



Treatment of perennial allergic rhinitis using Shi-Bi-Lin, a Chinese herbal formula

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ABSTRACT

Aim of the study: Shi-Bi-Lin (SBL) is modified from the classic formula Cang-Er-Zi-San which has been used to treat chronic rhinitis, paranasal sinusitis and allergic rhinitis by herbal practitioners. The present study aimed at patients with moderate to severe perennial allergic rhinitis. SBL which has been shown effective in treating a guinea-pig model of allergic rhinitis, was evaluated for its efficacy and safety.

Materials and methods: 126 allergic rhinitis patients were recruited in a double-blind randomized control trial. Half of the patients received SBL capsules and the others half received placebo for 4 weeks. Symptoms scores, physician's evaluation, nose examination, quality of life, adverse effects, serum cytokines were evaluated before and after treatment.

Results: SBL was found to be safe and effective in relieving some symptoms of perennial allergic rhinitis, improving the nose condition, and enhancing some domains of quality of life when compare to placebo, ($p < 0.05$). In the 2 weeks follow up after treatment completion, the SBL enjoyed a prolongation of symptom control ($p = 0.05$).

Conclusion: SBL relieved symptoms of nose blockage among patients with perennial allergic rhinitis, and some aspects of the quality of life were also improved. The improvement was sustained for at least 2 weeks after treatment. No serious adverse events were encountered.

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1. Introduction

Allergic rhinitis (AR) is a common condition that significantly affects the patient's quality of life. Traditional Chinese Medicine has been widely used in Asian communities for centuries and some formulae claimed efficacy in treating allergic conditions (Kung et al., 2006; Xue et al., 2006; Guo et al., 2007; Yang and Yu, 2008). Shi-Bi-Lin (SBL) is a formula developed by the Institute of Chinese Medicine, the Chinese University of Hong Kong, based on the classic formula Cang-Er-Zi-San by Yan (1253) which was created over 700 years ago for the treatment of chronic rhinitis, paranasal sinusitis and allergic rhinitis (Xu et al., 2001; Zeng, 2002; Han, 2003).

In early laboratory studies, we tested the therapeutic effects of SBL in a well-characterized ovabumin-induced guinea-pig model of allergic rhinitis (Zhao et al., 2005a,b, 2006; Lenon et al., 2008), and found it effective in the relief of nasal symptoms resulting from the induced allergic rhinitis. In addition, SBL apparently suppressed eosinophilic infiltration in the animals' nasal tissues, and inhibited

the expression of endothelial nitric oxide synthase (ENOS) and the release of thromboxane B2 (TXB2). In our earlier cell culture studies, SBL also demonstrated inhibitory effects on some cytokines, such as IL-4 and TNF- α , released from human mast cells (HMC-1).

We therefore hypothesized that this modified classic herbal formula might improve the symptoms of perennial allergic rhinitis (PAR) and offer an alternative treatment for PAR. Accordingly, a prospective, double-center, double blind, placebo controlled clinical trial was designed and conducted to evaluate the clinical efficacy and safety of SBL in treating PAR.

2. Methodology

2.1. Patient selection and randomization

The research was approved by both the Clinical Research Ethics Committees of the Chinese University of Hong Kong and the Hospital Authority Kowloon West Cluster and followed the guidelines of the Declaration of Helsinki and Tokyo for humans. Patients were recruited as volunteers from the Prince of Wales hospital, the Yan Chai hospital and the Alice Ho Mui Ling Nethersole Hospital specialist clinics. Informed consent was obtained prior to the treatment

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Table 1
Inclusion and exclusion criteria of the clinical trial.

Inclusion criteria	A subject was eligible for inclusion if the following items applied:
	1. Aged from 18 to 65 years old 2. Total symptom score ≥ 4 3. Has a history of typical symptoms of perennial allergic rhinitis (PAR) including watery rhinorrhea, sneezing, nasal obstruction and itching in nose and eyes or palate for at least 2 previous consecutive years 4. Has a positive skin test to house-dust mite, mold antigens and/or animal (dog and cat) dander (to be carried out by registered medical doctor in standard procedures). Those with regular medications should stop medication for 7 days prior to the test 5. Informed consent was obtained and signed before initiation
Exclusion criteria	Patients with on or more of the following conditions will be excluded:
	1. Lactating or pregnant women and women of child-bearing potential not using reliable contraceptive method 2. Patients who received allergen injections during the previous 2 years 3. Patients on regular medications for AR, or for cold and other allergic disorder 4. Seasonal allergic rhinitis, vasomotor rhinitis and rhinitis and rhinitis medicamentosa 5. Nasal structure deformities, nasal polyps and hypertrophic rhinitis 6. Systematic corticosteroid used within recent 3 months or nasal corticosteroid within 15 days 7. Other active respiratory disorders 8. Mental retardation 9. Active medical disorders: cancer, infection, hematological, renal, hepatic, cardiovascular, metabolic diseases and HIV infection

start. Patients ages between 18 and 65 years old, and had a history of perennial allergic rhinitis for at least two consecutive years, and fulfilled the allergic rhinitis diagnostic criteria for enrolment required for trials (US Department of Health and Human Services, 2000). A positive skin test to house-dust mite, mold antigens and/or animal dander was required.

The trial was undertaken at the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong, and Yan Chai Hospital. Because PAR had no seasonal predominance, recruitment was conducted throughout the year. The physicians and patients were blinded to the medications. Randomization was organized by allocating a computer generated random number to each patient on the list. All patients were informed that there was a 50% chance of receiving placebo treatment. The strict inclusion and exclusion criteria are shown in Table 1. The assessment for each patient was conducted by the same ear, nose and throat (ENT) specialist.

2.2. Study design

Visit 1 was a screening visit. During the visit, participants were explained thoroughly about how the trial would be conducted and a consent form was signed. Physical examination included nose examination and grading of symptoms and skin sensitivity tests. In the nose examination included appearance of mucous membrane, nose obstruction and secretion. Blood samples were collected for total serum IgE, Eosinophil Cationic Protein (ECP), liver and kidney function tests, and a full blood picture. Pregnancy was excluded for females, because of possibility of extra adverse effect. Subjects then entered a 1-week run-in-period, during which a symptom diary was given to each subject for the evaluation of symptoms. The data from

this 1-week run-in period were used to determine the eligibility of the patient for inclusion in the trial.

At visit 2, the eligible subjects were evaluated for the final inclusion. Those included received a 2-week daily symptom and medication chart and capsules of either SBL or placebo for the first 2-week trial consumption. The placebo contained brown colored starch resembling the SBL powder. Participants completed a quality of life (QOL) questionnaire, filled up a visual analogue scale (VAS) and a concomitant medication form. Qualified patients were thus randomized for 4 weeks of treatment with either SBL or color-matched placebo capsules with dose of 1 g (two capsules), twice daily.

At visit 3, patients returned to the clinic for evaluation of their clinical conditions. Daily symptoms and medication diaries were collected, and new diaries for the next 2 weeks were issued. The medication container was returned for the counting of remaining capsules, before the next 2-weeks trial medication was supplied. Patients should have completed a VAS form, a concomitant medication form and an adverse event (AE) report form.

At visit 4, a final clinical evaluation and physical examination and nose examination were carried out. The medication container was again checked. Blood and urine samples were collected. The investigator discussed with the patient, so as to enter the physician's overall evaluations of global symptoms at the end of the study. Patients completed the QOL questionnaire, the VAS form, the concomitant medication form and the AE report form.

Visit 5 was an additional visit, which was designed for the evaluation of sustained effects of the medication after treatment had been completed for 2 weeks. All the participants were required to provide information about their symptoms using the same VAS.

2.3. Skin prick tests

These tests were performed by two physicians with positive control (histamine 1 mg/mL), negative control (albumin saline), and using the following allergens (Bayer Corporation, Spokane, US): *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, mold mix, cockroach, cat, and dog. A skin test was considered positive when it produced a wheal with a diameter of at least 7 mm within 10 min after beginning the test. At least one positive skin test was required for inclusion into the study.

2.4. SBL capsules and placebo

The major components of SBL included 7.5 g *Xanthium sibiricum* Patr. ex Widder (Asteraceae, Fructus), 20 g *Angelica dahurica* (Fisch. ex Hoffm.) Benth. (Apiaceae, Radix), 7.5 g *Saposhnikovia divaricata* (Turcz.) Schischk. (Apiaceae, Radix), 15 g *Magnolia biondii* Pamp. (Magnoliaceae, Flos), 5 g *Gentiana scabra* Bunge (Gentianaceae, Radix) and 5 g *Verbena officinalis* L. (Verbenaceae, Herba). The composition of each herb was standardized prior to manufacturing by thin layer chromatography (TLC) with reference to methods recommended by the Chinese Pharmacopoeia (State Pharmacopoeia Commission, 2000) (Zhao et al., 2005c). The reference herbs and reference chemical standards used for authentication were purchased from the National Institute for the Control of Pharmaceutical and Biological Products, People's Republic of China. SBL capsules were manufactured, packaged and labeled by a pharmaceutical manufacturer with GMP license. Gas chromatography-mass spectrometry (GC-MS) and inductively coupled Argon plasma spectrometry (ICAPS) tests were carried out to rule out contamination in the SBL capsules. The tests included toxic heavy metals, microbial contaminations and pesticides residues.

2.5. Efficacy evaluation instruments

Efficacy outcomes were evaluated by four instruments, viz. symptom diary, quality of life questionnaire, the visual analog scale (VAS), and the physician's overall evaluation.

2.5.1. Symptom diary

The severity of PAR was evaluated by means of a daily symptom diary chart. Patients were instructed to grade retrospectively everyday before bed time, their general well-being, nasal symptoms (nasal blockage, rhinorrhea, nose itching, sneezing) and non-nasal symptoms (itching eyes, tearing eyes, redness of eyes, itching of ears or palate) on the diary chart. A 4-point severity scale from no symptoms (0), mild (1), moderated (2) to severe (3) was used (Prenner et al., 1996).

2.5.2. SF-36 QOL questionnaire

Medical outcomes were studied by QOL questionnaire before and after treatment. The validated and authorized Cantonese version of SF-36 QOL was adopted. It has 36 questions that have been validated to measure general health status by evaluating eight domains: general health (GH), physical functioning (PF), social functioning (SF), role limitation caused by physical problems (RP), bodily pain (BP), role limitations caused by emotional problem (RE), mental health (MH), and vitality (VT) (Brazier et al., 1992; Ware and Sherbourne, 1992). Each domain was started from 0 (worst health) to 100 (best health).

2.5.3. Visual analogue scale (VAS)

A VAS evaluation (Miller and Ferris, 1993) was completed by patients at each follow-up visit. VAS consisted of a 10-cm line related to each symptom of PAR with "no symptom at all" on the left end of the line (0%) and "very severe and intolerable symptoms" on the right end of the line (100%). The VAS was used to evaluate whether there was any change of the symptoms during the treatment of PAR with SBL or placebo.

2.5.4. Physician's overall evaluation

After completion of the evaluations of QOL and VAS at visit 4, the physician discussed with the patients about the overall symptom responses. The impression obtained was recorded as excellent, good, fair, poor or failure.

2.6. Credibility evaluation

For assessing compliance, daily medication was recorded in the daily medication diary, and trial medication containers were checked at each visit for any remaining capsules. Data checking was completed before breaking the double-blind code. Analysis was performed by independent biostatisticians.

2.7. Serum Total Immunoglobulin (IgE) and Eosinophil Cationic Protein (ECP) concentrations

These were measured for all the patients before and after the trial. Patients' sera were stored at -70°C before analysis. Serum total IgE was measured by chemiluminescence immunoassay using the IMMULITE Analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum ECP was measured by fluorescent enzyme immunoassay (AutoCAP system, Pharmacia Diagnostics AB, Uppsala, Sweden).

2.8. Statistical analysis

Analyses were performed on an intention-to-treat basis. All the outcome variables were tested at the baseline for their equivalence

with *t*-test, ANOVA and χ^2 test, respectively, depending on their nature. For the analysis of difference between treatment groups, the score of VAS, self-report symptom and SF-36, were compared with paired-*t*-test and ANCOVA, with the baselines adjustment. SF-36 consisted of eight domains, viz., physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. For laboratory outcomes, IgE and ECP concentrations, Student's *t*-test and ANOVA were used to compare the differences between SBL and placebo group.

All statistical tests were two-sided with 0.05 alpha levels. The statistical analyses were performed with SPSS 14.0 for Windows.

3. Results

3.1. Patient characteristics

A total of 182 patients were screened, among them 126 satisfied the selection criteria. The most common reason for exclusion was negative skin test and low total symptom score (below 4). Sixty-three patients were recruited into the treatment and placebo groups, respectively. There were no significant differences between the two groups in age, sex, body weight and baseline total symptom score.

3.2. Effect of SBL on symptom scores

3.2.1. Symptom diary

Each symptom score in the diary was calculated and the differences between the two groups, and self-comparison with the baselines was analysed. Starting from baselines, there were improvements of general well-being (GF), nose-blockage (NB) and eye-itchiness (EI) in both groups. The SBL treatment group developed effectiveness earlier than the placebo group, i.e. starting in 1–2 weeks (Table 2). Although in week 1, both the SBL and placebo groups showed one parameter significantly different from the baseline; in week 2 the placebo group showed more parameters significantly improved. However, in week 3, the SBL group was having less rhinorrhea and sneezing compare with the placebo ($p \leq 0.05$).

3.2.2. Visual analogue scale

Based on patients' own evaluation, both groups showed alleviation of symptoms of nasal blockage, rhinorrhea, sneezing, nose itchiness, eye itchiness, tearing, eye congestion and ear congestion. When SBL group was compared with placebo group, no significant difference was found (Table 3). After the treatment was completed, each subject was followed up for 2 weeks and the VAS was also evaluated at the end of follow-up period (visit 5). The results indicated that in the 2 weeks where no treatment was given, symptoms recurred in the placebo group. However, in the SBL group all symptoms except nose blockage were still improved (Fig. 1).

3.2.3. Physicians' overall evaluation and nose examination

Physicians' overall evaluation was performed at visit 4 after completion of treatment. As shown in Table 4, there was a tendency of improvement in favour of SBL treatment but the difference did not reach statistical significance.

At the beginning of the study (screening visit), careful nose examination was done for all patients. The gross appearance of mucous membrane, obstruction and secretion were assessed and recorded. Grading was scored as normal, mild, moderate and severe. Only 4.8% in both groups were normal looking. After 4 weeks' treatment, 28.6% subjects in the SBL group turned normal, while in the placebo group only 8.5% turned normal ($p = 0.005$).

Table 2

Daily symptom weekly mean score analysis.

Symptom	Group	Run-in	Week 1	Week 2	Week 3	Week 4
GF	SBL	3.31(0.58)	3.11(0.57) (–6%) ^c	3.00(0.66) (–9%) ^c	2.91(0.74) (–12%) ^c	2.82(0.80) (–15%) ^c
	Placebo	3.30(0.70)	3.21(0.62) (–3%)	3.02(0.66) (–8%) ^c	2.91(0.74) (–12%) ^c	2.80(0.78) (–15%) ^c
NB	SBL	1.53(0.77)	1.42(0.62) (–7%)	1.32(0.61) (–14%) ^b	1.27(0.62) (–17%) ^b	1.19(0.68) (–22%)
	Placebo	1.35(0.71)	1.50(0.71) (–2%)	1.36(0.78) (–11%)	1.31(0.79) (–14%)	1.21(0.77) (–21%) ^c
RV	SBL	1.47(0.74)	1.44(0.75) (–2%)	1.48(0.70) (1%)	1.40(0.73) (–5%) ^a	1.26(0.71) (–14%)
	Placebo	1.64(0.66)	1.55(0.66) (–5%)	1.45(0.72) (–12%) ^b	1.24(0.76) (–24%) ^c	1.24(0.70) (–24%) ^c
SF	SBL	1.48(0.73)	1.37(0.67) (–7%)	1.33(0.61) (–10%)	1.29(0.72) (–13%) ^a	1.15(0.64) (–22%) ^b
	Placebo	1.47(0.72)	1.36(0.73) (–7%)	1.24(0.75) (–16%) ^b	1.14(0.75) (–22%) ^c	1.18(0.70) (–20%) ^c
NI	SBL	1.35(0.76)	1.30(0.74) (–4%)	1.31(0.69) (–3%) ^a	1.14(0.70) (–16%) ^a	1.11(0.58) (–18%)
	Placebo	1.46(0.72)	1.18(0.76) (–19%) ^b	1.07(0.74) (–27%) ^c	0.96(0.74) (–34%) ^c	0.99(0.75) (–32%) ^c
EI	SBL	0.97(0.79)	0.91(0.67) (–6%)	0.79(0.68) (–19%) ^b	0.67(0.63) (–31%) ^b	0.73(0.67) (–25%)
	Placebo	0.78(0.72)	0.76(0.67) (–3%)	0.67(0.81) (–14%)	0.53(0.70) (–32%) ^c	0.56(0.76) (–28%) ^c
T	SBL	0.54(0.74)	0.54(0.69) (0%)	0.55(0.66) (2%)	0.51(0.66) (–6%)	0.52(0.71) (–4%)
	Placebo	0.44(0.66)	0.41(0.64) (–7%)	0.44(0.71) (0%)	0.39(0.65) (–11%)	0.43(0.67) (–2%)
EC	SBL	0.36(0.67)	0.33(0.51) (–8%)	0.23(0.43) (–36%)	0.32(0.56) (–11%)	0.37(0.60) (3%)
	Placebo	0.29(0.58)	0.26(0.60) (–10%)	0.35(0.71) (21%)	0.27(0.58) (–7%)	0.26(0.58) (–10%)
EAR	SBL	0.98(0.69)	0.96(0.76) (–2%)	0.89(0.66) (–9%)	0.86(0.78) (–12%)	0.81(0.65) (–17%)
	Placebo	0.88(0.73)	0.83(0.78) (–6%)	0.78(0.79) (–11%)	0.68(0.78) (–23%)	0.61(0.78) (–31%)

GF—general well-being; NB—nose blockage; RV—rhinorrhea volume; SF—sneeze frequency; NI—nose itching; EI—eyes itching; T—tears; EC—eye congestion; EAR—ear itching.

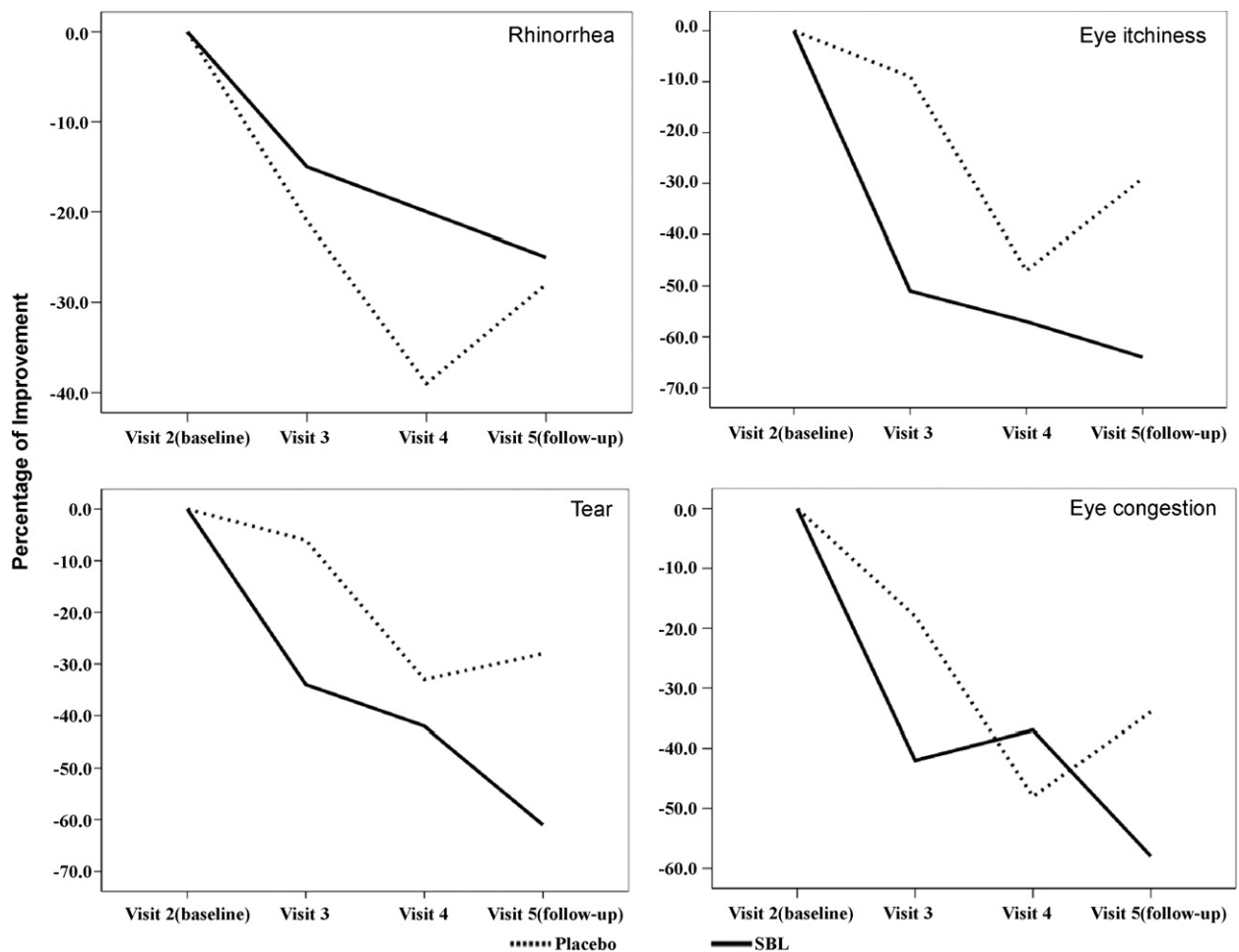
^a $p < 0.05$ compared with placebo group.^b $p < 0.05$ compared with baseline.^c $p < 0.01$ compared with baseline.**Fig. 1.** Improvement of visual analogue scale.

Table 3
General assessment of self-reported symptoms.

Symptom	Group	Run-in	Weeks 1–2	Weeks 3–4	p value ^a
GF	SBL	3.33(0.70)	3.05(0.70)	2.74(0.79)	0.000
	Placebo	3.39(0.82)	3.05(0.72)	2.66(0.79)	0.000
	p value	0.812	0.985	0.635	
NB	SBL	1.56(0.85)	1.46(0.60)	1.40(0.69)	0.117
	Placebo	1.65(0.83)	1.50(0.85)	1.26(0.77)	0.001
	p value	0.674	0.819	0.316	
RV	SBL	1.67(0.77)	1.64(0.72)	1.51(0.80)	0.226
	Placebo	1.89(0.68)	1.58(0.72)	1.35(0.72)	0.000
	p value	0.129	0.522	0.358	
SF	SBL	1.70(0.68)	1.54(0.71)	1.38(0.77)	0.015
	Placebo	1.76(0.74)	1.48(0.79)	1.26(0.81)	0.001
	p value	0.644	0.845	0.455	
NI	SBL	1.57(0.90)	1.50(0.85)	1.17(0.64)	0.001
	Placebo	1.63(0.75)	1.18(0.79)	1.09(0.79)	0.000
	p value	0.818	0.036	0.378	
EI	SBL	1.18(0.92)	0.93(0.78)	0.77(0.78)	0.003
	Placebo	0.90(0.78)	0.75(0.86)	0.58(0.78)	0.001
	p value	0.097	0.155	0.139	
T	SBL	0.69(0.90)	0.66(0.82)	0.55(0.67)	0.053
	Placebo	0.60(0.78)	0.45(0.72)	0.39(0.62)	0.028
	p value	0.735	0.099	0.155	
EC	SBL	0.48(0.79)	0.30(0.54)	0.36(0.65)	0.322
	Placebo	0.31(0.62)	0.32(0.68)	0.21(0.56)	0.109
	p value	0.204	0.654	0.160	
EAR	SBL	1.13(0.88)	1.02(0.86)	0.96(0.81)	0.065
	Placebo	0.95(0.91)	0.82(0.81)	0.63(0.82)	0.004
	p value	0.224	0.196	0.016	

Remark: GF—general well-being; NB—nose blockage; RV—rhinorrhea volume; SF—sneeze frequency; NI—nose itching; EI—eyes itching; T—tears; EC—eye congestion; EAR—ear itching.

^a Weeks 3–4 compared with run-in.

3.2.4. Effects of SBL on quality of life (SF-36)

The domains of physical function, emotional role were significantly improved in the SBL group from baseline ($p=0.006$ and $p=0.003$), while no significant changes were observed in the placebo group. However, the domain of body pain was significantly decreased in the placebo group from baseline ($p=0.005$) while SBL had apparently no effect. The domain of physical role was significantly improved in both the SBL and placebo group (Fig. 2).

3.3. Effect of SBL on serum total IgE and EPC concentrations

The changes in either the treatment or placebo group were insignificant.

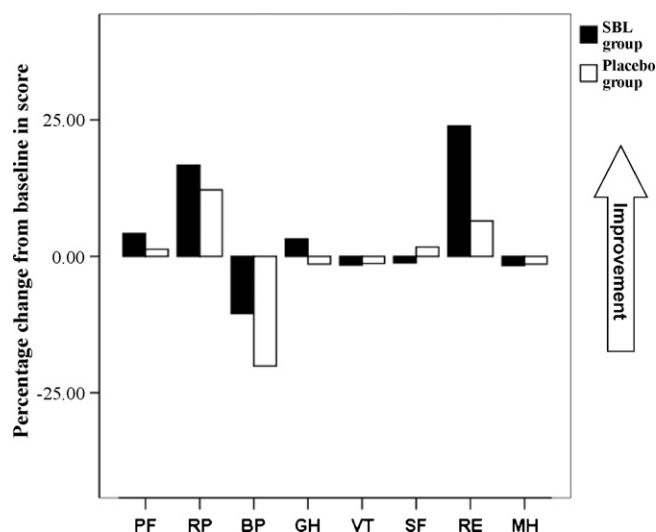
3.4. Adverse event

The adverse events reported included abdominal pain, diarrhea, sore throat, skin itchiness, dry mouth, etc. These occurred in 12 patients of the SBL group and 10 patients of the placebo group. They were apparently unrelated to the administration of either SBL or placebo.

Table 4
Efficacy of symptoms (global physician assessment).

Group	Response to treatment					Total
	Excellent	Good	Fair	Poor	Failure	
SBL	0	33(54%)	21(34%)	4(7%)	3(5%)	61
Placebo	2(3%)	24(39%)	28(45%)	7(11%)	1(2%)	62
Total	2	57	49	11	4	123

$\chi^2 = 7.418$, $p = 0.191$.

**Fig. 2.** Percentage change from baseline in scale score of each domain of QOL.

Remark: PF—physical functioning, RP—role limitations caused by physical problems, BP—bodily pain, GH—general health, VT—vitality, SF—social functioning, RE—role limitations caused by emotional problem and MH—mental health.

3.5. Concurrent medication

Thirteen patients in SBL group and eleven patients in placebo group took extra medicine to control their symptoms of PAR. There were no statistical differences, in the incidence of taking concomitant medicine to control symptoms of PAR, between the two groups ($p=0.821$). Those patient who mistakenly took antihistamine had been excluded from the analysis. Other patients' who occasionally took concurrent medications were found to be consuming unrelated items like vitamins, pain killers, anti-cholesterols or anti-hypertensive.

4. Discussion and conclusion

Chinese herbal medicine has been used for the treatment of allergic diseases for centuries. A large number of clinical studies conducted for allergic rhinitis published in Chinese medical journals were deficient of appropriate randomization, blinding, and control. This study was a well designed randomized, double blinded, placebo-controlled trial using the herbal preparation, SBL, in the treatment of perennial allergic rhinitis. Four main instruments, viz. daily symptom diaries, VAS of symptoms, physicians' overall evaluations and SF-36 QOL indices were used to measure the clinical efficacy of SBL.

Symptom diary evaluation was a continuous evaluation which is quite commonly used in clinical trials. In the present study, no significant difference was detected between the two groups. However in terms of general well-being, relief of nose blockage, sneezing and eye itching, there appeared a trend of better results with SBL.

VAS scales are commonly used to measure patients' perception of their well being and symptoms. However, this type of survey was well recognized to have practical limitations (Leopold et al., 1997). Many other studies showed poor or variable correlations with VAS and other outcome measures (Rechtweg et al., 2004). The VAS scale used in the present study had eight symptom measurements. It failed to show significant differences between the study groups. However, both groups showed significant alleviation in the symptoms of nasal blockage, rhinorrhea, sneezing, nose itching, eye congestion, tearing and ear itching, when compared with the baseline levels.

Apart from specific symptoms, allergic rhinitis has a profound impact on patients overall QOL. Although not a disease-specific QOL measurement for allergic rhinitis, SF-36 has been widely used to evaluate outcomes in many patient populations. The Task Force on Rhinosinusitis also recommended the use of SF-36 to measure the general health-related QOL for individuals suffering from sinusitis and AR (Kaliner et al., 1997; Leopold et al., 1997). In the present study, although no statistically significant differences of each domain between the SBL and placebo groups were observed, scores of social function, and emotional role in the SBL group were significantly improved when compared with the baseline, while the placebo group has no such improvement. It must be noted that the low sensitivity of SF-36 survey and the small sample size were limitations to this study.

Although the average scores of physician's overall evaluation showed no statistically significant difference between the two groups, a tendency of predominance of improvement in the SBL group was observed. Good efficacy rate was higher in the SBL group than in the placebo group. In the nose examination, the SBL group showed significant improvement compared with the placebo group.

It is difficult to explain the, significant placebo effects observed. Some clinical trials with Chinese Medicine encountered significant placebo effects which could be as high as 55% although the herbal formula gave better results (Yuan and Lin, 2000). According to the study protocol, all the participants were treated with SBL or placebo for 4 weeks. After the drug treatment was completed, each subject was checked 2 weeks later and the VAS indicated that during the follow-up period all symptoms recurred in the placebo group, but in the SBL group they remained under control. One explanation to this encouraging observation was that the placebo effects wore off after treatment stopped whereas the SBL effects were remained. After all, the use of herbal medicine was known to require prolonged administration and its effects wear off slowly (Lai, 2002).

The present clinical trial was conducted to investigate the efficacy and safety of the daily treatment of perennial allergic rhinitis using SBL and placebo as control for a limited period of 4 weeks.

Although the results of this study did not overwhelmingly support the efficacy of SBL, the trend appears to favour the efficacy of SBL over placebo. May be a larger sample size trial lasting a longer period of treatment could lead to better understanding of the efficacy of SBL. Since it was a preliminary study and we wanted to avoid adverse effects, we were conservative in determining the dose and treatment period in our planning. The dose of two capsules twice daily in fact, was about one third of the maximal recommended dose, and the treatment period of 4 weeks could be lengthened when prevention of a severe attack of AR is considered. Since prolonged effects of SBL was already observed, a larger dose with a longer administration would be adopted in our next study.

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References

- Brazier, J.E., Harper, R., Jones, N.M., O'Cathain, A., Thomas, K.J., Usherwood, 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *British Medical Journal* 305, 160–164.
- Guo, R., Pittler, M.H., Ernst, E., 2007. Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Annals of Allergy, Asthma and Immunology* 99, 483–495.
- Han, X.L., 2003. Application of CangErZiSan in the rhinology. *Shandong Journal of Traditional Chinese Medicine* 22, 121–122.
- Kaliner, M.A., Osguthorpe, J.D., Fireman, P., Anon, J., Georgitis, J., Davis, M.L., 1997. Sinusitis: Bench to Bedside. Current findings, future directions. *Otolaryngology and Head and Neck Surgery* 116, S1–S20.
- Kung, Y.Y., Chen, Y.C., Hwang, S.J., Chen, T.J., Chen, F.P., 2006. The prescriptions frequencies and patterns of Chinese herbal medicine for allergic rhinitis in Taiwan. *Allergy* 61, 1316–1318.
- Lai, S.L., 2002. *Clinical Trials of Traditional Chinese Materia*. Guang dong People's Publishing House, Guangzhou.
- Lenon, G.B., Li, C.G., Xue, C.C., Thien, C.K., Story, D.F., 2008. Inhibition of inducible nitric oxide production and iNOS protein expression in lipopolysaccharide-stimulated rat aorta and Raw 264.7 macrophages by ethanol extract of a Chinese herbal medicine formula (RCM-101) for allergic rhinitis. *Journal of Ethnopharmacology* 116, 547–553.
- Leopold, D., Ferguson, B.J., Piccirillo, J.F., 1997. Outcomes assessment. *Otolaryngology and Head and Neck Surgery* 117, S58–S68.
- Miller, M.D., Ferris, D.G., 1993. Measurement of subjective phenomena in primary care research: the Visual Analogue Scale. *The Family Practice Research Journal* 13, 15–24.
- Prenner, B.M., Chervinsky, P., Hampel Jr., F.C., Howland, W.C., Lawrence, M., Meltzer, E.O., 1996. Double-strength beclomethasone dipropionate (84 micrograms/spray) aqueous nasal spray in the treatment of seasonal allergic rhinitis. *Journal Allergy Clinical Immunology* 98, 302–308.
- Rechtweg, J.S., Moinuddin, R., Houser, S.M., Mamikoqlu, B., Corey, J.P., 2004. Quality of life in treatment of acute rhinosinusitis with clarithromycin and amoxicillin/clavulanate. *Laryngoscope* 114, 806–810.
- U.S. Department of Health and Human Services, Food and Drug Administration, April 2000. Allergic Rhinitis: Clinical Development Programs for Drug Products. Available at <http://www.fda.gov/cder/guidance/2718dft.pdf>.
- Ware Jr., J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 30, 473–483.
- Xu, C.H., Song, R.H., Zhong, Y., Gao, S.J., 2001. A clinical observation on the influence of irrigating solution supplemented Xanthii powder on the therapeutic effect of ESS for chronic sinusitis and nasal polyps. *Chinese Journal of Otorhinolaryngology of Integrated Traditional of Western Medicine* 9, 274–276.
- Xue, C.C., Li, C.G., Hugel, H.M., Story, D.F., 2006. Does acupuncture or Chinese herbal medicine have a role in the treatment of allergic rhinitis? Outcome measures. *Current Opinion in Allergy & Clinical Immunology* 6, 175–179.
- Yan, Y.H., 1253. *Jisheng Fang, Cang-Er-Zi-San*. Song Dynasty, China.
- Yang, S.H., Yu, C.L., 2008. Antiinflammatory effects of Bu-zhong-yi-qi-tang in patients with perennial allergic rhinitis. *Journal of Ethnopharmacology* 115, 104–109.
- Yuan, R., Lin, Y., 2000. Traditional Chinese Medicine: an approach to scientific proof and clinical validation. *Pharmacology & Therapeutics* 86, 191–198.
- Zeng, H., 2002. Treatment of allergic rhinitis with YuPingFeng plus JiaWai-CangErZiSan. *Journal of North Sichuan Medical College* 17, 72–73.
- Zhao, Y., Woo, J.K., Leung, P.C., Chen, G.G., Wong, Y.O., Liu, S.X., 2005a. Symptomatic and pathophysiological observations in a modified animal model of allergic rhinitis. *Rhinology* 43, 47–54.
- Zhao, Y., Leung, P.C., Woo, K.S., Chen, G.G., Wong, Y.O., Wang, L.H., 2005b. The effect and therapeutic mechanism of a Chinese herbal formula Shu-Bi-Lin (SBL) in the treatment of allergic rhinitis-animal study and in vitro study. *Journal Allergy Clinical Immunology* 115, S139.
- Zhao, Y., van Hasselt, C.A., Woo, J.K.S., Chen, G.G., Wong, Y.O., Wang, L.H., 2005c. Effects of the Chinese herbal formula Shi-Bi-Lin on cytokine release from the human mast cell line. *Annals of Allergy Asthma Immunology* 95, 79–85.
- Zhao, Y., van Hasselt, C.A., Woo, J.K.S., Chen, G.G., Wong, Y.O., Li, H., et al., 2006. Effect of a Chinese herbal formula, Shi-Bi-Lin, on an experimental model of allergic rhinitis. *Annals of Allergy Asthma Immunology* 96, 844–850.