Original Article

Preliminary Study on Safety and Efficacy of a Thai Herbal Remedy in Persistent Allergic Rhinitis: A Randomized Double-blind Placebo-controlled Trial

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Background: Globally, the prevalence of allergic rhinitis has increased significantly. However, herbal remedies for allergic rhinitis were recorded on Wat Pho's marble inscription in 1832, yet have never been scientifically studied.

Objective: To identify the safe and appropriate dose of an herbal remedy comprising six herbs in healthy adults, and to explore the safety and preliminary efficacy of the remedy.

Materials and Methods: Phase I, a randomized, non-blinded study focusing on safety of the studied drug included 16 healthy participants. Phase IIa, a randomized, double-blind, placebo-controlled trial, included 44 patients with persistent allergic rhinitis.

Results: Generally the Thai herbal remedy was safe. However, diarrhea was reported significantly move often in the group that received the remedy than in the placebo group (p = 0.029). The appropriate dose was determined to be two capsules (1.12 g) after meals, three times per day. Preliminary efficacy according to symptom-score evaluation by a physician revealed significant improvements in 3 symptoms. The more than 25% improvement in peak nasal inspiratory flow was detected in participants who received herbal remedy (p = 0.018).

Conclusion: This herbal remedy was well tolerated, with a somewhat increased occurrence of diarrhea. Although the study showed some symptom improvement.

Keywords: Thai herbal remedy, Allergic rhinitis, Clinical trial, Safety, Efficacy

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Globally, the prevalence of allergic rhinitis has increased significantly[1]. In Thailand, Allergy is one of the 10 chronic diseases of concern to the Ministry of Public Health[2]. The Kana-harissaroke in the Canon of Harissaroke of Wat Pho's marble inscription refers to the following symptoms of allergic rhinitis[3,4]. The Wat Pho's marble inscription was made in 1832 and for more than three generations it has been accepted as a high level of supporting evidence for herbal treatment properties[5]. The inscription indicates three Thai traditional medicine formulas appropriate for treating allergic rhinitis. The formula evaluated in this study consisted of equal part of Plumbagidis Indicae Radix, Telosmae Cordatae Radix, Zingiberis Officinalidis Rhizoma, Gloriosae Superbae Radix and Piperis retrofracti Fructus each, and three parts of Piperis Nigri Fructus[3].According to the principles of Thai traditional medicine theory, this formula is considered highly effective in resolving rhinosinusitis by affecting disease pathogenesis. This herbal remedy is cited in the Thai herbal guidebook[6], which has been the reference for most Thai traditional pharmacies for the past 40 years. Independent studies are needed to verify that this medicine is safe and effective in addition to treatment recommendations from references based on traditional use. A WHO meeting report on traditional treatments addressed the clinical evaluation of traditional treatments and stated that the national drug assessment policy might accept herbal clinical treatment evaluation with a high level of supporting evidence without toxicology and preclinical testing[5]. The dosage of the formulation is not explicitly known. However, the National List of Essential Medicines[7] shows a treatment dosage for a similar traditional remedy of 3.0 to 6.5 g/day. Hence, the recommended dosage is 3.0 to 4.5 g/day.

The present study reports a preliminary Phase I

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and IIa clinical trial to investigate the safety with proper dosage and preliminary efficacy of the Thai herbal remedy against chronic allergic rhinitis over a 4-week period.

Materials and Methods

The present study was approved by the Institutional Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, number MUTM 2015-005-01 and the Mahasarakham University, numbers 0136/2556 and 207/2557. The present study was conducted following Good Clinical Practice guidelines and trial registered under the Thai Clinical Trial Registry number 20150123003.

Research design

Phase I was an open-labeled safety trial in a group of 16 healthy participants. All participants were randomly assigned by a researcher to receive one of two doses: two (Group one) or three (Group two) capsules of the study medication three times/day for 4 consecutive weeks. Safety was assessed on the basis of physical examinations and blood samples at weeks 0 (baseline), 2 and 4 following safety parameters[8]. Participants were asked to report any adverse events occurring in week 2 and 4. The appropriate dosage was then selected after 4 weeks.

Phase IIa was a randomized, double-blind, placebo-controlled safety and preliminary efficacy trial in individuals with allergic rhinitis. The 44 enrolled participants were randomly assigned by a researcher to take a Thai herbal remedy (Group one) or a placebo (Group two). Safety blood investigations at week 0 (baseline), 2 and 4 following safety parameters[8]. Preliminary efficacy was determined by measuring peak nasal inspiratory flow (PNIF)[9] with a portable Youlten flow meter (In-check Nasal; Clement Clarke International, Essex, England). Physicians also assessed symptoms with a 7-level visual-analog scale[10]. Five satisfactory maximal inspirations were obtained and the average flow of the three highest results was taken as the PNIF.

Study participants

Healthy adults (determined with a physical examination) aged 18 to 59 years were included in the phase I trial at Suddhavej Hospital, Faculty of Medicine, Mahasarakham University. Phase IIa was conducted at the Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University. Each patient was pricked with the following common allergen extracts (ALK Laboratories, Port Washington, NY)[11]. The test was interpreted as positive if the mean wheal diameter at 15 min was 3 mm larger than the negative control to diagnose allergic rhinitis for study enrolment.

All participants signed a consent form and understood the details of the trial before study enrolment. The following exclusion criteria were used: 1) addicted to alcohol or drugs; 2) those participating in other ongoing projects or required to take daily medications; 3) those concurrently taking herbal medications that had the same components as the studied drug; 4) pregnant or lactating or planning to become pregnant within 6 months; and 5) showing a history of allergy to any herbal component used in the study regimen. For phase IIa, additional exclusion criteria included: 1) patients concurrently taking antihistamines or steroid medications and not willing to interrupt their daily medication regimen; and 2) patients with chronic diseases that could affect the results of study assessments.

Study medicine

Thai herbal remedy was prepared as a capsule, with each capsule containing 560±11 mg of Plumbagidis Indicae Radix, Telosmae Cordatae Radix, Zingiberis Officinalidis Rhizoma, Gloriosae Superbae Radix and Piperis retrofracti Fructus at 70 mg each and Piperis Nigri Fructus at 210 mg. Two materials which have side effects were Gloriosae Superbae Radix has diarrhea, stomach irritation and warming sensation effects[12] and Plumbagidis Indicae Radix has uterine compression effects[13]. Therefore, the medicine is contraindicated in pregnant women and in those presenting with fever. The process of obtaining the study medicine started with assessment of the quality of the above-mentioned components as set out by the Thai Herbal Pharmacopoeia guidelines[14]. After quality assessments, Gloriosae Superbae Radix was detoxified as recommended by five experts on Thai traditional medicine; the root was ground and roasted at 130°C and passed through an 80 µm sieve. The other ingredients were ground and passed individually through the 80 µm sieve. The ingredients were then combined into a capsule, as previously described and packed into an opaque plastic bottle. The bottle was then sterilized with gamma radiation and the quality of the capsules was assessed. The placebo capsule was composed of 96.8% powdered cream and 3.2% powdered cinnamon at 365±7 mg/capsule. The capsules passed quality assessment and microbial and heavy metal contamination[14].

Sample size

For phase I, the sample size was calculated to be 10 participants per group. However, because this medication had never been studied before, the sample size was reduced to five participants per group for the first round because of safety concerns about severe drug reactions. Once the appropriate dosage had been established, another six participants were added.

For phase IIa, the sample size was calculated with a power and sample-size calculation program, version 3.1.2, assuming a 10% withdrawal, to be 20 patients per group.

Statistical analysis

Statistical analysis was conducted on the intention-to-treat population. All categorical data were analyzed with the Chi-square test and relative risk. Continuous data were analyzed with a dependent t-test and independent t-test, respectively. Both tests were based on 2-sided t-tests where $\alpha = 0.05$ was considered statistically significant.

All statistical analyses were conducted with SPSS. version 11.5

Results

Phase I

Out of 12 participants screened, five were randomly assigned to Group 1 and six to Group 2. In Group 2, one participant withdrew from the study at week 2 because of liver enzyme elevation. The appropriate medication dose was determined to be two capsules three times daily. An additional five participants were enrolled to take the medication for 4 weeks.

The average age of study participants was 22.8±1.2 years, 75% were females, and all participants had an undergraduate degree. Baseline assessments, including physical examinations and blood tests, showed that all participants were healthy, with no significant difference between Groups 1 and 2 (p>0.05), (data not shown).

Dosage assessment for Thai herbal remedy

At week 2, one participant in Group 2 had an alanine aminotransferase (ALT) of 88 U/L and an aspartate aminotransferase (AST) of 49 U/L, which are approximately 1.5 times the upper normal limits (baseline ALT, 32 U/L and AST, 21 U/L). Concomitant paracetamol use for 3 days to relieve headache was also noted in the participant's medical history. He was clinically asymptomatic but withdrew from the study. After discontinuation of the study drug and paracetamol for 1 week, the participant's liver enzymes returned to normal (ALT, 55 U/L; AST, 29 U/L). Hence, we decided to set the dosage of the Thai herbal remedy at two capsules, taken three times per day.

Safety assessment

The safety assessment was conducted in Group 1 (taking two capsules/meal) only. This was because Group 1 had received the appropriate dosage of the Thai herbal remedy. The physical examination, vital signs and blood tests of all participants were normal value range. There were no serious adverse events throughout the study. The reported adverse events at week 4 were mild nose irritation in two participants, mild stomach irritation in two, moderate stomach irritation in one, mild diarrhea in two, moderate diarrhea in two and mild warming sensation in four participants.

Phase IIa

The study recruitment and screening were conducted from April 2015 to March 2016. Among 59 patients screened, 44 were enrolled in the study. The participants were randomly divided into two groups in a 1: 1 ratio (Figure 1). All enrolled participants had moderate to severe chronic allergic rhinitis. There were no statistically significant differences in baseline demographic data, blood tests, symptom scores between the groups (Table 1).

Safety assessment

Comparisons of vital signs and blood tests between

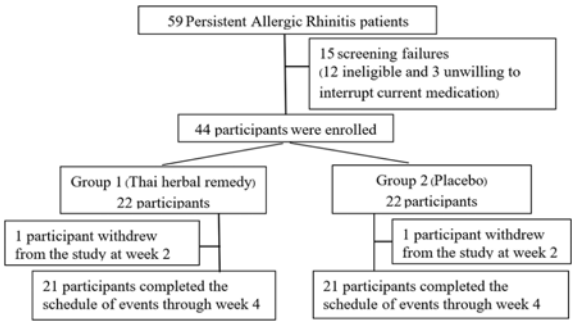

Figure 1. Overview of participants with persistent allergic rhinitis enrolled in the Phase IIa clinical trial.

Table 1. Demographic data at baseline (Phase IIa)

Demographic data	Group 1 (n = 22)	Group 2 (n = 22)	p-value
Demographics			
Age, years (mean ± SD)	45.23±16.85	38.95±13.26	0.177
Females, n (%)	15 (68)	14 (64)	>0.05**
Body mass index, kg/m^2 (mean ± SD)	22.60±3.16	21.50±2.96	0.241
Education			
Secondary school, n (%)	6 (27)	5 (23)	0.213**
Bachelor's degree, n (%)	10 (45)	15 (68)	
Higher than bachelor's degree, n (%)	6 (27)	2 (9)	
Moderate-severe allergic rhinitis, n (%)	22 (100)	22 (100)	NA
Positive skin-prick test			
Dermatophagoides pteronyssinus, n (%)	20 (91)	18 (82)	0.664**
Dermatophagoides farinae, n (%)	19 (86%)	18 (82%)	1.000**
PNIF (L/sec) (mean ± SD)	96.84±39.78	102.41±32.07	0.612

p-value = independent t-test, p** value = Chi-square test

the Thai herbal remedy and placebo groups at week 4 revealed no significant differences between groups. In addition, no severe adverse events were observed in either group during the trial period. At week 4, patients taking the Thai herbal remedy had a risk ratio of 2.14: 1 for diarrhea; this difference was statistically significant (p = 0.029, 95% CI 1.10 to 4.16; Figure 2).

Preliminary efficacy assessment

Although, no statistically significant difference in change in PNIF was observed between the groups. We also assessed the percentage of participants with improved PNIF at week 4 compared with baseline. At the end of the study a significantly higher percentage of participants receiving the studied drug showed more than 25% improvement in PNIF than those in the placebo group (47.6% vs. 19.0%, p = 0.018).

The physician assessed symptoms found 13 out of 15 symptoms improved significantly from baseline in both groups (Table 2). We compared between Thai herbal remedy group and placebo group by the best symptom scores. The results showed three symptoms improved significantly from baseline: itchy eyes (p = 0.016; 95% CI = -2.37 to -0.26), eye irritation (p = 0.017; 95% CI = -2.02 to -0.21) and brain fog (p = 0.034; 95% CI = -1.94 to -0.08) (Table 3).

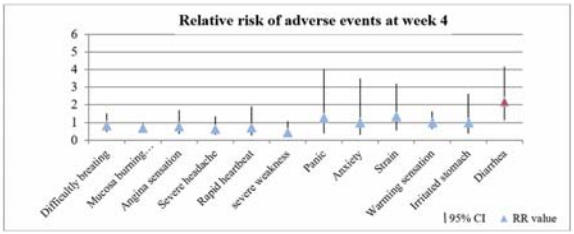

Figure 2. Relative risk of adverse events at week 4.

Discussion

In the Wat Pho inscription, this medication is described as a powder to be dissolved in water for consumption. However, using a powdered formula without an effective device for drug delivery may skew the dose used at each intake, making it difficult to assess results accurately. In this study, we converted the medication into a capsule of fixed dosage (560±11 mg per capsule) that can be easily taken orally.

The phase I medication dosage used in the present study was 1.12 g/meal, which is in accordance with the normally recommended dosage of 0.5 to 1.0 g/meal for three meals/day for any Thai traditional remedy in the Thai Traditional Pharmacy guidebook[15]. In the present study, we did not further investigate all possible causes of the liver enzyme elevation seen at week 2; however, the authors presumed the elevation to be a drug-related event because of its spontaneous resolution after drug interruption and the history of concomitant paracetamol use. Therefore, we cannot provide a specific warning regarding consumption of the studied drug, but we caution against using it at a high dose or in combination with paracetamol or other hepatotoxic drugs.

Diarrhea occurred significantly more often in the Thai herbal remedy group. This adverse event is predictable and dose-dependent (type A) because the remedy is made

Table 2. Physician assessment: symptoms of allergic rhinitis according to each group

Symptom assessment (score 1 to 7) (mean ± SD)	Group 1 (Thai herbal remedy)			Group 2 (placebo)		
	At baseline (n = 22)	At week 4 (n = 21)	p-value	At baseline (n = 22)	At week 4 (n = 21)	p-value
Rhinorrhea	3.82±2.26	2.62±1.32	**0.009**	4.00±2.35	2.29±1.19	**0.003**
Nasal itching	4.23±1.93	2.48±1.86	**0.002**	4.05±1.84	2.86±1.80	**0.020**
Nasal obstruction	4.59±1.79	3.10±1.70	**0.007**	4.64±1.84	3.29±1.68	**0.012**
Sneezing	3.73±2.03	2.81±1.50	0.069	4.05±1.79	2.38±1.60	**0.003**
Cough	3.00±1.88	1.76±1.09	**0.018**	3.00±2.41	1.52±0.81	**0.004**
Dry throat	4.82±1.99	3.62±2.11	**0.009**	4.23±2.16	3.48±2.10	0.181
Cough and phlegm	4.32±2.32	3.10±2.25	**0.001**	4.14±2.42	3.00±2.32	**0.047**
Itchy eyes	3.41±2.06	1.71±0.84	**0.000**	3.82±2.15	2.90±1.73	**0.010**
Eye irritation	3.14±1.93	1.62±0.86	**0.001**	3.64±2.17	2.81±1.75	**0.041**
Eye tearing	2.05±1.36	1.62±0.97	0.153	2.59±2.17	1.76±1.18	0.071
Brain fog	3.18±1.99	1.95±1.66	**0.006**	3.23±1.90	2.45±1.70	**0.035**
Weakness	3.23±2.04	1.81±1.12	**0.001**	3.59±2.08	2.43±1.72	**0.016**
Breathlessness	4.09±1.95	2.90±2.14	**0.021**	4.55±1.82	2.71±1.87	**0.001**
Headache	3.14±1.96	1.76±1.04	**0.004**	3.14±1.91	1.81±1.29	**0.003**
Somnolence	3.82±2.28	2.71±1.95	**0.006**	4.18±2.08	2.71±1.95	**0.006**
Insomnia	3.23±2.18	2.57±2.0	0.130	3.77±1.93	1.86±1.50	**0.000**

p-values = dependent t-test, values in bold indicate p<0.05

Table 3. Physician assessment: symptoms of allergic rhinitis compared between group 1 and 2

Symptom assessment (score 1 to 7) (mean ± SD)	At week 0 (baseline)			Best symptoms scores at week 4		
	Group 1 (n = 22)	Group 2 (n = 22)	*p*-value	Group 1	Group 2	*p*-value
Rhinorrhea	3.82±2.26	4.00±2.35	0.795	n = 13, 2.00±1.22	n = 15, 1.87±0.99	0.753
Nasal itching	4.23±1.93	4.05±1.84	0.750	n = 17, 2.06±1.68	n = 16, 2.25±1.34	0.721
Nasal obstruction	4.59±1.79	4.64±1.84	0.934	n = 16, 3.06±1.84	n = 18, 2.83±1.29	0.675
Sneezing	3.73±2.03	4.05±1.79	0.584	n = 13, 2.23±1.42	n = 16, 1.88±1.09	0.452
Cough	3.00±1.88	3.00±2.41	>0.05	n = 15, 1.27±0.59	n = 20, 1.50±0.83	0.361
Dry throat	4.82±1.99	4.23±2.16	0.351	n = 14, 3.07±2.13	n = 15, 3.00±1.96	0.926
Cough and phlegm	4.32±2.32	4.14±2.42	0.800	n = 17, 2.76±2.33	n = 13, 1.69±1.18	0.142
Itchy eyes	3.41±2.06	3.82±2.15	0.523	n = 18, 1.61±0.78	n = 14, 2.93±2.02	**0.016**
Eye irritation	3.14±1.93	3.64±2.17	0.425	n = 20, 1.55±0.83	n = 15, 2.67±1.76	**0.017**
Eye tearing	2.05±1.36	2.59±2.17	0.324	n = 17, 1.35±0.86	n = 18, 1.56±1.10	0.549
Brain fog	3.18±1.99	3.23±1.90	0.939	n = 15, 1.27±0.59	n = 18, 2.28±1.67	**0.034**
Weakness	3.23±2.04	3.59±2.08	0.562	n = 19, 1.74±1.15	n = 18, 2.06±1.39	0.451
Breathlessness	4.09±1.95	4.55±1.82	0.428	n = 14, 2.21±1.72	n = 16, 2.38±1.75	0.802
Headache	3.14±1.96	3.14±1.91	>0.05	n = 15, 1.33±0.82	n = 17, 1.47±1.07	0.689
Somnolence	3.82±2.28	4.18±2.08	0.584	n = 16, 2.25±1.84	n = 18, 2.28±1.60	0.963
Insomnia	3.23±2.18	3.77±1.93	0.384	n = 15, 1.87±1.60	n = 18, 1.44±0.92	0.350

p-values = independent t-test, values in bold indicate $p<0.05$

from dried plants. Therefore, taking the medicine involves taking a large amount of fiber. Individuals with easy excretion may experience diarrhea. Therefore, the studied drug is considered safe, a finding in accordance with the Wat Pho inscription and the Thai herbal guidebook. The preliminary efficacy data obtained in the present study suggest that the Thai herbal remedy can help to relieve at least three symptoms of chronic allergic rhinitis. Weather changes and allergen exposure may affect efficacy assessment. The study data were collected throughout the year: 55% of participants enrolled in the rainy season, 21% in winter, 14% in summer and 10% between winter and summer. Physician-assessment of symptoms of disease revealed significant improvement in the rainy season only. Temperature and moisture changes in the rainy season may stimulate more symptoms of allergic rhinitis, which improved for some symptoms after taking Thai herbal remedy. The major allergens were indoor aeroallergens, which stimulate symptoms of disease year round. Therefore, a participant's behavior to avoid allergens is a cofactor in assessing allergic rhinitis. A specific season for the study or additional research lasting longer than 4 weeks is required for further evaluation.

Conclusion

The Thai herbal remedy the authors used as the study medicine was shown to be safe for treatment of allergic rhinitis at a dosage of two capsules (1.12 g) taken three times per day. The common side effect of diarrhea was observed, which was considered to be in the acceptable range for medication side-effects. In addition, the present study showed that the Thai herbal remedy can relieve some symptoms of chronic allergic rhinitis.

What is already known on this topic?

The Thai herbal remedy for allergic rhinitis treatment from wat Pho's marble inscription has been high level of traditional supporting evidence for safety and efficacy. However, the dosage of the herbal remedy is not explicitly known and never been clinically studied on safety and efficacy against allergic rhinitis.

What this study adds?

Current study revealed that This herbal remedy is safe with an appropriate dose of 2 capsules (1.12 g/meal) three times a day, after meals. Mild diarrhea can be found as non-serious and acceptable side effect. The herbal remedy can relieve at least 3 symptoms of allergic rhinitis. This clinical study was scientific evidence for further study.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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