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Potential effectiveness of Chinese herbal medicine *Yu ping feng san* for adult allergic rhinitis: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Chinese herbal medicine formula *Yu ping feng san* (YPFS) is commonly used for allergic rhinitis (AR). Previous review had summarized the effectiveness and safety of YPFS, however without any subgroup analysis performed to provide detailed evidence for guiding clinical practice. YPFS was recommended for the management of AR by Chinese medicine clinical practice guideline, but the treatment duration of YPFS was also not specified. The aim of this study is to evaluate the effectiveness and safety of YPFS in treating adult AR with the most recent evidence, and attempt to specify the duration of utilisation through subgroup meta-analyses.

Methods: Seven databases were searched from their inceptions to September 2017. Randomized controlled trials (RCTs) evaluating YPFS for adult AR were included. Methodological quality of studies was assessed using the Cochrane risk of bias tool. Meta-analysis and subgroup meta-analyses were conducted for evaluating the effectiveness of YPFS. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used for rating the quality of evidence.

Results: Twenty-two RCTs involving 23 comparisons were included in this review. YPFS was compared to placebo, pharmacotherapy, and used as an add-on treatment compared to pharmacotherapy. Meta-analyses were feasible for the outcomes of four individual nasal symptom scores and "effective rate". Four individual nasal symptom scores decreased after YPFS' combination treatment: itchy nose (MD-0.46, 95% CI[-0.50, -0.42]), sneezing (MD-0.41, 95% CI[-0.47, -0.35]), blocked nose (MD-0.46, 95% CI[-0.54, -0.39]) and runny nose (MD-0.42, 95% CI[-0.58, -0.26]). Based on "effective rate", meta-analysis showed that YPFS did not achieve better effect than pharmacotherapy (RR1.07, 95%CI [0.94, 1.22]), but its combination with pharmacotherapy seemed more effective than pharmacotherapy alone (RR1.27, 95%CI [1.19, 1.34]) (low quality). Subgroup analysis suggested that YPFS was not superior to the second-generation antihistamine (RR1.04, 95%CI [0.90, 1.19]) (low quality). Further, YPFS' combination treatment seemed more beneficial when it was used for more than three weeks (RR1.15, 95%CI [1.01, 1.32]). In addition, YPFS was well-tolerated for treating adult AR.

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Conclusion: Chinese herbal medicine formula YPFS seems beneficial for adult AR. This potential benefit need to be further evaluated by more rigorous RCTs.

Keywords: *Yu ping feng san*, Chinese herbal medicine, Allergic rhinitis, Treatment duration, Systematic review, Meta-analysis

Background

Allergic rhinitis (AR) is the most common type of non-infectious rhinitis; it is defined as a “symptomatic disorder of the nose induced by the IgE-mediated inflammation after allergen exposure” [1]. AR is characterized mainly by nasal symptoms including sneezing, itching, rhinorrhoea and nasal congestion, as well as a group of non-nasal symptoms involving eyes, ears, throat or chest. AR patients may also develop sinusitis and asthma, or be accompanied by malaise, weakness, and fatigue [2, 3]. Globally, AR affects 10% to 20% of the population, and an increase of the prevalence has been observed in the past 40 years [1, 4]. Clinically, AR is one of the most common diseases affecting adults [5], and it is considered a major chronic respiratory disease due to its high prevalence, impairments on patients’ quality of life (QoL) and work/school performance, substantial economic impact and its co-morbidities [1, 6].

Allergic rhinitis has traditionally been categorized as seasonal or perennial types according to the predilection time and triggering allergens, or may be classified as intermittent or persistent types based on its frequency and severity. However, both of these classifications have certain limitations [1, 5–7]. Regardless of the classification types, their clinical management are all same. Recommended by the most recent clinical guideline, effective treatments of AR are topical steroids, oral antihistamines, and immunotherapy [5]. This guideline also pointed out that Chinese herbal medicine (CHM) has often been utilized for managing AR in clinical practice, although the evidence supporting its efficacy and mechanism of action is uncertain [5]. As suggested by a systematic review published in 2012, CHM might be more effective than placebo for persistent allergic rhinitis, but a confirmed conclusion could not be drawn since all included studies suffered certain methodological limitations [8]. One CHM formula, *Yu ping feng san* (YPFS), was recommended by Chinese medicine clinical practice guideline to manage AR despite its classification and severity, but the effective treatment duration is not clear [9]. YPFS formula contains three key herbs: *Astragalus membranaceus* (*huang qi*), *Rhizoma Atractylodis Macrocephalae* (*bai zhu*) and *Radix Ledebouriellae Divaricatae* (*fang feng*) [10]. In clinical practice, YPFS usually is used together with other herbs, e.g., *Lilymagnolia* (*xin yi*), *Fructus xanthii* (*cang er zi*) and *Radix Angelicae*

Dahuricae (*bai zhi*) etc. The effectiveness and safety of YPFS for AR treatment has been investigated by a number of clinical studies, and been summarized by a review article published in Chinese [11]. Although the overall effectiveness of YPFS seems promising, the treatment details were not suggested due to the lack of subgroup analyses. Therefore, in depth meta-analyses of current evidence are needed for guiding the use of YPFS for adult AR treatment in clinical practice.

Methods

The review protocol was registered on PROSPERO (CRD42015024821), and the review was constructed following the PRISMA guidelines (Additional file 1).

Study selection criteria

This systematic review was designed to evaluate the effectiveness and safety of CHM formula YPFS for AR. No limits on language and publication type were placed on study selection. Studies were considered if they recruited adult AR participants (aged 18 years and above) without classification limited. Included studies were RCTs comparing oral YPFS in any preparation forms to placebo CHM or pharmacotherapy being recommended by clinical practice guidelines [1, 7], or comparing the combination of YPFS and pharmacotherapy to the same pharmacotherapy. If YPFS was used together with other CHM herbs, only the studies using YPFS as the chief formula with other herbs as additional modification were included.

Studies were included if they reported one of the pre-defined outcomes, these are: the primary outcome measures being total nasal symptom score (TNSS) or individual nasal symptom scores; the secondary outcomes are effective rate (a composite outcome measure which calculates the change of nasal symptoms scores and nasal signs), QoL, recurrence rate in follow-up phase, serum specific immunoglobulin E (sIgE) level, serum interleukin 4 (IL-4), and adverse events (AEs).

Search strategy

A comprehensive search was conducted in seven major English and Chinese databases from their inceptions to September 2017. Searched databases are: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Chinese Biomedicine (CBM), China

Network Knowledge Infrastructure (CNKI), Wanfang Database and Chinese Scientific Journals Database (VIP). Reference lists of all full text articles were hand-searched for additional studies. The ongoing trials were searched from clinical trial registries. The search strategies for PubMed and Chinese Databases are provided as examples (see Additional file 2). Abstracts and full texts were screened for eligibility by two authors (QL and CSZ) independently according to the selection criteria. Disagreement was solved through discussion with the third author (LY).

Data extraction

Data were extracted and entered into a pre-defined Excel spread sheet, including study design, participants' demographic data, details of CHM and control treatments, outcome data and AEs.

Methodological assessment

Two authors (QL and LY) assessed the methodological quality of the included studies independently using the risk of bias tools according to the Cochrane Handbook version 5.1.0 [12]. Disagreements were resolved through discussion with another author (XG). Each item was assessed as low, high or unclear risk, with reasons recorded to support the judgments.

Statistical analysis

The RevMan 5.3 software was used for performing meta-analyses. Studies were grouped for analyses according to their comparisons and outcome measures. Dichotomous data were expressed as risk ratio (RR) and continuous data were presented as mean difference (MD), both with 95% confidence intervals (CI). A fixed-effect model was used when heterogeneity (I^2) was less than 50%; otherwise a random effects model was applied. Subgroup analysis was performed based on the type of pharmacotherapy medicine used in the control groups (e.g., second-generation antihistamine, intranasal glucocorticosteroids) and treatment duration (two weeks or more than three weeks). Publication bias was assessed using a funnel plot and Egger's test where more than ten trials in a meta-analysis.

GRADE

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [13] was used to summarize and rate the quality of evidence. Summary of Findings (SOF) tables were prepared using the online software program "GRADE pro GDT" (<https://gradepro.org/>). The main comparisons being assessed using GRADE methods were identified through discussion.

Results

In total, 1244 records were obtained through database searches, and 334 potentially relevant articles were identified after screening titles and abstracts. According to the selection criteria, 312 articles were further excluded. Twenty-two RCTs were included in the review [14–35], twenty of them were included meta-analyses [16–35]. Twenty-one included trials were conducted in the mainland China and published in Chinese [15–35], and one was conducted in China Hong Kong and published in English [14]. The search and study selection process is shown in Fig. 1, and the characteristics of included RCTs are presented in Table 1.

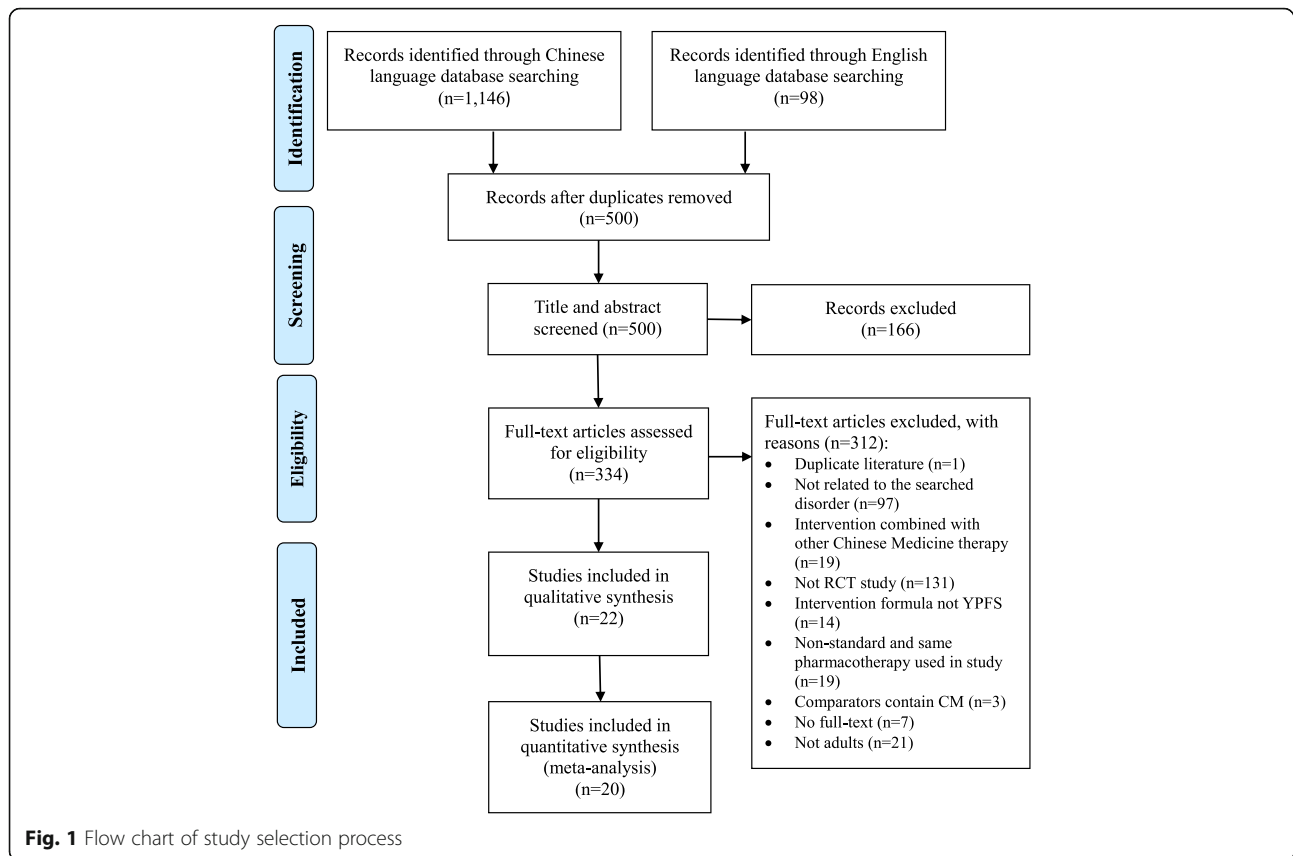
Participants

In total, 2309 participants with AR were involved in the 22 RCTs, 309 participants were diagnosed with perennial allergic rhinitis, and 2000 participants were AR without specified subtype. All participants aged between 18 to 70 years. Of the reported gender information, there were a total of 1153 males and 1098 females. Participants were allocated to the YPFS group ($n = 552$), placebo group ($n = 126$), pharmacotherapy group ($n = 1044$) and the combination of CHM and pharmacotherapy group ($n = 587$). Five studies did not provide information on participants' duration of disease [17, 21, 26, 29, 31], the remaining 17 RCTs reported the duration of disease with a median of 4.5 years.

Interventions

Nine studies employed the original YPFS formula of only three herbs as treatment [16, 21, 24–26, 31, 33–35], the remaining 13 studies used modified YPFS formulas. The dosage and composition of YPFS formulas used in different studies are presented in Table 2. The preparation forms of the CHM were decoctions (10 studies) [17, 18, 20, 22, 23, 27–30, 32], granule (eight studies) [19, 21, 25, 26, 31, 33–35], capsule (one study) [16], pill (one study) [24], and liquid extract (two studies) [14, 15]. In regards to the comparator, two studies compared YPFS to placebo [14, 15], seven studies compared YPFS to pharmacotherapy [16–22], 12 studies compared the combination of YPFS and pharmacotherapy to pharmacotherapy alone [24–35], and one three-arm study [23] contained both pharmacotherapy and YPFS plus pharmacotherapy as controls. In addition, two studies had an arm of a different CHM formula which are not included in our review [14, 15].

Pharmacotherapy being used as comparators were: 1) oral [17–22, 24, 28–30, 34, 35] or intranasal [23, 32, 33] second generation H1-antihistamines, 2) intranasal glucocorticosteroids [26, 31], and 3) the combination of



second generation H1-antihistamines and intranasal glucocorticosteroids [16, 25, 27].

Outcomes

The primary outcome measures of individual nasal symptom scores were reported in four studies [29, 32, 34, 35]. In terms of the secondary outcome measures, effective rate was reported in 20 studies [15–32, 34, 35], with two methods of calculating the effective rate being used as stated in Chinese clinical guidelines [36–39]. Patients' QoL using Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score was assessed by one study [14]. Reported laboratory tests results were serum sIgE [15] and IL-4 [15, 16, 30, 33, 34]. In addition, the recurrence rate in follow-up phase was reported in two studies [18, 20].

Treatment duration and follow-up

All included studies provided treatment of equal duration to the intervention and control groups. The treatment duration was two weeks or fifteen days in eight studies [17, 19–21, 23, 25, 31, 34], four weeks or one month in 12 studies [14, 16, 18, 22, 24, 26–30, 33, 35], three weeks [32] and eight weeks [15] each in one study. Six studies [14, 18, 20, 25, 27, 29] reported a post treatment follow-up phase, being one month [20], eight

weeks [25], three month [14, 27], six months [29] and one year [18].

Dropouts

Three studies reported dropouts during treatment phase with reasons provided [14, 28, 30]. None of the dropouts was due to serious AE. The other 19 studies were considered to have no dropouts since they reported equal numbers of participants at randomization and study completion.

Risk of bias assessment

Eight studies were assessed as “low” risk for “sequence generation” since they used random number “tables” [14, 16, 20, 22, 23, 29, 33, 35], others were “unclear”. For “allocation concealment”, one study was “low” risk because it used a sealed envelope method [14], others were “unclear” due to lack of information. One study employed placebo control and made effort to blind participants, personnel and outcome assessors, thus this study was assessed as “low” risk for these items [14]; the other 21 studies were “high” risk for “blinding of participants and personnel” and “unclear” risk for “blinding of outcome assessors”. All studies were “low” risk for the “incomplete outcome data”, since they were considered having no dropouts

Table 1 Characteristics of included RCTs

First author, publication year, country	Treatment duration, follow-up duration	Duration of AR (mean (SD))	Number of participants of randomized/ assessed	Age (mean (SD) or range in years), gender (M/F)	Intervention (route of administration)	Control (route of administration, dosage)	Adverse events (number of events)
1 YPFS vs placebo							
Chan 2014 [14], Hong Kong China	4 weeks, 3 months	I: >1 year; C: >1 year	I: 83/80; C: 83/79	I: 18–25, 32/48; C: 18–25, 35/44	Modified YPFS (oral)	Placebo (oral, 70 ml each time, once per day)	Increased acne and abdominal distension (4)
Feng 2004 [15], China	8 weeks, NS	I: 10.57 (7.31) years C: 11.31 (8.17) years	I: 43/43; C: 43/43	I: 37.74 (14.57), 22/21; C: 38.17 (14.21), 22/21	Allergic Rhinitis oral liquid (oral)	Saline (oral, 20 ml each time, three times a day)	NS
2 YPFS vs pharmacotherapy							
Fang 2014 [16], China	1 month, NS	I: 3.26 (1.27) years; C: 3.17 (1.12) years	I: 118/118; C: 102/102	I: 35.18 (13.72), 53/65; C: 36.03(12.85), 43/59	<i>Yu ping feng</i> capsule (oral)	Cetirizine Hydrochloride (oral, 10 mg once per day), Budesonide aerosol (nasal spray, twice per day)	No AE
Wang 2014 [17], China	14 days, NS	I: NS; C: NS	I: 30/30; C: 30/30	I: 33 (10.78), 14/16; C: 35 (11.94), 15/15	Modified YPFS (oral)	Cetirizine Hydrochloride (oral, 10 mg once per day)	NS
Luo 2012 [18], China	28 days, 1 year	I: 4.34 (4.29) years C: 4.52 (4.45) years	I: 60/60; C: 60/60	I: 34.64 (11.35), 38/22; C: 35.20 (10.43), 34/26	Modified YPFS (oral)	Cetirizine Hydrochloride (oral, 10 mg once per day)	NS
Wu 2013 [19], China	14 days, 1 year	I: 5 (1–11) years; C: 6 (1–8) years	I: 50/50; C: 50/50	I: 36, 22/28; C: 39, 27/23	<i>Yu ping zhi ti</i> granule (oral)	Loratadine (oral, 10 mg before bedtime)	NS
Wang 2009 [20], China	14 days, 1 month	I: 4.34 (4.29) years; C: 4.52 (4.45) years	I: 30/30; C: 30/30	I: 34.64 (11.35), 19/11; C: 35.2 (10.43), 17/13	Modified YPFS (oral)	Cetirizine Hydrochloride (oral, 10 mg once per day)	NS
Guo 2015 [21], China	15 days, NS	I: NS; C: NS	I: 35/35; C: 35/35	I: 26.5 (6.3), 20/15; C: 32 (4.3), 16/19	<i>Yu ping feng</i> granule (oral)	Cetirizine Hydrochloride (oral, 10 mg once per day)	NS
Yao 2015 [22], China	4 weeks, NS	I: 8.8(3.5) years; C: 8.6 (3.1) years	I: 43/43; C: 40/40	I: 41.8 (5.5), 18/25; C: 40.3 (4.9), 17/23	Modified YPFS (oral)	Cetirizine Hydrochloride (oral, 10 mg before bedtime)	No AE
3 YPFS + pharmacotherapy vs pharmacotherapy							
Shi 2014 [24], China	28 days, No follow up	I: 4.18 (2.82) years; C: 4.67 (2.33) years	I: 44/44; C: 32/32	I: 36.5 (17.5), 23/21 C: 37.5 (16.5), 17/15	<i>Yu ping feng</i> drop pill and Cetirizine (oral)	Cetirizine (oral, 10 mg once per day)	No AE
Lu 2014 [25], China	2 weeks, 8 weeks	I: (1 month–3 years); C: (1 month–2.5 years)	I: 40/40 C: 40/40	I: 40.3 (10.5), 28/12; C: 38.0 (11.2), 27/13	<i>Yu ping feng</i> granule (oral) + Ebastine (oral), Fluticasone propionate (nasal spray, (nasal spray)	Ebastine (oral, 10 mg once per day), Fluticasone propionate (nasal spray, two sprays each nostril, once per day)	No AE
Zhou 2010 [26], China	1 month, NS	I: NS; C: NS	I: 36/36; C: 36/36	I: 45.5, 15/21; C: 43.6, 15/21	<i>Yu ping feng</i> granule (oral) + Budesonide aerosol (nasal spray)	Budesonide aerosol (nasal spray, two sprays each nostril, twice per day)	No AE

Table 1 Characteristics of included RCTs (Continued)

First author, publication year, country	Treatment duration, follow-up duration	Duration of AR (mean (SD))	Number of participants of randomized/ assessed	Age (mean (SD) or range in years), gender (M/F)	Intervention (route of administration)	Control (route of administration, dosage)	Adverse events (number of events)
Huang 2014 [27], China	4 weeks; 3 months	I: 12.7 (3.1) months; C: 11.2 (2.5) months	I: 74/74; C: 71/71	I: 30.3 (3.4), 40/34; C: 31.2 (2.7), 38/33	Modified YPFS (oral) + Cetirizine Hydrochloride (oral); Budesonide aerosol (nasal spray)	Cetirizine Hydrochloride (oral, one spray each nostril, twice per day), Budesonide aerosol (nasal spray, 10 mg once per day)	NS
Liu 2012 [28], China	30 days; NS	I: 4 years; C: 4 years	I: 30/28; C: 30/29	I: 39.25 (5.58), 13/15; C: 39.97 (4.15), 15/14	Modified YPFS + Loratadine (oral)	Loratadine (oral, 10 mg once per day)	No AE
Chen 2014 [29], China	28 days; 6 months	I: NS; C: NS	I: 60/60; C: 60/60	I: NS, NS; C: NS, NS	Modified YPFS + Cetirizine (oral)	Cetirizine (oral, 10 mg once per day)	I: skin rash (2), vomit (1), nausea (2), C: skin rash (5), vomit (4), nausea (3)
Lin 2014 [30], China	30 days; NS	I: 4.25 (1) years; C: 4.28 (1.05) years	I: 30/28; C: 30/29	I: 33.18 (11.42), 16/12; C: 33.89 (9.35), 16/13	Modified YPFS + Cetirizine (oral)	Cetirizine (oral, 10 mg once per day)	No AE
Guan 2013 [31], China	14 days; NS	I: NS; C: NS	I: 27/27; C: 26/26	I: NS, NS; C: NS, NS	YPFS (oral) + Budesonide aerosol (nasal spray)	Budesonide aerosol (nasal spray, 64µg each nostril, twice per day)	I: sedation (1), local mucosa irritation (2); C: local mucosa irritation (2), skin rash (2)
Chen 2015 [32], China	21 days; NS	I: 5.92(4.07) years; C: 6.16(4.39) years	I: 63/63; C: 63/63	I: 35.36 (7.19), 35/28; C: 34.18 (6.82), 33/30	Modified YPFS (oral) + Azelastine (nasal spray);	Azelastine (nasal spray, one spray each nostril, twice per day)	NS
Ma 2017 [33], China	4 weeks; NS	I: 5.1(0.3) years; C: 5.3(0.6) years	I: 37/37; C: 37/37	I: 38.6 (6.9), 21/16; C: 37.9 (6.5), 20/17	Yu ping feng granule (oral) + Azelastine (nasal spray);	Azelastine (nasal spray, one spray each nostril, twice per day)	NS
Qiu 2017 [34], China	2 weeks; NS	I: 7.83(1.35) years; C: 7.68(1.40) years	I: 50/50; C: 50/50	I: 35.41 (7.35), 28/22; C: 36.07 (7.18), 29/21	Yu ping feng granule (oral) + Ebastine (oral);	Ebastine (oral, 10 mg once per day)	NS
Zheng 2017 [35], China	4 weeks; NS	I: 7.7(1.3) years; C: 8.1(1.5) years	I: 36/36; C: 36/36	I: 42.7 (12.3), 18/18; C: 43.1 (11.6), 20/16	Yu ping feng granule (oral) + Levocetirizine (oral);	Levocetirizine (oral, 5 mg once per day)	No AE
4 YPFS + pharmacotherapy vs pharmacotherapy vs YPFS							
Yu 2012 [23], China	14 days; NS	I: 2.7 (0.5) years; C1: 2.8 (0.4) years; C2: 2.5 (0.6) years	I: 60/60; C1: 60/60; C2: 60/60;	I: 32.9 (6.4), 33/27; C1: 34.0 (5.9), 31/29; C2: 33.0 (6.1), 32/28	YPFS plus Cang er zi san (oral)	C1: Azelastine Hydrochloride (nasal spray, one spray each nostril, twice per day); C2: YPFS plus Cang er zi san (oral) + Azelastine Hydrochloride (nasal spray, one spray each nostril, twice per day)	I: no AE; C1 and C2: dryness in the nasal cavity (6)

Note: RCT: randomized controlled trial; YPFS: *yu ping feng san*; M/F: male/female; I: intervention group; C: control group; NS: not stated; SD: standard deviation; AE: adverse event

Table 2 CHM used in all included studies

First author, publication year, country	Name	Form of the CHM	Ingredients (dosage)	Packaging dosage; Dosage and times of administration	Modification
Chan 2014 [14], Hong Kong China	Modified YPFS	Syrup	Huangqi 15 g, baizhu 12 g, fangfeng 3 g, xinyi 3 g, cangerzi (NS), gancao (NS).	NS; 70 ml of syrup once a day	Add xinyi 3 g, cangerzi (NS), gancao (NS).
Feng 2004 [15], China	Allergic Rhinitis oral liquid	Oral liquid	Huangqi (NS), baizhu (NS), fangfeng (NS), guizhi (NS), baishao (NS), dazao (NS), shanyao (NS), fuling (NS), baibandou (NS), xinyi (NS), cangerzi (NS), mudanpi (NS), gancao (NS).	10 ml each bottle; 20 ml each time, three times per day	Add guizhi (NS), baishao (NS), dazao (NS), shanyao (NS), fuling (NS), baibandou (NS), xinyi (NS), cangerzi (NS), mudanpi (NS), gancao (NS).
Fang 2014 [16], China	Yu ping feng capsule	Capsule	Huangqi (NS), baizhu (NS), fangfeng (NS).	0.5 g each capsule, 20 capsules in one box; Two capsules each time, three times per day	None
Wang 2014 [17], China	Modified YPFS	Decoction	Huangqi 10 g, baizhu 10 g, fangfeng 10 g, guizhi 6 g, cangerzi 10 g, xinyi 10 g, baizhi 6 g, wumei 10 g, gancao 6 g.	NS; One dosage for twice per day	Add guizhi 6 g, cangerzi 10 g, xinyi 10 g, baizhi 6 g, wumei 10 g, gancao 6 g.
Luo 2012 [18], China	Modified YPFS	Decoction	Huangqi 20 g, baizhu 15 g, fangfeng 9 g, dangshen 20 g, fuling 15 g, dilong 12 g, wuweizi 12 g, jingjie 9 g, xinyi 9 g, chantui 9 g, ganjiang 6 g, xixin 6 g, gancao 6 g.	NS; One dosage each time, twice per day	Add dangshen 20 g, fuling 15 g, dilong 12 g, wuweizi 12 g, jingjie 9 g, xinyi 9 g, chantui 9 g, ganjiang 6 g, xixin 6 g, gancao 6 g.
Wu 2013 [19], China	Yu ping zhi ti granule	Granule	Huangqi 15 g, baizhu 10 g, fangfeng 10 g, jiangcan 10 g, chantui 9 g, jianghuang 6 g, dahuang 3 g, xinyi 9 g.	One herb granule in one small sized sachet; One sachet each time, twice per day	Add jiangcan 10 g, chantui 9 g, jianghuang 6 g, dahuang 3 g, xinyi 9 g.
Wang 2009 [20], China	Modified YPFS	Decoction	Huangqi 20 g, baizhu 15 g, fangfeng 6 g, bajiji 10 g, jingjie 10 g, xixin 3 g.	NS; One dosage per day	Add bajiji 10 g, jingjie 10 g, xixin 3 g.
Guo 2015 [21], China	Yu ping feng granule	Granule	Huangqi (NS), baizhu (NS), fangfeng (NS).	5 g each sachet; One sachet each time, three times per day	None
Yao 2015 [22], China	Modified YPFS	Decoction	Huangqi 60 g, baizhu 20 g, fangfeng 15 g, cangerzi 10 g, xinyi 10 g, jingjie 15 g, baizhi 15 g, manjingzi 10 g, fuling 20 g, sharen 10 g.	NS; 100 ml each time, twice per day	Add cangerzi 10 g, xinyi 10 g, jingjie 15 g, baizhi 15 g, manjingzi 10 g, fuling 20 g, sharen 10 g.

Table 2 CHM used in all included studies (Continued)

First author, publication year, country	Name	Form of the CHM	Ingredients (dosage)	Packaging dosage; Dosage and times of administration	Modification
Yu 2012 [23], China	YPFS plus <i>Cang er zi san</i>	Decoction	<i>huangqi</i> 30 g, <i>baizhu</i> 10 g, <i>fangfeng</i> 10 g, <i>xixin</i> 9 g, <i>cangerzi</i> 15 g, <i>huangqin</i> 12 g, <i>baizhi</i> 20 g, <i>jingjie</i> 10 g, <i>shichangpu</i> 15g, <i>guizhi</i> 5g.	NS; One dosage each time, three times per day	Add <i>xixin</i> 9 g, <i>cangerzi</i> 15 g, <i>huangqin</i> 12 g, <i>baizhi</i> 20 g, <i>jingjie</i> 10 g, <i>shichangpu</i> 15 g, <i>guizhi</i> 5 g.
Shi 2014 [24], China	<i>Yu ping feng</i> drop pill	Drop pill	<i>Huangqi</i> (NS), <i>baizhu</i> (NS), <i>fangfeng</i> (NS).	2.4 g each sachet; One sachet each time, three times per day	None
Lu 2014 [25], China	<i>Yu ping feng</i> granule	Granule	<i>Huangqi</i> (NS), <i>baizhu</i> (NS), <i>fangfeng</i> (NS).	5 g each sachet; One sachet each time, three times per day	None
Zhou 2010 [26], China	<i>Yu ping feng</i> granule	Granule	<i>Huangqi</i> (NS), <i>baizhu</i> (NS), <i>fangfeng</i> (NS).	5 g each sachet; One sachet each time, three times per day	None
Huang 2014 [27], China	Modified YPFS	Decoction	<i>Huangqi</i> 30 g, <i>baizhu</i> 10 g, <i>fangfeng</i> 10 g, <i>shanyao</i> 15 g, <i>zexie</i> 12 g, <i>zhiqiao</i> 12 g, <i>cheqianzi</i> 12 g, <i>shengma</i> 12 g, <i>cangerzi</i> 10 g, <i>xinyi</i> 10 g, <i>chaihu</i> 10 g, <i>hezi</i> 10 g, <i>dilong</i> 8 g.	NS; One dosage for twice per day	Add <i>shanyao</i> 15 g, <i>zexie</i> 12 g, <i>zhiqiao</i> 12 g, <i>cheqianzi</i> 12 g, <i>shengma</i> 12 g, <i>cangerzi</i> 10 g, <i>xinyi</i> 10 g, <i>chaihu</i> 10 g, <i>hezi</i> 10 g, <i>dilong</i> 8 g.
Liu 2012 [28], China	Modified YPFS	Decoction	<i>Huangqi</i> 30 g, <i>baizhu</i> 12 g, <i>fangfeng</i> 12 g, <i>cangerzi</i> 9 g, <i>xinyi</i> 9 g, <i>baizhi</i> 9 g, <i>zisu</i> 9 g, <i>gancao</i> 6 g.	NS; One dosage each time, twice per day	Add <i>cangerzi</i> 9 g, <i>xinyi</i> 9 g, <i>baizhi</i> 9 g, <i>zisu</i> 9 g, <i>gancao</i> 6 g.
Chen 2014 [29], China	Modified YPFS	Decoction	<i>Huangqi</i> 30 g, <i>baizhu</i> 20 g, <i>fangfeng</i> 12 g, <i>dangshen</i> 20 g, <i>danggui</i> 15 g, <i>xinyi</i> 12 g, <i>gancao</i> 12 g.	NS; 200 ml of one dosage, once per day	Add <i>dangshen</i> 20 g, <i>danggui</i> 15 g, <i>xinyi</i> 12 g, <i>gancao</i> 12g.
Lin 2014 [30], China	Modified YPFS	Decoction	<i>Huangqi</i> 30 g, <i>baizhu</i> 30 g, <i>fangfeng</i> 15 g, <i>baizhi</i> 10 g, <i>xixin</i> 3 g.	NS; One dosage each time, twice per day	Add <i>baizhi</i> 10g, <i>xixin</i> 3 g.
Guan 2013 [31], China	YPFS	Granule	<i>Huangqi</i> (NS), <i>baizhu</i> (NS), <i>fangfeng</i> (NS).	5 g each sachet; One sachet each time, three times per day	None
Chen 2015 [32], China	Modified YPFS	Decoction	<i>Huangqi</i> 30 g, <i>baizhu</i> 15 g, <i>fangfeng</i> 15 g, <i>cangerzi</i> 9 g, <i>baizhi</i> 9 g, <i>gancao</i> 6 g, <i>xixin</i> 3 g, <i>zisu</i> 9 g.	NS; 200 ml each time, twice per day	Add <i>cangerzi</i> 9 g, <i>baizhi</i> 9 g, <i>gancao</i> 6 g, <i>xixin</i> 3 g, <i>zisu</i> 9 g.
Ma 2017 [33], China	<i>Yu ping feng</i> granule	Granule	<i>Huangqi</i> (NS), <i>baizhu</i> (NS), <i>fangfeng</i> (NS).	15 g each sachet; 5 g each time, three times per day	None

Table 2 CHM used in all included studies (Continued)

First author, publication year, country	Name	Form of the CHM	Ingredients (dosage)	Packaging dosage; Dosage and times of administration	Modification
Qiu 2017 [34], China	Yu ping feng granule	Granule	Huangqi (NS), baizhu (NS), fangfeng (NS).	5 g each sachet; 5 g each time, three times per day	None
Zheng 2017 [35], China	Yu ping feng granule	Granule	Huangqi (NS), baizhu (NS), fangfeng (NS).	NS; One sachet each time, three times per day	None

Note: YPFS: *yu ping feng san*; g: gram; ml: milliliters; NS: not stated

[15–27, 29–35], or reported similar number of dropouts from both groups which was unlikely to cause bias [14, 28, 30]. One study reported all outcomes pre-defined in its registered protocol therefore it received a “low” risk for the “selective outcome reporting” [14], others were “unclear”. Due to lacking of information, all studies were “unclear” for “other bias” focusing on the funding resources.

Effectiveness

The effectiveness of YPFS were firstly analysed according to the comparators as follow. All meta-analyses results are summarised in Table 3.

YPFS versus placebo

Two studies compared YPFS with oral placebo [14, 15]. Meta-analysis was not possible because they reported data on different outcomes.

One study reported data on RQLQ, it was found that the post-treatment total RQLQ score of the YPFS group was lower than that of the placebo group ($n = 159$, MD-8.57, 95%CI [-16.37, -0.77]) [14]. Another study reported post-treatment data on effective rate, serum sIgE and IL-4. Significant difference between the YPFS group and the placebo group was found for all these outcomes ($n = 86$, effective rate: RR13.33, 95%CI [4.46, 39.83]; sIgE: MD-16.18, 95%CI [-22.50, -9.86]; IL-4: MD-19.65, 95%CI [-25.32, -13.98]) [15]. However, these results are only from single study, the small sample size and wide confidence interval makes the results unconvincing.

YPFS versus pharmacotherapy

Seven studies compared YPFS to pharmacotherapy [16–22], and one three-arm study also contained this comparison [23]. None of these studies reported nasal symptom scores.

All these studies reported post-treatment data on effective rate, the overall meta-analysis showed that YPFS did not achieve superior effect than overall pharmacotherapy ($n = 833$, RR1.07, 95%CI [0.94, 1.22], $I^2 = 70%$) [16–23]. Subgroup analyses were conducted to further explore the effectiveness of YPFS comparing to different types of pharmacotherapy. It was found that, when comparing YPFS to the second-generation antihistamines, there was no significant difference between two groups for the outcome of effective rate ($n = 613$, RR1.04, 95%CI [0.90, 1.19], $I^2 = 64%$) [17–23]. On the other hand, one study showed that YPFS was more effective than the combination of the second-generation antihistamine and intranasal glucocorticosteroids ($n = 220$, RR1.27, 95%CI [1.10, 1.48]) [16] (Fig. 2).

Subgroup analysis based on treatment duration was also conducted. Results showed that, in terms of the effective rate, there was no significant difference between

the YPFS and pharmacotherapy when it was tested for two weeks ($n = 410$, RR1.04, 95%CI [0.92, 1.18], $I^2 = 6%$) [17, 19–21, 23]; or being tested for more than three weeks ($n = 423$, RR1.08, 95%CI [0.82, 1.42], $I^2 = 90%$) [16, 18, 22] (Fig. 3).

In addition, one study found that YPFS achieved better effect than intranasal glucocorticosteroids for IL-4 ($n = 220$, MD-37.94, 95%CI [-49.47, -26.41]) [16]. Another study reported the recurrence rate at the end of follow-up phase, it was found that the number of recurrence of the YPFS group was less than that of pharmacotherapy (Cetirizine) ($n = 103$, RR0.37, 95%CI [0.18, 0.78]) [18].

YPFS plus pharmacotherapy versus pharmacotherapy

Twelve studies compared the combination of YPFS and pharmacotherapy to pharmacotherapy alone [24–35], and one three-arm study also contained this comparison [23].

For the primary outcome measure, four studies using second-generation antihistamines as control reported data on individual symptoms scores [29, 32, 34, 35]. It was found that the combined intervention was more effective than second-generation antihistamines alone for four nasal symptoms: itchy nose ($n = 418$, MD-0.46, 95%CI [-0.50, -0.42], $I^2 = 0%$), sneezing ($n = 418$, MD-0.41, 95%CI [-0.47, -0.35], $I^2 = 54%$), blocked nose ($n = 418$, MD-0.46, 95%CI [-0.54, -0.39], $I^2 = 60%$) [29, 32, 34, 35] and runny nose ($n = 318$, MD-0.42, 95%CI [-0.58, -0.26], $I^2 = 70%$) [29, 32, 35].

Meta-analysis was also feasible for the outcome of effective rate. Of these 1 comparisons, meta-analysis showed that the combination was more effective than pharmacotherapy alone ($n = 1077$, RR1.27, 95%CI [1.19, 1.34], $I^2 = 22%$) [23–32, 34, 35]. Subgroup analysis on effective rate was conducted according to the pharmacotherapy used in the control groups. The results showed that the combination was more effective than different types pharmacotherapy as follow: the combination versus second-generation antihistamines ($n = 727$, RR1.28, 95%CI [1.19, 1.37], $I^2 = 43%$) [23, 24, 28–30, 32, 34, 35] and the combination versus the second-generation antihistamine plus intranasal glucocorticosteroids ($n = 225$, RR1.29, 95%CI [1.14, 1.46], $I^2 = 0%$) [25, 27]. However, the combined intervention was not superior to intranasal glucocorticosteroids alone ($n = 125$, RR1.15, 95%CI [0.97, 1.36], $I^2 = 0%$) [26, 31]. (Fig. 4).

Subgroup analysis for effective rate was performed based on the treatment duration [23–31, 34, 35]. Superior effects towards the combination therapy was found when it was tested for more than three weeks, ($n = 725$, RR1.15, 95%CI [1.01, 1.32], $I^2 = 74%$) [24, 26–30, 32, 35], but it was not found in the subgroup of two weeks treatment ($n = 353$, RR1.13, 95%CI [0.84, 1.54], $I^2 = 88%$) [23, 25, 31, 34] (Fig. 5).

Table 3 Summary of meta-analyses results

Intervention vs control	Overall analysis or subgroup analysis	Subgroup details	Outcome measure	Number of studies	References	Number of participants	Results	I ²
YPFS vs Pharmacotherapy	Overall	N/A	Effective rate	8	[16–23]	833	RR1.07, 95%CI [0.94, 1.22]	70%
YPFS vs Pharmacotherapy	Subgroup analysis (Pharmacotherapy)	Second-generation antihistamines	Effective rate	7	[17–23]	613	RR1.04, 95%CI [0.90, 1.19]	64%
YPFS vs Pharmacotherapy	Subgroup analysis (treatment duration)	Two weeks	Effective rate	5	[17, 19–21, 23]	410	RR1.04, 95%CI [0.92, 1.18]	6%
YPFS vs Pharmacotherapy	Subgroup analysis (treatment duration)	Three weeks or more	Effective rate	3	[16, 18, 22]	423	RR1.08, 95%CI [0.82, 1.42]	90%
YPFS plus pharmacotherapy versus pharmacotherapy	Overall	Second-generation antihistamines	Itchy nose	4	[29, 32, 34, 35]	418	MD-0.46, 95%CI [-0.50, -0.42]*	0
YPFS plus pharmacotherapy versus pharmacotherapy	Overall	Second-generation antihistamines	Sneezing	4	[29, 32, 34, 35]	418	MD-0.41, 95%CI [-0.47, -0.35]*	54%
YPFS plus pharmacotherapy versus pharmacotherapy	Overall	Second-generation antihistamines	Blocked nose	4	[29, 32, 34, 35]	418	MD-0.46, 95%CI [-0.54, -0.39]*	60%
YPFS plus pharmacotherapy versus pharmacotherapy	Overall	Second-generation antihistamines	Runny nose	3	[29, 32, 35]	318	MD-0.42, 95%CI [-0.58, -0.26]*	70%
YPFS plus pharmacotherapy versus pharmacotherapy	Overall	N/A	Effective rate	12	[23–32, 34, 35]	1077	RR1.27, 95%CI [1.19, 1.34]*	22%
YPFS plus pharmacotherapy versus pharmacotherapy	Subgroup analysis (Pharmacotherapy)	Second-generation antihistamines	Effective rate	8	[23, 24, 28–30, 32, 34, 35]	727	RR1.28, 95%CI [1.19, 1.37]*	43%
YPFS plus pharmacotherapy versus pharmacotherapy	Subgroup analysis (Pharmacotherapy)	Second-generation antihistamine + intranasal glucocorticosteroids	Effective rate	2	[25, 27]	225	RR1.29, 95%CI [1.14, 1.46]*	0
YPFS plus pharmacotherapy versus pharmacotherapy	Subgroup analysis (Pharmacotherapy)	Intranasal glucocorticosteroids	Effective rate	2	[26, 31]	125	RR1.15, 95%CI [0.97, 1.36]	0
YPFS plus pharmacotherapy versus pharmacotherapy	Subgroup analysis (treatment duration)	Two weeks	Effective rate	4	[23, 25, 31, 34]	353	RR1.13, 95%CI [0.84, 1.54]	88%
YPFS plus pharmacotherapy versus pharmacotherapy	Subgroup analysis (treatment duration)	Three weeks or more	Effective rate	8	[24, 26–30, 32, 35]	725	RR1.15, 95%CI [1.01, 1.32]*	74%

Note: YPFS; *yu ping feng san*; RR: risk ratio; MD: mean difference; CI: Confidence interval. *: significant difference between two groups was detected

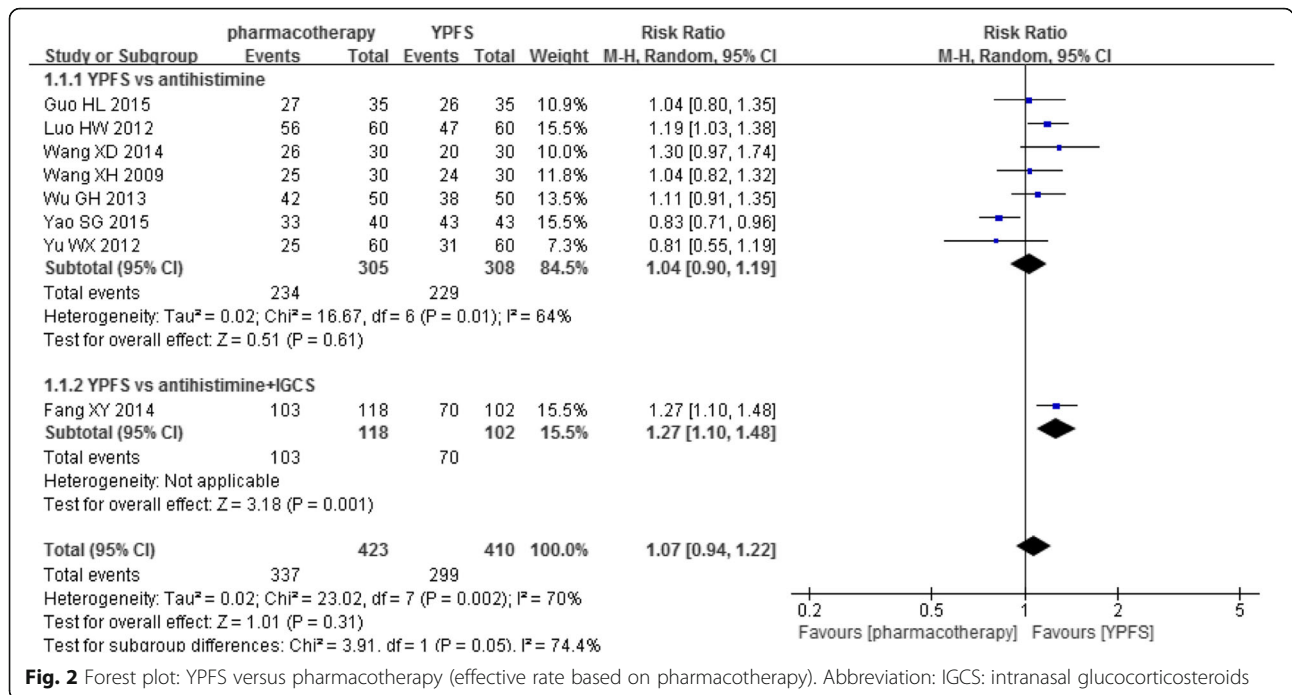


Fig. 2 Forest plot: YPFS versus pharmacotherapy (effective rate based on pharmacotherapy). Abbreviation: IGCS: intranasal glucocorticosteroids

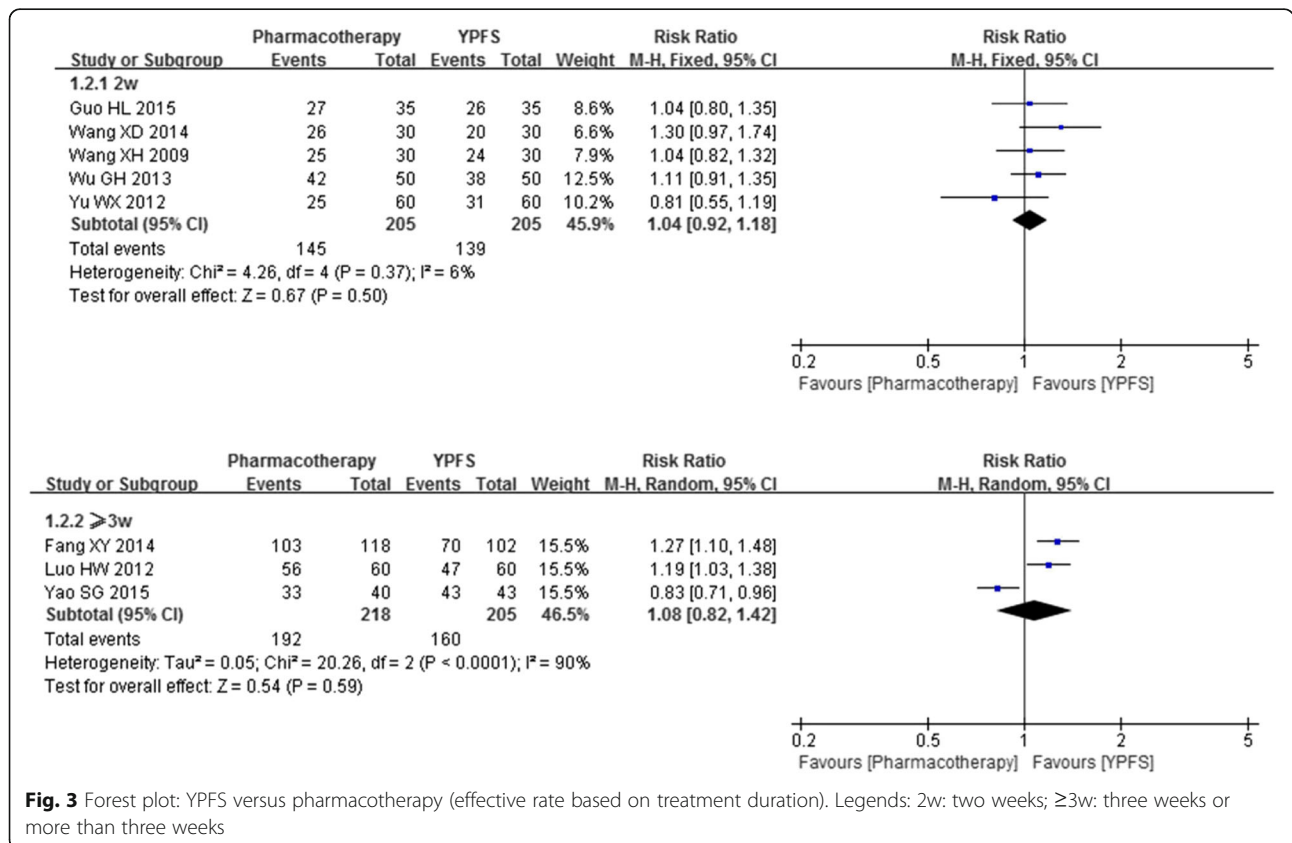


Fig. 3 Forest plot: YPFS versus pharmacotherapy (effective rate based on treatment duration). Legends: 2w: two weeks; ≥3w: three weeks or more than three weeks

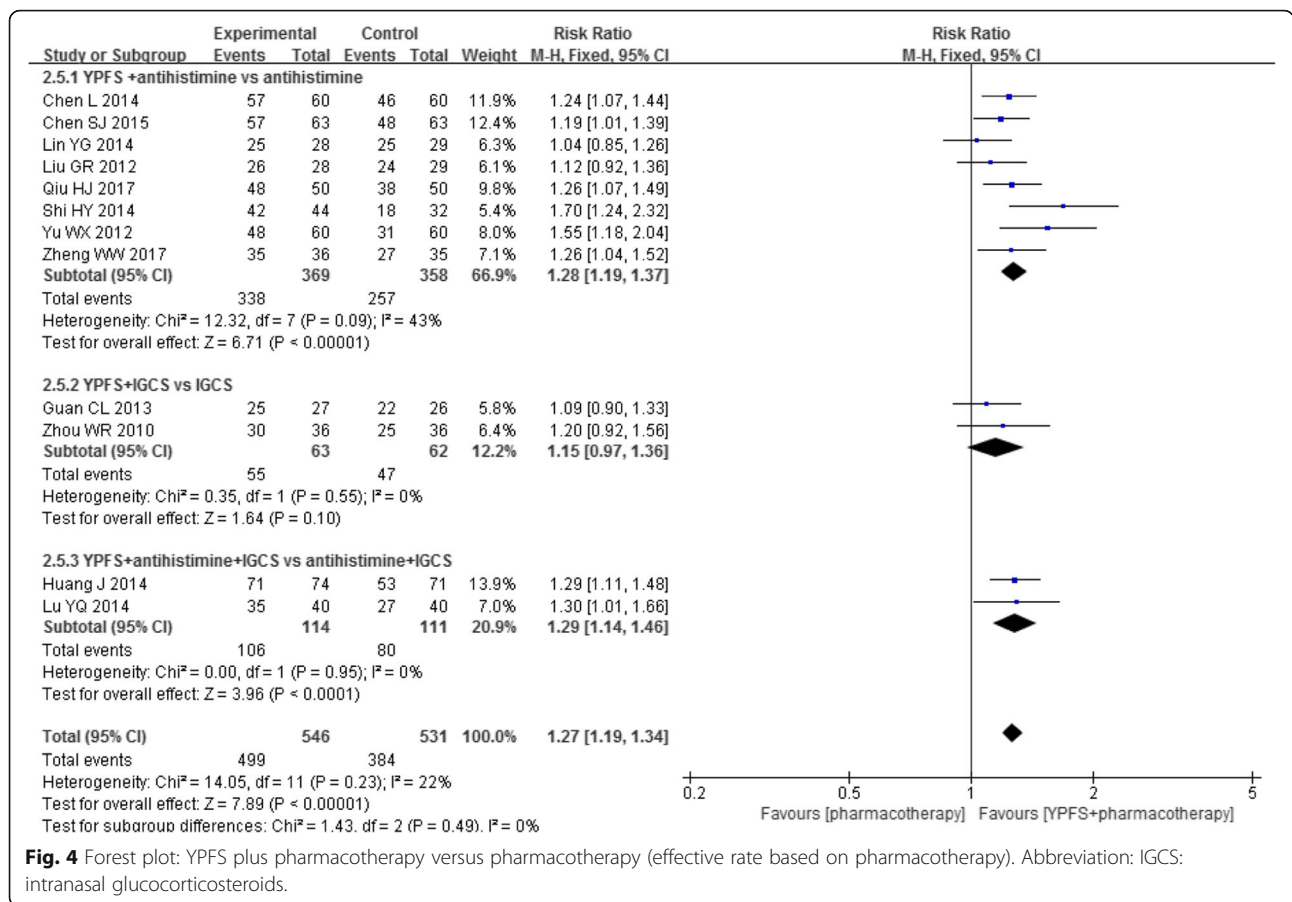


Fig. 4 Forest plot: YPFS plus pharmacotherapy versus pharmacotherapy (effective rate based on pharmacotherapy). Abbreviation: IGCS: intranasal glucocorticosteroids.

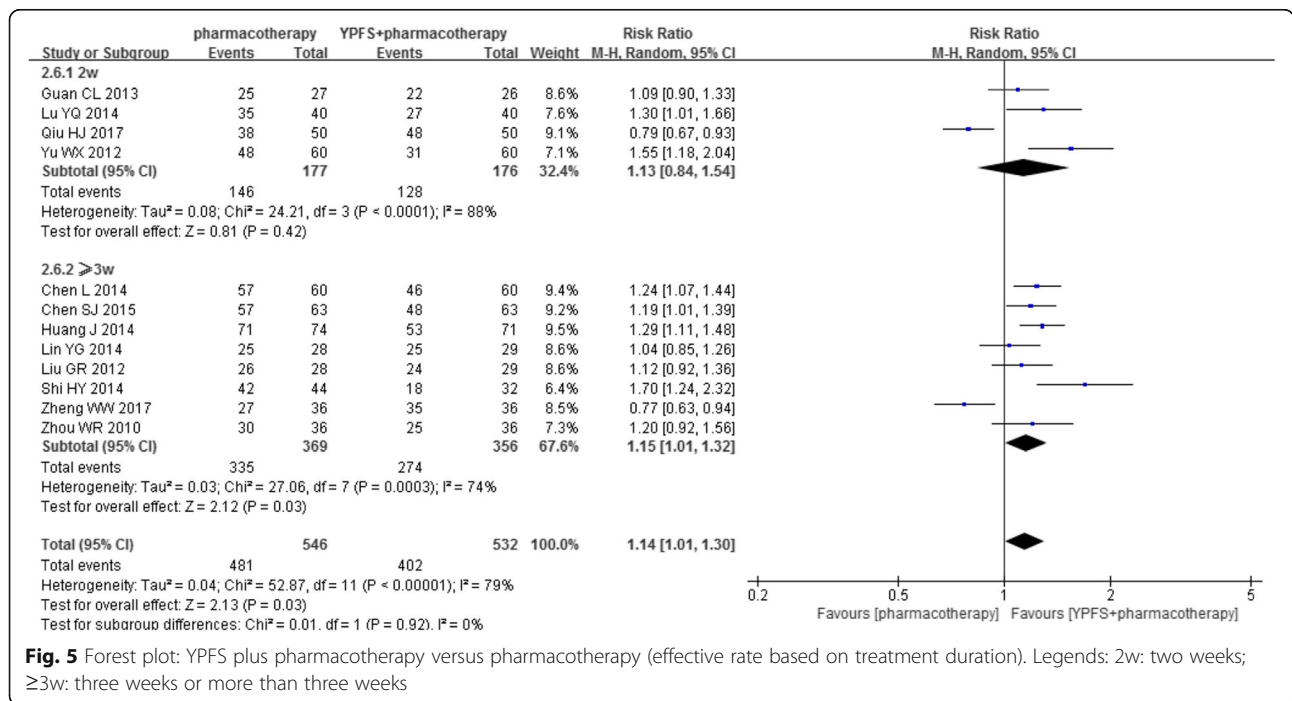


Fig. 5 Forest plot: YPFS plus pharmacotherapy versus pharmacotherapy (effective rate based on treatment duration). Legends: 2w: two weeks; ≥3w: three weeks or more than three weeks

In addition, biomarker IL-4 was reported by three studies and it showed that the YPFS and second-generation antihistamines combination treatment were superior to second-generation antihistamines alone ($n = 231$, MD-14.43, 95%CI [-28.58, -0.29]) [30, 33, 34].

Safety

Ten studies did not report information on AEs [15, 17–21, 27, 32–34]. Eight studies reported there was no AE occurred in both groups [16, 22, 24–26, 28, 30, 35]. The remaining four studies reported AEs in treatment group [14, 23, 29, 31], and control groups [23, 29, 31] during the treatment phase. According to these studies, the AEs possibly associated with the use of YPFS were acne and abdominal distension [14]; while the AEs possibly caused by pharmacotherapy included dryness in the nasal cavity [23], local mucosa irritation [31], sedation [31], skin rash [29, 31], vomit and nausea [29]. All above AEs were transient and no medical intervention was required. Serious AE was not reported by any study. It was worth noting that the number of AEs occurred in the combination group was less than that of the pharmacotherapy group. For example, one study reported five cases of AEs in the combination group and 12 cases in the pharmacotherapy group [29], and another study reported three cases of AEs in the combination group and four cases in the pharmacotherapy group [31]. These studies concluded that adding YPFS to pharmacotherapy is safe and it may be beneficial for reducing the AEs caused by pharmacotherapy. All detailed information of AEs is provided in Table 1.

Publication bias

The publication bias could not be assessed for the comparison of YPFS versus pharmacotherapy since there were not enough studies included in one meta-analysis. For the comparison of YPFS plus pharmacotherapy vs. pharmacotherapy alone, there were 12 trials in the meta-analysis of effective rate. No publication bias was detected based on the funnel plot (Fig. 6) and the Egger’s test ($t = 1.30$, 95% CI [-1.26, 4.79], $p = 0.223$).

GRADE for the main comparisons of YPFS

GRADE assessment was conducted for two main comparisons. The quality of evidence was low. Table 4 summarises the results.

Discussion

This systematic review evaluated RCTs of CHM YPFS including the most recently published articles. Studies compared CHM YPFS to placebo or pharmacotherapy, and those used YPFS as add-on therapy were all included in our evaluation. The evidence of YPFS effectiveness has been revealed through meta-analyses.

Effectiveness and safety of YPFS

In this review, meta-analyses were feasible for the outcomes of four individual nasal symptom scores and “effective rate”. Based on these outcomes, it was found that: 1) in terms of the nasal symptoms, adding YPFS to the second-generation antihistamines achieved better treatment effects (low quality evidence); 2) for “effective rate”, although YPFS was not superior to

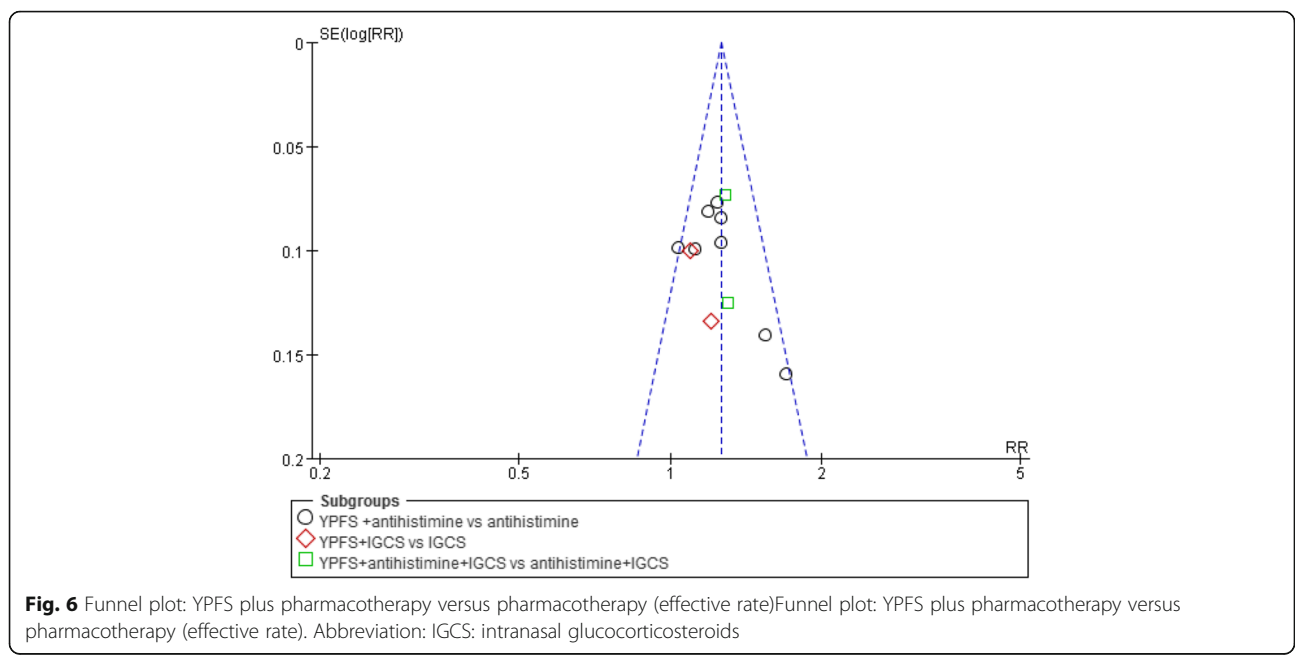


Table 4 Summary of GRADE

Quality assessment		Effect										Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Relative (95% CI)	Absolute (95% CI)	Quality	Importance	
							YPFS or its combi-nation	therapy					
Effective rate: YPFS vs Antihistamine for Adult Allergic Rhinitis													
7 [17–23]	Randomized trials	serious ^a	serious ^b	not serious	not serious	none	229/308 (74.4%)	234/305 (76.7%)	RR 1.04 (0.90 to 1.19)	29 more per 1000 (from 75 fewer to 141 more)	⊕⊕⊕⊕ LOW	NOT IMPORTANT	
Score of Itchy nose: YPFS + Antihistamine vs Antihistamine for Adult Allergic Rhinitis													
4 [29, 32,34,35]	Randomized trials	serious ^a	not serious	not serious	serious ^c	none	209	209	MD -0.46 (-0.50 to -0.42)	0.46 fewer (0.5 fewer to 0.42 fewer)	⊕⊕⊕⊕ LOW	IMPORTANT	
Score of sneezing: YPFS + Antihistamine vs Antihistamine for Adult Allergic Rhinitis													
4 [29,32,34, 35]	Randomized trials	serious ^a	serious ^b	not serious	not serious	none	209	209	MD -0.41 (-0.47 to -0.35)	0.41 fewer (0.47 fewer to 0.35 fewer)	⊕⊕⊕⊕ LOW	IMPORTANT	
Score of blocked nose: YPFS +Antihistamine vs Antihistamine for Adult Allergic Rhinitis													
4 [29, 32,34,35]	Randomized trials	serious ^a	serious ^b	not serious	not serious	none	209	209	MD -0.46 (-0.54 to -0.39)	0.46 fewer (0.54 fewer to 0.39 fewer)	⊕⊕⊕⊕ LOW	IMPORTANT	
Score of runny nose: YPFS +Antihistamine vs Antihistamine for Adult Allergic Rhinitis													
3 [29, 32, 35]	Randomized trials	serious ^a	serious ^b	not serious	not serious	none	209	209	MD -0.42 (-0.58 to -0.26)	0.42 fewer (0.58 fewer to 0.26 fewer)	⊕⊕⊕⊕ LOW	IMPORTANT	
Effective rate: YPFS +Antihistamine vs Antihistamine for Adult Allergic Rhinitis													
8 [23,24, 28–30,32, 34,35]	Randomized trials	serious ^a	not serious	not serious	not serious	none	338/369 (91.6%)	257/358 (71.8%)	RR 1.28 (1.19 to 1.37)	201 more per 1000 (from 136 more to 265 more)	⊕⊕⊕⊕ LOW	NOT IMPORTANT	

Abbreviations: YPFS *Yu ping feng san*, CI confidence interval, RR risk ratio, MD mean difference

Note: ^aLacking of blinding, randomisation and allocation concealment are unclear. ^bSubstantial heterogeneity. ^cSmall sample size

pharmacotherapy, adding YPFS to common pharmacotherapy was also more effective than using pharmacotherapy alone. Further, subgroup analysis showed that there was no significant difference between YPFS and the second-generation antihistamine in terms of “effective rate” (low quality evidence).

In order to provide evidence for the duration of clinical administration, subgroup analysis regarding the treatment duration was conducted. Our results showed that adding YPFS to pharmacotherapy was beneficial when it was administered for more than three weeks, but this was not seen in the studies of only two weeks treatment. It is worth noting that, there has been experimental research evidence showing that six days’ high and middle dosages of YPFS powder significantly increased the IFN- γ , the antibody of infectious laryngotracheitis and the immune organ indexes, and also reduced IL-4 in chickens [40]. One study reported that 14 days of oral YPFS could stimulate immune responses in allergic rhinitis mice [41]. Another study reported that after five to seven days intervention, different concentration of the glucosidic which extracted from YPFS produced anti-inflammatory and immune-regulatory effects [42]. These experimental studies indicated that YPFS alone may show immune-modulatory and anti-inflammatory effects after one to two weeks. In clinical management of AR, pharmacotherapies usually are fast-acting for symptom control but leaving 10% to 20% AR patients to endure bothersome symptoms [43, 44]. Our results suggest that, although YPFS is not superior to pharmacotherapy, adding CHM YPFS to common pharmacotherapy for at least three weeks is helpful to improve the overall symptoms. Since YPFS has been recommended as AR management by current Chinese Medicine clinical practice guideline [9], but without recommendation on the treatment duration, our results may potentially have filled this gap and provide indication for further clinical practice. Nevertheless, these finding was only based on the outcome of “effective rate” since there were not enough data on nasal symptoms scores supporting these analyses. Further studies using globally well-accepted outcome measures to assess the treatment effects at different time points are needed to confirm such findings.

Reported AEs caused by YPFS were mild and transient. It was also reported that adding YPFS could reduce the number of AEs caused by cetirizine [29] or budesonide aerosol [31], though detailed explanation was not provided by these studies. Similar findings were reported by other clinical trials of YPFS for AR management [45, 46] but without further exploration of the mechanisms. It is worth noting that some toxicity tests of YPFS also suggested that its toxicity is either minor or without any adverse effects [47, 48].

Potential mechanisms of YPFS

Results from experimental studies showed that YPFS reduced the eosinophilic cells’ infiltration and degranulation reaction, decreased the tissue edema [49, 50], and reduced the immune factors including histamine, IgE, IL-4 and tumor necrosis factor- α (TNF- α) in serum [50]. Other researches indicated that YPFS was effective for AR through down-regulating the activity of IL-6 and TNF- α [51], activating interleukin 3 (IL-3), growth factor of mast cells, and inhibiting granulocyte colony stimulating factor (GM-SCF) and an inhibitory factor of mast cells proliferation [52]. IL-4 is one of the important Th2 cytokines related to AR, it can accelerate the synthesis of B cell and secrete a large number of IgE [7]. The result from five included studies in this review illustrated that the IL-4 level decreased after YPFS or its combination treatments [15, 16, 30, 33, 34], and one of these studies also reported the sIgE level declined after YPFS treatment [15]. Furthermore, a review article [53] suggested that YPFS may lead to immunoregulatory effects through the following pathways: 1), to promote the generation of IgA and IgG, the peripheral blood levels of CD3⁺, CD4⁺ and CD4⁺/CD8⁺; 2), to increase the amount of C3, C4 and the receptor of C3b, and activate the complement system involved in immune response; 3), to protect the phagocytosis of macrophage; and 4) to regulate the cyclic adenosine monophosphate (cAMP) in the cells of mice spleen bi-directionally.

There has been evidence showing that glucosides were the principal active ingredients of YPFS which are related to the anti-inflammatory and immunoregulatory effects [42], and claycosin and formononetin may be the effective compounds which could produce the anti-inflammatory function by reducing thymic stromal lymphopoietin production via regulating Nuclear factor (NF)- κ B activation [54].

Furthermore, the three chief herbs of YPFS (*huang qi*, *fang feng*, *bai zhu*) have also been researched previously. Studies found that these herbs may have certain anti-allergy and anti-inflammatory effects [55–58]. For instance, in mice with allergen-induced airway hypersensitivity, *huang qi* injection suppressed the allergic reaction, enhanced interferon-gamma levels (important immune responsive cytokine) and decreased allergen-induced elevations of important allergy related interleukins IL-5 and IL-13 [53]. Aqueous extracts of *huang qi* inhibited nitric oxide production in lipopolysaccharide -stimulated murine macrophage RAW 264.7 cells in a dose-dependent manner and this may be associated with the inhibition of inducible nitric oxide synthase mRNA expression [56]. In RAW 264.7 cells, *fang feng* compound anomalin reduced several pro-inflammatory cytokines, including tumor necrosis factor- α and IL-6, by inhibiting NF- κ B DNA binding [57]. Five *bai zhu* compounds

(atractylenolide III 1, atractylenolide I 2, 14-acetoxy-12-seneciolyxotetradeca-2E,8E,10E-trien-4,6-diy-1-ol 3, 14-acetoxy-12-alpha-methylbutyl-2E,8E,10E-trien-4,6-diy-1-ol 4 and 14-acetoxy-12-beta-methylbutyl-2E,8E,10E-trien-4,6-diy-1-ol 5) significantly inhibited mice ear edema induced by xylene, showing anti-inflammatory activities [58].

In brief, there has been certain pre-clinical evidence supporting the use of YPFS for AR management due to its anti-inflammatory and immunoregulatory function. More details about its mechanism and the active compounds of YPFS are yet to be explored.

Limitations of the included studies

Proper randomization and allocation is essential to reduce selection bias for randomized controlled trials. However, in our systematic reviews, only 36.4% of the included studies (eight trials) applied appropriate methods for sequence generation, and only 4.5% (one trial) for allocation concealment. Blinding of participants, personnel and outcome measures was only achieved by one study, while other studies did not utilize proper placebo control to ensure blinding, and therefore they were not free of performance bias or detection bias.

In regards to the outcome measures, it was found the individual nasal symptom scores was reported by four studies but without TNSS being reported, and QoL was only reported by one study, while the “effective rate” was reported by the majority of the included studies. The “effective rate” assesses the proportion of participants who had achieved certain improvement of the nasal symptoms and signs. Considering that this outcome measure only reflects the overall improvement, it makes it indirect to compare the effectiveness results of these studies to other RCTs which reported data on nasal symptom scores and QoL, even though this outcome measure was recommended by several previous clinical guidelines [36–39, 59] and had been widely used in China.

Considering AR is a chronic and recurrent condition, the long-term effects or the recurrence rate after treatment is of clinicians’ interests. Two included studies reported data on the recurrence rate in follow-up phase [18, 20]. However, there is no clear definition of “recurrence” stated by these studies. Further studies should consider using the internationally well-accepted outcome measures to evaluate the long-term treatment effects of YPFS, for example, the nasal symptom scores and QoL.

In terms of clinical trial reporting, none of the included study reported all items recommended by CONSORT 2010 and its Extension for Herbal Intervention [60, 61]. Also, in the absent of trial registration information or published protocol of the included studies, evaluation of selective reporting bias was not applicable in all of the included studies.

All these limitations reduced the certainty of our results. Future research should take all these aspects into consideration and improve the methodological quality of clinical trials’ design and conduct.

Strengths and limitations of this review

The review synthesised the most recent clinical research following rigorous methodology recommended by the Cochrane Handbook, with GRADE approach being used to assess the quality of evidence. This review focused on YPFS treating adult AR, it not only included studies comparing YPFS to placebo or pharmacotherapy, but also evaluated the add-on effects of YPFS to pharmacotherapy. Outcome measures included symptoms scores, QoL, effective rate, recurrence rate, as well as objective outcomes such as serum sIgE and IL-4.

However, a few limitations downgraded the certainty of our results, they are: 1). The majority of included studies (21 out of 22) were all conducted in China and published in Chinese. 2). outcome measures in most included studies were not consistent with international guidelines. This leads to indirectness when interpreting the findings; 3). the overall methodological quality of included studies was low; 4). the long-term effects of YPFS were uncertain due to the lack of follow-up phase of most studies.

Implication for clinical practice and further research

The results of this review suggest that YPFS is effective for the management of adult AR as an add-on therapy. Clinical practice could consider adding oral YPFS to routine pharmacotherapy management and it may improve the effectiveness and safety of routine pharmacotherapy. A correlation of treatment duration and effects of YPFS was observed in this review, however, it requires further exploration. The mechanism of YPFS herbs and their active compounds are also worth more investigation.

Nevertheless, although YPFS in general is effective regarding individual nasal symptoms and the overall “effective rate”, but there is insufficient data supporting the effectiveness towards TNSS and QoL. Further research should consider employing outcome measures recommended by international guidelines (nasal symptom scores and QoL) to evaluate the effectiveness of YPFS. A follow-up phase with well-accepted outcome measures is also important to confirm the long-term effects of YPFS. Lack of blinding is the major methodological flaw of most included studies in this review, further research should consider adapting placebo control and making efforts to the blinding of participants and outcome assessors.

In addition, although it was seen that adding YPFS to pharmacotherapy may reduce the common AEs caused by pharmacotherapy, the mechanism of such herb-drug

interaction is unknown. This may be worth exploring for future research to provide evidence of the safety aspect.

Conclusion

Oral CHM YPFS seems to have add-on effects to pharmacotherapy for the treatment of adult AR, when it was administered for at least three weeks. Further, the use of YPFS in clinical practice is safe. Also, there has been available pre-clinical evidence supporting the use of YPFS and the three chief herbs for AR. However, the overall methodological quality of included studies was low. More RCTs following rigorous methodology and using internationally well-accepted outcome measures are needed to further define the effectiveness of YPFS.

Additional files

Additional file 1: PRISMA 2009 checklist. (DOC 66 kb)

Additional file 2: Search Strategies. (DOCX 18 kb)

Abbreviations

AE: Adverse event; AR: Allergic rhinitis; CHM: Chinese herbal medicine; CI: Confidence intervals; G-CSF: Granulocyte colony stimulating factor; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IL-3: Interleukin 3; IL-4: Interleukin 4; MD: Mean difference; QoL: Quality of life; RCT: Randomized controlled trial; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; RR: Risk ratio; sIgE: Specific immunoglobulin E; SOF: Summary of Findings; TNF- α : Tumor necrosis factor- α ; TNSS: Total nasal symptom score; YPFS: *Yu ping feng san*

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Availability of data and materials

All data supporting the conclusions of this article are included in this published article.

Authors' contributions

CX and CL initiated the research. QL, CZ and LY conducted the database search, study screening, data extraction and data analyses. AZ and XG were involved in data analysis, interpretation and resolving disagreements. QL and CZ drafted the manuscript. All co-authors provided critical comments on the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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