Current Allergy and Asthma Reports (2021) 21: 25
https://doi.org/10.1007/s11882-021-00999-9

RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Herbal Medicines for Allergic Rhinitis: a Systematic Review and Meta-analysis

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Accepted: 23 February 2021 / Published online: 25 March 2021

Abstract

Purpose of Review To assess the effects of herbal medicine (HM) therapy in various durations and analyze the effects of HM separately by mechanism of action in the treatment of allergic rhinitis (AR).

Recent Findings Thirty-two studies were included (2,697 patients, mean age 34.6 years). For the ≤ 4 weeks of treatment duration, HM brought greater benefits over placebo in reduction of total nasal symptoms score (standardized mean difference (SMD) −0.68; 95% confidence interval (CI) −0.98, −0.38; p <0.01) and improvement in Rhinoconjunctivitis Quality of Life Questionnaire score (SMD −0.53; 95% CI −0.81, −0.25; p <0.01). For the 4–12 weeks duration, total nasal symptoms score (SMD −0.22; 95%CI −0.4, −0.05; p =0.01) and Rhinoconjunctivitis Quality of Life Questionnaire score (SMD −0.48; 95% CI −0.89, −0.06; p =0.03) favored the HM. However, HM therapy for longer than 12 weeks was related to tachyphylaxis and showed no benefit over placebo in any outcomes. There was no difference between the HM and standard treatment on symptoms improvement. Anti-allergic effect, anti-inflammatory effect, anti-leukotriene effect, and anti-histaminic effect of HM were revealed. HM was safe and their adverse effects were comparable placebo.

Summary HM therapy is safe and provides better results than placebo in improving nasal symptoms and disease-specific quality of life in patients with AR. Its beneficial effects are demonstrated only in less than 12 weeks of treatment.

Trial Registration PROSPERO ID: CRD42020168367

Keywords Herbal medicine · Allergic rhinitis · Rhinoconjunctivitis · Anti-allergic · Anti-inflammatory · Anti-leukotriene effect · Anti-histamine

Introduction

Herbal medicine (HM) has been used as a treatment for allergic diseases for centuries [1] and can decrease nasal symptoms of allergic rhinitis (AR) [2]. Herbal usage has increased in the past three decades [3]. A self-report survey in Germany demonstrated that 26.5% of the participants used alternative medicine for allergy diseases [4]. To date, there are several potential HMs for treating AR worldwide. *Yu ping feng san* is a Chinese formula commonly used in Asian countries, especially in East Asia [5]. In Western countries, butterbur has become one of the most common herbs used as an adjunct treatment for AR since the first human trial in 2002 [6•]. The mechanisms of action of HM include anti-inflammatory, anti-allergic, and immunological effects [7]. Anti-inflammatory effects of HM interfere with type 1 hypersensitivity and inhibit the production of inflammatory cells such as mast cells, basophils, eosinophils, and monocytes. Anti-allergic effects of HM reduce the release of histamine, leukotriene, cytokine, and chemokine from inflammatory cells. The active compounds in HM modulate the immunological activities of mast cells [7, 8•]. As a

This article is part of the Topical Collection on *Rhinosinusitis*

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result, these effects significantly relieve nasal symptoms of AR, including sneezing, itching, rhinorrhea, nasal obstruction [9].

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision suggests conventional treatment options for treating AR including antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists [10]. In addition to conventional therapies, HM is acknowledged as an alternative therapy [2, 11•]. Although the beneficial effects of HM have been extensively investigated, the findings are inconsistent [8•, 11•]. In some systematic reviews, the data consisted of different kinds of HM and various mechanisms of action. The extracted data were pooled without being categorized [9, 12•]. There is no systematic review that focuses on the mechanisms of action of HM [8•, 9, 12•]. The optimal duration of HM treatments to reach their maximum effects is unknown. It is unclear whether HM works only in a short period of duration or it has long-lasting benefit in controlling the symptoms of AR. This review aimed to assess the effects of HM therapy in patients with AR, in various durations and to analyze the effects of HM separately by mechanism of action.

Recent Findings

Study Selection, Data Extraction, and Analysis

The protocol of this systematic review was registered on PROSPERO (ID: CRD42020168367). Electronic searches were conducted on PubMed and EMBASE. Additional sources were manually searched for published and unpublished trials. The last search was performed on February 9, 2020. Combination of MeSH terms and keywords were "rhinitis, allergic, seasonal", "rhinitis, allergic, perennial", "rhinitis", "*allergic rhinitis", "hay fever", "rhinoconjunctivitis", "pollen allergy", "herbal medicine", "Chinese herb*", "plant extract", "phytomedicine*", "herbaceous agent", "eastern medicine", "oriental medicine", "alternative medicine". Only clinical trials in humans and trials published in English were selected. The systematic review was performed under The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format [13].

Randomized controlled trials (RCTs) studying AR patients of any age were included. Diagnostic criteria of AR followed the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. Patients who had characteristic clinical symptoms of AR and allergies were confirmed by either skin prick test (SPT) or serum IgE test [14]. HM in any formulation (decoction, tablet, pill, powder, herbal patch, and nasal spray/drop). Duration of treatment was at least 1 week. There was no limit of the length of treatment. The comparison pairs of interest in this review were (1) HM versus placebo, (2) HM versus standard treatment, and (3) HM plus standard treatment versus standard treatment alone. Antihistamines and intranasal corticosteroids were acknowledged as standard treatments in this review. The outcomes were nasal symptoms, ocular symptoms, disease-specific quality of life (QOL), objective measurement for nasal patency, and adverse events. Exclusion criteria included trials related to homeopathy and immunotherapy, studies that were conducted with experimental extracts containing synthetic chemicals, conference abstracts, and crossover studies with the washout period less than one week (due to possible carry-over effects). Two authors (MPH and WC) independently screened the titles and the abstracts based on the predetermined eligibility criteria and reviewed the selected articles comprehensively. The senior author (KS) resolved disagreements on study selection when necessary.

The extracted data were AR subtypes, number of patients who received HM and comparators, age, gender, formulation of HM, duration of treatment, and therapeutic outcomes. The mechanism of action of each HM was assessed. HMs were categorized into subgroups according to their actions. Data of HM with similar type of effects were pooled. One HM may have multiple effects and could be categorized into more than one subgroup. Anti-inflammatory effect was defined when the HM decreased the migration of inflammatory cells, including mast cells, eosinophils, basophils, and monocytes. Anti-allergic effect was defined when the HM reduced the release of cytokines, chemokines, or mast cell mediators, including histamine, leukotrienes, or prostaglandins [7, 15]. Anti-leukotriene effect was defined when the HM worked as leukotriene biosynthesis inhibitors or leukotriene receptors antagonists [16]. Anti-histaminic effect was defined when the HM diminished the skin wheal and flare responses in SPT [17]. In addition, anti-cholinergic and vasoconstrictor effects were extracted from the experimental trials where available.

Two authors independently reviewed the quality of the included studies following the Cochrane Handbook for Systematic Reviews of Interventions [18]. Five domains were assessed: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each domain was determined as "low risk of bias" if the domain was well-described; "high risk of bias" if the method or data of the respective domain had not been mentioned; or "unclear risk of bias" if the domain data were only mentioned without a clear explanation.

The extracted data were pooled for meta-analysis. Risk ratio (RR) and 95% confidence interval (CI) were used for dichotomous data. Continuous outcomes were presented as mean difference (MD) or standardized mean difference (SMD) with standard deviation (SD) and 95%CI. Subgroup analysis by the AR subtype, quality of the included studies, and mechanism of the effects were conducted. If the change from baseline to endpoint was not available, the final scores were extracted. The standard error, interquartile range, range, and 95% CI were imputed if the SD was not reported.

Discrepancies in treatment effects among different trials were assessed using a heterogeneity (I^2) statistic. An I^2 of <40%, 40-60% and >60% represented low, moderate and substantial heterogeneity, respectively. A fixed-effect model was used in low heterogeneity and a random-effects model was used if the heterogeneity was high for a more conservative estimate of the differences. All statistical assessments were conducted using Review Manager (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

A total of 2032 articles were retrieved for screening (2,030 from electronic search and two from manual search). Finally, 32 studies were included in qualitative synthesis [19–50] and 29 studies in quantitative synthesis [19, 20, 22–25, 27–43, 45–50] (Fig. 1). Data from three included studies [21, 26, 44] were not pooled for meta-analysis due to incomplete outcome data. The characteristics of the included studies are summarized in Table 1.

There were 2697 participants with the mean age of 34.57 years. Fifty-two percent of the patients were female. Nineteen RCTs included patients with perennial allergic rhinitis (PAR) [20, 24, 28, 30, 31, 35–38, 40–47, 49, 50], and 12 RCTs included seasonal allergic rhinitis (SAR) [19, 21–23, 25–27, 29, 33, 34, 39, 48]. One RCT studied patients with both PAR and SAR [32]. Four RCTs recruited the patients under 18 years of age [28, 32, 41, 45].

1. Effects of Herbal Medicine

HMs by Mechanism of Action Both anti-inflammatory effect and anti-allergic effect were in 18 RCTs [20, 22, 28, 30–32, 35, 36, 38–40, 42, 43, 45–48, 50], sole anti-inflammatory effect 4 RCTs [23, 26, 37, 41], sole anti-allergic effect 4 RCTs [19, 29, 33, 44, 49], anti-leukotriene effect 5 RCTs [21, 24, 25, 27, 34], and anti-histaminic effect 4 RCTs [32, 36, 46, 47]. There was insufficient data to assess anticholinergic and vasoconstriction effects.

HMs by Formulation Oral HM were in 26 RCTs [19–31, 33–40, 43, 45, 47, 49, 50], intranasal spray or oil inhalation 3 RCTs [42, 44, 48], and external herbal patch or moxibustion 3 RCTs [32, 41, 46]. Data are shown in Table 1.

The *duration of treatments* ranged from 1 to 16 weeks.

The Comparison Pairs HM versus placebo were in 27 RCTs, HM versus standard treatment 3 RCTs [21, 41, 50]. There were two RCTs investigating three arms of HM versus placebo and standard treatment [24, 27]. There was no study comparing HM plus standard treatment versus standard treatment.

Standard Treatments Four RCTs used antihistamine [21, 24, 27, 41] and 1 RCT used a combination of intranasal corticosteroid spray and antihistamine [50].

2. Risk of Bias in the Included Studies

In general, the included studies had some selection bias: 25% had low risk of bias in allocation concealment and 59% had low risk in random sequence generation; 62% had low risk of bias in blinding of outcome assessment and incomplete outcome data while 78% had low risk of bias in selective reporting.

3. Total Nasal Symptom Score

Sixteen RCTs compared total nasal symptom score (TNSS) between HM and placebo [22, 24, 25, 27, 29, 33–36, 39, 40, 42, 45–48] and three RCTs compared TNSS between HM and standard treatment [24, 27, 50].

When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo (SMD −0.68; 95%CI −0.98, −0.38; $p < 0.01$; 11 RCTs) (Fig. 2). HM and standard treatment brought similar effects (MD −0.01; 95%CI −0.24, 0.21; $p = 0.93$; 3 RCTs). When the duration of treatment was 4–12 weeks, the effects still favored HM over placebo (SMD −0.22; 95%CI −0.4, −0.05; $p = 0.01$; 7 RCTs). Nevertheless, the effects were not statistically different from placebo when the duration of treatment was ≥12 weeks (SMD −0.49; 95%CI −1.13, 0.15; $p = 0.13$; 5 RCTs).

4. Individual Nasal Symptom Score

Sneezing, rhinorrhea, and nasal obstruction scores were assessed by fifteen RCTs [20, 25, 28, 30–32, 37, 38, 40, 42, 45–49] while itching score was assessed by eleven RCTs [20, 25, 31, 32, 37, 42, 45–49]. Data from two studies could not be pooled because the SDs could not be imputed [25, 31].

When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo in sneezing (SMD −0.23; 95%CI −0.44, −0.02; $p = 0.03$; 12 RCTs), rhinorrhea (SMD −0.32; 95%CI −0.58, −0.06; $p = 0.02$; 12 RCTs), nasal obstruction (SMD −0.36; 95%CI −0.57, −0.16; $p < 0.01$; 12 RCTs), and itching (SMD −0.36; 95%CI −0.62, −0.09; $p < 0.01$; 9 RCTs). When the duration of treatment was > 4 weeks, the effects favored HM over placebo only in nasal obstruction (SMD −0.34; 95%CI −0.66, −0.02; $p = 0.04$; 3 RCTs), the effects in other individual symptoms were not different from placebo. Two RCTs compared individual nasal symptom score between HM and standard treatment [41, 50]. HM brought similar effects with standard treatment in each symptom.

Table 1 Characteristics of included studies investigating herbal medicine categorized by the mechanism of action

First author, year	Patient				Herbal medicine			Route		
	Mean age (years)	Female (%)	Total number (n)	AR subtype	Name	Number (n)	Duration (weeks)	Oral	IN spray/ inhalation	External application
Anti-allergic effect										
Berstein [19], 2002	39.5	66.7	51	SAR	Grape seed extract	25	8	X		
Hu [20], 2002	38.8	36.2	58	PAR	Bimine	26	12	X		
Xue [22], 2003	39.5	60.0	55	SAR	CHM	28	8	X		
Brinkhaus [23], 2004	33.5	51.9	54	SAR	CHM	28	6	X		
Enomoto [28], 2006	33.2	72.7	33	PAR	Apple Polyphenols	22	4	X		
Segawa [29], 2007	40.8	64.1	39	SAR	Hop water extract	20	12	X		
Yoshimura [30], 2007	35.1	57.5	33	PAR	Tomato extract	17	8	X		
Zhao [31], 2009	NR	NR	126	PAR	Shi-bi-lin	63	4	X		
Hsu [32], 2010	22.4	51.5	33	Mixed	CHM	18	8			X
Matkovic [33], 2010	32.4	53.7	41	SAR	Astragalus membranaceus	27	6	X		
Yang [35], 2010	29.5	45	100	PAR	Xin-yi-san	62	12	X		
Yonekura [38], 2011	30.2	47.2	89	PAR	Ten-Cha	47	4	X		
Lenon [39], 2012	40.8	53.7	95	SAR	RCM-102 (CHM)	47	8	X		
Masuda [40], 2014	39.6	70.6	51	PAR	Green tea	26	16	X		
Choi [42], 2016	30	NR	54	PAR	Aromatherapy oils	27	1		X	
Hoffmann [44], 2016*	25.5	61.2	31	PAR	Lemon, quince	31	1		X	
Arpornchayanon [45], 2019	34.9	68.8	16	PAR	Shallot	8	4	X		
Dai [46], 2019	42.0	52.2	92	PAR	Tian Jiu	46	8			X
Kim [47], 2019	22.8	38.9	154	PAR	So-Cheong-Ryong-Tang	78	12	X		
Steels [48], 2019	43.3	61.7	60	SAR	Cinnamon bark	30	1		X	
Tandhavadhana [49], 2019	42.1	85.7	42	PAR	Thai herbal medicine	21	4	X		
Zhao [50], 2019	37.4	43.9	98	PAR	Bimin	51	4	X		
Anti-inflammatory effect										
Hu [20], 2002	38.8	36.2	58	PAR	Bimine	26	12	X		
Schapowal [21], 2002	37.0	67.2	125	SAR	Butterbur	61	2	X		
Xue [22], 2003	39.5	60.0	55	SAR	CHM	28	8	X		
Brinkhaus [23], 2004	33.5	51.9	54	SAR	CHM	28	6	X		
Lee [24], 2004*	43.0	56.3	16	PAR	Butterbur	16	1	X		
Schapowal [25], 2004	42.7	64.0	186	SAR	Butterbur	125	2	X		
Takano [26], 2004	33.1	44.8	29	SAR	Perilla frutescens	19	3	X		
Schapowal [27], 2005	38.1	65.7	330	SAR	Butterbur	110	2	X		
Enomoto [28], 2006	33.2	72.7	33	PAR	Apple Polyphenols	22	4	X		
Yoshimura [30], 2007	35.1	57.5	33	PAR	Tomato extract	17	8	X		
Zhao [31], 2009	NR	NR	126	PAR	Shi-bi-lin	63	4	X		
Hsu [32], 2010	22.4	51.5	33	Mixed	CHM	18	8			X
Wilson [34], 2010	43.8	65	60	SAR	Pycnogenol	30	12-14	X		
Yang [35], 2010	29.5	45	100	PAR	Xin-yi-san	62	12	X		
Jung [36], 2011	26.4	62.7	59	PAR	Fermented red gingseng	30	4	X		
Nikakhlagh [37], 2011	20.8	74.6	59	PAR	Nigella sativa	30	4	X		
Yonekura [38], 2011	30.2	47.2	89	PAR	Ten-Cha	47	4	X		
Lenon [39], 2012	40.8	53.7	95	SAR	RCM-102 (CHM)	47	8	X		
Masuda [40], 2014	39.6	70.6	51	PAR	Green tea	26	16	X		
Min [41], 2015	17.9	49	355	PAR	CHM	182	8			X

Table 1 (continued)

Choi [42], 2016	30	NR	54	PAR	Aromatherapy oils	27	1		X		
Fujiwara [43], 2016	25	48.5	66	PAR	Chlorophyll c2	33	12	X			
Arpornchayanon [45], 2019	34.9	68.8	16	PAR	Shallot	8	4	X			
Dai [46], 2019	42.0	52.2	92	PAR	Tian Jiu	46	8			X	
Kim [47], 2019	22.8	38.9	154	PAR	So-Cheong-Ryong-Tang	78	12	X			
Steels [48], 2019	43.3	61.7	60	SAR	Cinnamon bark	30	1		X		
Tandhavadhana [49], 2019	42.1	85.7	42	PAR	Thai herbal medicine	21	4	X			
Zhao [50], 2019	37.4	43.9	98	PAR	Bimin	51	4	X			
Anti-leukotriene effect											
Schapowal [21], 2002	37.0	67.2	125	SAR	Butterbur	61	2	X			
Lee [24], 2004*	43.0	56.3	16	PAR	Butterbur	16	1	X			
Schapowal [25], 2004	42.7	64.0	186	SAR	Butterbur	125	2	X			
Schapowal [27], 2005	38.1	65.7	330	SAR	Butterbur	110	2	X			
Wilson [34], 2010	43.8	65	60	SAR	Pycnogenol	30	12-14	X			
Anti-leukotriene effect											
Hsu [32], 2010	22.4	51.5	33	Mixed	CHM	18	8			X	
Jung [36], 2011	26.4	62.7	59	PAR	Fermented red gingseng	30	4	X			
Dai [46], 2019	42.0	52.2	92	PAR	Tian Jiu	46	8			X	
Kim [47], 2019	22.8	38.9	154	PAR	So-Cheong-Ryong-Tang	78	12	X			

First author, year	Control			Outcome					
	Placebo	Standard treatment	Number (n)	TNSS	INSS	TOSS	Quality of life	OMNP	Safety
Anti-allergic effect									
Berstein [19], 2002	X		26		X		X		X
Hu [20], 2002	X		32		X		X		X
Xue [22], 2003	X		27	X		X	X		X
Brinkhaus [23], 2004	X		26				X		X
Enomoto [28], 2006	X		11		X				X
Segawa [29], 2007	X		19	X					
Yoshimura [30], 2007	X		16		X		X		X
Zhao [31], 2009	X		63		X		X		X
Hsu [32], 2010	X		15		X		X		
Matkovic [33], 2010	X		14	X			X		X
Yang [35], 2010	X		38	X				X	X
Yonekura [38], 2011	X		42		X		X		X
Lenon [39], 2012	X		48	X		X	X		X
Masuda [40], 2014	X		25	X		X	X		X
Choi [42], 2016	X		27	X	X	X	X		
Hoffmann [44], 2016*	X		31					X	
Arpornchayanon [45], 2019	X		8	X	X	X		X	X
Dai [46], 2019	X		46	X	X	X	X		X
Kim [47], 2019	X		76	X	X		X		X
Steels [48], 2019	X		30	X	X	X	X		X
Tandhavadhana [49], 2019	X		21		X			X	X
Zhao [50], 2019		X	47	X	X	X	X	X	X
Anti-inflammatory effect									
Hu [20], 2002	X		32		X		X		X

Table 1 (continued)

Schapowal [21], 2002		X	65				X		X
Xue [22], 2003	X		27	X		X	X		X
Brinkhaus [23], 2004	X		26				X		X
Lee [24], 2004*	X	X	16	X				X	
Schapowal [25], 2004	X		61	X	X				X
Takano [26], 2004	X		10		X		X		X
Schapowal [27], 2005	X	X	220	X					X
Enomoto [28], 2006	X		11		X				X
Yoshimura [30], 2007	X		16		X		X		X
Zhao [31], 2009	X		63		X		X		X
Hsu [32], 2010	X		15		X		X		
Wilson [34], 2010	X		30	X		X			X
Yang [35], 2010	X		38	X				X	X
Jung [36], 2011	X		29	X			X		X
Nikakhlagh [37], 2011	X		29		X				
Yonekura [38], 2011	X		42		X		X		X
Lenon [39], 2012	X		48	X		X	X		X
Masuda [40], 2014	X		25	X		X	X		X
Min [41], 2015		X	173		X		X		X
Choi [42], 2016	X		27	X	X	X	X		
Fujiwara [43], 2016	X		33				X		
Arpornchayanon [45], 2019	X		8	X	X	X		X	X
Dai [46], 2019	X		46	X	X	X	X		X
Kim [47], 2019	X		76	X	X		X		X
Steels [48], 2019	X		30	X	X	X	X		X
Tandhavadhana [49], 2019	X		21		X			X	X
Zhao [50], 2019		X	47	X	X	X	X	X	X
Anti-leukotriene effect									
Schapowal [21], 2002		X	65				X		X
Lee [24], 2004*	X	X	16	X				X	
Schapowal [25], 2004	X		61	X	X				X
Schapowal [27], 2005	X	X	220	X					X
Wilson [34], 2010	X		30	X		X			X
Anti-leukotriene effect									
Hsu [32], 2010	X		15		X		X		
Jung [36], 2011	X		29	X			X		X
Dai [46], 2019	X		46	X	X	X	X		X
Kim [47], 2019	X		76	X	X		X		X

CHM, Chinese herbal medicine; *AR,* allergic rhinitis; *SAR,* seasonal allergic rhinitis; *PAR,* perennial allergic rhinitis; *IN,* intranasal; *TNSS,* total nasal symptom score; *TOSS,* total ocular symptom score; *OMNP,* objective measurement for nasal patency; *n,* number

* Crossover study

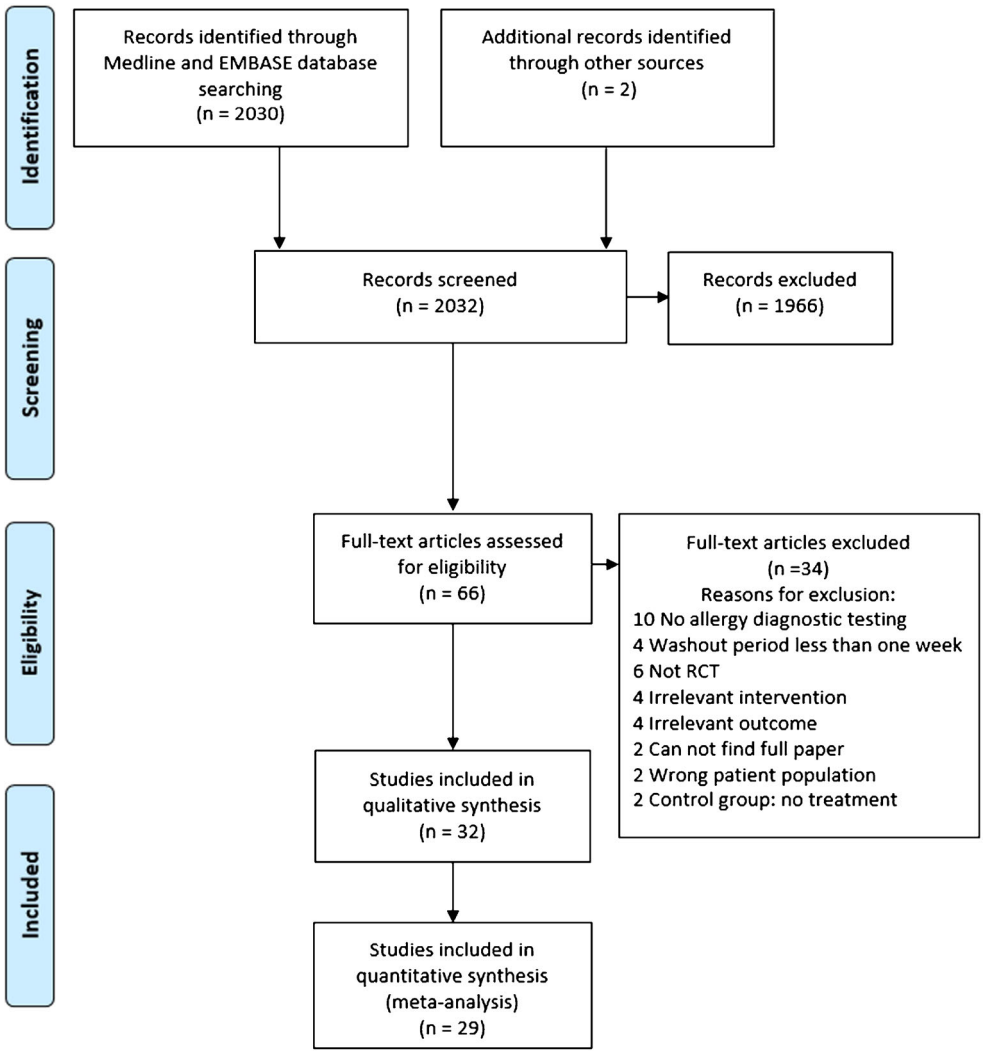

Fig. 1 Flow diagram of the study selection

5. Total Ocular Symptom Score

Eight RCTs compared the total ocular symptom score (TOSS) between HM and placebo [22, 34, 39, 40, 42, 45, 46, 48]. When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo (SMD −0.32; 95% CI −0.58, −0.05; p = 0.02; 4 RCTs) (Fig. 3). When the duration of treatment was > 4 weeks, there was no statistically significant difference between the groups.

6. Disease-Specific QOL

Seventeen RCTs compared Rhinoconjunctivitis Quality of life Questionnaire (RQLQ) [19, 20, 22, 23, 30, 33, 36, 38–43,

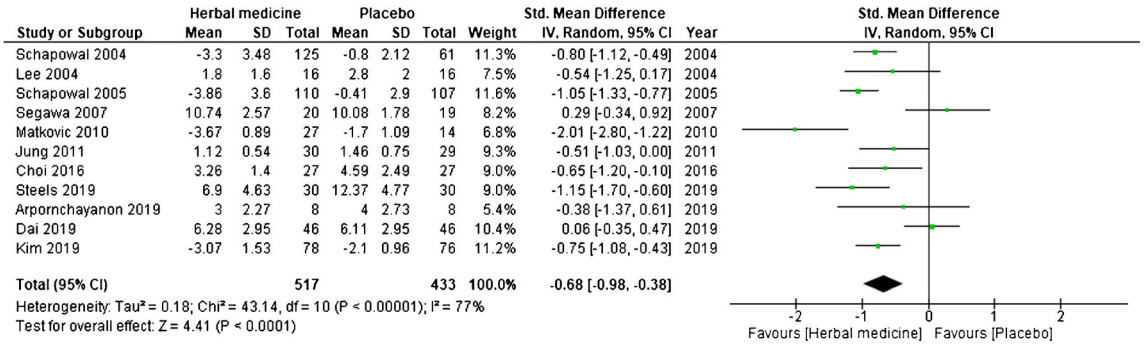

Fig. 2 Improvement on total nasal symptom score: herbal medicine versus placebo at ≤ 4-week time point. CI confidence interval; df degrees of freedom; Std. mean difference standardized mean difference

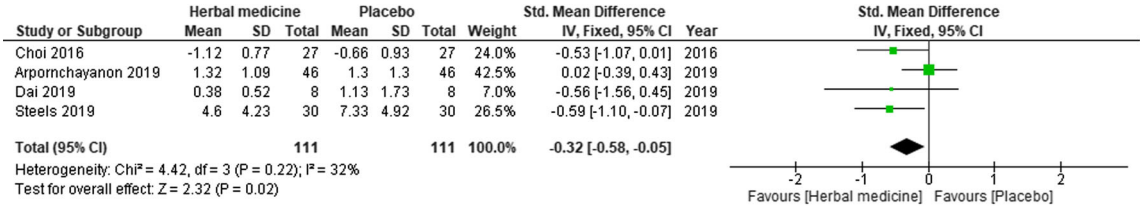

Fig. 3 Improvement on total ocular symptom score: herbal medicine versus placebo at ≤ 4-week time point. CI confidence interval; df degrees of freedom; Std. mean difference standardized mean difference

46–48, 50]. Data in five RCTs were not pooled because the SDs could not be imputed [22, 38–41].

When the duration of treatment was ≤ 4 weeks, the effects favored HM over placebo (SMD −0.53; 95%CI −0.81, −0.25; $p < 0.01$; 9 RCTs) (Fig. 4) and over standard treatment (SMD −1.89; 95%CI −2.37, −1.41; $p < 0.01$; 1 RCT) [51]. When the duration of treatment was 4–12 weeks, the effects still favored HM over placebo (SMD −0.48; 95%CI −0.89, −0.06; $p = 0.03$; 7 RCTs). Nevertheless, the effects were not statistically different between the groups when the duration of treatment was ≥12 weeks (SMD −0.17; 95%CI −0.47, 0.12; $p = 0.24$; 3 RCTs).

7. Objective Measurement for Nasal Patency

Nasal airway resistance (NAR) and peak nasal inspiratory flow (PNIF) were assessed. Four RCTs assessed anterior NAR in the inhalation phase [35, 44, 45, 50]. One RCT did not report the mean NAR [44]. There were no significant differences between the effects of HM and placebo (MD −0.07; 95%CI −0.19, 0.04; $p = 0.22$; 2 RCTs) [35, 45] and between the HM and standard treatment (MD −0.01; 95%CI −0.06, 0.04; $p = 0.68$; 1 RCT) [50]. Two trials assessed peak nasal inspiratory flow, however, neither of two trials had sufficient data for analysis [24, 49].

8. Subgroup Analysis by Mechanism of Action

The effects of HM on TNSS improvement were better than placebo in all subgroups of mechanism of action: anti-allergic effect (SMD −0.55; 95%CI −0.69, −0.4; $p < 0.01$, 12 RCTs), anti-inflammatory effect (SMD −0.61; 95%CI −0.88, −0.33; $p < 0.01$, 13 RCTs), anti-leukotriene effect (SMD −0.67; 95%CI −1.07, −0.27; $p < 0.01$, 4 RCTs), and anti-histaminic effect (SMD −0.5; 95%CI −0.91, −0.08; $p < 0.01$, 4 RCTs). The effects of HM on RQLQ improvement were better than placebo in anti-allergic effect (SMD −0.61; 95% CI −1, −0.21; $p < 0.01$, 9 RCTs) and anti-inflammatory effect (SMD −0.5; 95%CI −0.79, −0.21; $p < 0.01$, 9 RCTs). There was no difference on RQLQ improvement between HM with anti-histaminic effect and placebo (SMD −0.16; 95% CI −0.40, 0.09; $p = 0.2$, 3 RCTs).

9. Subgroup Analysis by AR Subtype

For the duration of treatment ≤ 4 weeks, the effects of HM on TNSS improvement were better than placebo in both the SAR (SMD −0.92; 95%CI −1.41, −0.43; $p < 0.01$; 5 RCTs) and PAR subgroups (SMD −0.47; 95%CI −0.77, −0.17; $p < 0.01$; 6 RCTs). For the duration of 4–12 weeks, the effects on TNSS favored HM only in the SAR subgroup (SMD −0.51; 95%CI −0.87, −0.16; $p < 0.01$; 3 RCTs), but not in the PAR subgroup (SMD −0.13; 95%CI −0.33, 0.06; $p = 0.18$; 4 RCTs). For the duration of ≥ 12 weeks, there were no differences between HM and placebo in both the SAR and PAR subgroups. The effects of HM on RQLQ improvement were better than placebo when the duration of treatment was ≤ 4 weeks in both the SAR (SMD −0.82; 95%CI −1.56, −0.08; $p < 0.01$; 3 RCTs) and PAR (SMD −0.38; 95%CI −0.61, −0.14; $p < 0.01$; 6 RCTs), but there were no differences after 4 weeks of treatments.

10. Subgroup Analysis by Quality of the Included Studies

The included studies that had at least one high risk of bias in one domain were defined as "Trials with high risk of bias"

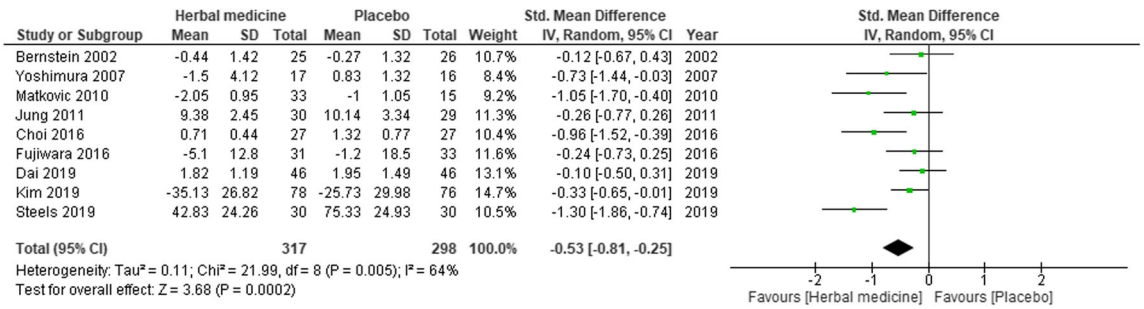

Fig. 4 Improvement on Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ): herbal medicine versus placebo at ≤ 4-week time point. CI confidence interval; df degrees of freedom; Std. mean difference standardized mean difference

where others were defined as "Trials without high risk of bias." In the trials without high risk of bias subgroup, HM significantly improved TNSS when the duration of treatment was ≤ 4 weeks (SMD −0.89; 95%CI −1.13, −0.65; $p < 0.01$; 8 RCTs) but there was no difference after 4 weeks. HM significantly improved RQLQ when the duration of treatment was < 12 weeks but there was no difference after this timepoint. In the trials with high risk of bias subgroup, there were no differences between the HM and placebo in both TNSS and RQLQ improvement regardless of the duration of treatment.

11. Adverse Events

Nine RCTs assessed headache, dry mouth/nose, dizziness, somnolence, and gastrointestinal pain/diarrhea events (Table 2). There were no significant differences in adverse events between the HM and other treatments.

Discussion

This systematic review and meta-analysis demonstrated the beneficial effects of HM for treating AR. HM improved total nasal symptoms, individual nasal symptoms, total ocular symptoms, and disease-specific quality of life. These beneficial effects persisted in the high quality RCTs subgroup analysis. In contrast, there were no differences between the HM and placebo in the trials with high risks of bias subgroup. In addition, HMs brought beneficial effects like standard treatments, including antihistamines and intranasal corticosteroids. HMs with anti-inflammatory activities contains plant steroids, of which the structure is close to corticosteroids [50]. Subgroup analyses showed that HMs with anti-allergic effect and anti-inflammatory effect were effective. These effects controlled the early-phase and late-phase symptoms. In addition, anti-histamine and anti-leukotriene effects were also revealed. Jung et al. [36] demonstrated the ability of fermented red ginseng to suppress the wheel and flare response in SPT as a part of the anti-histamine effect. Butterbur and Pycnogenol showed the ability to inhibit leukotriene biosynthesis, like zileuton [21, 24, 25, 27, 34]. These effects decrease mucus hypersecretion in the airways and enhance mucociliary functions [51]. Choosing an appropriate HM should be based on the mechanisms of action of the HM that could improve the prominent symptoms of AR.

The results of this study showed the benefits of HMs up to twelve weeks duration then the benefits decreased. Tachyphylaxis has been known for a long time in other medicines such as antihistamines, intranasal decongestants, and opioids. To the best of our knowledge, this is the first systematic review showing evidence of tachyphylaxis of herbal medicine. There is no evidence regarding whether increasing the dose of HM can restore the original response. Physicians should be aware that the HM response decreases after three months of treatment. The subgroup analyses by AR subtype showed that both the patients with SAR and PAR benefited from the HMs. However, the patients with PAR experienced tachyphylaxis after 4 weeks.

To date, the evidence supporting the HM treatments for AR is unclear. The recommendation of HM is controversial [8•]. A systematic review utilized a modified Delphi method by Wu et al. [6•] showed that butterbur extract was one of the potential alternative treatments for sinusitis and rhinitis. Unlike Western HMs, Eastern HMs have composite ingredients containing different herbs. Therefore, it is difficult to identify the original or individual component that provides the primary beneficial effects. Lenon et al. [39] studied a new formula that was developed from an existing HM formula, by selecting 7 out of the 18 individual herbal ingredients and found no differences between the HM and placebo. There are four meta-analyses evaluating the effects of Chinese HMs. These meta-analyses included several studies that were published in Chinese. However, those studies were not included in our review. A meta-analysis by Wang et al. [9] showed the benefits of Chinese HM over placebo or inactive comparator in the assessment of TNSS. In contrast, Zhang et al. [12•] reported no differences in TNSS or individual nasal symptom scores between the HM and placebo or inactive comparator. Although they found beneficial effects on RQLQ favoring the HM, the heterogeneity was substantial. Another meta-analysis by Zheng et al. [52] assessed pediatric AR from 19 RCTs and showed benefits of Chinese HM over antihistamines. Luo et al. [3] assessed adult patients with AR from 23 RCTs and showed that the Chinese HM formula, *Yu ping feng san*, was effective for managing adult AR.

Based on the results of this meta-analysis, HM decreased nasal and ocular symptoms related to allergic rhinitis and improved quality of life with no difference from standard treatments. Nevertheless, beneficial effects did not persist after 12 weeks. In addition to the benefits of HM as a sole therapy, its role as an addition to standard treatment also had favorable therapeutic outcomes [17]. Arpornchayanon et al. [45] assessed the effects of cetirizine and HM combination and showed that the combination was superior to cetirizine and placebo. The findings of this study showed that HM was safe and tolerable. This is in agreement with previously published articles which reported no differences in adverse events between the HM and control groups. However, diarrhea or liver toxicity was reported in some cases [8•, 11, 49]. In clinical practice, the authors suggest that HM should be considered as a primary treatment only for a short-term treatment. Standard treatments such as antihistamines and intranasal corticosteroids are the first-line drugs for the long-term treatment while HM can be used as an option or as an adjunct to standard treatment to boost up the treatment effect [6•].

This study had several limitations. The systematic search did not search for articles published in languages other than English. Therefore, our meta-analysis could not cover all

Table 2 Adverse events of herbal medicine and risk ratio

Adverse events	Number of studies	Herbal medicine		Control		Risk ratio (95% CI)	*p* value
		Number of participants	Number of events	Number of participants	Number of events		
Headache	7	356	19	364	18	1.09 (0.66-1.81)	0.73
HM vs Placebo	6	246	18	251	18	1.04 (0.62-1.73)	0.76
HM vs ST	1	110	1	113	0	3.08 (0.13-74.83)	0.49
Dry mouth/nose	3	126	3	122	6	0.51 (0.14-1.82)	0.30
HM vs Placebo	2	75	1	75	2	0.60 (0.08-4.38)	0.61
HM vs ST	1	51	2	47	4	0.46 (0.09-2.40)	0.36
Dizziness	5	301	10	308	12	0.86 (0.38-1.92)	0.71
HM vs Placebo	4	191	6	195	6	1.02 (0.35-2.98)	0.97
HM vs ST	1	110	4	113	6	0.68 (0.20-2.36)	0.55
Somnolence	2	59	3	55	4	0.76 (0.23-2.56)	0.66
HM vs Placebo	1	8	2	8	4	0.50 (0.13-2.00)	0.33
HM vs ST	1	51	1	47	0	2.77 (0.12-66.36)	0.53
Gastrointestinal pain/diarrhoea	7	471	17	414	13	1.09 (0.57-2.09)	0.80
HM vs Placebo	6	361	15	301	13	0.96 (0.49-1.90)	0.91
HM vs ST	1	110	2	113	0	5.14 (0.25-105.76)	0.29

HM, herbal medicine; *ST*, standard treatment; *CI*, confidence interval

current studies. In addition, the included studies had high heterogeneity for outcomes assessment. Subgroup analyses, by mechanism of action of the HM, the AR subtype, and quality of the included studies, were conducted to investigate the heterogeneity. The heterogeneity persisted because different kinds of HM were investigated together.

Conclusion

Evidence from this meta-analysis showed the benefits of HM for treating AR patients. HMs improved nasal symptoms, ocular symptoms, and disease-specific QOL when compared to placebo. Beneficial effects of HMs were similar to standard treatments but only revealed in a short-term treatment, less than 12 weeks. In general, HM is considered safe. In practice, standard treatments such as antihistamines and intranasal corticosteroids should be considered for a long-term treatment.

Author Contribution Minh P. Hoang: study design, search, study selection, data collection, data analysis, drafting the article, and final approval.

Wirach Chitsuthipakorn: search, study selection, data collection, revising the article, and final approval.

Kornkiat Snidvongs: conception, study design, data analysis, drafting the article, and final approval.

Declarations

Conflict of Interest Kornkiat Snidvongs has served on speakers' bureau for Merck Sharp Dolme, Mylan, GSK, and Menarini. Minh Phuoc Hoang and Wirach Chitsuthipakorn declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1_Suppl):S1–S43.
2. Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. Allergy Asthma Immunol Res. 2018;10(4):300–53.
3. MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. Prev Med. 2002;35(2):166–73.
4. Schaefer T, Riehle A, Wichmann HE, Ring J. Alternative medicine in allergies–prevalence, patterns of use, and costs. Allergy. 2002;57(8):694–700.

5. Luo Q, Zhang CS, Yang L, Zhang AL, Guo X, Xue CC, et al. Potential effectiveness of Chinese herbal medicine Yu ping feng san for adult allergic rhinitis: a systematic review and meta-analysis of randomized controlled trials. BMC Complement Altern Med. 2017;17(1):485.
6.• Wu AW, Gettelfinger JD, Ting JY, Mort C, Higgins TS. Alternative therapies for sinusitis and rhinitis: a systematic review utilizing a modified Delphi method. Int Forum Allergy Rhinol. 2020;10(4):496–504 **A good review yielded the experts' recommendation of alternative treatments for sinusitis and rhinitis. Butterbur is recommended as an adjunctive treatment for allergic rhinitis.**
7. Xue CC, Hugel HM, Li CG, Story DF. Efficacy, chemistry and pharmacology of chinese herbal medicine for allergic rhinitis. Curr Med Chem. 2004;11(11):1403–21.
8.• Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of allergic rhinitis: a systematic review. Ann Allergy Asthma Immunol. 2007;99(6):483–95. https://doi.org/10.1016/S1081-1206(10)60375-4. **The first systematic review investigated a wide spectrum of herbal medicine in the field treating allergic rhinitis**.
9. Wang S, Tang Q, Qian W, Fan Y. Meta-analysis of clinical trials on traditional Chinese herbal medicine for treatment of persistent allergic rhinitis. Allergy. 2012;67(5):583–92.
10. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140(4):950–8.
11.• Kern J, Bielory L. Complementary and alternative therapy (CAM) in the treatment of allergic rhinitis. Curr Allergy Asthma Rep. 2014;14(12):479 **The comprehensive review of the literature regarding the efficacy and safety of herbal medicine in treating allergic rhinitis.**
12.• Zhang X, Lan F, Zhang Y, Zhang L. Chinese Herbal Medicine to Treat Allergic Rhinitis: Evidence From a Meta-Analysis. Allergy Asthma Immunol Res. 2018;10(1):34–42 **The latest meta-analysis displays the efficacy of Chinese herbal medicine and the limitation of lacking well-designed randomized controlled studies.**
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
14. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63(Suppl 86):8–160.
15. Seresirikachorn K, Chitsuthipakorn W, Kanjanawasee D, Khattiyawittayakun L, Snidvongs K. Leukotriene Receptor Antagonist Addition to H1-Antihistamine Is Effective for Treating Allergic Rhinitis: A Systematic Review and Meta-analysis. Am J Rhinol Allergy. 2019;33(5):591–600.
16. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database Syst Rev. 2012;5.
17. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, et al. International consensus statement on allergy and rhinology: allergic rhinitis. Int Forum Allergy Rhinol. 2018;8(2):108–352.
18. Higgins JPT, Green S. Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. 2011. https://handbook-5-1.cochrane.org. Accessed 13 Apr 2020.
19. Bernstein DI, Bernstein CK, Deng C, Murphy KJ, Bernstein IL, Bernstein JA, et al. Evaluation of the clinical efficacy and safety of grapeseed extract in the treatment of fall seasonal allergic rhinitis: a pilot study. Ann Allergy Asthma Immunol. 2002;88(3):272–8.
20. Hu G, Walls RS, Bass D, Ramon B, Grayson D, Jones M, et al. The Chinese herbal formulation biminne in management of perennial allergic rhinitis: a randomized, double-blind, placebo-controlled, 12-week clinical trial. Ann Allergy Asthma Immunol. 2002;88(5):478–87.
21. Schapowal A, Petasites SG. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. BMJ. 2002;324(7330):144–6.
22. Xue CC, Thien FC, Zhang JJ, Da Costa C, Li CG. Treatment for seasonal allergic rhinitis by Chinese herbal medicine: a randomized placebo controlled trial. Altern Ther Health Med. 2003;9(5):80–7.
23. Brinkhaus B, Hummelsberger J, Kohnen R, Seufert J, Hempen CH, Leonhardy H, et al. Acupuncture and Chinese herbal medicine in the treatment of patients with seasonal allergic rhinitis: a randomized-controlled clinical trial. Allergy. 2004;59(9):953–60.
24. Lee DK, Gray RD, Robb FM, Fujihara S, Lipworth BJ. A placebo-controlled evaluation of butterbur and fexofenadine on objective and subjective outcomes in perennial allergic rhinitis. Clin Exp Allergy. 2004;34(4):646–9.
25. Schapowal A, Petasites SG. Butterbur Ze339 for the treatment of intermittent allergic rhinitis: dose-dependent efficacy in a prospective, randomized, double-blind, placebo-controlled study. Arch Otolaryngol Head Neck Surg. 2004;130(12):1381–6.
26. Takano H, Osakabe N, Sanbongi C, Yanagisawa R, Inoue K, Yasuda A, et al. Extract of Perilla frutescens enriched for rosmarinic acid, a polyphenolic phytochemical, inhibits seasonal allergic rhinoconjunctivitis in humans. Exp Biol Med (Maywood). 2004;229(3):247–54.
27. Schapowal A, Study G. Treating intermittent allergic rhinitis: a prospective, randomized, placebo and antihistamine-controlled study of Butterbur extract Ze 339. Phytother Res. 2005;19(6):530–7.
28. Enomoto T, Nagasako-Akazome Y, Kanda T, Ikeda M, Dake Y. Clinical effects of apple polyphenols on persistent allergic rhinitis: A randomized double-blind placebo-controlled parallel arm study. J Investig Allergol Clin Immunol. 2006;16(5):283–9.
29. Segawa S, Takata Y, Wakita Y, Kaneko T, Kaneda H, Watari J, et al. Clinical effects of a hop water extract on Japanese cedar pollinosis during the pollen season: a double-blind, placebo-controlled trial. Biosci Biotechnol Biochem. 2007;71(8):1955–62.
30. Yoshimura M, Enomoto T, Dake Y, Okuno Y, Ikeda H, Cheng L, et al. An evaluation of the clinical efficacy of tomato extract for perennial allergic rhinitis. Allergol Int. 2007;56(3):225–30.
31. Zhao Y, Woo KS, Ma KH, van Hansselt CA, Wong KC, Cheng KF, et al. Treatment of perennial allergic rhinitis using Shi-Bi-Lin, a Chinese herbal formula. J Ethnopharmacol. 2009;122(1):100–5.
32. Hsu WH, Ho TJ, Huang CY, Ho HC, Liu YL, Liu HJ, et al. Chinese medicine acupoint herbal patching for allergic rhinitis: a randomized controlled clinical trial. Am J Chin Med. 2010;38(4):661–73.
33. Matkovic Z, Zivkovic V, Korica M, Plavec D, Pecanic S, Tudoric N. Efficacy and safety of Astragalus membranaceus in the treatment of patients with seasonal allergic rhinitis. Phytother Res. 2010;24(2):175–81.
34. Wilson D, Evans M, Guthrie N, Sharma P, Baisley J, Schonlau F, et al. A randomized, double-blind, placebo-controlled exploratory study to evaluate the potential of pycnogenol for improving allergic rhinitis symptoms. Phytother Res. 2010;24(8):1115–9.
35. Yang SH, Yu CL, Chen YL, Chiao SL, Chen ML. Traditional Chinese medicine, Xin-yi-san, reduces nasal symptoms of patients with perennial allergic rhinitis by its diverse immunomodulatory effects. Int Immunopharmacol. 2010;10(8):951–8.
36. Jung JW, Kang HR, Ji GE, Park MS, Song WJ, Kim MH, et al. Therapeutic effects of fermented red ginseng in allergic rhinitis: a randomized, double-blind, placebo-controlled study. Allergy Asthma Immunol Res. 2011;3(2):103–10.
37. Nikakhlagh S, Rahim F, Aryani FH, Syahpoush A, Brougerdnya MG, Saki N. Herbal treatment of allergic rhinitis: the use of Nigella sativa. Am J Otolaryngol. 2011;32(5):402–7.

38. Yonekura S, Okamoto Y, Yamasaki K, Horiguchi S, Hanazawa T, Matsune S, et al. A randomized, double-blind, placebo-controlled study of ten-cha (Rubus suavissimus) on house dust mite allergic rhinitis. Auris Nasus Larynx. 2011;38(5):600–7.
39. Lenon GB, Li CG, Da Costa C, Thien FC, Shen Y, Xue CC. Lack of efficacy of a herbal preparation (RCM-102) for seasonal allergic rhinitis: a double blind, randomised, placebo-controlled trial. Asia Pac Allergy. 2012;2(3):187–94.
40. Masuda S, Maeda-Yamamoto M, Usui S, Fujisawa T. 'Benifuuki' green tea containing o-methylated catechin reduces symptoms of Japanese cedar pollinosis: a randomized, double-blind, placebo-controlled trial. Allergol Int. 2014;63(2):211–7.
41. Min CY, Peng CJ, Wei GJ, Huang XH, Fu TT, Du Y, et al. Moxibustion with Chinese herbal has good effect on allergic rhinitis. Int J Clin Exp Med. 2015;8(9):16480–7.
42. Choi SY, Park K. Effect of Inhalation of Aromatherapy Oil on Patients with Perennial Allergic Rhinitis: A Randomized Controlled Trial. Evid Based Complement Alternat Med. 2016;2016:7896081.
43. Fujiwara T, Nishida N, Nota J, Kitani T, Aoishi K, Takahashi H, et al. Efficacy of chlorophyll c2 for seasonal allergic rhinitis: single-center double-blind randomized control trial. Eur Arch Otorhinolaryngol. 2016;273(12):4289–94.
44. Hoffmann A, Klein SD, Grundemann C, Garcia-Kaufer M, Wolf U, Huber R. Efficacy of a Nasal Spray from Citrus limon and Cydonia oblonga for the Treatment of Hay Fever Symptoms-A Randomized, Placebo Controlled Cross-Over Study. Phytother Res. 2016;30(9):1481–6.
45. Arpornchayanon W, Klinprung S, Chansakaow S, Hanprasertpong N, Chaiyasate S, Tokuda M, et al. Antiallergic activities of shallot (Allium ascalonicum L.) and its therapeutic effects in allergic rhinitis. Asian Pac J Allergy Immunol. 2019;18 [Epub ahead of print].
46. Dai L, Zhong LLD, Kun W, Lam WC, Yang Z, Huang T, et al. An External CAM Therapy (Tian Jiu) versus Placebo in Treatment of Allergic Rhinitis: A Pilot Single-Blinded, Three-Arm, Randomized Controlled Study. Evid Based Complement Alternat Med. 2019;2019:6369754.
47. Kim MH, Hong SU, Kim HT, Seo HS, Kim K, Ko SG, et al. A multicenter study on the efficacy and safety of So-Cheong-Ryong-Tang for perennial allergic rhinitis. Complement Ther Med. 2019;45:50–6.
48. Steels E, Steels E, Deshpande P, Thakurdesai P, Dighe S, Collet T. A randomized, double-blind placebo-controlled study of intranasal standardized cinnamon bark extract for seasonal allergic rhinitis. Complement Ther Med. 2019;47:102198.
49. Tandhavadhana S, Maek ANW, Phonrat B, Picheansoonthon C, Pitisuttithum P. Preliminary study on safety and efficacy of a Thai herbal remedy in persistent allergic rhinitis: A Randomized Double-blind Placebo-controlled Trial. J Med Assoc Thai. 2019;102(8):24–9.
50. Zhao J, Yan X, Gai J, Han J, Zhang H, Luo H, et al. Efficacy of Bimin decoction for patients with perennial allergic rhinitis: an open-label non-inferiority randomized controlled trial. Trials. 2019;20(1):802.
51. Thomet OA, Schapowal A, Heinisch IV, Wiesmann UN, Simon HU. Anti-inflammatory activity of an extract of Petasites hybridus in allergic rhinitis. Int Immunopharmacol. 2002;2(7):997–1006.
52. Zheng Z, Sun Z, Zhou X, Zhou Z. Efficacy of Chinese herbal medicine in treatment of allergic rhinitis in children: a meta-analysis of 19 randomized controlled trials. J Int Med Res. 2018;46(10):4006–18.