Original Article

A Comparative Study of the Clinical Efficacy and Safety of Benjakul Extract and Loratadine in Allergic Rhinitis Patients: Double Blind, Randomized Controlled Trial

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Background: Benjakul remedy (BJK) is a traditional Thai herbal medicine prescribed as an adaptogen and for treatment of several diseases. Previous *in vitro* study showed that ethanolic extract of BJK exhibited potent anti-allergic activity by reducing the release of β-hexosaminidase in RBL-2H3 cells.

Objective: To investigate the clinical efficacy and safety of BJK extract in allergic rhinitis patients compared with loratadine treatment.

Materials and Methods: A phase 2, double blind clinical trial, randomized controlled trial was designed to investigate efficacy and safety of BJK in mild to moderate allergic rhinitis patients. In the present study, 60 patients diagnosed as allergic rhinitis by otolaryngologist were recruited. The patients were divided into two groups. During six weeks of treatment, the experimental group received 300 mg/day of the BJK extract and the control group was treated with 10 mg/day of loratadine. All patients were followed up at 21 and 42 days. The changes of total nasal symptom score (TNSS), acoustic rhinometry were evaluated as efficacy parameters. Regarding safety issue, clinical signs and symptoms, complete physical examination, and blood chemistries and components were evaluated.

Results: Sixty patients completed this clinical investigation. After treatments, TNSS parameters of both groups decreased from baseline, but the acoustic rhinometry parameters of both groups did not significantly decrease. Between the groups, comparison showed no differences. The blood analysis of both groups did not change after treatments.

Conclusion: Oral administration of 100 mg BJK extract three times daily for 42 days in allergic rhinitis patients can reduce allergic rhinitis symptoms and it showed safety on all parameters.

Keywords: Benjakul, Loratadine, Allergic rhinitis, Phase II, Efficacy and Safety

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The incidence of allergy is markedly increasing both worldwide and in Thailand. A survey found that the incidence has increased three to four times within the last 40 years in Thailand[(1)]. In large cities, air pollution has raised the incidence steadily of allergic rhinitis, which is the most common allergic disease. Although allergic rhinitis is not a severe disease, it affects the quality of life of patients in all physical, mental, and social aspects[(2)].

Benjakul (BJK), a traditional Thai herbal medicine, consists of five plant species, which are fruits of *Piper retrofractum* Vahl, root of *Piper sarmentosum* Roxb, stem of *Piper interruptum* Opiz, root of *Plumbago indica* Linn, and rhizome of *Zingiber officinale* Roscoe. It was approved in

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Thailand National List of Essential Medicines as adaptogenic medicine[3]. Previous survey study of 35 traditional Thai clinics, found that BJK is widely used by traditional Thai doctors as adaptogenic medicine and for treatment of several diseases such as allergies, fatigue, aches, stuffy nose, and abnormal menstruation[4]. A previous study reported *in vitro* anti-allergic activity of ethanolic extract of BJK by inhibiting β-hexosaminidase enzymes in RBL-2H3 rat basophilic leukemia cells. The results showed that BJK exhibited anti-allergic potency with IC_{50} of 12.69±1.25 µg/ml better than positive control, chlorpheniramine (17.98±0.78 µg/ml). Moreover, BJK exhibited more powerful anti-allergic activity than its plant components[5]. A clinical pharmacokinetic study of BJK extract in healthy volunteers showed that piperine as a major marker of BJK, could be gradually absorbed and its blood level reached maximum concentration within two hours. Furthermore, piperine was eliminated from body within six hours for a 100 mg dose and nine hours for a 200 mg dose. There was no serious adverse effect observed in any subjects indicating the safety of single dose BJK extract in healthy volunteers[6]. Previous clinical study of BJK extract in patients with osteoarthritis of knee reported that patients had no sign or symptoms of severe adverse effects or toxicity of renal and liver functions during the 28 days administration of 100 mg BJK extract three times daily[7].

According to evidence of BJK prescribed by traditional Thai doctors and the *in vitro* anti-allergic potential, the authors investigated the clinical efficacy of BJK extract compared with the conventional anti-allergic drug, loratadine, in allergic rhinitis patients. Concomitantly, the authors evaluated its clinical safety in the present six weeks of continuous treatment. To the best of the authors' knowledge, the present study is the first report indicating clinical efficacy and safety of BJK extract in allergic rhinitis patients to prove the phase 2 clinical study for further development of BJK extract to be used in allergic rhinitis patients with clinical confidence.

Materials and Methods

Recruitment of patients

The present clinical study was conducted at Thammasat Hospital, Pathum Thani, Thailand. The trial was approved by the Medical Ethics Committee of the Faculty of Medicine, Thammasat University. The committee was accepted by FDA Thai Government (registry number MTU-EC-TM-4-183/57), and the present study was registered in the ClinicalTrials.gov with identifier code: NCT03376594.

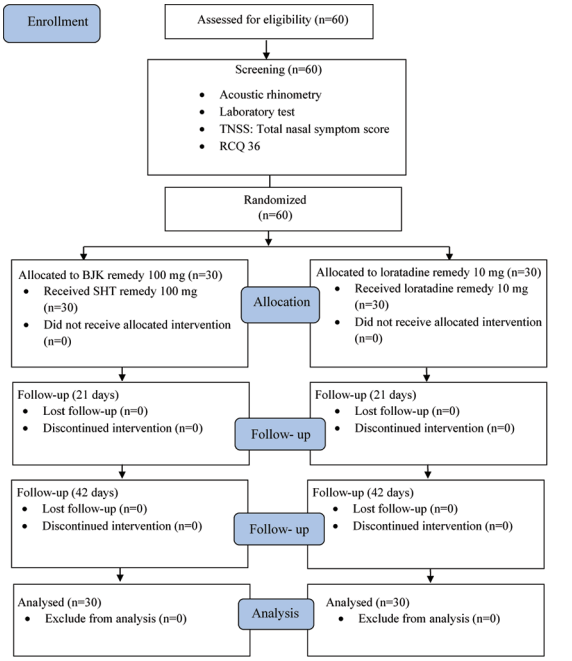

Figure 1. Flow of volunteers.

Patients were diagnosed with mild to moderate allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline. Sixty patients aged 20 to 70 years old from the Department of Otolaryngology, Thammasat Hospital were enrolled according to inclusion and exclusion criteria. Patients diagnosed with the total nasal symptom score (TNSS) of at least 5 were recruit. The volunteers must not have underlying disease such as tuberculosis, nasal polyps, heart disease, kidney disease, liver disease, epilepsy, hypertension, or severe asthma. The results of blood tests for liver and kidney function were normal. Patients were not pregnant during trial period. Body mass index were (BMI) 18 to 35 kg/m², all showed willingness to participate, and all had normal vital signs. All volunteers accepted the project explanation and agreed to participate by signing the ethically approved consent form.

Research design and sample size

Double-blind, randomized controlled trial was designed to evaluate the clinical efficacy and safety of BJK extract for treating allergic rhinitis compared with loratadine. Sample size determination was calculated by the following equation: $N = (Z_{\alpha/2} + Z_{\beta})^2 \times 2SD^2/d^2$

Where $Z_{\alpha/2}$ is the critical value of the normal distribution at α/2 (confidence level of 95%, α=0.05,

the critical value is 1.96), Z_β is the critical value of the normal distribution at β (power of 80%, β is 0.2 and the critical value is 0.84), SD is standard deviation of the difference=2.9, and d is the difference between groups=1.6. Therefore, $N=(1.96+0.84)^2\times2(2.9)^2/(1.6)^2$, N=52, and considering a 20 percent drop out, we required 60 of volunteers. These were divided into two groups of 30[8].

Preparation of drug formulation

Each plant component of BJK was equally weighed and combined. The plant mixture was then macerated in 95% ethanol for three days at room temperature. The extract was filtered and evaporated under reduced pressure. The residue of plant mixture was re-macerated using similar procedure and repeated two times. All three extracts were combined and dried. The BJK extract was formulated as capsules with dose strength of 100 mg per capsule. Each 10 mg loratadine tablet was filled into other capsules and used as control.

Drug administration

First group of 30 patients received an oral dose of 100 mg BJK extract per capsule three times daily. Second group of 30 patients received 10 mg oral dose of loratadine one capsule daily in the morning and received the placebo twice daily in the midday and evening (1 capsule each). Both groups received the drug continually for six weeks.

Procedure

The patients who met the inclusion criteria were informed, signed the consent form, and divided randomly to either the BJK extract treatment group or loratadine group using computer generated program by individual who were not involved in the trial.

Each patient received the same appearance of treatment with a randomized code number sequentially from a secret random list, which was not revealed until data collecting was completed or medical emergency developed. All treatment's assignment was blind to all investigators involved in the present trial.

Demographic data, clinical signs and symptoms, complete physical examination, laboratory test that included complete blood count (CBC), lipid profile, liver function test, renal function test, and urine analysis, TNSS, and acoustic rhinometry (ARM) were collected on the first visit for baseline data and again after receiving treatment on day 21 and 42.

Efficacy and safety assessments

The treatment period was completed in 42 days with the clinical and laboratory investigation follow-up assessments at day 21 and day 42 (third week and sixth week). Nasal symptoms were assessed using the TNSS by calculating the sum of scores for nasal congestion, rhinorrhea, itchy nose, and sneezing. The nasal congestion was measured by evaluating the nasal cavity, using ARM to estimate the minimal cross-sectional area (MCA), nasal volume (Vol) and distance of MCA (Dis). Hematological tests including CBC, lipid profile, fasting blood sugar, renal function, and liver function were conducted for clinical safety.

Statistical analysis

All data were expressed as mean ± SD and statistical analyses were performed by using a computerized program, SPSS version 17.0 (IBM Corp., USA). Differences of within treatment group were conducted by using one-way repeated ANOVA. The between groups differences were performed by the student t-test or chi-square test or Mann-Whitney U test. Significant difference was considered when calculated p-value was less than 0.05.

Results

Baseline characteristics

Baseline characteristics including demographic data (average age, weight, height, blood pressure, and BMI), TNSS, and ARM parameters of the two groups are shown in Table 1. There was no significant difference of the baseline data between the two groups except the volume of left nasal cavity (Vol_L).

Efficacy

Sixty patients completed the study. The treatment outcomes of BJK and loratadine groups were investigated at the time of follow-up (day 21 and day 42). As shown in Table 2, all TNSS parameters of both BJK and loratadine groups measured at day 21 and the end of treatments decreased significantly. There were no differences of TNSS between BJK group and loratadine group. However, all observed ARM parameters (MCA, Vol, and Dis) after treatment of both groups showed no significant difference from baseline as shown in Table 3. The between group parameters also showed no significant difference except Vol_L.

Safety

As shown in Table 4, after six weeks of treatment, the liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], and direct bilirubin) of

Table 1. Baseline characteristics of the two patient groups

Parameters	BJK (n=30) Mean±SD	Loratadine (n=30) Mean±SD	p-value
Demographic data			
Age (years)	31.20±8.25	35.16±12.47	0.15
Weight (kg)	61.45±11.65	59.55±10.23	0.50
Height (cm)	161.33±7.42	161.86±5.91	0.76
BMI	23.56±3.80	22.66±3.38	0.34
Systolic (mm/Hg)	119.0±6.48	117.66±6.66	0.41
Diastolic (mm/Kg)	62.13±8.38	63.13±7.83	0.93
TNSS			
Total score	6.60±1.76	7.13 ±1.40	0.18
Rhinorrhea	1.56±0.77	1.73±0.73	0.31
Itchy nose	1.43±0.81	1.70±0.95	0.28
Nasal congestion	2.13±0.68	2.13±0.62	0.97
Sneezing	1.53±0.86	1.56±0.72	0.77
Acoustic rhinometry			
MCA_L	0.35±0.12	0.40±0.12	0.09
MCA_R	0.37±0.13	0.36±0.12	0.72
Vol._L	1.33±0.21	1.47±0.29	0.01[t]
Vol._R	1.41±0.28	1.44±0.51	0.59
Dis._L	1.91±0.45	1.83±0.56	0.94
Dis._R	1.95±0.44	2.05±0.33	0.18

BJK=Benjakul remedy; SD=standard deviation; BMI=body mass index; TNSS=total nasal symptom score; MCA=minimal cross-sectional area; Vol.=nasal volume; Dis.=distance of MCA; L=left; R=right

[t] Statistically different with independent t-test

both groups showed no significant difference from the baseline. Regarding evaluation of renal function, blood urea nitrogen (BUN) level increased slightly in BJK group but not over the normal range and the creatinine levels did not differ from the baseline. White blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), and platelets levels were also normal and were not different from the baseline. The result of the present study analyses showed that BJK extract and loratadine did not induce liver and renal toxicity along the treatment periods. Thus, BJK extract and loratadine are safe throughout the six weeks of consecutive treatment.

Discussion

BJK is a traditional Thai herbal medicine approved in the Thai National List of Essential Medicines as adaptogenic drug. Previous study[5] showed that ethanolic extract of BJK exhibited *in vitro* anti-allergic by inhibiting β-hexosaminidase released from rat basophil cells (IC_{50}=12.69 μg/ml) and exhibited anti-inflammatory activities by inhibiting nitric oxide production in macrophage cells (IC_{50}=16.60 μg/ml, which is encouraging for using the extract in patients with allergy and inflammation. Moreover, the responsive components, 6-shogaol, plumbagin, exhibited potent anti-allergic activity better than the antihistamine, chlorpheniramine. The 6-shogaol and plumbagin were also the potent inhibitors of inflammatory associated mediators, nitric oxide and TNF-α[5]. These *in vitro* experiments demonstrated the inhibitory activities of BJK, its plant components and active compounds on the mediators related to progression of allergic rhinitis symptoms[9].

A study on the evidence of BJK prescribed by traditional Thai doctors showed that BJK was prescribed in most Thai traditional clinics as adaptogenic drug and for treatment of allergy and inflammation related diseases[4]. To confirm the evidences of the uses of BJK according to traditional Thai wisdom, the authors investigated clinical efficacy and safety of BJK in allergic rhinitis patients. In the present study, a dose of 300 mg BJK extract per day (100 mg, three times) can minimize the nasal symptoms including rhinorrhea, itchy nose, nasal congestion, and sneezing. The efficacy of BJK extract did not differ from the conventional medicine, loratadine. During six weeks-continuous treatment, BJK extract did not induce the liver and renal toxicity similar to the conventional drug, loratadine. These results related to the safety data of previous clinical study of BJK extract over four weeks in osteoarthritis patients[7]. The present phase II clinical study is the first report of BJK extract that provides the efficacy and safety information for treatment of mild to moderate allergic rhinitis.

Regarding measurements of nasal cavity by using acoustic rhinitis, all observed parameters (MCA, Vol, and DIS) of both groups did not show statistical differences from baseline, although the TNSS showed improvements. Considering the MCA parameter which is the main parameter using for describing the relationship between nasal cavity and nasal obstruction symptom[10]. Although the statistical results did not show differences, the MCAs trended to increase by approximately 5% to 8% at the end of treatments of both groups. These results caused small expansions of the nasal valve in the nasal cavity that

Table 2. Evaluation of allergic rhinitis symptoms by TNSS

Symptom	Follow-up	BJK (n=30)	Loratadine (n=30)	p-value
		Mean±SD	Mean±SD	
Total score	Week 0	6.60±1.76	7.13±1.40	0.18
	Week 3	4.30±2.08	4.50±1.96	0.61
	Week 6	2.90±1.97	3.13±1.75	0.42
Rhinorrhea	Week 0	1.56±0.77	1.73±0.74	0.31
	Week 3	0.90±0.80	1.13±0.73	0.19
	Week 6	0.73±0.69	0.73±0.78	0.89
Itchy nose	Week 0	1.43±0.81	1.70±0.95	0.28
	Week 3	1.00±0.74	0.93±0.91	0.65
	Week 6	0.60±0.62	0.73±0.63	0.41
Nasal congestion	Week 0	2.13±0.68	2.13±0.63	0.97
	Week 3	1.36±0.92	1.40±0.67	0.76
	Week 6	0.80±0.66	0.93±0.64	0.42
Sneezing	Week 0	1.53±0.86	1.56±0.73	0.77
	Week 3	1.03±0.76	1.03±0.61	0.75
	Week 6	0.73±0.67	0.73±0.45	0.89

BJK=Benjakul remedy; SD=standard deviation

Table 3. Comparison of measurement parameters evaluating by acoustic rhinometry of BJK extract and loratadine treated groups

Parameters	Follow-up	BJK (n=30)	Loratadine (n=30)	p-value
		Mean±SD	Mean±SD	
MCA_L	Week 0	0.35±0.12	0.40±0.12	0.09
	Week 3	0.36±0.12	0.41±0.12	0.11
	Week 6	0.37±0.12	0.42±0.14	0.17
MCA_R	Week 0	0.37±0.13	0.36±0.12	0.72
	Week 3	0.41±0.10	0.37±0.15	0.22
	Week 6	0.40±0.15	0.39±0.17	0.94
VoI._L	Week 0	1.33±0.21	1.47±0.29	0.02[t]
	Week 3	1.34±0.20	1.46±0.28	0.02[t]
	Week 6	1.38±0.19	1.49±0.28	0.15
VoI._R	Week 0	1.41±0.28	1.44±0.51	0.58
	Week 3	1.42±0.25	1.46±0.50	0.43
	Week 6	1.41±1.95	1.49±0.45	0.15
Dis._L	Week 0	1.91±0.45	1.83±0.56	0.94
	Week 3	1.89±0.50	1.77±0.64	0.69
	Week 6	1.93±0.38	1.89±0.47	0.98
Dis._R	Week 0	1.95±0.44	2.05±0.33	0.19
	Week 3	2.02±0.36	1.90±0.50	0.70
	Week 6	2.00±0.46	1.94±0.53	0.74

BJK=Benjakul remedy; SD=standard deviation; MCA=minimal cross-sectional area; Vol.=nasal volume; Dis.=distance of MCA; L=left; R=right

[t] Statistically different with independent t-test

Table 4. Liver functions, renal function, and complete blood count in safety issue

Indicators (normal level)	Follow-up	BJK (n=30) Mean±SD	Loratadine (n=30) Mean±SD	p-value
Liver functions				
AST (15 to 37 U/L)	Week 0	21.10±9.38	18.83±8.14	0.17
	Week 3	20.90±9.53	20.53±6.49	0.67
	Week 6	20.06±9.38	19.63±5.79	0.47
ALT (30 to 65 U/L)	Week 0	28.26±11.07	26.63±13.22	0.39
	Week 3	25.46±10.19	26.43±9.25	0.59
	Week 6	28.90±16.60	25.46±9.52	0.44
ALP (50 to 136 U/L)	Week 0	65.50±18.26	62.40±16.88	0.49
	Week 3	64.70±18.14	61.60±17.06	0.49
	Week 6	63.93±17.58	61.73±16.21	0.61
Direct bilirubin (0 to 0.3 mg/dL)	Week 0	0.14±0.49	0.12±0.55	0.09
	Week 3	0.14±0.67	0.12±0.69	0.45
	Week 6	0.13±0.60	0.15±0.10	0.47
Renal function				
BUN (5 to 23 mg/dL)	Week 0	10.56±3.26	11.87±0.67	0.21
	Week 3	11.17±3.30	12.45±0.69	0.18
	Week 6	14.11±14.15	12.51±0.59	0.26
Creatinine (0.6 to 1.4 mg/dL)	Week 0	0.71±0.15	0.72±0.15	0.95
	Week 3	0.70±0.14	0.71±0.16	0.91
	Week 6	0.72±0.14	0.71±0.15	0.73
Complete blood count				
WBC (4K to 11K/cu.mm)	Week 0	5.70±1.54	6.18±1.89	0.28
	Week 3	6.00±1.86	6.06±1.82	0.90
	Week 6	5.90±1.73	6.44±1.52	0.20
RBC count (4.5 to 6.0 $\times 10^6$/cu.mm)	Week 0	4.64±0.56	4.72±0.62	0.61
	Week 3	4.67±0.58	4.63±0.64	0.82
	Week 6	4.71±0.57	4.65±0.56	0.71
Hb (14 to 18 gm/dL)	Week 0	12.55±1.28	12.77±1.07	0.47
	Week 3	12.54±1.29	12.52±1.08	0.96
	Week 6	12.63±1.24	12.55±0.90	0.77
Platelets count (150K to 400K/cu.mm)	Week 0	295.46±65.08	265.80±53.33	0.05
	Week 3	285.33±60.81	255.93±46.60	0.04
	Week 6	288.33±57.77	272.73±53.84	0.28

BJK=Benjakul remedy; SD=standard deviation; AST=aspartate transaminase; ALT=alanine transaminase; ALP=alkaline phosphatase; BUN=blood urea nitrogen; WBC=white blood cell; RBC=red blood cell; Hb=hemoglobin

may infer improvement of stuffiness symptom[11].

For the safety evaluation, liver function (AST, ALT, alkaline phosphatase and direct bilirubin) and renal function (BUN and creatinine) parameters were monitored closely to detect any abnormality and none were found in either group. Regarding hematological test, no notable results were reported after continuously receiving both treatments for three and six weeks. Thus, the patients who received the BJK extract (similar to loratadine) did not experience

liver toxicity, renal toxicity, or a serious adverse effect on their blood cells.

A common adverse effect after the BJK extract treatment was the burning sensation in the stomach. This may relate to piperine and gingerol, which are the markers of BJK[12]. Piperine and gingerols are agonist of human TRPV1 receptor located in gastro-intestinal tract that can induce the burning sensation[13]. However, the BJK extract does not exhibit the sedative effect associating with antihistamines.

Conclusion

In conclusion, the present study performed the first clinical efficacy and safety of BJK extract for treatment of mild to moderate allergic rhinitis by comparison with the conventional anti-allergic drug, loratadine. BJK extract can relieve the symptoms of allergic rhinitis with clinical safety. BJK extract capsules can be considered as a non-sedative, alternative treatment for allergic rhinitis. This is the first report or first indication in human of BJK for being anti-allergy drug.

What is already known on this topic?

The BJK remedy extract has good anti-allergic activity in allergic rhinitis patients with no adverse effect on liver and kidney functions including hematology.

What this study adds?

This study provided background knowledge for clinical trial phase 2 of BJK extract.

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Conflicts of interest

The authors declare no conflict of interest.

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