Original Article

Efficacy of *Zingiber cassumunar* Roxb (Phlai capsule) Compare with Loratadine as Treatment in Allergic Rhinitis Patients (Preliminary Results)

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Abstract

Introduction: Phlai capsules can inhibit skin reactivity in allergic rhinitis patients.

Objectives: The aim of this study was to compare the efficacy of Phlai capsules with Loratadine in allergic rhinitis patients.

Methods: This was a multi-center, prospective, randomized, double-blinded, placebo-controlled study in 50 patients, aged 18-50 years old, who randomly received 4 mg or 8 mg Phlai capsules or Loratadine for 8 weeks. The primary efficacy endpoint was Total Symptoms Score at 4 and 8 weeks. The secondary endpoints were peak nasal inspiratory flow and quality of life.

Results: Demographic data was similar between groups. The change in 6-Total symptoms score decreased significantly from baseline. Peak nasal inspiratory flow increased with no significant differences between groups. According to the RCQ-36 questionnaire, there was significant improvement in quality of life for every domain, including sleep and emotion.

Conclusions: Phlai capsules reduced rhinitis symptoms and improved quality of life.

Keywords: *Zingiber cassumunar,* Phlai, Allergic rhinitis, Antihistamine, Quality of life

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Introduction

Allergic rhinitis (AR) is a serious health problem because of its prevalence and its impact on patients' social life, school performance, and work productivity.[1] Pharmaceutical treatments of AR are generally divided into two groups: oral H1-antihistamines and intranasal corticosteroids. Antihistamines play an important role in the treatment of AR. For example, loratadine is a once-daily, second-generation, non-sedating antihistamine which is commonly used to relieve allergic rhinitis symptoms.

Zingiber cassumunar Roxb. (Zingiberaceae), known as "Phlai" in Thai, has been used as traditional medicine in Thailand for treatment of various diseases, including allergic rhinitis and asthma. The major bioactive component is (E)-4-(3', 4'-dimethoxyphenyl) but-3-en-1-ol (compound D), which has anti-inflammatory activity, is a smooth muscle relaxant, is an antihistamine, and has mucin-lowering secretion properties.[2-4] In a molecular docking and molecular dynamic simulation, compound D molecules bound to arachidonic acid on 5-lipoxygenase (5-LO) enzyme at the same binding site as an inhibitor of 5-LO (Zileuton).[5] Therefore, the active constituent, compound D, has potential anti-allergic and anti-inflammatory effects.

Previous study showed that *Zingiber cassumunar* Roxb (Phlai) can inhibit skin reactivity to histamine and to mite-skin-prick test in AR patients.[6] Studies of pharmacokinetics and safety (acute and chronic) of *Zingiber cassumunar* have been conducted with animals.[7,8] Phlai capsules, once daily 8 mg (of compound D) over 12 weeks, did not cause serious adverse events or laboratory abnormalities in healthy volunteers.[9]

Traditional herbal medicines are widely used in Asia, including Thailand. They are more affordable and accessible for local communities and align with patients' concerns about adverse effects of modern medicines. *Zingiber cassumunar* Roxb., known as "Phlai" in Thai, is commonly used in Thailand to relieve myofascial pain and for aromatherapy. However, the antihistaminic effect of Phlai has not yet been compared to that of second-generation H1-antagonist drugs which are now recommended for treatment of allergic rhinitis. The aim of this study was to compare the efficacy of Phlai capsule and Loratadine for treatment of AR patients.

Methods

Study Design

This study was a multi-center, prospective, randomized, double-blinded, placebo-controlled, interim analysis trial of 50 allergic rhinitis patients. It evaluated the efficacy of Phlai capsule 4 mg and Phlai capsule 8 mg compared with Loratadine 10 mg in treatment of AR patients for 8 weeks. The trials were conducted at the out-patient department, Thammasat University Hospital and at the ENT department, Siriraj Hospital, Thailand. Blinded co-investigators conducted informed consent interviews and exchanged information with the patients. Informed written consent forms were obtained from all enrolled patients. The study was approved by the human ethics committee of both trial sites and registered with http://www.clinicaltrials.in.th (TCTR 20171111002).

Patients

Fifty allergic rhinitis patients, 18-50 years old, who met inclusion and exclusion criteria were eligible for the study. Inclusion criteria were positive skin prick test for at least one of five aeroallergens (house dust mite, cockroach, Bermuda grass, cat hair, and dog dander), and total nasal symptoms score 6-10 from 12 on 3 consecutive days. Exclusion criteria were asthma, immunotherapy treatment, underlying chronic disease, history of nasal cavity surgery within 6 months, anatomical defect of nasal cavity, rhinosinusitis, women with pregnancy or lactation, and patients who received sedative or anxiolytic drugs. All patients provided written informed consent.

Trial Treatment

Before randomization, patients entered a run-in period lasting 2 weeks during which they had to cease any antihistamine for 7 days prior to the trial, and any topical or systemic steroids for 2 weeks prior to and during the trial. Eligible patients were randomly assigned to receive either Phlai 4 mg, Phlai 8 mg, or Loratadine 10 mg once a day for 8 weeks. Phlai capsules were provided by the Government Pharmaceutical Organization and were identical in appearance. In case of severe symptoms such as severe nasal obstruction or rhinorrhea, patients were permitted to use rescue medication, i.e., oral pseudoephedrine or normal saline irrigation and medication scores were recorded. Follow-up

visits were scheduled at 2, 4, and 8 weeks after study participation. Participants were asked to report any unusual symptoms occurring after the drug intake such as sedation, dizziness, dry mouth, or headache.

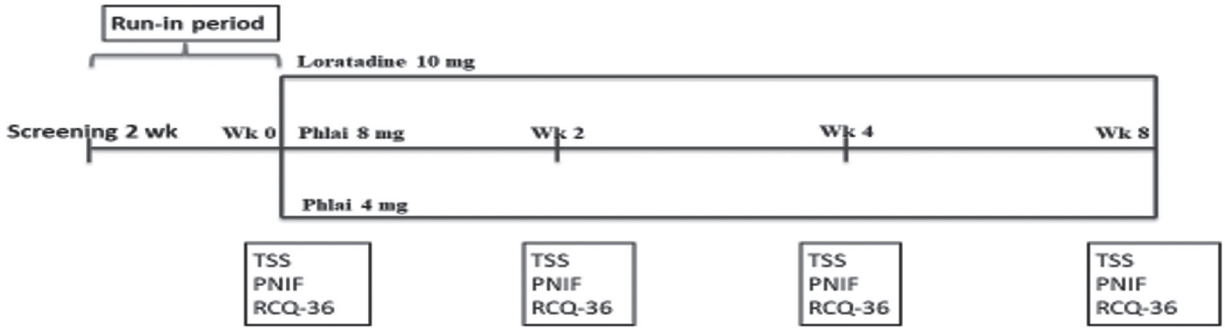

Figure 1 Trial design.

Endpoints and Assessments

The primary efficacy endpoint was the change in 6-Total Symptoms Score (TSS) at 4 and 8 weeks. The 6-total symptoms score included 4 nasal (sneezing, nasal itching, nasal obstruction, and rhinorrhea) and 2 ocular (eye itching and tearing) scores. During the trial, patients were assigned to record daily scores of nasal symptoms, ocular symptoms and rescue medication use. The 6-total symptoms scores (TSS) were calculated as mean ± SD, compared between baseline, 4 and 8 weeks of treatment in all groups (Figure 1).

The secondary endpoints were the change in peak nasal inspiratory flow (PNIF) and quality of life (QOL). A peak nasal inspiratory flow meter was used to measure the level of nasal obstruction and recorded at baseline, 2-, 4-, and 8-week visits. The other secondary endpoint was the change in quality of life, measured as the mean of the RCQ-36 questionnaire scores. The 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) [119]. The score of each item ranged from 1 to 5 (lower is better). The RCQ-36 assessment was performed over the screening period, 2, 4, and 8 weeks after treatment. Nasal symptom scores (NSS) and ocular symptom scores (OSS), were analyzed to study the efficacy of treatment. Descriptive analysis was used for demographic data and one-way ANOVA for drug efficacy.

Results

Demographic Data

The 50 allergic rhinitis patients (37 females, 13 males) were randomly allocated to Phlai 4 mg (16 patients), Phlai 8 mg (16 patients) and Loratadine (18 patients). Demographic and clinical characteristics of participants were not significantly different in all groups (Table 1).

Table 1 Patients' demographic and clinical characteristic data

	Loratadine (n = 18, 36%)	**Phlai 8 mg (n = 16, 32%)**	**Phlai 4 mg (n = 16, 32%)**
Gender (male, n, %)	4 (22.22)	4 (25)	5 (31.25)
Age (years; range)	33.27 (23-49)	32.62 (20-49)	30.87 (21-45)
Baseline TSS - Mean ± SD	8.71 ± 1.84	8.56 ± 2.14	9.25 ± 2.78
Baseline TNSS - Mean ± SD	7.01 ± 1.35	6.86 ± 1.47	7.68 ± 2.06
Baseline OS - Mean ± SD	1.69 ± 1.28	1.69 ± 1.36	1.82 ± 1.27
Baseline PNIF - Mean ± SD	91.11 ± 33.54	94.68 ± 34.81	92.18 ± 34.11
Baseline VAS - Mean ± SD	6.77 ± 1.77	7.43 ± 1.20	6.62 ± 1.86
Positive skin test			
• Dust mite	13 (72.22)	13 (81.25)	15 (93.75)
• Cockroach	12 (66.67)	10 (62.50)	11 (68.75)
• Dog	0	2 (12.50)	4 (25)
• Cat	6 (33.33)	5 (31.25)	8 (50)
• Grass	3 (16.67)	4 (25)	9 (18)
• Dust mite+ Cockroach	8 (32)	7 (28)	10 (40)

Primary Efficacy Outcomes

At 4 and 8 weeks, the 6-total symptom scores were significantly reduced compared to baseline in all groups. There were no significant TSS differences between the groups (Figure 2).

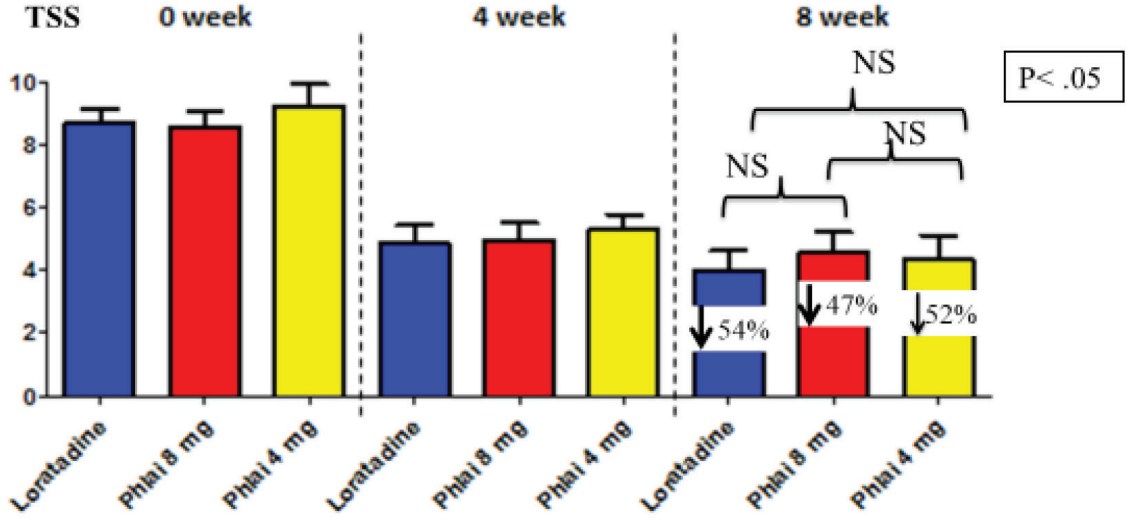

Figure 2 The 6-total symptoms score at baseline, 4 and 8 weeks. (mean ± SD); NS = not significant.

We note the reduction in 6-TSS began after a week of trial in all groups. Besides the TSS, the change in Total Nasal Symptom Scores (TNSS) and Ocular Scores (OS) similarly decreased significantly compared to the baseline for all groups, and there were no significant differences between groups in TNSS or OS (Figure 3).

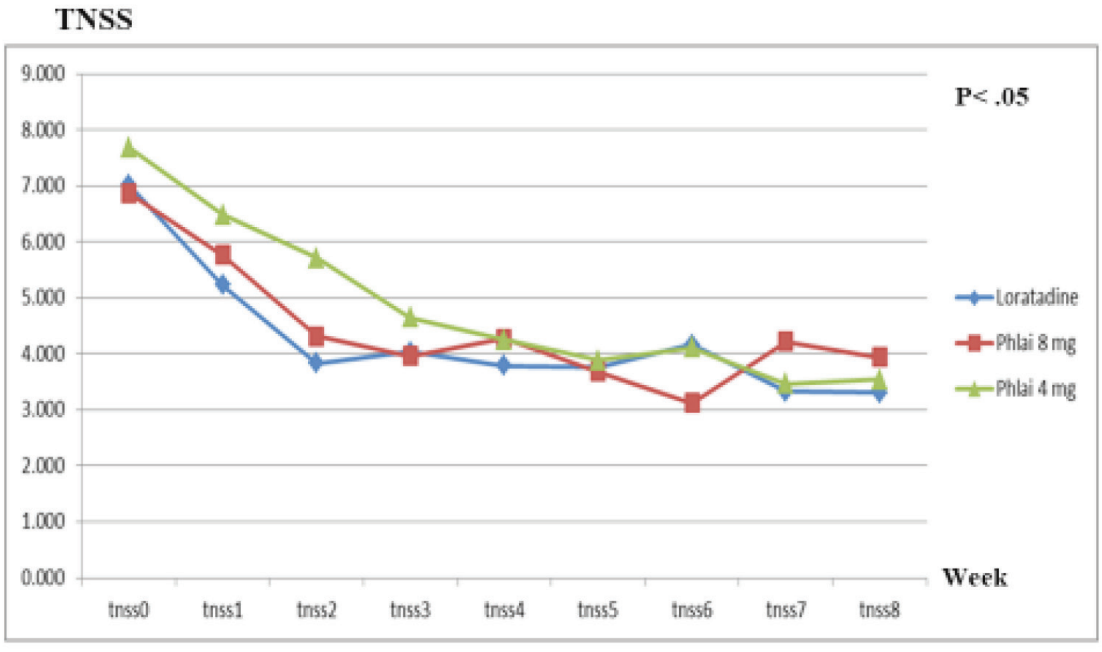

Figure 3 The total nasal symptom score (TNSS) at baseline and weekly mean scores (mean ± SD).

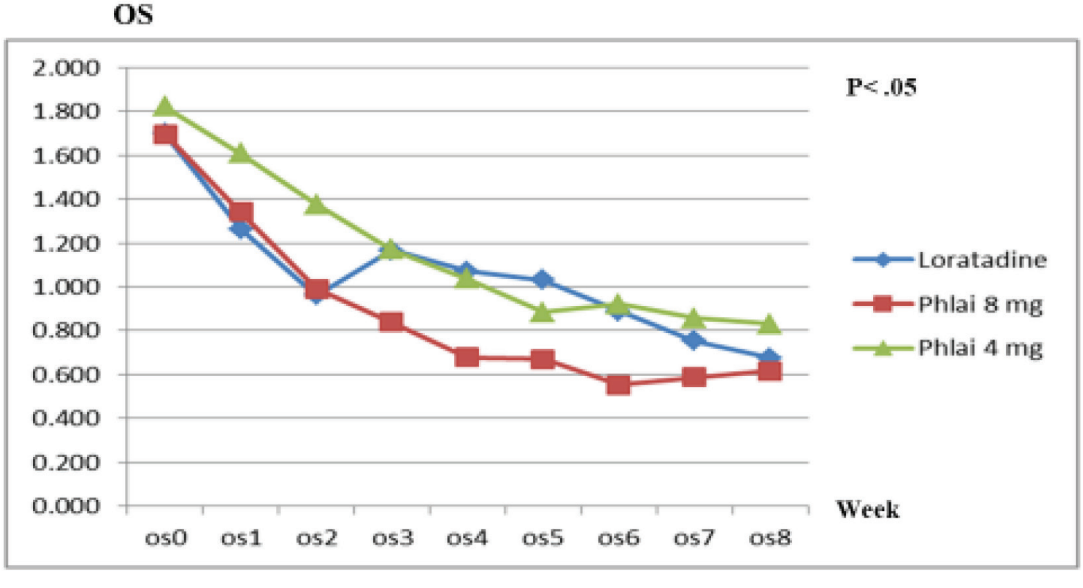

Figure 4 The ocular score (OS) at baseline and weekly mean scores, (mean ± SD).

Secondary Efficacy Outcomes

Peak nasal inspiratory flow (PNIF) and quality of life (QOL) were evaluated as secondary efficacy outcomes. PNIF increased from baseline in Phlai 4 mg, Loratadine 10 mg and Phlai 8 mg respectively, but there were no significant differences between the groups (Figure 5).

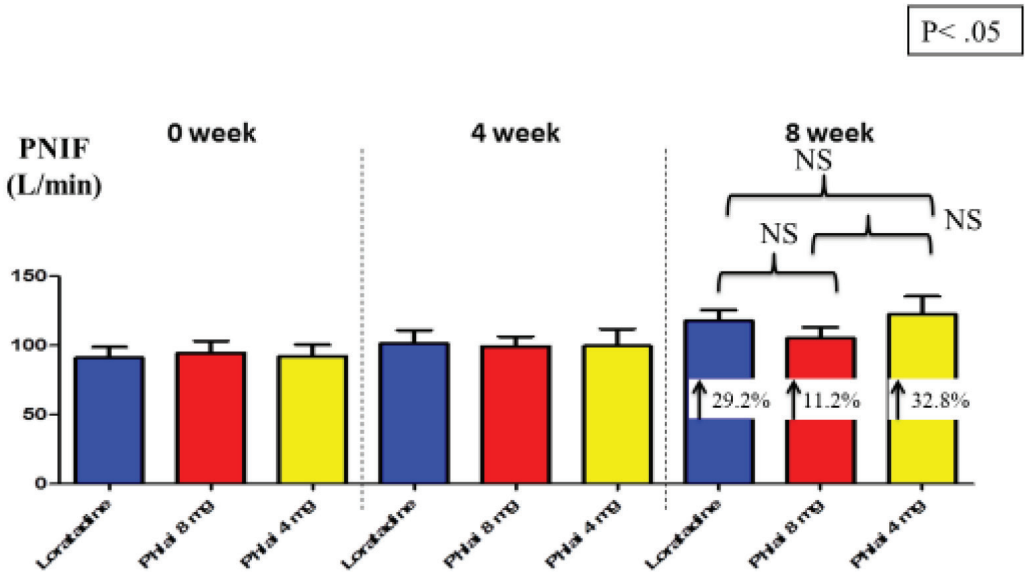

Figure 5 Peak nasal inspiratory flow at baseline, 4- and 8-week follow-up (mean ± SD).

Evaluation of quality of life was another important domain in allergic rhinitis patients because moderate to severe symptoms impair the quality of life and work. RCQ-36 questionnaires reflected significant improvement from baseline in all dimensions of QOL for all three groups, and there were no significant differences between groups (Figure 6). Both doses of Phlai capsules were well-tolerated and there were no adverse events.

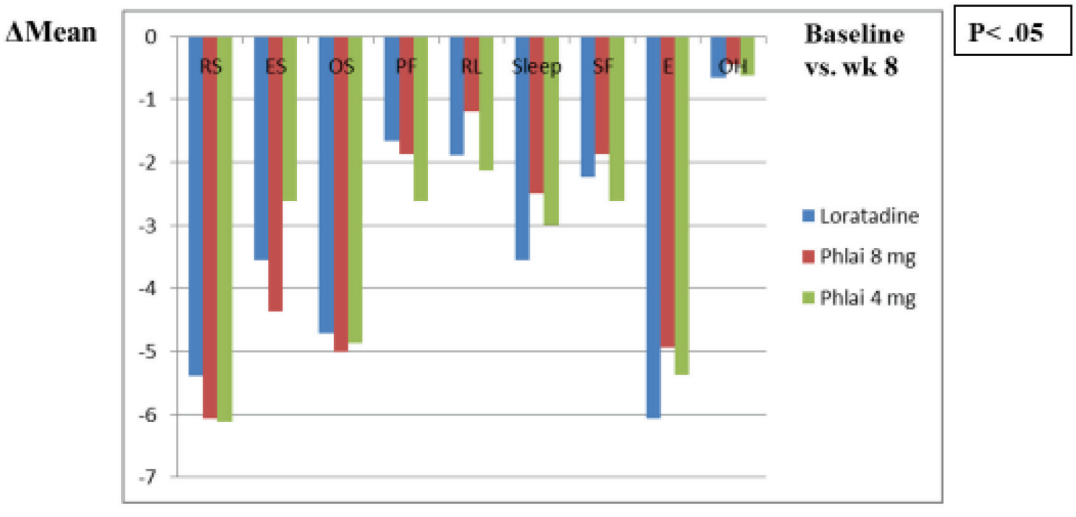

Figure 6 The change in Quality of Life (QOL) from RCQ-36 questionnaires between baseline and at 8 week followed up. RS- Rhinitis Symptoms; ES- Eye Symptoms; OS- Other Symptoms; PF- Physical Functioning; RL- Role Limitation; SF- Social Functioning; E- Emotion; OH- Overall Health.

Discussion

In this preliminary study, we compared the efficacy of Phlai capsules, both 4 mg and 8 mg, and Loratadine 10 mg, for 8 weeks in treatment of allergic rhinitis. The trial showed that Phlai capsules had same efficacy as Loratadine, a second-generation antihistamine which is the standard of care for AR. All three treatments reduced nasal and ocular symptoms, and improved peak nasal inspiratory flow and quality of life. There were no significant differences in efficacy between any of the three groups, including between the 4 mg and 8 mg dosages of Phlai.

Phlai is found in Thailand and other Asian countries.[10] However, there is little clinical evidence of how Phlai affects AR symptoms. Our previous study demonstrated that Phlai capsules could suppress histamine-induced wheal and flare similarly to loratadine.[6] A previous study found that *Zingiber officiale* improved clinical symptoms of AR and reduced serum total IgE. However, no studies have been published about *Zingiber cassumunar* Roxb (Phlai capsule) and allergic rhinitis symptoms. In this clinical trial, Phlai capsules reduced TNSS and PNIF and improved quality of life in AR patients. We found that Phali could reduce all rhinitis symptoms including ocular and nasal obstruction.

The strength of this study was its design: prospective, randomized, double-blind, and placebo-controlled. Its limitations were small sample sizes and lack of cytokine evaluation for treatment response measurement.

In conclusion, this trial showed that for treatment of allergic rhinitis, the efficacy of Phlai capsules is similar to that of loratadine for reducing total nasal and ocular symptoms and improving quality of life. Both 4 mg and 8 mg doses of Phlai capsules reduced total symptoms score of allergic rhinitis symptom and improved quality of life in AR patients.

Acknowledgements

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