

The effectiveness and safety of sanfu acupoint herbal patching for treating allergic rhinitis

A protocol for systematic review and meta-analysis

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Abstract

Background: Allergic rhinitis (AR) is one of the most common chronic disease of the nasal mucosa globally. Several clinical studies have shown that sanfu acupoint herbal patching (SAHP) has obvious advantages in treating AR. Therefore, the purpose of this systematic review is to evaluate the effectiveness and safety of SAHP for treating AR.

Method: The following 9 electronic databases will be searched from January 2010 to October 2020: PubMed/Medline, Web of Science, Cochrane Library, EMBASE, China National Knowledge Infrastructure, VIP Database, WANFANG Database, China Biology Medicine disc. The selection of the studies and the extraction of the data are independently completed by 2 reviewers. The qualities of the studies are evaluated by Cochrane risk-of-bias tool. The main outcome of included studies is total effective rate. Secondary outcomes are Total Nasal Symptom Score, recurrence rate, Rhinitis Quality of Life Questionnaire, adverse events and laboratory indicators: serum immunoglobulin E (IgE). And the STATA 14.0 software will be implemented for data synthesis and meta-analysis.

Results: The review is ongoing, no results can be reported.

Conclusions: The systematic review will provide a better option for patients to treat AR.

Registration number: INPLASY2020100101.

Abbreviations: AR = allergic rhinitis, IgE = immunoglobulin E, RCT = randomized controlled trial, SAHP = sanfu acupoint herbal patching.

Keywords: allergic rhinitis, meta-analysis, sanfu acupoint herbal patching

1. Introduction

Allergic rhinitis (AR) is defined as a non-infectious inflammatory disease of the nasal mucosa. The mechanism of this disease is due to immunoglobulin E (IgE)-mediated mast cell degranulation and mediator release, which can cause rapid response to allergens, leading to a series of clinical symptoms,^[1] such as nasal congestion, nasal itching, sneezing, and runny nose.^[2] According

to epidemiological surveys, the prevalence of AR has risen rapidly in recent years. It has been calculated that 10% to 30% of the world population suffered from this disease approximately.^[3] A study which target the number of AR patients and the burden of this disease in America, Latin America and Asia-Pacific shows that the prevalence of American adults is 14% and children account for 13%, Latin American adults about 7%, Asia-Pacific adults about 9%.^[4] AR is known as a chronic disease, hence, quality of patients life has been disturbed impressively with its recurrence more and more frequently.^[5] Besides the original symptoms of AR have been mentioned above, quality of patients life has been weaken in the following aspects: physical function decreasing, social difficulties, sleep disturbance, fatigue during the day, lethargy, irritability, depression, lack of learning and memory.^[6] In the meanwhile, the economic burden of AR patients is substantial, the total cost of treatment reaches \$3.4 billion per year and the main components of the cost are prescription drugs and outpatient visits.^[7] Patients always easily neglect the comorbidities of AR, such as headache, allergic conjunctivitis, otitis media, sinusitis, cough, asthma, which also exert a huge impact on their health.^[6] The relationship between AR and asthma should be taken into consideration because 78% of asthma patients have AR according to the study,^[8] which enlightens us that AR may be a high risk factor for asthma. Considering so many comorbidities, AR patients are required to pay more attention to the treatment of original disease and prevention of comorbidities so that we can reduce indirect economic investment.

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Nowadays, oral H1 antihistamines and intranasal corticosteroids spray are widely acknowledged as the mainstream therapy for treating AR.^[9,10] These 2 major classes of drugs block inflammatory pathways to relieve nasal symptoms. Intranasal corticosteroids and H1 antihistamines are treated as first-line treatments with its own efficacy.^[11] The mechanism of Histamine is inhibiting basophils and mast cells from releasing, thereby reducing the binding to various histamine receptors of glandular, neurogenic and vascular target cells, which can decrease sensory nerve stimulation and subsequent parasympathetic activity.^[12] However, the disadvantages of this therapy has become obvious. With the recurrence of symptoms, the efficacy of the drugs will decrease; there is no doubt that the inhibition of symptoms requires more money and more dosage of drugs as well.^[6]

Consequently, complementary and alternative therapy becomes a better option to treat AR,^[13] particularly traditional Chinese medicine (TCM).^[14–16] According to theory of TCM, sanfu refers to the 3 specific periods of the Chinese lunar year from July to August, each fu period includes 10 days.^[17] Sanfu period is characterized as the hottest temperature and the strongest power of Yang, which is defined as a metaphysical energy with a nature of hotness inside of the body to protect body from illness.^[18] Sanfu acupoint herbal patching (SAHP), as one of complementary and alternative therapy derived from Qing dynasty (1636–1912), also has good effect in treating AR. SAHP is a herbal pad that contains powdered Chinese herbals and is being used to stick to specific acupoints during sanfu period.^[19] The purpose of this treatment is to utilize the comprehensive effect of herbal medicine absorbed by skin, acupoint stimulation and time effect so that therapeutic effects can be produced.^[18] The efficacy of SAHP has been reported by a great number of randomized controlled trails (RCTs).^[20–24] However, no systematic review or meta-analysis about SAHP for treating AR has been reported yet. In this review, we aim to evaluate the effectiveness and safety of SAHP for treating AR.

2. Methods

2.1. Study registration

The protocol of this meta-analysis has been registered in INPLASY (<https://inplasy.com/>) with ID INPLASY 2020100101. Moreover, the protocol will comply with the Cochrane Handbook for Systematic Reviews and Meta-Analysis Protocol guidelines.^[25] Ethical approval can be skipped because this is a systematic literature research. Any changes will be explained if necessary.

2.2. Eligibility criteria

2.2.1. Types of studies. All of RCTs published in English and Chinese about SAHP for treating AR will be included.

2.2.2. Types of participants. Patients diagnosed with AR^[5] can be included into study regardless of nation, gender, race, courses of disease.

2.2.3. Type of interventions. SAHP (No restriction on herbal medicine composition, course of disease, selection of acupoints, etc.) or SAHP plus other therapy (such as oral Chinese medicine, moxibustion, acupuncture, placebo, western medicine) as control group. However, some of RCTs with SAHP as an adjunctive treatment will be excluded.

2.2.4. Types of comparisons. The intervention of comparator could be no treatment, placebo, sham acupoint herbal patching, or other therapy which involved in the control group. The possibilities of therapy combination will be listed:

1. SAHP vs no treatment.
2. SAHP vs other common therapy.
3. SAHP + other common therapy vs other common therapy.
4. SAHP vs placebo or sham acupoint herbal patching.

2.2.5. Outcomes

2.2.5.1. Primary outcomes. Total effective rate will be defined as main outcome in this meta-analysis.

2.2.5.2. Secondary outcomes. TNSS (Total Nasal Symptom Score), recurrence rate, RQLQ (Rhinitis Quality of Life Questionnaire), adverse events, laboratory indicators: IgE will be used as secondary outcomes.

2.3. Exclusion criteria

1. Patients with AR accompany by other diseases.
2. Systematic review or meta-analysis, case report, animal experiments, conference papers will be excluded.
3. Repeated publications and missing data researches will be excluded.

2.4. Search methods for identification of studies

2.4.1. Electronic searches. Owing to popularity of SAHP and high-quality researches published in recent 10 years, we will search the following databases from January 2010 to October 2020: PubMed, Web of Science, Cochrane Library, EMBASE, China National Knowledge Infrastructure, VIP Database, WANFANG Database, China Biology Medicine disc. The languages of included studies are restricted in English and Chinese. The keywords contain: “allergic rhinitis,” “sanfu acupoint herbal patching,” “randomized controlled trial”. In addition, clinical researches which are not completed will be searched on the mainstream registries such as Chinese Clinical Trial Registry and ClinicalTrials.gov trials registry.

2.4.2. Search strategy. The search strategy of PubMed is shown in Table 1, and other databases will be the same way to be searched.

2.5. Data collections and analysis

2.5.1. Selection of studies. All retrieved studies will be managed with Note Express 3.0. Firstly, 2 reviewers (Xiaohui Tian and Qiaochu Zhu) will exclude some studies that are not in accordance with the inclusion criteria by reading titles and abstracts of the articles independently, then they will download included studies and read full text in order to check the studies whether they are available for inclusion criteria. Besides, if there is a dispute during the process of systematic review, consensus will be reached by discussion with the third reviewer (Aiqun Song). The process of screening will be shown in Figure 1.

2.5.2. Data extraction and management. Two reviewers (Yan Wang and Yangpu Zhang) will extract data of included studies independently, and the following items will be extracted:

Search number	Query
#1	"Rhinitis, Allergic" [Mesh]
#2	((Allergic Rhinitides [Title/Abstract]) OR (Rhinitides, Allergic [Title/Abstract])) OR (Allergic Rhinitis [Title/Abstract])
#3	Rhinitis, Allergic, Seasonal [MeSH Terms]
#4	((((((((((Seasonal Allergic Rhinitis [Title/Abstract]) OR (Allergic Rhinitides, Seasonal [Title/Abstract])) OR (Allergic Rhinitis, Seasonal [Title/Abstract])) OR (Rhinitides, Seasonal Allergic [Title/Abstract])) OR (Rhinitis, Seasonal Allergic [Title/Abstract])) OR (Seasonal Allergic Rhinitides [Title/Abstract])) OR (Pollen Allergy [Title/Abstract])) OR (Allergies, Pollen [Title/Abstract])) OR (Allergy, Pollen [Title/Abstract])) OR (Pollen Allergies [Title/Abstract])) OR (Pollinosis [Title/Abstract])) OR (Pollinoses [Title/Abstract])) OR (Hay Fever [Title/Abstract])) OR (Fever, Hay [Title/Abstract])) OR (Hayfever [Title/Abstract])
#5	#1 OR #2 OR #3 OR #4
#6	acupuncture points [MeSH Terms]
#7	((((((((((Acupuncture Point [Title/Abstract]) OR (acupoint [Title/Abstract])) OR (Acupoints [Title/Abstract])) OR (sanfu moxibustion [Title/Abstract])) OR (Sanfu acupoint herbal patching [Title/Abstract])) OR (sanfu herbal patch [Title/Abstract])) OR (acupoint sticking [Title/Abstract])) OR (summer acupoint herbal patching [Title/Abstract])) OR (Sanfuju [Title/Abstract])) OR (Sanfutie [Title/Abstract])
#8	#6 OR #7
#9	randomized controlled trial [Publication Type] OR (randomized [Title/Abstract] AND controlled [Title/Abstract] AND trial [Title/Abstract])
#10	#5 AND #8 AND #9

1. The first author, publication year, number of each group, average age.
2. Courses of disease, interventions, comparisons, courses of treatment.
3. Main outcome, secondary outcomes, blinding, missing data.

If included studies data are missing without any description or wrong data, we intend to contact the corresponding author to get an explanation. And consensus will be reached by discussion with a third party (Zhongyu Zhou) if there is a dispute in data extraction.

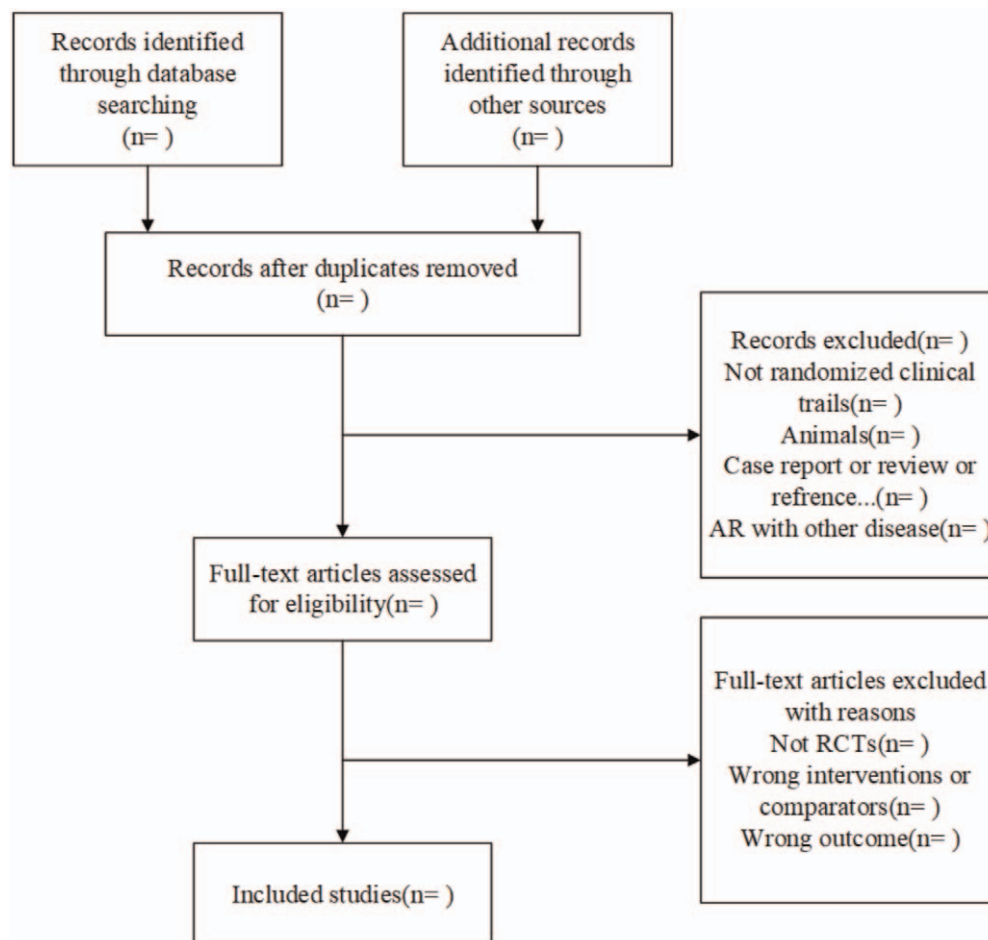


Figure 1. Flow diagram of the study selection process.

2.5.3. Assessment of risk of bias and reporting quality of included studies. Two reviewers (Dan Wei and Yang Jiao) will use Cochrane risk-of-bias tool (ROB 2.0 (Centre for Evidence-Based Medicine Odense (CEBMO), Odense, DK)) to evaluate the quality of included studies respectively.^[25] The following 5 domains will be used:

1. bias arising from the randomization process,
2. bias due to deviations from intended interventions,
3. bias due to missing outcome data,
4. bias in measurement of the outcome,
5. bias in selection of the reported result.

At last, there is an overall risk of bias of a study after evaluation. Any disagreements about quality of included studies will be solved by discussion with the third reviewer (Fu Dong).

2.5.4. Measurement of treatment effect. In this meta-analysis, statistical analyses will be operated by STATA14.0 software. Dichotomous data will be expressed by the risk ratio (RR) and 95% confidence interval (CI). Continuous data will be expressed by the mean difference (MD) of 95% CI. If different measurement scales are used, standardized mean difference (SMD) will be operated to analyze it.

2.5.5. Dealing with missing data. We will contact the first author or corresponding author to ask for an explanation when data is insufficient. If we receive no response, this study will be moved out of our meta-analysis.

2.5.6. Assessment of heterogeneity. I^2 test is used to evaluate the heterogeneity of included studies. If there is no significant heterogeneity ($I^2 < 50\%$), the fixed-effects model is used. If there is a large heterogeneity ($I^2 \geq 50\%$), use a random-effects model.

2.5.7. Assessment of publication bias. If included studies > 10 , a funnel plot analysis will be used to assess publication of bias.

2.5.8. Subgroup analysis. If data is reasonable, we are going to conduct subgroup analysis of different types of groups, the following subgroups we will conduct: different treating time, herbal medicine on patch, different control measures (western medicine, placebo herbal patch, no treatment, acupuncture, moxibustion, etc.)

2.5.9. Sensitivity analysis. Sensitivity analysis can find the source of heterogeneity and confounding factors in the research. When we end up with assessing the quality of included studies. Then we will obtain a stable consolidated result of our study.

2.5.10. Quality of evidence. Quality of evidence will be evaluated by the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE). In this system, evidence quality will be graded by 4 levels (very low, low, moderate, and high) and 5 factors will degrade (study limitations, inconsistency, indirectness, publication bias, and imprecision) level of evidence quality.

3. Discussion

AR is a totally tricky health problem that nearly 1 in every 6 American suffered from this disease and generated \$2 to \$5 billion expenses in global public health system according to published survey.^[26] Federally funded national health surveys, such as NHIS and NHANES, point out that it affects 30 to

60 million people in the United States annually, including 10% to 30% of adults and 40% of children.^[27] With disturbance of symptoms, patients can do nothing but to seek medicines for help. However, adverse effects of western medicines cannot be ignored. Using oral H1 antihistamines and intranasal corticosteroids spray frequently no doubt makes medicines less effective and the dosage of drugs will be increasing. So how to treat AR without drug resistance has perplexed clinical doctors for a long time. Thus, researchers shift their focus on complementary and alternative therapies, and find some of them indeed reduce the incidence of comorbidities.^[28] SAHP, a special acupoint herbal patching mixed acupoint stimulation and time effect, has become a popular therapy to treat AR with prosperity of TCM. Compared to western medicine, SAHP has advantages in safety, low expense, no drug resistance and fewer adverse effects. According to the historical finding about ancient China, the first appearance of SAHP derived from Zhangs Treatise on General Medicine which was wrote by Zhang Lu in Qing dynasty (1636–1912). He insisted that some diseases would occur in winter when yang was insufficient, so doctors use SAHP positively during the summer months on the sanfu days for the reason that this special period has strongest power of yang.^[29] In the theory of TCM, this is the principle which is called “treating winter diseases in summer”. Several systematic reviews have proved that SAHP is an effective treatment for chronic diseases, especially in AR.^[30,31] Based on theory of meridians, modern biologists have discovered that linkages between qi and blood of organs are expressed by meridians,^[32] applying some Chinese herbals on the skin and making it fully absorbed can stimulate reaction of meridians.

With increasing attention to individual health, thousands of people go to medical institutions for SAHP therapy vigorously in summer.^[33] Nowadays, an increasing number of clinical studies have reported that SAHP is an effective and safety therapy for treating AR.^[24,34] However, systematic review with protocol which use the total effect rate as main outcome has not been published up to now. There are also some limitations on previous studies either meta-analysis without protocol or no secondary outcomes. Therefore, we aim to perform a meta-analysis to assess the effectiveness and safety of SAHP for treating AR. We sincerely wish our research can be a better option therapy for patient with AR, and offer a high quality evidence to explore AR disease.

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