ORIGINAL ARTICLE

The Effect of *Zingiber cassumunar* (Phlai Capsule) on Bronchial Hyperresponsiveness in Asthmatic Patients: A Randomized Controlled Trial

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Background: Bronchial hyperresponsiveness (BHR) is a key feature of asthma. Compound D, an active compound in Phlai, can bind cysteinyl leukotrienes receptors that play a role for asthma treatment.

Objective: To determine the effect of Phlai capsules on BHR measured by the methacholine challenge test.

Materials and Methods: A randomized, double-blind, placebo-controlled, crossover study was conducted in adult asthmatic patients with partly controlled symptoms. Each patient received four weeks of treatment with either Phlai or placebo separated by a 2-week washout period. The main outcome was provocative concentration of methacholine causing a 20% drop in FEV_1 (PC_{20}). Asthma control test (ACT) scores, and fractional exhaled nitric oxide (FeNO) levels were secondary end points.

Results: Thirty patients were randomly allocated to either the Phlai or the placebo group. All patients had allergic rhinitis and received inhaled corticosteroid and long-acting beta2-agonist (ICS/LABA) or ICS alone. Four weeks after treatment, mean PC_{20} in the Phlai group was higher than in the placebo group at 9.76±1.56 mg/mL versus 6.05±1.65 mg/mL (p=0.151). The improvement of ACT scores in the Phlai group was significantly higher than in the placebo group. FeNO levels decreased after treatment in the Phlai group. All patients tolerated the treatment well and had no side effects.

Conclusion: In adult asthmatic patients with partly controlled symptoms, concomitant treatment with Phlai capsules tended to decrease BHR and significantly improve symptom scores.

Keywords: Asthma; Asthma control test; Bronchial hyperresponsiveness; *Zingiber cassumunar*; Phlai

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Asthma is a chronic respiratory disease of the airway characterized by variable airflow limitation, airway inflammation, and airway hyperresponsiveness[1]. The most common signs and symptoms of asthma are cough, especially at night or during exercise, chest tightness, shortness of breath, and wheezing which impacts on patient's social life, performance, and work productivity[1]. The prevalence of asthma in children in Bangkok, Thailand is 13% to 15%[2]. The asthma prevalence in Thai adults aged 20 to 44 years from a nationwide survey is 2.9%[3]. The main mechanism of asthma is type 2 inflammation, such that immune responses mainly mediated by eosinophil, mast cell, type 2 T-helper cells, and immunoglobulin E (Ig E)-producing B cell[1]. The key medications for treatment of asthma are anti-inflammatory and bronchodilator drugs that help to decrease airway inflammation, relieve asthma symptoms, and prevent asthma exacerbations. The main types of anti-inflammatory drug are inhaled corticosteroids (ICS). Other anti-inflammatory treatments include leukotriene modifiers, anticholinergics, and immunomodulators.

Zingiber cassumunar Roxb., known as "Phlai" in Thai has been used as traditional medicine in Thailand for treatment of allergy and allergic-related diseases. The major bioactive component is (E)-4-(3', 4'-dimethoxyphenyl) but-3-en-1-ol or compound D,

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which has anti-inflammatory activity, smooth muscle relaxant, antihistamine, mucin-lowering secretion properties[4-7], and inhibits 5-lipoxygenase enzyme[8] and a cysteinyl leukotriene receptor antagonist[8]. It is safely tolerated in animals for both acute and chronic administration of *Z. cassumunar* extract[9]. Compound D and DMPBD are compounds extracted from Phlai or *Z. cassumunar* Roxb. They can bind at the same binding site of its natural substrate or arachidonic acid, on 5-lipoxygenase enzyme, which is similar to the binding of commercial asthma drug, zileuton[8]. In an in vivo study, oral Phlai capsules 200 mg/day for 12 weeks did not cause serious adverse events or laboratory abnormalities in healthy subjects[10]. A previous clinical study showed that *Z. cassumunar* Roxb (Phlai) could inhibit skin reactivity to histamine and mite-skin-prick test in patients with allergic rhinitis (AR)[11]. Moreover, *Z. cassumunar* capsule exhibited antihistamine effects similar to oral antihistamine as demonstrated by inhibition of skin reactivity to histamine and reduction of total nasal symptoms score in AR individuals[11].

This herbal medication has not been investigated in adults with asthma. Therefore, the authors hypothesized that Phlai capsules might be an effective therapy in asthmatic patients resulting from effects of anti-inflammatory property, antihistamine, bronchial smooth muscle relaxant, and reducing mucous secretion. The aim of the present study was to investigate the effect of Phlai capsules on bronchial hyperresponsiveness (BHR) measured by the methacholine challenge test (MCT) in adult asthmatic patients.

Materials and Methods

Study design and participants

A prospective, randomized, double-blinded placebo-controlled, crossover study was conducted at the Center of Excellence for Allergy, Asthma and Pulmonary Diseases, Thammasat University Hospital, Thailand between February and November 2019. Written informed consent was obtained before trial participation.

Inclusion criteria were 1) patients aged 18 years or older with diagnosis of asthma for at least one year by allergists or pulmonologists followed the Global Initiative for Asthma (GINA) Guidelines[1], 2) history of partly controlled or uncontrolled symptoms assessed according to GINA 2019 guidelines[1] while taking a medium-dose to high-dose ICS or combination of ICS and long-acting beta2-agonists (ICS/LABA) for at least three months prior to the study recruitment, 3) Asthma Control Test (ACT) scores of 19 or higher at baseline, and 4) baseline forced expiratory volume in one second (FEV_1) of 70% or more of predicted value.

Exclusion criteria were 1) 10 or more pack-years smoking history, 2) inability to perform effective spirometry, 3) taking medications including leukotriene receptor antagonists (LTRA), antihistamines, xanthines, and cyclooxygenase inhibitors within two weeks prior to the study recruitment, 4) taking systemic corticosteroids within two weeks before the first visit, 5) taking biologics such as monoclonal anti-Ig E (omalizumab) within six months before the first visit, 6) having chronic diseases such as chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, coronary artery disease, ischemic or hemorrhagic stroke, chronic kidney disease with a creatinine clearance of less than 50 mL/minute, chronic liver disease with liver enzymes of more than 1.5 times of upper normal limit, 7) allergic reaction to compound of Phlai, 8) pregnancy or lactation, and 9) conditions or diseases that might influence the results of the study as judged by the investigators.

Ethic approval was obtained from the Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine), Thailand (IRB No. MTU-PE-IM-0-261/61), and in compliance with the Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and The International Practice (ICH-GCP). All methods were performed in accordance with these guidelines and regulations. All participants provided written informed consents.

Randomization

Randomization and blinding were carried out by an independent nurse unrelated to the present study. Each eligible participant was randomized to one of two groups by block of four randomization. The study flowchart is shown in Figure 1. Phlai capsule and placebo were provided by the Government Pharmaceutical Organization and were identical by their appearance.

Study intervention

Before randomization, patients with partly or uncontrolled asthma entered a run-in period lasting two weeks. Patients were required to meet eligibility requirements at the end of the 2-week run-in period before randomization. After screening and fitting to study criteria, eligible patients were blinded and randomly divided into two groups to take Phlai

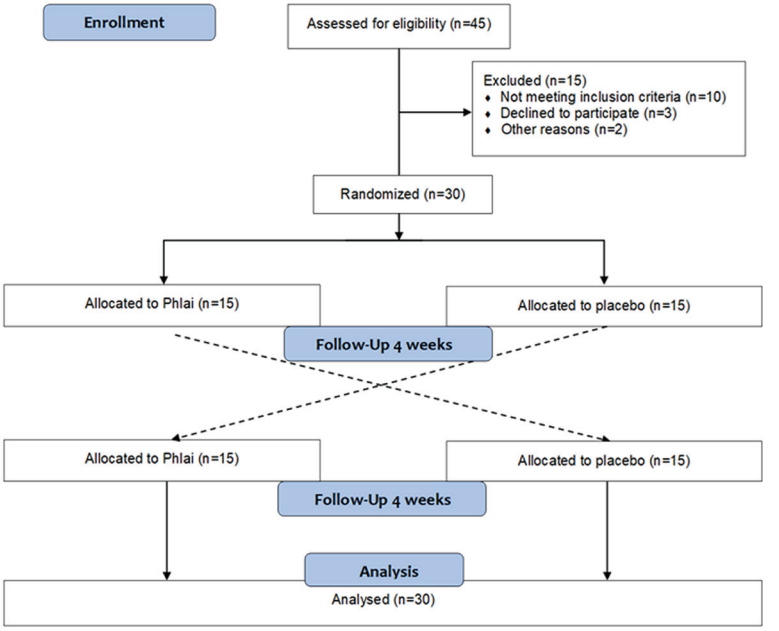

Figure 1. Flowchart of prospective, randomized, double-blinded placebo-controlled, crossover study.

capsules containing 16 mg of compound D, thus four capsules, or placebo once daily for four weeks (Figure 1). At baseline, all patients performed MCT, the fraction of exhaled nitric oxide (FeNO) measures and spirometry. Spirometry was performed according to the American Thoracic Society (ATS) and the European Respiratory Society Guidelines[12,13] using PC spirometer (Vyntus® SPIRO, Vyaire Medical, Inc., Mettawa, IL, USA). Complete blood count with blood eosinophil count (BEC), serum blood urea nitrogen, creatinine, liver function test, urine pregnancy test, electrocardiogram, and chest X-ray were collected and done at first visit. Following the initial four weeks of treatment, there was a 2-week washout period followed by four weeks of crossover treatment with Phlai capsules or placebo, as shown in Figure 1. MCT according to ATS guidelines[14], ACT scores, FeNO using a portable analyzer (NIOX VERO®, Aerocrine, Solna, Sweden) according to the standard guidelines[15], and spirometry were performed at the end of week 4 or visit 2, week 6 or visit 3, and week 10 or visit 4. Medications were withheld before MCT following ATS guidelines[14]. Briefly, MCT with the five-breath dosimeter method was performed by quadrupling increments between steps from lower initial to higher last concentration as 0.0625, 0.25, 1, 4, and 16 mg/mL[14]. PC_{20} was concentration of methacholine between second-to-last and final concentration causing a 20% fall in FEV_1[14]. In the present study, the final concentration of subjects with PC_{20} of more than 16 mg/mL were reported as 16 mg/mL.

Basic laboratory tests were collected every visit. Subject compliance was assessed by capsule count at each follow-up visit.

Endpoints and assessments

The primary endpoint was the provocative concentration of methacholine causing a 20% drop in FEV_1 (PC_{20}). The secondary endpoints were changes in ACT scores, FeNO levels, and pulmonary functions including FEV_1, forced vital capacity (FVC), forced expiration flow rate at 25% to 75% of forced viral capacity (FEF_{25-75}), and peak expiratory flow rate (PEFR). Adverse events were recorded.

Statistical analysis

Because Phlai has not been studied in asthmatic patients, the authors supposed a sample size for two groups of 30 patients with 80% power to detect PC_{20} difference between the two treatment groups for the primary end points. Categorical data were presented as number (%). Continuous data was presented as mean ± standard deviation (SD) or median (interquartile range). PC_{20} was presented as mean ± standard error of mean (SEM). Chi-squared test was used to compare categorical variables between the two groups. Student t-test was used to compare continuous

variables between the two groups. Wilcoxon signed-rank test was used to compare FeNO before and after treatment in each group and Mann-Whitney U test was used to compare FeNO between Phlai and placebo group. A two-sided p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

Results

After the randomization, no patient was lost to follow-up through the study (Figure 1). Baseline demographic and spirometric data of asthmatic patients are shown in Table 1 and 2. The thirty adult asthmatic patients, including nine males and 21 females, were aged 42.90±13.12 years. All patients had AR. Three patients (10.3%) had allergic conjunctivitis and one patient (3.3%) had atopic dermatitis. Nine patients or 30% had previous LTRA treatment. Ninety-six-point-seven percent of the patients took ICS/LABA. There were no significant differences in baseline characteristics between the Phlai and the placebo groups.

Methacholine challenge test

The mean PC_{20}±SEM increased from 8.53±1.94 to 9.76±1.56 mg/mL after the 4-week Phlai treatment (p=0.194) but decreased from 8.25±1.96 to 6.05±1.65 mg/mL after the 4-week placebo treatment (p=0.265). PC_{20} in the Phlai group after the 4-week treatment was higher than the placebo group (p=0.151) (Table 3, Figure 2).

Asthma control test scores

In the Phlai group, mean ACT scores improved significantly from 21.07±1.68 to 22.10±1.69 (p=0.001), whereas in the placebo group, the mean ACT scores changed from 21.13±1.81 to 20.40±4.25 (p=0.385). The improvement of ACT scores in the Phlai group after treatment was significantly higher than in the placebo group at 22.10±1.69 versus 20.40±4.25 (p=0.046) (Table 3, Figure 3).

Fractional exhaled nitric oxide

In the Phlai group, FeNO levels decreased from 23.00 (13.75, 45.50) to 20.00 (10.00, 48.50) ppb, (p=0.355), whereas in the placebo group, FeNO levels changed from 25.00 (14.50, 48.25) to 24.00 (12.75, 53.75) ppb, (p=0.690). There were no significant differences in FeNO levels after treatment in either the Phlai or the placebo group (p=0.641) (Figure 4). Subgroup analysis of the low or less than 20 ppb,

Table 1. Baseline characteristics of 30 adult asthmatic patients

Characteristics	Data (n=30)
Age (years); mean±SD	42.90±13.12
Sex; n (%)	
Male	9 (30.0)
Female	21 (70.0)
Height (cm); mean±SD	162.60±9.52
Weight (kg); mean±SD	68.93±12.90
Body mass index (kg/m^2); mean±SD	26.07±4.36
Smoking history; n (%)	
Never smoking	22 (73.3)
Formerly smoking	6 (20.0)
Actively smoking	2 (6.7)
Partly controlled asthma; n (%)	30 (100)
Comorbidity; n (%)	
Allergic rhinitis	30 (100)
Allergic conjunctivitis	3 (10.3)
Atopic dermatitis	1 (3.3)
Others	10 (33.3)
Medications before enrollment	
ICS/LABA	29 (96.7)
ICS	1 (3.3)
INS	28 (93.3)
Antihistamines	30 (100)
LTRA	9 (30.0)
Xanthine	5 (16.7)
Daily baseline dose of ICS as beclomethasone equivalent (μg/day); mean±SD	522.67±65.26
ACT scores; mean±SD	21.26±1.98
PC_{20} (mg/mL); mean±SD	8.39±1.35

SD=standard deviation; LTRA=leukotriene receptor antagonist; ICS=inhaled corticosteroids; LABA=long-acting beta2-agonists; INS=intranasal steroid; ACT=Asthma Control Test; PC_{20}=provocative concentrations of MCT causing a 20% drop in FEV_1

Table 2. Baseline spirometric and inflammatory biomarker data

Characteristics	Data (n=30)
FeNO (ppb); median (IQR)	24.50 (14.25, 44.50)
Blood eosinophil counts (cells/mm^3); mean±SD	281.31±195.67
Spirometric data; mean±SD	
FEV_1 (L)	2.25±0.59
FEV_1 (%predicted)	82.06±5.30
FEV_1/FVC (%)	74.71±8.86
FEF_{25-75} (%predicted)	58.85±22.13
PEFR (L/minute)	399.17±92.27

SD=standard deviation; IQR=interquartile range; FeNO=fraction of exhaled nitric oxide; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FEF_{25-75}=forced expiration flow rate at 25% to 75% of forced viral capacity; PEFR=peak expiratory flow rate; ppb=parts per billion

Table 3. Methacholine challenge test results, asthma symptoms, lung functions, and blood eosinophil counts after 4 weeks of Phlai and placebo treatment

Data	Phlai; mean±SD				Placebo; mean±SD				Mean difference (95% CI)*	p-value*
	Before	After	Mean change (95% CI)	p-value	Before	After	Mean change (95% CI)	p-value		
PC_{20} (mg/mL)	8.53±1.94	9.76±1.56	1.23 (–0.12 to 2.34)	0.194	8.25±1.96	6.05±1.65	–2.54 (–2.21 to 7.29)	0.265	3.73 (–1.24 to 5.78)	0.151
ACT scores	21.07±1.68	22.10±1.69	0.93 (0.64 to 1.27)	0.001	21.13±1.81	20.40±4.25	–1.53 (–2.41 to 0.26)	0.576	2.45 (0.56 to 3.78)	0.046
FEV_1 (L)	2.25±0.58	2.25±0.60	0.00 (0.04 to 0.04)	0.950	2.25±0.62	2.23±0.63	–0.02 (–0.07 to 0.02)	0.330	0.02 (–0.04 to 0.09)	0.445
FEV_1/FVC (%)	75.02±8.80	74.79±9.51	–0.23 (1.60 to 1.13)	0.729	74.41±9.07	74.21±9.69	–0.20 (–1.39 to 0.99)	0.730	–0.03 (–1.80 to 1.73)	0.970
FEF_{25-75} (%predicted)	59.97±23.67	60.13±23.84	0.17 (–2.78 to 3.11)	0.409	57.73±20.81	56.97±21.53	–0.77 (–3.85 to 2.32)	0.610	–0.93 (–5.10 to 3.24)	0.656
PEFR (L/minute)	398.00±95.90	410.67±101.64	12.67 (0.03 to 25.30)	0.049	400.33±90.11	400.67±94.90	0.33 (14.49 to 15.16)	0.960	7.03 (–12.76 to 26.82)	0.200
BEC (cells/mm^3)	295.73±219.34	282.88±166.37	–12.85 (–34.71 to 60.41)	0.585	266.89±171.32	271.03±161.41	–4.14 (–42.94 to 34.66)	0.829	–8.65 (–35.53 to 42.36)	0.575

SD=standard deviation; CI=confidence interval; PC_{20}=provocative concentrations of methacholine causing a 20% drop in FEV_1; ACT=Asthma Control Test; PEFR=peak expiratory flow rate; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FEF_{25-75}=forced expiration flow rate at 25% to 75% of forced viral capacity; BEC=blood eosinophil counts

* Comparison between Phlai and placebo treatment

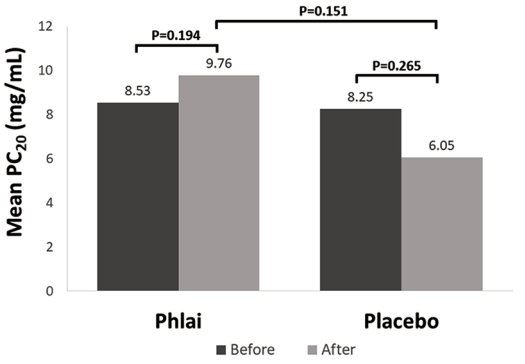

Figure 2. Provocative concentration of methacholine causing a 20% drop in FEV_1 (PC_{20}) before and after treatment.

FEV_1=forced expiratory volume in one second

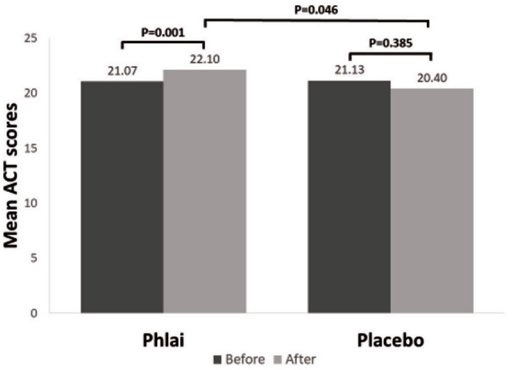

Figure 3. Asthma control test (ACT) scores before and after treatment.

and high FeNO or the 20 ppb or more groups found positive MCT of PC_{20} less than 16 mg/mL was 21.74% and 70.27%, respectively.

Subgroup analyses of low and high FeNO groups are summarized in table 4. There were no statistically significant differences in PC_{20} and other outcome parameters between the Phlai and the placebo groups both the low and the high FeNO groups (Table 4).

In the high FeNO group, there were no statistically significant differences in PC_{20}, lung function parameters, and BEC between before and after treatments of both the Phlai and the placebo groups including mean differences in their parameters between the Phlai and the placebo groups (Table 5). Interestingly, the significant improvement of ACT scores in the Phlai group was observed only in the high FeNO subgroup (Table 4, 5).

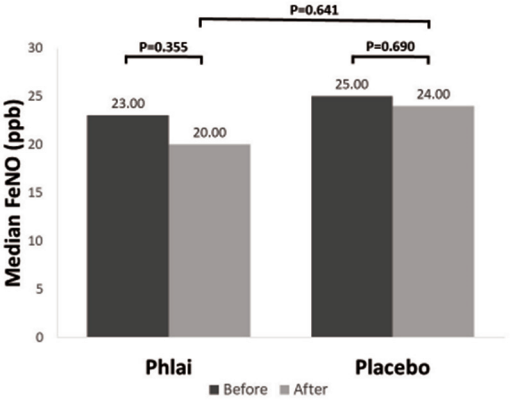

Figure 4. Fraction of exhaled nitric oxide (FeNO) levels before and after treatment.

Lung functions

Table 3 shows that mean FEV_1 and FEV_1/FVC did not change after treatment in the Phlai and placebo groups. FEF_{25-27} was higher after treatment in the Phlai group but not in the placebo group. However, mean change of FEF_{25-27} was not statistically significant between two groups after treatment. Furthermore, PEFR significantly improved from the baseline in

Table 4. Data on methacholine challenge test results, asthma symptoms, pulmonary functions and blood eosinophil counts comparing asthmatic patients with high and low fractional exhaled nitric oxide (FeNO) levels after 4-week treatment

Data	Low FeNO (<20 ppb); mean±SD				High FeNO (≥20 ppb); mean±SD			
	Phlai (n=12)	Placebo (n=11)	Mean difference (95% CI)	p-value	Phlai (n=18)	Placebo (n=19)	Mean difference (95% CI)	p-value
ΔPC_{20} (mg/mL)	8.50±3.50	−0.75±0	7.75 (−5.35 to 10.45)	0.675	6.33±7.29	−2.30±2.03	8.63 (−5.98 to 23.24)	0.234
ΔACT scores	0.58±0.34	0.45±0.28	0.13 (−0.79 to 1.05)	0.774	1.33±0.37	−0.42±0.39	1.75 (0.66 to 2.85)	0.003
ΔPEFR (L/minute)	12.5±7.99	2.73±6.19	9.77 (−11.53 to 31.07)	0.351	12.78±9.00	−1.05±11.00	13.83 (−15.2 to 42.86)	0.340
ΔFEV_1 (L)	−0.03±0.02	−0.03±0.02	0.00 (−0.05 to 0.06)	0.900	0.02±0.03	−0.02±0.03	0.04 (−0.06 to 0.14)	0.433
ΔFEV_1/FVC (%)	−0.24±0.90	−0.46±0.78	0.22 (−2.29 to 2.73)	0.858	−0.23±0.96	−0.05±0.81	−0.18 (−2.71 to 2.35)	0.887
ΔFEF_{25-75} (%predicted)	−1.17±2.34	−1.73±2.55	0.56 (−6.62 to 7.74)	0.873	1.06±1.85	−0.21±1.91	1.27 (−4.14 to 6.67)	0.637
ΔBEC (cells/mm^3)	8.72±12.96	14.2±11.77	−5.48 (−42.12 to 31.15)	0.759	−27.23±37.87	−1.68±29.42	−25.54 (−122.31 to 71.22)	0.595

Δ=changes in each parameter after 4-week treatment; SD=standard deviation; CI=confidence interval; FeNO=fraction of exhaled nitric oxide; PC_{20}=provocative concentrations of methacholine causing a 20% drop in FEV_1; ACT=Asthma Control Test; PEFR=peak expiratory flow rate; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FEF_{25-75}=forced expiration flow rate at 25% to 75% of forced viral capacity; BEC=blood eosinophil counts; ppb=parts per billion

Table 5. Data on methacholine challenge test results in the patient subgroup with high fractional exhaled nitric oxide levels

Data	Phlai (n=18); mean±SD				Placebo (n=19); mean±SD				Mean difference (95% CI)*	p-value*
	Before	After	Mean change (95% CI)	p-value	Before	After	Mean change (95% CI)	p-value		
PC_{20} (mg/mL)	7.36±2.22	13.69±8.06	6.33 (−9.72 to 22.38)	0.404	8.77±2.03	6.46±1.72	−2.68 (−7.89 to 2.52)	0.277	8.63 (−5.98 to 23.24)	0.234
ACT scores	21.11±1.78	22.44±1.62	1.33 (0.55 to 2.12)	0.002	21.47±1.84	20.05±5.19	0.58 (−0.11 to 1.27)	0.285	1.75 (0.66 to 2.85)	0.003
PEFR (L/minute)	430.00±84.51	442.78±100.63	12.78 (−6.20 to 31.76)	0.174	409.47±97.78	408.42±105.58	−1.05 (−24.16 to 22.06)	0.925	13.83 (−15.2 to 42.86)	0.340
FEV_1 (L)	2.36±0.63	2.38±0.64	0.02 (−0.05 to 0.09)	0.578	2.29±0.74	2.27±0.72	−0.02 (−0.09 to 0.05)	0.584	0.04 (−0.06 to 0.14)	0.433
FEV_1/FVC (%)	72.81±8.17	72.57±9.14	−0.23 (−2.25 to 1.79)	0.813	71.45±9.97	71.40±10.73	−0.05 (−1.75 to 1.65)	0.950	−0.18 (−2.71 to 2.35)	0.887
FEF_{25-75} (%predicted)	53.44±18.40	54.50±20.08	1.06 (−2.85 to 4.96)	0.576	50.63±18.41	50.42±19.09	−0.21 (−4.22 to 3.80)	0.913	1.27 (−4.14 to 6.67)	0.637
BEC (cells/mm^3)	355.40±232.59	328.17±153.26	−27.23 (−107.13 to 52.68)	0.482	292.21±174.39	290.52±160.87	−1.68 (−63.50 to 60.13)	0.955	−25.54 (−122.31 to 71.22)	0.595

Δ=changes in each parameter after 4-week treatment; SD=standard deviation; CI=confidence interval; PC_{20}=provocative concentrations of methacholine causing a 20% drop in FEV_1; ACT=Asthma Control Test; PEFR=peak expiratory flow rate; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FEF_{25-75}=forced expiration flow rate at 25% to 75% of forced viral capacity; BEC=blood eosinophil counts

* Comparison between Phlai and placebo treatment

Table 6. Blood test results in Phlai and placebo treatment

Data	Phlai ; mean±SD				Placebo ; mean±SD				Mean difference (95% CI)*	p-value*
	Before	After	Mean change (95% CI)	p-value	Before	After	Mean change (95% CI)	p-value		
Hemoglobin (g/dL)	13.20±1.23	13.17±1.12	−0.04 (−0.22 to 0.15)	0.687	13.21±1.14	13.10±1.10	−0.11 (−0.28 to 0.06)	0.180	0.08 (−0.17 to 0.32)	0.532
WBC (cells/mm^3)	7,020.00±2,154.45	6,853.33±1,875.38	−166.67 (−811.51 to 478.18)	0.601	6,906.67±2,273.37	6,726.67±1,736.61	−180.00 (−851.3 to 491.3)	0.588	13.33 (−897.71 to 924.37)	0.977
Platelet (×10^3/mm^3)	269.10±58.18	265.70±55.76	−3.40 (−11.39 to 4.59)	0.391	268.07±39.82	274.73±52.56	6.67 (−5.05 to 18.38)	0.254	−10.07 (−23.95 to 3.81)	0.152
BEC (cells/mm^3)	295.73±219.33	282.88±166.37	−12.85 (−60.41 to 34.71)	0.585	266.89±171.33	271.03±161.41	4.14 (−34.66 to 42.94)	0.829	−16.99 (−77.06 to 43.08)	0.573
BUN (mg/dL)	12.21±2.97	12.72±3.37	0.52 (−0.25 to 1.28)	0.178	12.94±2.77	13.27±2.93	0.33 (−0.68 to 1.34)	0.515	0.19 (−1.05 to 1.43)	0.758
Creatinine (mg/dL)	0.79±0.22	0.81±0.21	0.03 (−0.02 to 0.08)	0.308	0.79±0.20	0.83±0.20	0.04 (−0.01 to 0.09)	0.110	−0.01 (−0.08 to 0.05)	0.683
AST (U/L)	21.47±7.06	20.87±4.78	−0.60 (−2.41 to 1.21)	0.503	21.83±6.02	24.77±9.90	2.93 (−0.07 to 5.94)	0.055	−3.53 (−6.97 to −0.10)	0.060
ALT (U/L)	25.47±12.92	23.07±11.70	−2.40 (−5.84 to 1.04)	0.164	25.60±12.31	26.9±13.04	1.30 (−3.16 to 5.76)	0.555	−3.70 (−9.21 to 1.81)	0.184
ALP (U/L)	73.57±20.48	73.53±24.50	−0.03 (−4.92 to 4.85)	0.989	74.53±17.11	74.87±20.24	0.33 (−4.04 to 4.71)	0.877	−0.37 (−6.78 to 6.05)	0.909
TB (mg/dL)	0.57±0.28	0.50±0.14	−0.07 (−0.16 to 0.01)	0.077	0.53±0.26	0.56±0.23	0.03 (−0.03 to 0.08)	0.364	−0.10 (−0.20 to 0)	0.060

SD=standard deviation; CI=confidence interval; WBC=white blood counts; BEC=blood eosinophil counts; BUN=blood urea nitrogen; AST=aspartate transaminase; ALT=alanine transaminase; TB=total bilirubin

* Comparison between Phlai and placebo treatment

the Phlai group at 398±95.90 to 410.67±101.64 L/minute (p=0.049) (Table 3).

Side effects and compliance

Phlai capsule did not have side effects compared to placebo. There were no changes in any blood chemistry (Table 6). Phlai capsule was well-tolerated in all patients, but most patients or 80% complained that Phlai capsule created an herbal smell after taking. However, the adherence to Phlai capsule was good as it was taken in about 85% of the prescribed doses.

Discussion

In the present prospective randomized, double-blind, placebo-controlled, crossover study, the authors evaluated the effect of *Z. cassumunar* (Phlai capsule) in asthmatic patients over a wide age range to make the results more applicable to clinical practice. The present research is the first study to investigate the effect of this medication on BHR in asthmatic patients with partly controlled symptoms.

The main study results showed short-term addition of Phlai treatment to a background of therapy with ICS or ICS/LABA for four weeks resulted in a reduction of BHR compared to placebo treatment, although this reduction was not statistically significant. This insignificant difference in PC_{20} following treatment might be due to low numbers of patients with positive MCT at the beginning of the study. The authors found only 53% of all patients or 16 patients from 30 patients, had positive MCT at first visit of enrollment and the mean PC_{20} before the enrollment was 8.39 mg/mL, which is borderline BHR. These findings might dilute the effect of Phlai in the study participants. Therefore, the limited analysis of PC_{20} changes after treatment may have led to less reliable PC_{20} results. The reason for low numbers of positive MCT test may be because most patients took ICS or ICS/LABA for at least one year prior to the study. An effect of long-term ICS treatment can be to suppress BHR and asthma symptoms[14,16,17], which was found in the present study. This can lead to normalization of the MCT[18].

The 2-week wash-out period of the present study could be sufficient for Phlai effect to MCT. The previous study by Tanticharoenwiwat et al. showed that Phlai capsule 200 mg or 4 mg of compound D, could inhibit mite allergen-induced wheal and flare responses for at least 24 hours with maximum effect four hours after treatment[11]. Pharmacokinetic data of this herb medicine in human has not been explored. The pharmacokinetic profiles of compound D, the major component of *Z. cassumunar*, in rats showed having good tissue distribution to most organs at one to four hours after administration[19]. Therefore, authors the stipulated that Phlai effect on MCT was unlikely to exceed the 2-week wash out period.

FeNO is a non-invasive biomarker for eosinophilic airway inflammation in asthma[20] and can be used to monitor for the asthma control with ICS treatment[21]. Phlai capsule also suppressed airway inflammation reflected by a fall in FeNO after treatment, although there was no statistically significant difference compared to placebo. Because the authors recruited both allergic and non-allergic types of asthmatic patients, some patients did not show significant eosionophilic airway inflammation as 38% of patients had low FeNO. However, subgroups of patients were analyzed with low and high FeNO. Interestingly, mean change of ACT scores significantly increased after treatment in only the high FeNO group compared to the low FeNO group. The authors assumed that Phlai capsule was more effective in asthmatic patients with type 2 inflammation than non-type 2 inflammation. However, the authors cannot explain how Phlai is effective in decreasing type 2 inflammation.

The present study showed no significant differences in changes of lung functions in either Phlai or placebo groups, except PEFR. The significant improvement of PEFR after treatment showed in only the Phlai group after 4-week treatment.

The authors had have tried to calculate the power of the test using the present study PC_{20} results and a sample size of 30. The calculated power would be 100%. Therefore, non-significant differences in these parameters might not be limited by a small size of participants.

The present study has limitations. Firstly, for safety reasons, the authors did not recruit steroid-naive asthmatic patients because it might increase risk of asthma exacerbation. All patients received long-term ICS prior to enrollment in the study, which could affect BHR or FeNO. Lastly, due to the short period of follow-up in spirometry, the finding could not show lung function changes in the Phlai group treatment.

Conclusion

In adult asthmatic patients with partly controlled symptoms with ICS treatment, concomitant treatment with Phlai capsule tends to decrease BHR and significantly improve symptom scores without side effects, especially in patients with the presence of BHR and high FeNO levels at baseline.

What is already known on this topic?

BHR is a key feature of asthma. Main treatment for asthma is anti-inflammatory agents including ICS. Compound D, which is an active compound in Phlai, can bind cysteinyl leukotrienes receptors that play a role for asthma treatment.

What this study adds?

This study aimed to determine the effect of Phlai capsules on BHR measured by the methacholine

challenge test.

In asthmatic patients with partly controlled symptoms with treatment with ICS, concomitant treatment with Phlai capsules tended to decrease BHR and significantly improve symptom scores.

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Conflicts of interest

The authors declare no conflict of interest.

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