding medication. Each study participant received two bags containing capsules with identical appearances. They were instructed to undertake one capsule in each bag after dinner per day. Study

investigators, care providers, and patients were blinded to treatment allocation. Study participants were randomized into three groups. Group 1 received a 4-week oral administration of 2 capsules of *Zingiber montanum* (J.König) Link ex A.Dietr. with a total of 200 mg of Phlai extract. Group 2 received a 4-week oral administration of one capsule of *Zingiber montanum* (J.König) Link ex A.Dietr. and one capsule of placebo with a total of 100 mg of Phlai extract. Group 3 received a 4-week oral administration of 2 capsules of placebo. The treatment duration was four weeks. There were two follow-up visits at 2 and 4 weeks. The study flow diagram is shown in Figure 3.

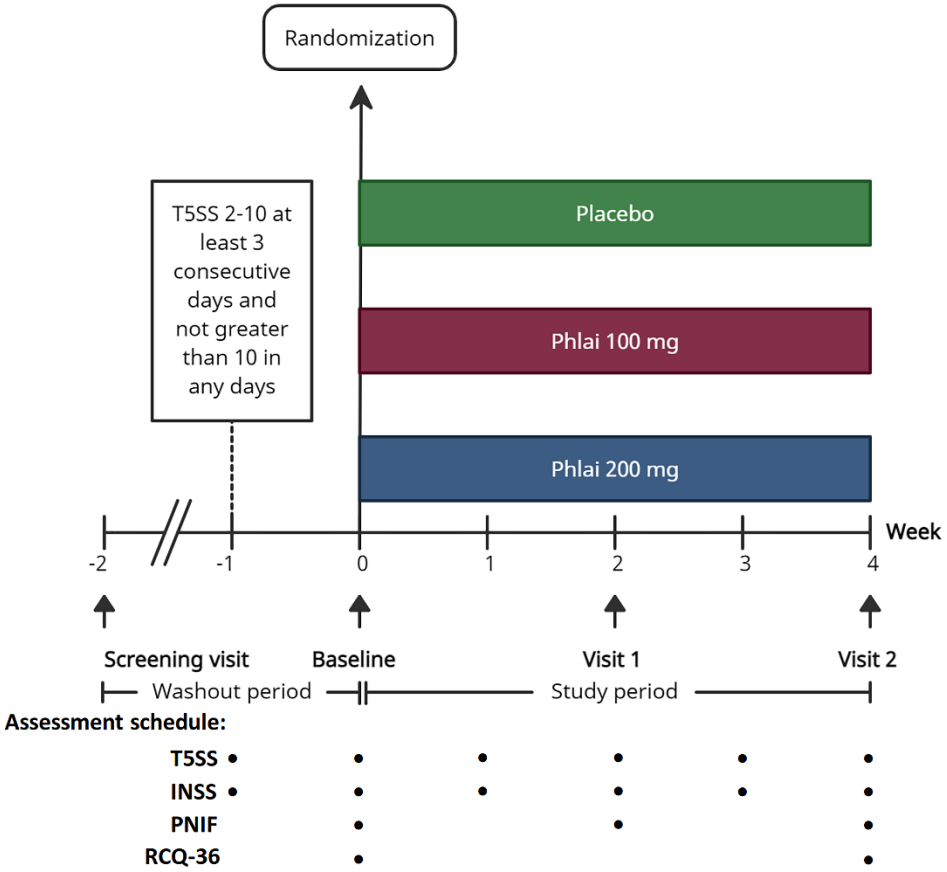


Figure 3. Study design

In the cases of worsening of AR symptoms with T5SS > 10, study participants were permitted to use isotonic nasal saline irrigation as rescue medication provided by researchers [99]. All rescue medicine use was daily self-recorded. Study participants were withdrawn when having one of the following criteria: (1) patient request; (2) serious illness during the study; (3) severe nasal symptoms score with T5SS > 10 without improvement by rescue medicine; (4) pregnancy.

We used an electronic software, REDCap (Vanderbilt University, Tennessee, USA), to manage clinical data. Each study site ensured the accuracy and completeness of the data entered in clinical report forms and the data derived from source documents. All data were inputted in the same coding format. Clinical report forms were kept on the databases with backup files. All data were locked after finishing the data validation.

4.1.4 Outcome measures

Study participants self-assessed AR symptoms twice a day in the morning (assessing the instantaneous T5SS) and at bedtime (assessing the reflective T5SS). The primary outcome was the reflective total five symptoms score (rT5SS) which evaluated a sum of five AR symptoms of the past 24 hours. The total score was 15. The secondary outcomes were the instantaneous T5SS (iT5SS), reflective individual symptom scores, overall Rhinoconjunctivitis Quality of Life-36 Questionnaire (RCQ-36) score, peak nasal inspiratory flow (PNIF), safety, and compliance. The instantaneous T5SS was an on-spot evaluation. The individual AR symptoms were scored on a 4-point scale (0-3). RCQ-36 is a validated Thai version of RQLQ, comprising 36 items in six domains (symptoms, physical functioning, role limitations, sleep, social functioning, emotions) and two independent items (general health and absenteeism) [100]. The score of each item ranged from 1 to 5 (lower is better). The RCQ-36 assessment was performed over the screening period and four weeks after treatment. PNIF meter (Clement Clarke International Ltd, Harlow, UK) was measured three times, and the highest value among three attempts was recorded. Outcome assessors were blinded to the treatment arm when analyzing patient-reported outcomes.

Adverse events were recorded daily. Complete blood counts (CBC), liver functions [aspartate transaminase (AST), alanine transaminase (ALT)] and renal functions [blood urea nitrogen (BUN), and creatinine levels] were measured over periods of screening and four weeks. Study participants recorded the recuse medicine use, concomitant drugs, and remaining capsules for calculating compliance during each week.

4.1.5 Statistical analysis

Sample size assumptions were based on the data from the previous study [101]. T5SS decreased by 1.14 for the active arm versus placebo after 4 weeks of study; the combined standard deviation was 2.5 [101]. Enrolling 74 participants (a total of 222 for three arms) would give 80% power to detect this difference in either of the active groups versus the placebo, at a 2-sided significance level of 5%.

All statistical analyses were conducted using Stata 17.0 (StataCorp, College Station, TX). Descriptive data are displayed as mean and standard deviation (SD) for continuous variables and n (%) for categorical variables. Repeated measures data (T5SS, T5SS component symptom scores, PNIF, RCQ-36) were analyzed using a mixed-effects model. The model included treatment group interacted with study week, baseline scores, sex, body mass index (BMI; < 30 vs. ≥ 30), AR symptom severity and duration (ARIA guideline) [21], recruitment season, and a random intercept for subjects. Baseline scores were defined as those on the day before undertaking the intervention. Changes from baseline outcome measures were calculated in the intention-to-treat (ITT) population that included all randomized participants, with missing data were handled by the mixed model under the missing at random assumption. A per-protocol analysis was also conducted, excluding data from participants with protocol violations. Time-to-response analysis was performed using Kaplan-Meier estimates. A patient with a reduction of T5SS from baseline > 1 point was defined as a responder [101]. Minimal clinically important differences (MCID) for T5SS and individual symptoms scores have not been determined. Therefore, we followed the recommendation of Meltzer et al. suggesting any difference between treatment groups ≥ 0.2 times the baseline SD is clinically significant (Table 1) [102]. Changes in overall RCQ-36 score ≥ 0.21 were considered clinically meaningful [103]. The estimated MCID for PNIF in AR was 5 L/min [102].

Table 1. Minimal clinically important differences of T5SS and individual symptom scores

Outcomes	**MCID***
T5SS	0.46
Rhinorrhea	0.17
Nasal congestion	0.16

Itchy nose	0.16
Sneezing	0.15
Itchy eyes	0.17

*MCID: difference between treatment groups ≥ 0.2 times the baseline SD is clinically significant

4.2 Results

Three hundred and ninety-eight patients were screened from February 2020 to November 2021. A total of 262 patients were randomized, 88 to Phlai capsule 200 mg, 88 to Phlai capsule 100 mg, and 86 to placebo (Figure 4). The baseline demographics and clinical characteristics were comparable across randomized groups (Table 2). Females comprised 70.4% of study participants. Persistent AR accounted for 64.1% of study participants. Forty-four percent of participants had moderate to severe AR symptoms. The majority (97.3%) of study participants completed the study. Patients who were lost to follow-up were 4.5%, 2.3%, and 1.2% in Phlai capsule 200 mg, Phlai capsule 100 mg, and placebo groups, respectively.

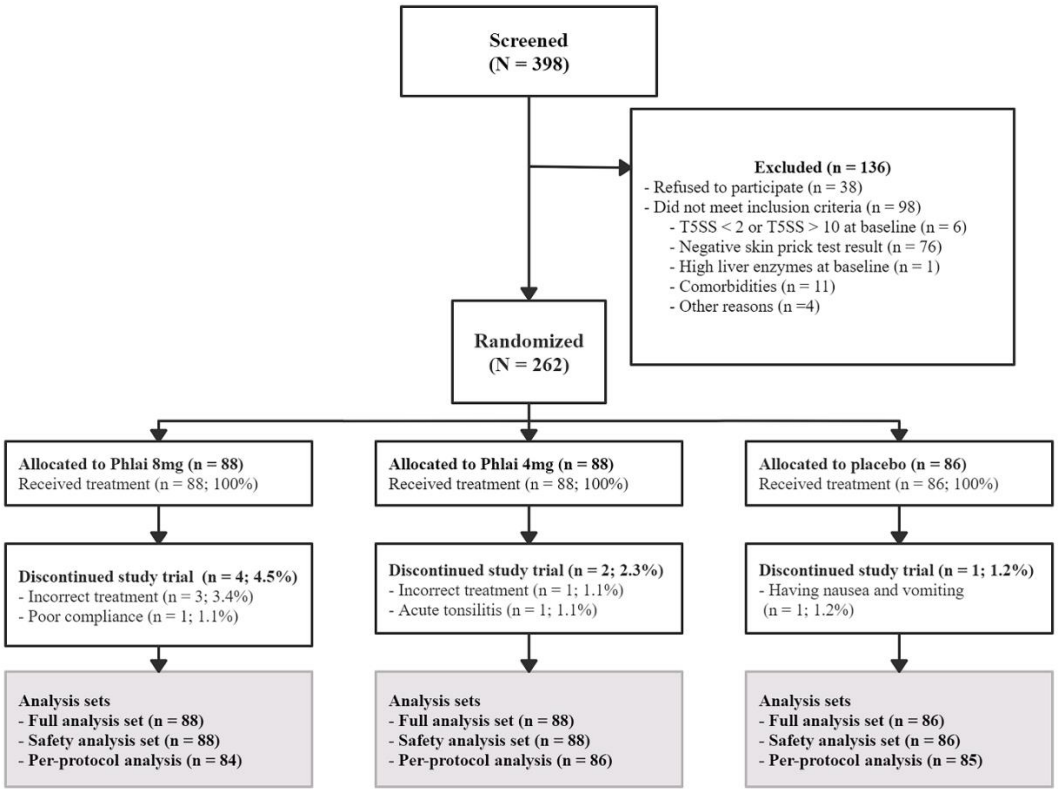


Figure 4. Patient disposition and trial profile

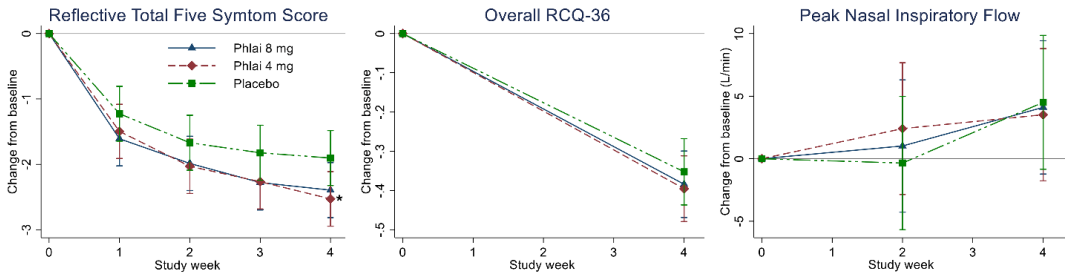


Figure 5. Adjusted changes from baseline to week 4 in reflective total five symptoms score, overall RCQ-36 score, and nasal peak inspiratory flow during the study period. Data are least-squares means ± 95% CI for the full analysis set. Total five symptoms score range, 0-15. Overall RCQ-36 range, 1-5. * p < 0.05 Phlai 100 mg versus Placebo

Table 2. Demographics, baseline characteristics in the three groups

	Phlai 8 mg (n = 88)	**Phlai 4 mg (n = 88)**	**Placebo (n = 86)**	**Overall population (n = 262)**
Female, n (%)	63 (71.6)	69 (78.4)	55 (64.0)	187 (71.4)
Age (year), mean (SD)	30.2 (7.7)	32.4 (9.0)	31.8 (7.5)	31.3 (8.1)
BMI, mean (SD)	23.5 (4.5)	23.8 (4.0)	23.7 (4.3)	23.6 (4.3)
Characteristics of AR condition, n (%)				
Intermittent	31 (35.2)	32 (36.4)	31 (36.1)	94 (35.9)
Persistent	57 (64.8)	56 (63.6)	55 (63.9)	168 (64.1)
Mild	49 (55.7)	50 (56.8)	50 (58.1)	149 (56.9)
Moderate to severe	39 (44.3)	38 (43.2)	36 (41.9)	113 (43.1)
Season recruitment, n (%)				
Winter	28 (31.8)	22 (25.0)	27 (31.4)	77 (29.4)
Rainy season	46 (52.3)	52 (59.1)	52 (60.5)	150 (57.2)
Summer	14 (15.9)	14 (15.9)	7 (8.1)	35 (13.4)
Allergens, n (%)				
Der p.	82 (93.2)	80 (90.9)	74 (86.1)	236 (90.1)
Der f.	80 (90.9)	75 (85.2)	70 (81.4)	225 (85.6)
Dog	16 (18.2)	16 (18.2)	9 (10.5)	41 (15.7)
Cat	10 (11.4)	6 (6.8)	11 (12.8)	27 (10.3)
Cockroach	31(35.2)	52 (59.0)	34 (39.5)	117 (44.7)
Para Grass	11 (12.5)	5 (5.7)	9 (10.5)	25 (9.5)
Careless Weed	11 (12.5)	6 (6.8)	5 (5.8)	22 (8.4)

Baseline scores, mean (SD)				
T5SS	5.01 (2.35)	5.01 (2.39)	4.74 (2.09)	4.92 (2.28)
Rhinorrhea	1.19 (0.87)	1.09 (0.87)	1.05 (0.84)	1.11 (0.86)
Nasal obstruction	1.16 (0.83)	1.10 (0.86)	1.15 (0.76)	1.14 (0.81)
Itchy nose	0.86 (0.76)	1.07 (0.83)	0.88 (0.74)	0.94 (0.78)
Sneezing	0.95 (0.76)	1.01 (0.73)	0.93 (0.73)	0.97 (0.74)
Itchy eyes	0.84 (0.81)	0.74 (0.81)	0.73 (0.86)	0.77 (0.83)
Overall RCQ-36	2.06 (0.58)	1.93 (0.47)	1.95 (0.56)	1.98 (0.54)
PNIF (L/min)	111.59 (37.78)	113.98 (40.12)	117.10 (43.18)	114.20 (40.30)
Anterior rhinoscopy, n (%)				
Nasal swelling	63 (71.6)	57 (64.8)	61 (70.9)	181 (69.1)
Pale	27 (30.7)	37 (42.1)	31 (36.1)	95 (36.3)
Nasal discharge	16 (18.2)	16 (18.2)	26 (30.2)	58 (22.1)

Table 3. Intention-to-treat analysis of adjusted mean change from baseline to week 4 of patient-reported symptoms and objective assessments parameters

Outcome	**Group**	**Adjusted mean change from baseline at week 4 (95% CI)**	**Difference between groups**			
			vs Placebo (95% CI)	**p value**	**Phlai 8 vs 4 mg (95% CI)**	**p value**
rT5SS (Scale 0-15)	Phlai 8 mg	-2.39 (-2.81, -1.97)	-0.49 (-1.09, 0.10)	0.17	0.13 (-0.46, 0.73)	0.66
	Phlai 4 mg	-2.53 (-2.95, -2.11)	-0.62 (-1.22, -0.03)	0.039		
	Placebo	-1.90 (-2.32, -1.48)				
iT5SS (Scale 0-15)	Phlai 8 mg	-2.12 (-2.53, -1.71)	-0.32 (-0.89, 0.26)	0.28	0.25 (-0.32, 0.82)	0.39
	Phlai 4 mg	-2.37 (-2.77, -1.97)	-0.57 (-1.14, 0.00)	0.05		
	Placebo	-1.80 (-2.21, -1.39)				
Rhinorrhea (Scale 0-3)	Phlai 8 mg	-0.53 (-0.66, -0.40)	-0.27 (-0.46, -0.09)	0.004	-0.09 (-0.27, 0.10)	0.36
	Phlai 4 mg	-0.44 (-0.57, -0.31)	-0.19 (-0.37, 0.00)	0.048		
	Placebo	-0.26 (-0.39, -0.12)				
Nasal obstruction (Scale 0-3)	Phlai 8 mg	-0.42 (-0.56, -0.28)	0.07 (-0.13, 0.26)	0.50	-0.04 (-0.23, 0.16)	0.69
	Phlai 4 mg	-0.38 (-0.52, -0.25)	0.11 (-0.09, 0.30)	0.28		
	Placebo	-0.49 (-0.63, -0.35)				
Itchy nose (Scale 0-3)	Phlai 8 mg	-0.46 (-0.59, -0.33)	-0.07 (-0.26, 0.11)	0.44	0.17 (-0.02, 0.35)	0.08
	Phlai 4 mg	-0.63 (-0.76, -0.50)	-0.24 (-0.43, -0.05)	0.011		
	Placebo	-0.39 (-0.52, -0.25)				
Sneezing (Scale 0-3)	Phlai 8 mg	-0.52 (-0.64, -0.39)	-0.09 (-0.26, 0.09)	0.33	0.03 (-0.15, 0.20)	0.75
	Phlai 4 mg	-0.54 (-0.67, -0.42)	-0.12 (-0.29, 0.06)	0.20		
	Placebo	-0.43 (-0.55, -0.30)				

Itchy eyes	Phlai 8 mg	-0.47 (-0.59, -0.35)	-0.12 (-0.30, 0.05)	0.16	0.06 (-0.11, 0.24)	0.47
(Scale 0-3)	Phlai 4 mg	-0.53 (-0.65, -0.41)	-0.19 (-0.36, -0.02)	0.033		
	Placebo	-0.34 (-0.47, -0.22)				
Overall	Phlai 8 mg	-0.38 (-0.47, -0.30)	-0.03 (-0.15, 0.09)	0.60	0.01 (-0.11, 0.13)	0.85
RCQ-36	Phlai 4 mg	-0.40 (-0.48, -0.31)	-0.04 (-0.16, 0.08)	0.48		
(Scale 1-5)	Placebo	-0.35 (-0.44, -0.27)				
PNIF	Phlai 8 mg	4.10 (-1.22, 9.43)	-0.40 (-7.95, 7.14)	0.92	0.59 (-6.91, 8.09)	0.88
(L/min)	Phlai 4 mg	3.51 (-1.77, 8.80)	-0.99 (-8.51, 6.53)	0.70		
	Placebo	4.50 (-0.84, 9.85)				

Abbreviations: rT5SS, reflective total five symptoms score; iT5SS, instantaneous total five symptom score; RCQ-36, The Rhinoconjuntivitis Quality of Life Questionnaire; PNIF, peak nasal inspiratory flow; SD, standard deviation; CI, confidence interval.

4.2.1 Reflective total five symptom score (rT5SS)

Adjusted changes in rT5SS over the study period are shown in Table 3 and Figure 5. Compared to placebo, there was a statistically significant improvement in rT5SS after four weeks [adjusted mean difference (aMD) -0.62; 95% CI -1.22, -0.03; p = 0.039] in Group 2. In Group 1, rT5SS also improved compared to placebo with a change of similar magnitude (aMD -0.49; 95% CI -1.09, 0.10; p = 0.17). Although the difference was not statistically significant, this change was greater than the MCD determined by the recommended method (Table 3) [102]. There was no statistically significant additional benefit of high dose (200 mg) over the low dose (100 mg) over all follow-up (Figure 6). The proportion of responders who achieved a reduction of rT5SS from baseline > 1 point was highest in Group 2 (85.2%), followed by Group 1 (81.4%) and Group 3 (72.1%) (Table 4 and Figure 7).

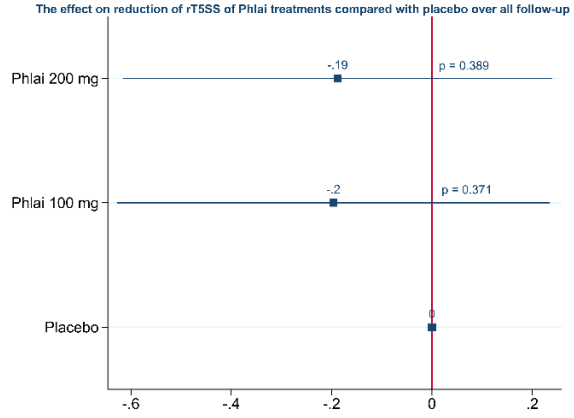


Figure 6. The effect on reduction of rT5SS of active treatments compared with placebo over all follow-up

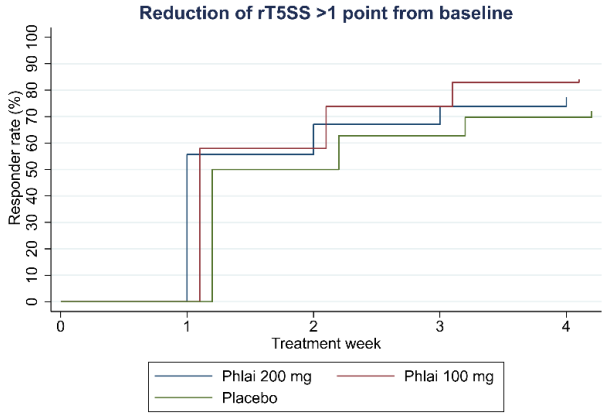


Figure 7. Time-response curves showing the percentage of patients exhibiting reduction of rT5SS from baseline >1 point by treatment week after treatment with Phlai 200 mg (n = 88), Phlai 100 mg (n = 88), and placebo (n = 86). Data are presented as mean proportion of participants. Phai 200 mg vs Phlai 100 mg: p = 0.34; Phlai 200 mg vs placebo: p = 0.28; Phlai 100 mg vs placebo: p = 0.044.

Table 4. Time advance of Phlai: treatment week at which responder rates were achieved

	Reduction of rT5SS from baseline >1 point		
Responder rate	**Phlai 200 mg**	**Phlai 100 mg**	**Placebo**
25%	1	1	1
50%	1	1	1
75%	3	2	-

Abbreviation: rT5SS, reflective total five symptom score

4.2.2 Instantaneous total five symptom score (iT5SS)

Compared to placebo, a trend was observed toward a greater reduction of iT5SS after week 4 in Group 2 receiving 100 mg of Phlai. (aMD -0.57; 95% CI -1.14, 0; p = 0.05) (Table 3).

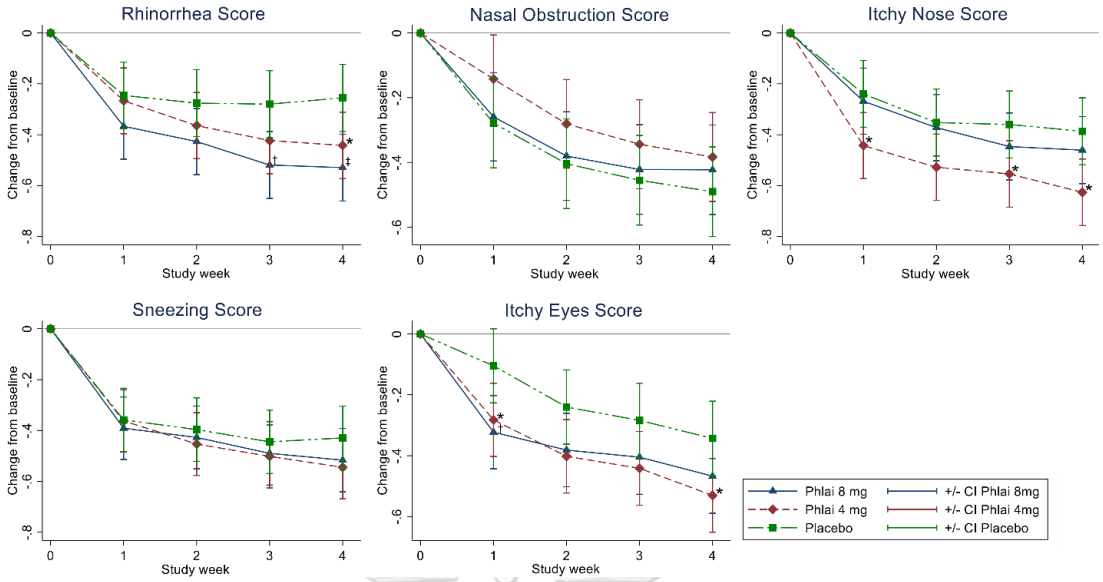


Figure 8. Adjusted changes from baseline to week 4 in individual reflective symptom scores (rhinorrhea, nasal obstruction, itchy nose, sneezing, itchy eyes). Data are least-squares means ± 95% CI for the full analysis set. Individual symptoms score range, 0-3. * $p < 0.05$ Phlai 100 mg versus Placebo; † $p < 0.05$ Phlai 200 mg versus Placebo, ‡ $p < 0.01$ Phlai 200 mg versus Placebo

4.2.3 Reflective individual symptom scores

Compared to placebo, there were statistically significant improvements in rhinorrhea (aMD -0.19; 95% CI -0.37, 0.002; p = 0.048), itchy nose (aMD -0.24; 95% CI -0.43, -0.05; p = 0.011), and itchy eyes (aMD -0.19; 95% CI -0.36, -0.02; p = 0.033) in Group 2 at 4 weeks. Improvement in itchy nose (aMD -0.2; 95% CI -0.39, -0.02; p = 0.03) and itchy eyes (aMD -0.18; 95% CI -0.35, -0.01; p = 0.04) in Group 2 were significantly better than placebo from week 1 (Figure 11, Table 3). Group 2 changes in nasal obstruction and sneezing were not statistically significant over follow-up. In Group 1, rhinorrhea was the only symptom which showed a significant improvement versus placebo at 3 weeks (aMD -0.24; 95% CI -0.43, -0.05; p = 0.01) and 4 weeks (aMD -0.27; 95% CI -0.46, -0.09; p = 0.004) (Figure 11, Table 3).

4.2.4 RCQ-36

Improvements in overall RCQ-36 score were greater in the active treatment groups versus placebo, but the differences were not statistically significant. (Figure 8, Table 3).

4.2.5 PNIF

Participants in all groups had improvements in peak nasal inspiratory flow, but the improvements in the active treatment groups were not statistically better than placebo. (Figure 8, Table 3).

4.2.6 Safety and adverse events

During the study period, 48.9%, 55.7%, and 55.8% of patients in Group 1, Group 2, and Group 3 experienced ≥ 1 adverse event (Table 5). The most common adverse events were sedation, dizziness, dry mouth/nose, and headache. The frequencies of common adverse events were not different among three groups. There was no significant change in the laboratory tests in any group (Table 6). Rescue medicine usage was similar for all groups, with 5.6%, 6.8%, and 7% of participants in Group 1, Group 2, and Group 3, respectively. Medication adherence to treatment was high over the study period, with of percentage of self-reported doses in Groups 1, 2 and 3 of 93.2%, 95.5%, and 94.2%, respectively (Tables 7 and 8). Three patients (0.01%) took concomitant drugs: in Group 1, one patient took a decongestant, and another an antidepressant; in Group 2, one participant used an intranasal corticosteroid.

Table 5. Adverse events from treatment

	Phlai 8 mg (n = 88)	**Phlai 4 mg (n = 88)**	**Placebo (n = 86)**
All adverse event n (%)			
Any-on treatment event	43 (48.9)	50 (56.8)	48 (55.8)
Grade 1	42 (47.8)	49 (55.7)	47 (54.7)
Grade 2*	1 (1.1)	1 (1.1)	1 (1.2)
Leading to study withdrawal	0 (0.0)	1 (1.1)	1 (1.2)
Most common adverse events n (%)**			
Sedation	23 (26.1)	19 (21.6)	28 (32.6)
Dizziness	11 (12.5)	10 (11.4)	8 (9.3)
Dry mouth/nose	20 (22.7)	28 (31.8)	27 (31.4)
Headache	6 (6.8)	10 (11.4)	6 (7.0)

* No grade 3 or 4 events were experienced by participants.

** Reported in 5% or more patients in any treatment group

Table 6. Changes in completed blood test, liver function, renal function tests from baseline to end of treatment

		Phlai 8 mg (n = 88)	**Phlai 4 mg (n = 88)**	**Placebo (n = 86)**
RBC (10^6/µL)	Mean (95% CI)	0.01 (-0.03, 0.05)	0.02 (-0.03, 0.06)	0.02 (-0.02, 0.07)
	p value	0.57	0.49	0.26
Hemoglobin (g/dL)	Mean (95% CI)	0.01 (-0.11, 0.12)	0.04 (-0.08, 0.15)	0.08 (-0.03, 0.2)
	p value	0.93	0.52	0.16
WBC (10^3/µL)	Mean (95% CI)	-0.2 (-0.57, 0.17)	0.15 (-0.22, 0.52)	0.08 (-0.29, 0.46)
	p value	0.29	0.42	0.66
Lymphocytes (%)	Mean (95% CI)	0.25 (-1.18, 1.69)	-0.27 (-1.69, 1.15)	0.35 (-1.09, 1.8)
	p value	0.73	0.71	0.63
Eosinophils (%)	Mean (95% CI)	-0.23 (-1.84, 1.38)	0.26 (-1.33, 1.85)	-0.24 (-1.86, 1.37)
	p value	0.78	0.75	0.77
Platelets (%)	Mean (95% CI)	0.10 (-0.17, 0.37)	-0.11 (-0.38, 0.16)	-0.13 (-0.4, 0.15)
	p value	0.47	0.41	0.37
AST (U/L)	Mean (95% CI)	-0.03 (-0.09, 0.03)	-0.02 (-0.07, 0.04)	-0.02 (-0.08, 0.04)
	p value	0.29	0.62	0.59
ALT (U/L)	Mean (95% CI)	-0.01 (-0.3, 0.29)	0.14 (-0.15, 0.43)	0.04 (-0.26, 0.33)
	p value	0.95	0.36	0.81
Creatinine (mg/dL)	Mean (95% CI)	-4.27 (-9.68, 1.13)	-1.15 (-6.5, 4.19)	-3.60 (-9.04, 1.84)
	p value	0.12	0.67	0.20
BUN (mg/dL)	Mean (95% CI)	0.09 (-1.37, 1.56)	-0.75 (-2.20, 0.71)	0.14 (-1.34, 1.62)
	p value	0.90	0.31	0.85

Abbreviation: RBC, red blood cell; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

Table 7. Summary of rescue medicine use to randomized therapy by week and randomized arm (intention-to-treat analysis)

		N (%)		
Study week	**Rescue Medicine**	**Phlai 8 mg (n = 88)**	**Phlai 4 mg (n = 88)**	**Placebo (n = 86)**
Week 1	Yes	1 (1.1)	2 (2.3)	1 (1.2)
	No	87 (98.9)	86 (97.7)	85 (98.8)
Week 2	Yes	3 (3.4)	4 (4.5)	2 (2.3)
	No	85 (96.6)	84 (95.5)	84 (97.7)
Week 3	Yes	3 (3.4)	2 (2.3)	3 (3.5)
	No	85 (96.6)	86 (97.7)	83 (96.5)
Week 4	Yes	4 (4.5)	3 (3.4)	2 (2.3)
	No	84 (95.5)	85 (96.6)	84 (97.7)

Table 8. Summary of adherence to randomized therapy by week and randomized arm (intention-to-treat analysis)

		N (%)		
Study week	**Rescue Medicine**	**Phlai 8 mg (n = 88)**	**Phlai 4 mg (n = 88)**	**Placebo (n = 86)**
Week 1	≥ 80%	86 (97.7)	86 (97.7)	85 (98.8)
	< 80%	2 (2.3)	2 (2.3)	1 (1.2)
Week 2	≥ 80%	84 (95.5)	87 (98.9)	82 (95.4)
	< 80%	4 (4.5)	1 (1.1)	4 (4.6)
Week 3	≥ 80%	83 (94.3)	87 (97.7)	84 (97.7)
	< 80%	5 (5.7)	2 (2.3)	2 (2.3)
Week 4	≥ 80%	83 (94.3)	84 (95.5)	85 (98.8)
	< 80%	5 (5.7)	4 (4.5)	1 (1.2)

4.2.7 Per-protocol analysis

The per-protocol analysis results were similar to the ITT analysis, with most outcome measures in the active treatment groups showing greater symptom improvement and quality of life versus placebo groups (Tables 9).

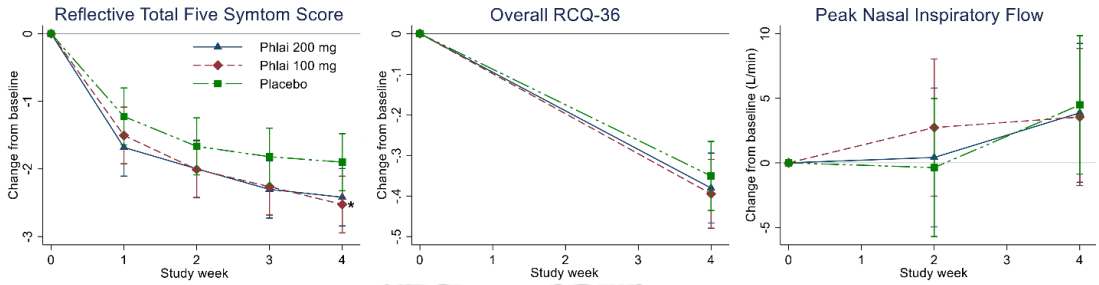


Figure 9. Adjusted changes from baseline to week 4 in reflective total five symptoms score, overall RCQ-36, and nasal peak inspiratory flow. Data are least-squares means ± 95% CI for the per-protocol set. Total five symptoms score range, 0-15. Overall RCQ-36 range, 1-5. * p <0.05 Phlai 100 mg versus Placebo.

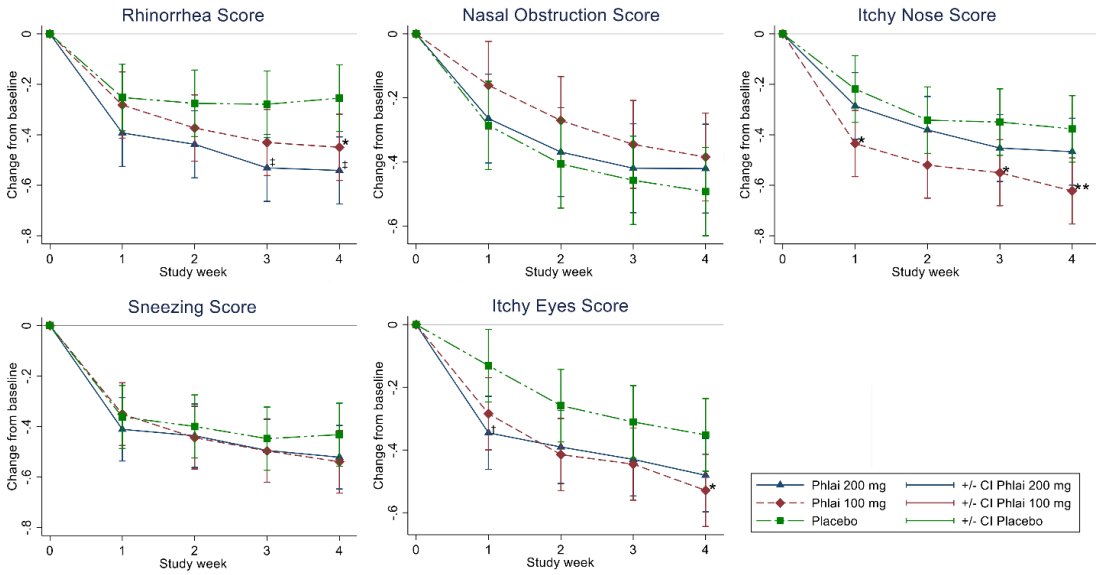


Figure 10. Adjusted changes from baseline to week 4 in reflective individual symptom scores (rhinorrhea, nasal obstruction, itchy nose, sneezing, itchy eyes). Data are least-squares means ± 95% CI for the per-protocol set. Individual symptoms score range, 0-3. * p <0.05 Phlai 100 mg versus Placebo; ** p <0.01 Phlai 100 mg versus Placebo; † p <0.05 Phlai 200 mg versus Placebo; ‡ p <0.01 Phlai 200 mg versus Placebo.

Table 9. Per-protocol analysis of adjusted mean change from baseline of patients-reported symptoms and objective assessments parameters at week 4

Outcome	Group	Adjusted mean change from baseline at week 4 (95% CI)	Difference between groups			
			vs Placebo (95% CI)	p value	Phlai 8 vs 4 mg (95% CI)	p value
rT5SS (Scale 0-15)	Phlai 8 mg	-2.42 (-2.84, -1.99)	-0.52 (-1.12, 0.08)	0.09	0.11 (-0.49, 0.70)	0.72
	Phlai 4 mg	-2.53 (-2.95, -2.11)	-0.63 (-1.22, -0.03)	0.039		
	Placebo	-1.90 (-2.32, -1.48)				
iT5SS (Scale 0-15)	Phlai 8 mg	-2.14 (-2.55, -1.73)	-0.34 (-0.92, 0.23)	0.28	0.22 (-0.35, 0.80)	0.45
	Phlai 4 mg	-2.37 (-2.77, -1.96)	-0.57 (-1.14, 0.01)	0.05		
	Placebo	-1.80 (-2.21, -1.39)				
Rhinorrhea (Scale 0-3)	Phlai 8 mg	-0.54 (-0.67, -0.41)	-0.29 (-0.47, -0.10)	0.003	-0.09 (-0.28, 0.09)	0.34
	Phlai 4 mg	-0.45 (-0.58, -0.32)	-0.19 (-0.38, -0.01)	0.040		
	Placebo	-0.25 (-0.39, -0.12)				
Nasal obstruction (Scale 0-3)	Phlai 8 mg	-0.42 (-0.56, -0.28)	0.07 (-0.12, 0.27)	0.47	-0.04 (-0.23, 0.16)	0.72
	Phlai 4 mg	-0.38 (-0.52, -0.25)	0.11 (-0.09, 0.30)	0.28		
	Placebo	-0.49 (-0.63, -0.35)				
Itchy nose (Scale 0-3)	Phlai 8 mg	-0.47 (-0.60, -0.33)	-0.09 (-0.28, 0.10)	0.34	0.16 (-0.03, 0.34)	0.10
	Phlai 4 mg	-0.62 (-0.75, -0.49)	-0.25 (-0.43, -0.06)	0.009		
	Placebo	-0.38 (-0.51, -0.24)				
Sneezing (Scale 0-3)	Phlai 8 mg	-0.52 (-0.65, -0.40)	-0.09 (-0.27, 0.09)	0.32	0.02 (-0.16, 0.19)	0.84
	Phlai 4 mg	-0.54 (-0.66, -0.42)	-0.11 (-0.28, 0.07)	0.23		
	Placebo	-0.43 (-0.56, -0.31)				
Itchy eyes (Scale 0-3)	Phlai 8 mg	-0.47 (-0.59, -0.34)	-0.12 (-0.30, 0.05)	0.16	0.06 (-0.11, 0.23)	0.48
	Phlai 4 mg	-0.53 (-0.65, -0.41)	-0.18 (-0.36, -0.01)	0.033		
	Placebo	-0.34 (-0.47, -0.22)				
Overall RCQ-36 (Scale 1-5)	Phlai 8 mg	-0.38 (-0.47, -0.29)	-0.03 (-0.15, 0.09)	0.63	0.01 (-0.11, 0.13)	0.82
	Phlai 4 mg	-0.39 (-0.48, -0.31)	-0.04 (-0.16, 0.08)	0.47		
	Placebo	-0.35 (-0.44, -0.27)				
PNIF (L/min)	Phlai 8 mg	3.87 (-1.50, 9.24)	-0.62 (-8.20, 6.97)	0.87	0.32 (-7.22, 7.87)	0.93
	Phlai 4 mg	3.55 (-1.76, 8.85)	-0.94 (-8.48, 6.60)	0.81		
	Placebo	4.49 (-0.87, 9.84)				

Abbreviations: rT5SS, reflective total five symptoms score; iT5SS, instantaneous total five symptom score, RCQ-36, The Rhinoconjuntivitis Quality of Life Questionnaire; PNIF, peak nasal inspiratory flow; SD, standard deviation; CI, confidence interval.

4.3 Discussion

In this randomized controlled trial of Phlai extract in patients with allergic rhinitis, the 100 mg and 200 mg doses provided an additional reduction in our main outcome of rT5SS, relative to the placebo group. The reduction in rT5SS to week 4 was statistically significant, and although the 8mg dose did not show a significant difference to placebo, the mean change in both active groups relative at week 4 was above the threshold for a clinically significant improvement [102].

The anti-inflammatory and anti-allergic effects of Phlai extract are mediated by compound D [10-15]. In a molecular docking and dynamic simulation study, compound D bound to the 5-lipoxygenase (5-LO) enzyme at the same binding site as arachidonic acid and Zileuton [104]. Therefore, it is likely that anti-asthmatic effects of compound D are mediated by competitive inhibition with arachidonic acid at the 5-LO binding site [104]. Preclinical studies revealed anti-inflammatory, anti-histaminic activity [14], smooth muscle relaxant [12]. Furthermore, *Zingiber montanum* (J.König) Link ex A.Dietr. suppressed inflammation and hypersensitiveness of airway epithelium in response to house dust mites [16].

Approximately two-thirds of study participants receiving *Zingiber montanum* (J.König) Link ex A.Dietr. experienced reduction in AR symptoms from the first visit onwards, versus 50% of the controls (Figure S2). The findings from our study showed that the magnitude of additional benefit of high dose (200 mg) over the low dose (100 mg) did not achieve the significance over all follow-ups regarding responder rate and effect on reduction of rT5SS. The reason that the 8 mg dose failed to achieve reductions of the same extent as the 100 mg dose is unclear, but possible explanations could include a higher proportion of incorrect treatment which influenced the subjective outcome assessments. The per-protocol analysis revealed a greater difference in rT5SS between the 200 mg dose and placebo group than in the intention-to-treat analysis, though it did not reach statistical significance.

The AR individual symptoms which improved in the active treatment groups over placebo were rhinorrhea, itching nose, and itching eyes reached statistical significance and MCID at one week (itching nose and itching eyes) and three weeks (rhinorrhea) and maintained thereafter. These symptoms are related to early phase allergic hypersensitivity [21] which is consistent with the findings of a previous study by

Tanticharoenwiwat et al. [11] showing inhibitory effect of compound D during the early phase on wheel and flare response to histamine, and house dust mite. Another other study by Limvuttegrijerat et al. [17] showed that a human pulmonary mucoepidermoid cell line significantly decreased phorbol12-myristate 13-acetate (PMA)-induced mucin (MUC2 and MUC5AC) production and gene expression when pretreated with *Zingiber cassumunar* Roxb. for two hours. These latter studies provide some evidence on the mechanism by which *Zingiber montanum* (J.König) Link ex A.Dietr. suppresses hypersecretion of mucus and improved rhinorrhea symptoms.

In contrast, our study did not demonstrate beneficial effects of *Zingiber montanum* (J.König) Link ex A.Dietr. on the late phase hypersensitivity response. Nasal obstruction improvements in the treatment groups were not different from the placebo group. Over two-thirds of participants in this study had persistent AR and hypertrophic inferior turbinate (Table 2) that could bring refractoriness to treatment. In addition, disease-specific quality of life in the treatment groups was not significantly different from the placebo group. *Zingiber montanum* (J.König) Link ex A.Dietr. improved nasal obstruction and disease-specific quality of life with greater reduction than the MCIDs when compared to baseline, but the comparison versus placebo was not statistically significant. Placebo arms in previously published randomized controlled trials of allergic diseases typically have a strong effect when evaluated by subjective rather than objective biochemical parameters [105]. In addition, when the questionnaire data of Israeli nurses' AR symptomatology while wearing face masks during the COVID-19 pandemic were evaluated, a decrease in symptom severity with mask usage was revealed when compared with no mask [106]. Since this study was conducted during the COVID-19 pandemic, and wearing masks was a habit for all study participants, face mask usage possibly minimized exposure of the respiratory system to provocative allergens, and reduced allergic rhinitis symptom severity in all participants including the placebo group.

Our study found that *Zingiber montanum* (J.König) Link ex A.Dietr. was safe with no moderate or serious adverse effects. Based on the findings of this Phase III study, we suggest *Zingiber montanum* (J.König) Link ex A.Dietr. can be as considered as an alternative treatment for patients with AR who suffer from rhinorrhea, itching nose,

and itching eyes. Further randomized controlled trials which compare *Zingiber montanum* (J.König) Link ex A.Dietr. with standard treatments are required to determine its role for the step-up and the step-down approach in the clinical practice guideline. Moreover, a long-term study of *Zingiber montanum* (J.König) Link ex A.Dietr. in treating AR is also required.

This study has limitations in several aspects. First, face mask usage by study participants may have confounded the study results by reducing exposure to airborne allergens. Second, biochemical parameters such as cytokine levels were not measured, and these would have provided more robust evidence of a therapeutic effect.

4.4 Conclusion

Zingiber montanum (J.König) Link ex A.Dietr. improved reflective total five symptom score, rhinorrhea, itchy nose, and itchy eyes after four weeks. There was no dose response relationship regarding different doses of *Zingiber montanum* (J.König) Link ex A.Dietr. extract. However, nasal obstruction, sneezing, overall RCQ-36, and PNIF did not reach a statistically significant difference compared to the placebo control group. Further randomized controlled studies are warranted to investigate the long-term effects of *Zingiber montanum* (J.König) Link ex A.Dietr.

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AWARD RECEIVED

1. Poster presentation award at MDCU congress 2020 for the study " Intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis" (2020)
2. Postgraduate outstanding student award in the Academic Year 2020. Faculty of Medicine, Chulalongkorn University
3. A traveling fellowship award. "Allergen-specific immunotherapy for local allergic rhinitis: a systematic review and meta-analysis". ERS 2021, Thessaloniki, Greece