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A multicenter study on the efficacy and safety of So-Cheong-Ryong-Tang for perennial allergic rhinitis

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ABSTRACT

Background: So-Cheong-Ryong-Tang (SCRT), also known as Xiao-Qing-Long-Tang or Sho-seiryo-to, is a mixed herbal formula that is used to treat allergic rhinitis, bronchitis, allergic asthma, and common cold in traditional Korean medicine.

Objective: To assess the efficacy and safety of the SCRT for the treatment of allergic rhinitis. Methods: We conducted a double-blind, randomized, placebo-controlled, parallel-group, multicenter study of Korean adults with perennial allergic rhinitis. The trial consisted of a 4-week oral administration of SCRT or placebo, with two visits at 2-week intervals, and an 8-week follow-up period, with two visits at 4-week intervals. The primary outcome was a change in the total nasal symptoms score. The secondary outcomes included changes in the Rhinoconjunctivitis Quality of Life Questionnaire score, total serum immunoglobulin E (IgE), cytokines levels, and nasal endoscopy index.

Results: SCRT improved nasal symptoms and quality of life in patients with PAR after 4 weeks medication, and these effects did not last 8 weeks after the end of medication. The level of serum IgE, eosinophil counts, and cytokines did not alter after medication. Nasal endoscopy index did not show significant difference. No serious AEs and safety assessment changes were observed in this trial.

Conclusion: SCRT is an effective and safe medication for patients with chronic, perennial, and moderate to severe AR. A clinical study with a > 4-week period of medication use, and more participants for immune material test is needed to investigate the long-term efficacy of SCRT in relieving the symptoms of nasal obstruction and identifying the underlying mechanisms of action and indications for traditional Korean medicine.

1. Introduction

Allergic rhinitis (AR) is an inflammatory disease of the nasal membranes that results from an immunoglobulin E (IgE)-mediated allergic reaction.[1] The prevalence of AR is 10–40% worldwide and 16.1% in South Korea.[2,3] AR can be classified as seasonal (SAR, occurring during specific seasons) or perennial (PAR, occurring year round). The major symptoms of AR are nasal congestion, rhinorrhea, nasal itching, and sneezing. AR is not a life-threatening disease; however, it has a considerable impact on the patients' quality of life and causes social and economic burden.[4] Furthermore, untreated AR is a risk factor for asthma, rhinosinusitis, nasal polyps, otitis media, and allergic conjunctivitis.[5]

In Korea, several herbal medicines have been used to treat AR. So-

Abbreviations: SCRT, So-Cheong-Ryong-Tang; TKM, traditional Korean medicine; PAR, perennial allergic rhinitis; IgE, immunoglobulin E; PI, pattern identification; SAR, seasonal allergic rhinitis; TM, traditional medicine; CRA, clinical research associate; TNSS, total nasal symptoms score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; AST, asparate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; KGMP, Korean Good Manufacturing Practice; IL, interleukin; CBC, complete blood counts; WBC, white blood cell; RBC, red blood cell; AE, adverse event; ITT, intent-to-treat; LOCF, last observation carried forward; PP, per-protocol; SD, standard deviation

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Cheong-Ryong-Tang (SCRT), also known as Xiao-Qing-Long-Tang or Sho-seiryo-to, is a mixed herbal formula that has been used in Asian countries for nasal symptoms for hundreds of years.[6,7] In an exploratory study, specialists in the department of otorhinolaryngology of traditional Korean medicine (TKM) selected SCRT as the most preferred medicine in treating AR.[8] In animal studies, SCRT has suppressed the progression of AR and allergic asthma.[9–11] A single randomized controlled clinical study which observed the efficacy of SCRT has been performed in Japan.[12] However, the treatment period for the study was only two weeks, and there was no follow up period after the treatment. Furthermore, outcome measurements to evaluate the mechanisms underlying anti-allergic and anti-inflammatory effects were not conducted, and the statistical analysis method that was used for primary outcome measurement was inappropriate.

Pattern identification (PI) is a tool that provides a diagnostic conclusion based on a cluster of concurrent symptoms and signs.[13] When diagnosing AR, many traditional medicine (TM) clinicians use nasal endoscopy not only for observing disease severity, but also for PI. For this reason, a nasal endoscopy index for PI of AR was developed, and inter- and intra-rater reliability studies were conducted in the same year.[14,15] In terms of PI, SCRT is used to treat wind-cold with internal phlegm-retention and this AR syndrome induce watery rhinorrhea, sneezing, and pale nasal mucosa in AR.[16] However, an exploration of the efficacy of SCRT based on PI has not been performed.

The aims of this study were as follows: first, to investigate the short- and long-term efficacy and safety of SCRT treatment in patients with PAR; second, to discover the underlying mechanisms resulting in anti-inflammatory effects of SCRT in patients with PAR; third, to investigate the efficacy of SCRT based on nasal endoscopy index for PI. We hypothesized as follows: (1) 4 weeks of SCRT administration would improve nasal symptoms and quality of life in patients with PAR and these effects would last for 8 weeks following the end of the treatment period; (2) total serum IgE, eosinophil count, and cytokines levels would be altered following SCRT administration; (3) SCRT will be more effective in patients who show cold pattern in the nasal endoscopy index for PI. We conducted a double-blind, randomized, placebo-controlled, parallel-group, multicenter trial of Korean adults with PAR.

2. Materials and methods

2.1. Study design

This was double-blind, randomized, placebo-controlled, parallel-group, multicenter trial (ClinicalTrials.gov, NCT03009136).[17] The trial consisted of a 4-week oral administration of SCRT with two visits at 2-week intervals and an 8-week follow-up period with two visits at 4-week intervals. Before enrollment, all participants underwent a 7-day run-in period. The enrolled participants were randomly allocated to two parallel groups (1:1): the SCRT group and the placebo group (Table 1).

This study was approved by the IRBs of the Kyung Hee University Hospital at Gangdong (KHNMC-OH-IRB 2015-04-009), Kyung Hee University Medical Center (KOMCIRB-160321-HRBR-011), Pusan National University Hospital, (2016-004) Dongguk University Medical Center (2016-03), and Semyung University hospital (2016-01). Written informed consent was obtained by the investigator from all participants prior to enrolment. The trial was performed in compliance with the Declaration of Helsinki, and according to Good Clinical Practices, as described by the Korea Food and Drug Administration.

In order to protect the rights and welfare of the participants and to maintain study quality, monitoring was performed. The contract research organization of this study sent a clinical research associate (CRA) to five centers at least four times (after the first participant was enrolled, after half of the planned enrolment was complete, after the planned enrolment was complete, and after all visits of participants were completed during the study) and the CRA visited each center additionally upon request. Before the initiation of the study, investigators at each centers were trained together following Standard Operation Procedures developed for this multicenter study.

Table 1
Study schedule (12 weeks).

Stage	Screening	Active treatment			Follow up	
Visit	−1	1	2	3	4	5
Weeks	−1	0	2	4	8	12
Informed consent and eligibility screening	○					
Demographic characteristics	○					
Medical/drug use history	○					
Skin prick test	○					
Allocation		○				
TNSS & RQLQ		○	○	○	○	○
Total IgE, eosinophil count		○		○		
Cytokines[a]		○		○		
Nasal endoscopy index for pattern identification		○		○		
Vital signs[b]	○	○	○	○	○	○
Laboratory tests for safety assessment[c]	○			○		
Adverse events			○	○	○	○

[a] Only for 32 participants recruited from the Kyung Hee University Korean Medicine Hospital at Gangdong (IL-4, IL-5, and IL-8).
[b] Blood pressure, pulse (heart rate), body temperature.
[c] Complete blood cell counts, levels of aspartate transaminase, alanine transaminase, blood urea nitrogen, and creatinine.

2.2. Sample size

Sample size calculations were performed to determine the number of participants who needed to be enrolled. The study aims to detect a difference between the two study groups in total nasal symptom score (TNSS) changes prior to (Visit 1) and following (Visit 3) medication. To our knowledge, only one randomized clinical trial for SCRT has been performed in patients with AR. [12] However, the primary outcome measurement that was collected in that study was not suitable for estimating sample size. We applied the effect size and standard deviation values that were obtained from other trials that used herbal medicines in patients with AR.[18–20] We thereby assumed that SCRT administration would improve TNSS by 2.68 points, placebo administration would improve TNSS by 1.25 points, and that the standard deviation would be 2.809. The following formula was used to estimate the sample size:

$$n = \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \sigma^2(r+1)/r\,(\mu_1 - \mu_2)^2$$

In the present study, the ratio (r) of number of subjects in the SCRT group to the number in the placebo group will be 1:1. With a power of 80% (1–β) and a significance level of 5% (α), the required sample size is approximately 61 for each group. Considering an assumed dropout rate of 20%, 154 subjects will be required.

2.3. Participants

The inclusion criteria were as follows: (1) age 18–60 years; (2) presence of two or more nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) with severity score ≥ 2 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms); (3) presence of nasal symptoms for over two consecutive years; and (4) positive reaction to one or more perennial allergens as evaluated in the skin prick test.

The exclusion criteria were as follows: (1) treatment with nasal/oral corticosteroids within the past month; nasal cromolyn or tricyclic antidepressants within the past two weeks, or with nasal/oral decongestants, nasal/oral antihistamines, or antileukotrienes within the past week; (2) presence of rhinosinusitis (paranasal sinus X-ray

demonstrating mucosal thickening, or partial or complete opacification of the paranasal sinuses); (3) presence of hypertension (systolic ≥ 180 mmHg or diastolic ≥ 100 mmHg); (4) presence of abnormal liver function (aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 100 IU/L) or abnormal renal function (blood urea nitrogen (BUN) ≥ 30 mg/dL or creatinine ≥ 1.8 mg/dL (male), 1.5 mg/dL (female)); (5) presence of neoplasm, severe systemic inflammation, or any other systemic disease that affects AR; (6) history of drug allergy; (7) history of anaphylaxis in response to allergic tests; (8) pregnancy or lactation; or (9) participation in another clinical study within the past 3 months.

The participant withdrawal criteria were as follows: (1) use of medication that can affect nasal symptoms (nasal/oral corticosteroids, nasal cromolyn, tricyclic antidepressants, nasal/oral decongestants, nasal/oral antihistamins, antileukotriens, and herbal medicines); (2) onset of rhinosinusitis (diagnosis with paranasal sinus X-ray); (3) onset or diagnosis of neoplasm, severe systemic inflammation, or any other systemic disease that affects AR; (4) pregnancy; (5) medication compliance < 80 percent at Visit 2 and 3; (6) occurrence of a serious adverse event; (7) participants' withdrawal of consent (8) detection of eligibility violations or the occurrence of other significant protocol violations during the study.

The skin prick test was performed to screen for patients with AR, in accordance with routine procedures. For this test, seven common aeroallergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, dog fur, cat fur, Alternaria tenuis, Aspergillus fumigatus, and cockroach),[21] negative controls, (50% glycerin saline) and positive controls (0.1% histamine phosphate) were used (Allergopharma GmbH & Co. KG, Reinbek, Germany).

2.4. Intervention

Hanpoong Pharm & Foods Co., Ltd. manufactured the SCRT and placebo in compliance with Korea Good Manufacturing Practice (KGMP) standards. The SCRT used in this study (Socheongryongtang extract granule Hangpoong) was comprised of dried, bitter, brown granules extracted with water. The extract was permitted and regulated by the Korean Food & Drug Administration and was composed of eight herbs (Table 2). The placebo was made of lactose, corn starch and caramel coloring, and had the appearance, shape, weight, taste, and color of the SCRT being administered. SCRT and placebo granules were sealed in opaque aluminium bags and administered to participants in doses of 3 g. The pharmacists instructed the participants to dissolve the SCRT or placebo from each package in water and take the solutions 30 min after each meal three times per day for 4 weeks. All participants were required to return remains of drugs for calculating compliance.

2.5. Primary outcomes

Primary outcome in the present study is the difference between the two study groups in TNSS change observed prior to (Visit 1) and subsequent to (Visit 3) medication. The TNSS evaluates symptoms of rhinorrhea, nasal congestion, nasal itching, and sneezing on a 4-point scale. The total score ranges from 0 to 12, where 0 = no symptoms, 1 = mild symptom(s) (present but bearable), 2 = moderate symptom(s) (present and uncomfortable), and 3 = severe symptom(s) (unbearable). It was filled by investigators based on participants' statements.

2.6. Secondary outcomes

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was measured to assess efficacy on the quality of life.[22,23] Serum IgE, eosinophil counts, and cytokines (IL-4, IL-5, and IL-8) were evaluated to discover the underlying mechanisms. Cytokines were not measured for all participants and cytokines levels were measured only in one center (32 participants), at the Kyung Hee University Hospital at Gangdong, as a pilot study. Nasal endoscopy index for PI was assessed to explore the efficacy of SCRT based on PI. Specialists in the department of otolaryngology of TKM at each center performed nasal endoscopy index. To avoid measurement bias, same endoscopic machine was provided at each centers and the color tone of computers and monitors were precisely corrected.

2.7. Safety assessment

The levels of aspartate aminotransferase (AST) / alanine aminotransferase (ALT), blood urea nitrogen (BUN) / creatinine, and complete blood counts (CBC) including white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, and platelet count was measured at screening, and during week 4 and week 12. The investigator asked participants questions regarding adverse events (AEs) during every visit and recorded AE details in case report forms. All AEs were monitored by independent clinical research associate.

To evaluate blinding, participants and investigators were respectively asked to guess the group to which they had been allocated, at week 4.

2.8. Statistical analysis

All statistical analyses were performed using the SPSS 21 (IBM Inc., Armonk, NY, USA). An intent-to-treat (ITT) analysis is an analysis method employed for evaluating data collected from a participant who takes the study drug at least once. In ITT analysis, missing data is replaced via the last observation carried forward (LOCF) method. A per-protocol (PP) analysis is used to evaluate data collected from a participant who completes all steps of the experimental protocol. Efficacy measurement analysis mainly utilized ITT analysis. Safety evaluation was conducted by PP analysis. Data was displayed as the mean and standard deviation (SD) for continuous variables and n (%) for categorical data. The baseline characteristics were compared by an independent *t*-test (parametric statistics) or Mann-Whitney test (non-parametric statistics) for continuous values and chi-square test or Fisher's exact test for categorical values. A repeated-measures ANOVA test with Bonferroni post hoc test was used to evaluate the changes in TNSS, RQLQ, and safety assessment measurements throughout the

Table 2
Components and standard materials of SCRT.

Botanical name	Herbal name	Amount*	Standard materials
Ephedra sinica Stapf	Ephedrae Herba	0.5	Ephedrine
Cinnamomum cassia Blume	Cinnamomi Ramulus	0.2	Cinnamaldehyde
Asiasarum sieboldi F. Maekawa	Asari Radix	0.5	Asarone
Zingiber officinale Roscoe	Zingiberis Rhizoma	0.5	6-Gingerol
Schisandra chinensis (Turcz.) Baillon	Schizandrae Fructus	2.67	Schizandrin
Paeonia lactiflora Pall.	Paeoniae Radix Alba	1	Paeoniflorin
Pinellia ternata Breitenbach	Pinelliae Rhizoma	2.67	Homogentistic acid
Glycyrrhiza uralensis Fischer	Glycyrrhizae Radix	1	Glycyrrhizic acid

* g, per day dose (9 g).

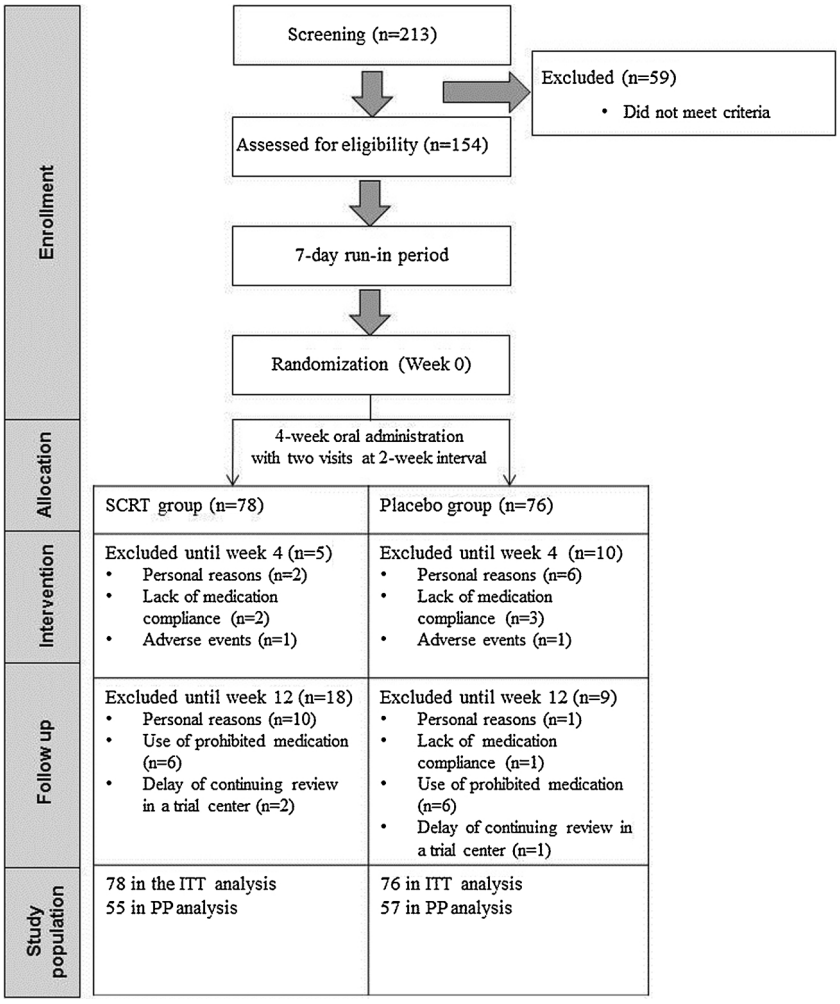

Fig. 1. Flow chart of participants recruitment and selection.

experiment. The differences of IgE, eosinophil count, cytokines, and credibility of blinding between the SCRT and placebo groups were compared using an independent *t*-test (parametric statistics) or Mann-Whitney test (nonparametric statistics). Within group differences of IgE, eosinophil count, cytokines, and credibility of blinding was compared using a paired *t*-test (parametric statistics) or a Wilcoxon signed rank test (nonparametric statistics). A pearson correlation test was used to analyze the relationship between cold and heat scores of nasal endoscopy index and TNSS changes. One-way analysis of variance was used to analyze the correlation between PI patterns and TNSS changes. In all tests, a value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Participants

From September 2016 to December 2017, a total of 213 patients were screened and 154 participants were included in this study. Fourty-two patients discontinued and a total of 112 patients completed the study. (Fig. 1). There were no significant differences in sex, age, body mass index, baseline TNSS, RQLQ score, serum IgE, eosinophil counts, and allergens between the SCRT and placebo groups (Table 3).

Table 3
Demographic characteristics of the participants at baseline.

Characteristics	SCRT (n = 78)	Placebo (n = 76)
Age (years)	33.68 ± 9.78	34.36 ± 11.31
Sex (male/female)	50/28	44/32
Body mass index	23.14 ± 3.25	22.51 ± 3.01
TNSS	7.55 ± 2.00	7.37 ± 2.17
RQLQ	77.43 ± 26.32	76.88 ± 29.15
IgE	321.42 ± 569.39	260.39 ± 361.65
Eosinophil counts	236.79 ± 171.35	209.42 ± 132.22
Allergens (%)		
Dermatophagoides farinae	86.7	83.1
Dermatophagoides pteronyssinus	85.0	83.1
Dog fur	6.7	15.3
Cat fur	20.0	27.1
Alternaria tenuis	8.3	10.2
Aspergillus fumigatus	5.0	0.0
Cockroach	10.0	13.6

3.2. TNSS

There were significant differences in primary outcome (between-group difference in TNSS change observed prior to and subsequent to medication). A statistically significant decrease in TNSS was observed after 2 weeks of medication (week 2), and this decrease lasted for the follow-up period in both groups. There were significant between-group differences at week 2 and 4 in TNSS reduction from baseline (Table 4 and Fig. 2). All nasal symptoms; rhinorrhea, nasal congestion, nasal itching and sneezing, significantly improved during treatment in each group. There were significant between-group differences in rhinorrhea and sneezing score changes (Table 5).

Table 4
Changes in TNSS.

	Week 0	Week 2†	Week 4†	Week 8	Week 12
SCRT	7.55 ± 2.00	−2.40 ± 1.37*	−3.07 ± 1.53*	−3.28 ± 1.58*	−3.57 ± 2.58*
Placebo	7.37 ± 2.17	−1.57 ± 0.96*	−2.10 ± 1.02*	−2.95 ± 1.31*	−3.22 ± 2.26*

Mean ± standard deviation.
* $p < 0.05$, within group analysis (vs. baseline).
† $p < 0.05$, between group analysis (SCRT vs. placebo).

3.3. Rhinoconjunctivitis quality of life questionnaire

A statistically significant decrease in RQLQ was observed after medication (week 4), and this decrease lasted for the follow-up period in both groups. There was significant between-group difference at week 4 in RQLQ reduction from baseline (Table 6 and Fig. 2).

3.4. The changes in serum IgE, eosinophil counts, and cytokines

There were no significant between and within group differences in IgE and eosinophil counts. A statistically significant decrease in IL-5 and IL-8 was observed after medication (week 4) in both groups. There were no significant between-group differences at any time points (Table 7).

3.5. Nasal endoscopy index

TNSS changes from week 0 to week 4 showed negative correlations with heat scores and positive correlations with cold scores; however, these differences were not statistically significant (Table 8).

3.6. Credibility of blinding

No difference was identified between the two groups ($p = 0.565$ (participants) and 0.491 (investigators)).

3.7. Adverse events

Some mild AEs (skin rash (n = 1) and dyspepsia (n = 1)) were identified; however, there was no significant difference between the two groups in the proportion of reported AEs, and no serious AEs were reported. There were no significant between- and within-group differences at baseline, week four, and week 12 in the safety assessment (AST / ALT, BUN / creatinine, WBC, RBC, hemoglobin, hematocrit, and platelet count).

4. Discussion

In this study, SCRT improved nasal symptoms and quality of life in patients with chronic, perennial, and moderate-to-severe AR after four weeks of treatment. However, the significant differences that were initially observed between the two groups were not maintained at follow-up visits.

Table 5
Changes of nasal symptoms.

	Week 0	Week 4	Difference
Rhinorrhea			
SCRT	1.93 ± 0.73	1.20 ± 0.82**	−0.73 ± 0.82
Placebo	1.90 ± 0.82	1.47 ± 0.88*	−0.42 ± 1.05
p value (between)	0.807	0.080	0.046†
Nasal congestion			
SCRT	1.92 ± 0.81	1.30 ± 0.87**	−0.62 ± 0.96
Placebo	2.12 ± 0.77	1.46 ± 0.93**	−0.66 ± 0.96
p value (between)	0.165	0.343	0.801
Nasal itching			
SCRT	1.80 ± 0.99	1.00 ± 0.86**	−0.80 ± 0.88
Placebo	1.69 ± 0.92	1.17 ± 0.89**	−0.53 ± 1.04
p value (between)	0.548	0.295	0.122
Sneezing			
SCRT	1.90 ± 0.80	0.98 ± 0.79**	−0.92 ± 0.79
Placebo	1.66 ± 0.78	1.17 ± 0.81**	−0.49 ± 0.97
p value (between)	0.101	0.208	0.010†

*$p < 0.05$, **$p < 0.001$, within group analysis (vs. baseline).
†$p < 0.05$, between group analysis (SCRT vs. placebo).

Previous studies reported that SCRT exhibits anti-allergic effects by inhibiting Th2 cytokine release and decreasing inflammatory cell infiltration into the nasal mucosa, in an ovalbumin-induced AR model.[9,10] Another study reported that SCRT exerts a preventive effect against asthma via neutrophil regulation, in an allergy-based asthma disease model.[11] Furthermore, in several previous studies, the main SCRT components; Ephedrae Herba, Cinnamomi Ramulus, and Paeoniae Radix Alba were observed to have anti-inflammatory, antiallergic, and antibacterial activities.[24–28] These mechanisms could explain the reason for the effects of SCRT in patients with AR.

In each nasal symptom analysis, rhinorrhea and sneezing scores decreased in the SCRT group, compared with the placebo group. Nasal congestion and nasal itching did not show significant differences between the two groups. When the nasal mucosa of patients with AR is

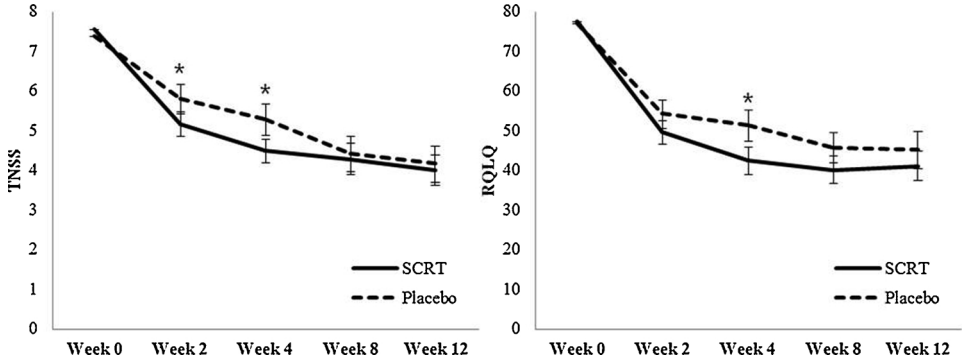

Fig. 2. TNSS and RQLQ reduction from baseline to week 12.
*$p < 0.05$, between group analysis (SCRT vs. placebo).

Table 6
Changes in RQLQ scores.

	Week 0	Week 2	Week 4[†]	Week 8	Week 12
SCRT	77.43 ± 26.32	−27.87 ± 20.47[*]	−35.13 ± 26.82[*]	−37.48 ± 27.40[*]	−36.53 ± 30.15[*]
Placebo	76.88 ± 29.15	−22.78 ± 19.54[*]	−25.73 ± 29.98[*]	−31.30 ± 27.33[*]	−31.85 ± 29.97[*]

[*] $p < 0.05$, within group analysis (vs. baseline).
[†] $p < 0.05$, between group analysis (SCRT vs. placebo).

Table 7
The changes in serum IgE, eosinophil counts, and cytokines.

	Week 0	Week 4	Difference
IgE			
SCRT	321.42 ± 569.39	328.78 ± 567.90	7.35 ± 52.79
Placebo	260.39 ± 361.65	298.59 ± 452.86	38.20 ± 249.50
Eosinophil counts			
SCRT	236.79 ± 171.35	231.13 ± 173.76	−5.66 ± 98.66
Placebo	209.42 ± 132.22	217.02 ± 160.18	7.60 ± 104.97
IL-4			
SCRT	7.73 ± 10.76	10.92 ± 9.79	3.19 ± 14.65
Placebo	5.90 ± 9.52	15.06 ± 10.97[*]	9.17 ± 17.00
IL-5			
SCRT	4.71 ± 0.35	1.79 ± 1.42[**]	−2.92 ± 1.38
Placebo	4.78 ± 0.46	1.65 ± 0.96[**]	−3.13 ± 1.08
IL-8			
SCRT	9.83 ± 3.61	8.35 ± 3.80[*]	−1.47 ± 1.79
Placebo	9.35 ± 4.00	7.02 ± 2.70[*]	−2.33 ± 3.71

[*] $p < 0.05$, within group analysis.

Table 8
The correlations between nasal endoscopy index and TNSS changes.

	Correlation	*p* value
Heat score	−0.049	0.708
Cold score	0.144	0.273

Pearson correlation test.

exposed to aeroallergens, symptoms such as rhinorrhea, sneezing, and itching begin within 30 min, and this is called an immediate allergic reaction. About six hours after the early phase, nasal congestion appears and slowly improves, and this is called the late phase. Inflammatory cells destroy and subsequently reconstruct the normal tissue of the nasal mucosa. As AR symptoms persist, this cycle occurs repeatedly and causes chronic nasal obstruction.[29] Every participant in this study had chronic, perennial, and moderate-to-severe nasal symptoms. Thus, they had a higher probability of having hypertrophic nasal mucosa that was refractory to treatment. Furthermore, in terms of TM, SCRT is used to treat lung-cold syndrome, which induces watery rhinorrhea, sneezing, and pale nasal mucosa in AR. As patients with chronic and severe nasal symptoms have a higher probability of having hyperemic and hypertrophic nasal membranes, the nasal congestion in the participants of this study may not match the indications for SCRT in TM. These two reasons may explain why SCRT did not improve nasal congestion, but still improved immediate allergic reaction symptoms, such as rhinorrhea and sneezing.

Against our hypothesis, color of nasal mucosa and rhinorrhea scores did not show any correlations with TNSS change. This study was the first to apply the nasal endoscopy index, and although the investigators at each center were pre-educated according to standard operating procedures, the variation in the color and resolution of nasal endoscope and monitors at each center may have impacted these results. The preparation of equal nasal endoscopes and monitors, and a more precise color tone correction, should be recommended for the next trial.

In many patients with AR, symptoms are prolonged for years. Therefore, it is necessary to develop medicines that have no adverse effects when employed as a long-term therapy. The main medications that are currently used for AR include antihistamines, nasal steroids, nasal decongestants, and leukotriene receptor antagonists. However, the long-term use of many of these AR medications can result in adverse effects. Antihistamines have limited efficacy in treating nasal congestion and commonly induce adverse effects, such as sedation and weight gain.[30,31] Nasal decongestants are useful against nasal obstructions, but using nasal decongestants for over a week is not recommended, owing to adverse effects and low drug tolerance.[32] For these reasons, traditional Chinese medicine (TCM), which involves the use of natural herbs, has recently gained much attention as a potential treatment for AR.[33] In this study, only one mild AE was reported in the SCRT group (skin rash), after four weeks of medication, and there were no changes safety assessments. Accordingly, SCRT is an alternative or supportive medication that supplements the disadvantages (side effects and short term of use) of conventional medicine.

Cytokines were measured for 32 participants in a pilot study, and no significant between-group differences were observed at any time point. However, the levels of IL-4 (Th2 type) increased significantly in the placebo group, while the SCRT group did not show a significant increase. These data are consistent with previous reports that showed a suppressed Th2 response with SCRT.[10,34] However, as IL-4 levels did not decrease after the medication, further clinical investigations with more participants are needed to reach a more definitive conclusion about the mechanisms of the action of SCRT in humans.

IgE and eosinophil counts increased in the placebo group; however, significant within- and between-group differences were not observed. A previous clinical study reported changes in serum IgE, cytokines, IL-4 stimulated prostaglandin E2 (PGE2), and polymorphonuclear leukocytes after a 12-week administration of traditional herbal medicine.[20,35] Thus, the duration of medication use needs to be longer than that used in our study to observe the immune response changes. Against our hypothesis, between-groups differences of nasal symptoms and quality of life did not persist at the follow-up period. As immune substances did not change after medication, the treatment efficacy could have been limited. Therefore, as described above, clinical trials with longer durations of medication could show positive results for maintaining the efficacy of SCRT.

To our knowledge, this is the first multicenter study with an eight-week follow-up period that investigated the efficacy of SCRT in patients with PAR. Based on our results, we suggest that SCRT can be used as an effective and safe medicine for patients with chronic, perennial, and moderate-to-severe AR. A clinical study with a > 4-week period of medication use and more participants is needed to investigate the long-term efficacy of SCRT in relieving the symptoms of nasal obstruction and identifying the underlying mechanisms of action and indications for TM.

Conflict of interest

The authors state no conflict of interest.

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