



## Review article

# The combined application of ear acupuncture in the treatment of allergic rhinitis: A meta-analysis

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## ABSTRACT

**Objective:** Meta-analysis was used to evaluate the clinical efficacy of auricular acupressure in the treatment of allergic rhinitis.

**Methods:** Randomised controlled trials (RCTs) on the treatment of allergic rhinitis with ear acupuncture were searched by computer in PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Database (Wanfang), VIP database, and China Biomedical Literature Service System (CBM). The search time was from the establishment of the database to September 18, 2022. Meta-analysis was performed using RevMan 5.4 software.

**Results:** A total of 15 papers with 1002 patients were included in the final study. ①Clinical efficiency: The clinical efficiency of ear acupuncture combined with control group was higher than that of control group, and the difference was statistically significant ( $P < 0.00001$ ); ② Nasal symptom score: the effect of ear acupuncture combined with control group on allergic rhinitis on nasal symptoms was more obvious than that of control group, and the difference was statistically significant ( $P = 0.004$ ); ③ Nasal itching symptom score: the efficacy of ear acupuncture combined with control group on allergic rhinitis on nasal itching symptom was significantly higher than that of control group, and the difference was statistically significant ( $P = 0.01$ ). ④Sneeze symptom score: the effect of ear acupuncture combined with control group on allergic rhinitis on nasal itching symptom was more effective than that of control group, and the difference was statistically significant ( $P < 0.00001$ ); ⑤Score of runny nose symptom: the effect of ear acupuncture combined with control group on allergic rhinitis on runny nose symptom was more obvious than that of control group, the difference was statistically significant ( $P = 0.004$ ); ⑥Nasal congestion symptom scores: The effect of ear acupuncture combined with control group on allergic rhinitis on nasal congestion symptom was more obvious than that of control group, and the difference was statistically significant ( $P = 0.003$ ). Conclusion: Ear acupuncture as an adjunctive therapy of allergic rhinitis can achieve better clinical efficacy.

Allergic rhinitis (AR) is characterized by symptoms of sneezing, runny nose, nasal obstruction, and pruritus caused by inhaled allergens and involving mucosal inflammation. AR is a disease with high prevalence all over the world and therefore should be examined thoroughly and treated appropriately [1]. Allergic rhinitis belongs to the category of “Biqiu” in Chinese medicine, also

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known as “Biti”, “Qiupen”, “Qiuti”, etc. The current treatment principle of allergic rhinitis is “combining prevention and treatment, four-in-one”, including environmental control, drug treatment, immunotherapy and health education. The common first-line therapeutic drugs for AR include nasal glucocorticoids, second-generation oral and nasal antihistamines, and oral leukotriene receptor antagonists. Although they can better control patients’ nasal symptoms, they are prone to trigger adverse reactions such as nasal burning sensation, dryness, stinging, and rhinorrhoea. Ear acupuncture (EAP) as a safe external treatment of Chinese medicine or can be used as an adjunctive therapy to reduce the use of drugs and reduce the chance of adverse reactions [2,3,19]. There is some literature on the efficacy of using ear acupuncture as an adjunctive method to treat AR, but there is still a lack of systematic analysis in this area. In this study, Meta-analysis was used to compare the efficacy of the combined application of EAP in the treatment of AR, and is reported below.

## 1. Introduction

### 1.1. Literature search

Both English (PubMed, Corhrane Library, Embase, Web of Science), and Chinese databases (Chinese National Knowledge Infrastructure, Wanfang Database, VIP Database, China Biomedical Literature Service) were used for Literature search to collect papers (including unpublished data such as dissertations) published from the establishment of these databases. To September 18, 2022. The full text was obtained by hand search for those who could not access the full text. The literature search was conducted within the scope of topics, abstracts and keywords, with a combination of subject terms and free words. English search terms included “Acupuncture, Ear”, “Auriculotherapy”, “Ear acupressure”, “Rhinitis, Allergic”, “Rhinitis, Allergic, Seasonal”, “Rhinitis, Allergic”, “Perennial”, etc.; qualifiers include randomised controlled trials (RCTs), etc. Chinese search terms included “鼻鼾”, “变应性鼻炎”, “过敏性鼻炎”, “鼾嚏”, “鼾嚏”, “耳穴压豆”, “耳穴压丸”, “耳穴按压”, “耳压”, “耳豆”, etc.

### 1.2. Inclusion criteria

- (1) Study type: RCT literature. (2) Study subjects: patients with AR, meeting the diagnostic criteria for AR in the “Guidelines for the diagnosis and treatment of allergic rhinitis (2015 - Tianjin)” [18] or “Guidelines for the diagnosis and treatment of allergic rhinitis (2009-Wuyishan)” [17]. The specific diagnosis is based on: ① Symptoms: Paroxysmal sneezing and clear watery discharge, Nasal itching and nasal congestion, etc., and the symptoms persist for more than 1 h per day or cumulatively. or accumulated for more than 1 h per day, may be accompanied by eye symptoms such as tearing, itchy eyes and red eyes. ② signs: common nasal mucosa pallor, edema, nasal watery discharge. ③ Allergen test: at least 1 allergen SPT and/or blood specific IgE positive, or positive nasal excitation test. (3) Interventions: The control group used non-EAP method to treat AR, the treatment group combined with EAP method on the basis of the control group, and other treatments were kept consistent. (4) Outcome indicators: include at least one of efficiency rate and symptom score.

### 1.3. Exclusion criteria

- (1) Non-RCTs, e.g. reviews, conferences, theoretical discussions, etc. (One conference was included because the data of which were complete and reasonable); (2) Studies from which data could not be extracted; (3) For duplicates include one of higher quality.

### 1.4. Literature screening and Data extraction

Literature screening was conducted independently by two investigators based on inclusion and exclusion criteria, with final cross-checking of inclusion results, and where there was disagreement, a third researcher to help adjudicate. Data extraction included first author, time of publication, information about the risk of bias assessment, sample size, age, interventions, duration of treatment, follow-up, and outcome indicators.

### 1.5. Literature quality assessment

The included studies were independently assessed according to the RCT risk of bias assessment tool recommended by the Cochrane Handbook, which included seven aspects of the literature: random sequence generation, allocation concealment, implementation of blinding of subjects and trial personnel, completeness of data, whether results were selectively reported, and whether there were other biases, and the quality of the literature was evaluated using RevMan 5.4 software.

### 1.6. Statistical processing

Meta-analysis was performed using RevMan 5.4 software, with effect sizes expressed as Risk Ratio (RR) and 95 % confidence interval (CI) for dichotomous variables and weighted mean difference (WMD) and 95 % CI for continuous variables. Statistical heterogeneity was analysed using the  $I^2$  index; if  $I^2 < 50$  %, heterogeneity was not significant and a fixed-effects model (FE) was selected; if  $I^2 \geq 50$  %, heterogeneity was significant and a random-effects model (RE) was selected. The combined statistic was considered statistically significant at  $P < 0.05$ . All effect sizes are expressed as 95 % CI.

## 2. Outcome

The results of the literature search yielded 758 documents, of which 730 were in Chinese, 28 were in English. After eliminating duplicates, time exclusion, and re-reading of titles and abstracts, 30 articles remained, which were further screened by reading the original texts, and 15 articles, all in Chinese, were finally included. The screening process is shown in Fig. 1.

### 2.1. Quality assessment of the included literature

15 RCTs [6,13–16,22,24,25,28–33,35] and 0 English literature were eventually included. A total of 1002 patients were classified into Internal Chinese Medicine, External Chinese medicine treatment and Western medicine therapies, depending on the control group interventions. The basic characteristics of the included studies are shown in Table 1.

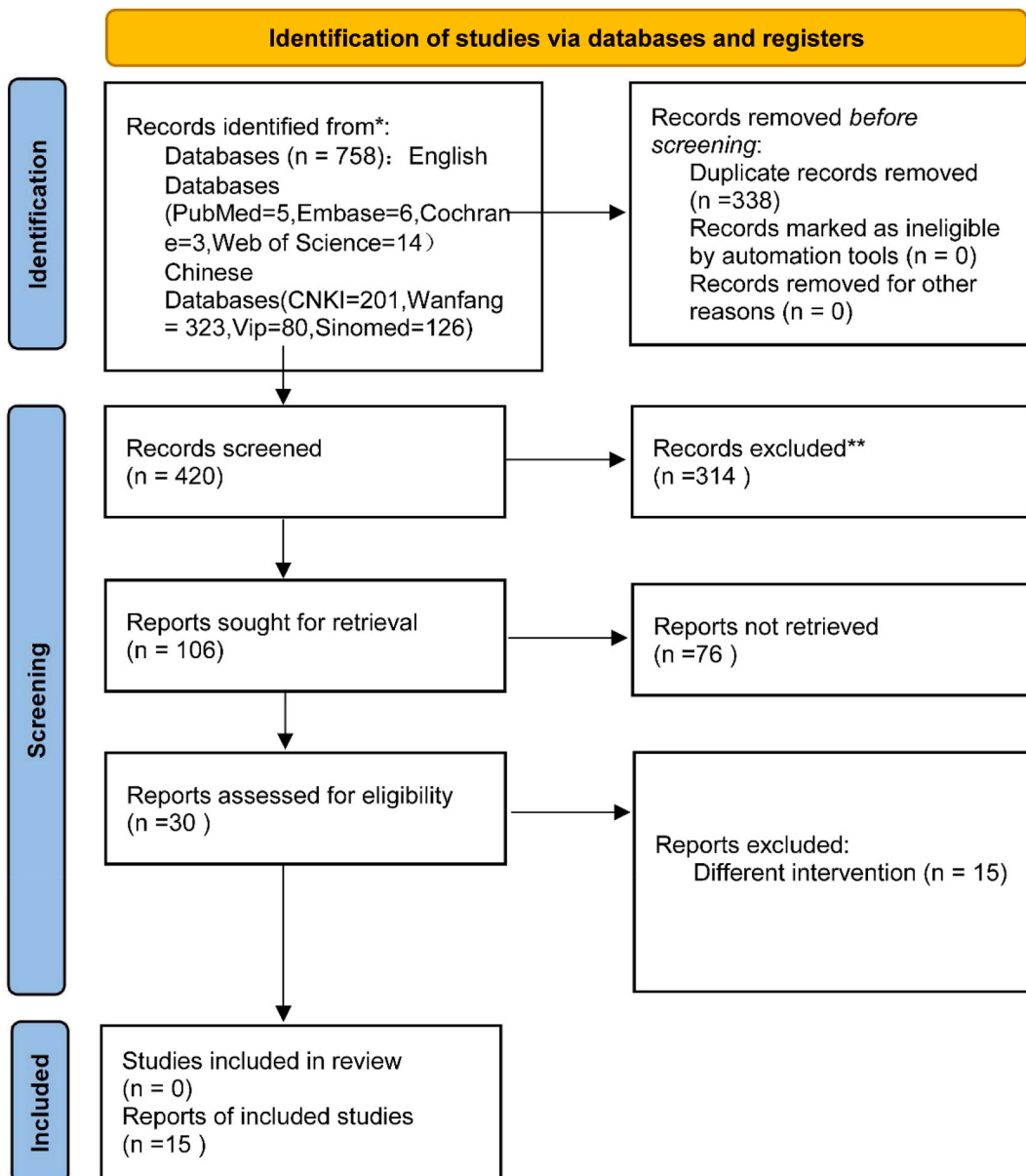


Fig. 1. Flow of literature search and selection process.

**Table 1**  
Characteristics of the included studies.

Studies	n		Age(years)		Gender(M/F)		disease duration		Interventions		DT	Outcome indicators
	T	C	T	C	T	C	T	C	T	C		
Zeng et al., 2022[16]	50	50	5.57 ± 1.80	5.22 ± 1.54	24/ 26	25/ 25	1.22 ± 0.48Y	1.17 ± 0.42Y	EAP + C	0.9% saline flush	1 M	①②
Huang 2017[24]	30	30	5–70	5–64	13/ 17	13/ 17	3M-7Y	3M-6Y	EAP + C	Xie's Warming Nose and Enlargement Soup	12D	①
Cao et al., 2021[32]	40	40	47.12 ± 2.59	47.08 ± 2.57	22/ 18	21/ 19	6.78 ± 1.48Y	6.12 ± 1.45Y	EAP + C	Loratadine syrup	2 M	②③④⑥
Zhao et al., 2020[14]	40	40	9.21 ± 4.13	9.16 ± 4.08	21/ 19	19/ 21	3-16Y	3-15Y	EAP + C	Cauliflower Powder Soup	30D	①②
Feng2022[6]	32	32	33.34 ± 8.03	34.17 ± 8.52	17/ 15	19/ 13	5.14 ± 3.04Y	5.57 ± 3.25Y	EAP + C	Gui Zhi Soup	3 M	①②③④⑤⑥⑦
Ren et al., 2022[25]	30	30	4.5	4.25	18/ 12	17/ 13	12.81 ± 2.58 M	12.75 ± 2.48 M	EAP + C	Terfenadine	6 M	①②⑦
Li 2017[13]	60	60	35.9 ± 1.5		62/58		7.5 ± 1.4Y		EAP + C	Endoscopic nasal microwave therapy	1 M	①②
Sun 2019[31]	30	30	37.2 ± 4.5		35/25		2.1 ± 3.6Y		EAP + C	Gui Zhi Soup with Allergy Soup	4W	①
Wang et al., 2020 [28]	30	30	19.6 ± 1.19	19.53 ± 1.17	16/ 14	17/ 13	–	–	EAP + C	Bloodletting of the ear tips	36D	①②
Wang et al., 2019 [29]	30	30	20.58 ± 0.93	20.03 ± 1.27	19/ 11	17/ 13	–	–	EAP + C	Moxibustion of Dazhui with ginger	24D	①②
Wang 2021[30]	30	30	40.54 ± 3.38	40.26 ± 3.45	16/ 14	18/ 12	13.28 ± 1.35 M	13.59 ± 1.25 M	EAP + C	Loratadine Tablet	4W	①②
Zhou et al., 2020[15]	30	30	5.33 ± 2.22	5.67 ± 1.58	19/ 11	8/12	22.43 ± 20.56 M	16.00 ± 12.13 M	EAP + C	Pediatric Tui Na	4W	①②
Zhang et al., 2021 [22]	45	45	7.41 ± 3.22	7.28 ± 3.16	28/ 17	27/ 18	3.26 ± 1.33Y	3.16 ± 1.23Y	EAP + C	Chinese herbal acupressure	50D	①②③④⑤⑥⑧
Zhao 2019[33]	29	29	31.65 ± 9.91	31.01 ± 10.12	11/ 18	16/ 13	4.48 ± 1.90Y	4.24 ± 2.08Y	EAP + C	She Ti Zhi Qiu Soup	4W	①②③④⑤⑥⑦
Zhuang 2022[35]	40	40	5.28 ± 1.10	5.21 ± 1.02	23/ 17	22/ 18	1.25 ± 0.16Y	1.21 ± 0.12Y	EAP + C	Pediatric Tui Na	4W	①②

n-Sample Size; T-Treatment group; C-Control group; DT-date of treatment; EAP-Ear acupuncture; Y-years; M-months; W-weeks; D-days.

①Efficient Rate; ②Nasal Symptom score; ③Nasal itching symptom score; ④Sneezing symptom score; ⑤Runny nose symptom score; ⑥Nasal congestion symptom score; ⑦Adverse reactions; ⑧Immune function.

## 2.2. Risk of bias assessment for study inclusion

Of the 15 included studies, 7 studies [15,16,22,25,29,30,35] used the random number table method, 1 study [14] adopted a blind sampling method, and 3 studies [28,32,33] were described by the word ‘random’, defined as ‘low risk’. The remaining 4 studies [6,13,24,31] were grouped according to the method of consultation, time of admission, and mean score, defined as ‘high risk’. One study [33] mentioned unblinding, defined as “high risk”, and the remaining 14 studies did not mention blinding, defined as “unclear risk”. Four studies [13,22,25,32] described follow-up information, defined as ‘low risk’, while the rest of the literature did not mention follow-up-related information, defined as ‘unclear risk’; all studies reported outcome indicators, defined as “All included studies did not show any other bias and were provisionally defined as “unclear risk”, and the specific risk of bias assessment is shown in Figs. 2 and 3.

## 2.3. Meta-analysis

### 2.3.1. Clinical efficiency

A total of 15 studies [6,13–16,22,24,25,28–33,35] were included for a total of 1002 patients. The  $Q$  test and  $I^2$  test reported low heterogeneity ( $P = 0.21$ ,  $I^2 = 22\%$ ), so the fixed effects model (FEM) was applied to the combined analysis. To clarify the source of heterogeneity, a subgroup analysis was used for this analysis, dividing the 15 studies into internal Chinese medicine [6,14,24,31,33], external Chinese treatment [15,22,28,29,35] and Western medical therapy [13,16,25,30,32] according to the control group interventions, with 5 studies in each group. The results of the subgroup analysis showed low heterogeneity between internal Chinese medicine ( $P = 0.67$ ,  $I^2 = 0\%$ ) and Western therapies ( $P = 0.48$ ,  $I^2 = 0\%$ ). In contrast, there was high heterogeneity between groups of TCM external therapies ( $P = 0.02$ ,  $I^2 = 67\%$ ). A manual exclusion of single literature methods for this subgroup to find the source of heterogeneity yielded that the heterogeneity originated from Zhang Xiaoyan’s study [22], considering that the reason could be the presence of conventional treatment (oral loratadine) on top of the intervention, resulting in a significantly higher efficiency rate than other studies. The results showed that the efficacy of EAP combined with control group therapy in the treatment of AR was higher than that of the control group, and the difference was statistically significant ( $RR = 1.18$ , 95%CI (1.13, 1.24),  $Z = 6.88$ ,  $P < 0.00001$ ). See Fig. 4.

### 2.3.2. Nasal symptom score

A total of 9 studies, 658 patients were included [13–16,25,28–30,33], The  $Q$  test and  $I^2$  test reported high heterogeneity ( $P < 0.00001$ ,  $I^2 = 99\%$ ), and the random effects model (REM) was applied to the combined analysis. The studies in which the control group intervention was TCM external therapy [15,28,29] were also separated from the other studies for subgroup analysis. After subgroup analysis a total of 3 studies with 180 patients were included within the TCM external treatment method subgroup, with less heterogeneity ( $P = 0.89$ ,  $I^2 = 0\%$ ), while the heterogeneity of the other studies was still greater ( $P < 0.00001$ ,  $I^2 = 99\%$ ). Meta-analysis showed that EAP combined with control therapy was significantly more effective in treating allergic rhinitis than the control group in terms of nasal symptoms, and the difference was statistically significant ( $MD = 1.92$ , 95%CI (0.87, 2.98),  $Z = 3.56$ ,  $P = 0.0004$ ). See Fig. 5.

### 2.3.3. Nasal itching symptom score

A total of 4 studies, 292 patients were included [6,22,32,33], The  $Q$  test and  $I^2$  test reported high heterogeneity ( $P < 0.00001$ ,  $I^2 = 97\%$ ), and the random effects model (REM) was applied to the combined analysis. Meta-analysis showed that EAP combined with control therapy was significantly more effective in treating allergic rhinitis than the control group in terms of nasal itching symptoms, and the difference was statistically significant ( $MD = 0.43$ , 95%CI (0.09, 0.77),  $Z = 2.49$ ,  $P = 0.01$ ). See Fig. 6.

### 2.3.4. Sneezing symptom score

A total of 4 studies, 292 patients were included [6,22,32,33], The  $Q$  test and  $I^2$  test reported high heterogeneity ( $P < 0.00001$ ,  $I^2 =$

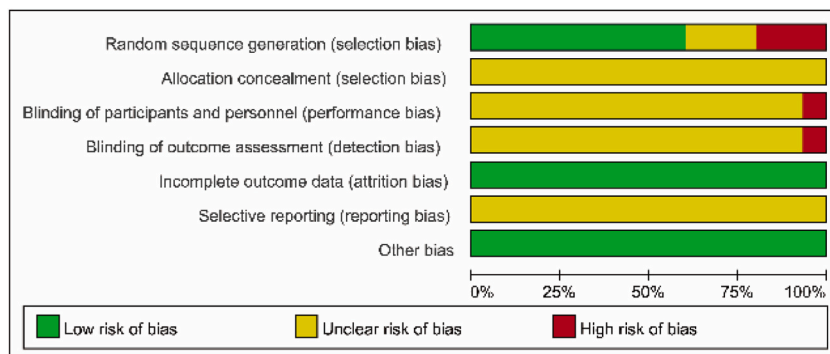


Fig. 2. Risk of bias graph.

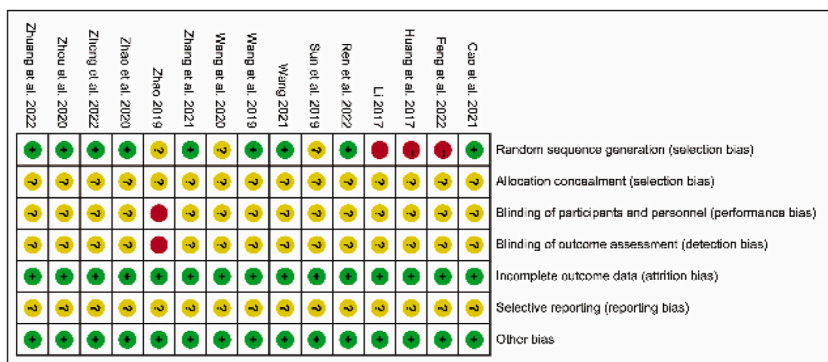


Fig. 3. Risk of bias summary.

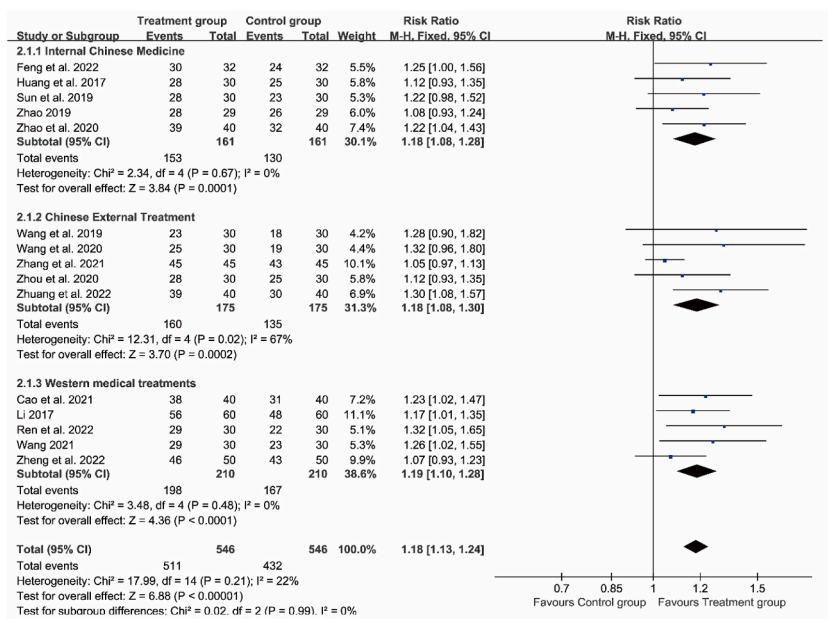


Fig. 4. Meta-analysis of clinical efficiency.

96 %), and the random effects model (REM) was applied to the combined analysis. Meta-analysis showed that EAP combined with control therapy was significantly more effective in treating AR than the control group in terms of sneezing symptoms, and the difference was statistically significant ( $MD = 0.68$ ,  $95\%CI (0.39, 0.98)$ ,  $Z = 4.51$ ,  $P < 0.00001$ ). See Fig. 7.

2.3.5. Runny nose symptom score

A total of 3 studies, 212 patients were included [6,22,33], The Q test and  $I^2$  test reported high heterogeneity ( $P = 0.03$ ,  $I^2 = 71\%$ ), and the random effects model (REM) was applied to the combined analysis. Meta-analysis showed that EAP combined with control therapy was significantly more effective in treating AR than the control group in terms of runny nose symptoms, and the difference was statistically significant ( $MD = 0.36$ ,  $95\%CI (0.12, 0.61)$ ,  $Z = 2.90$ ,  $P = 0.004$ ). See Fig. 8.

2.3.6. Nasal congestion symptom score

A total of 4 studies, 292 patients were included [6,22,32,33], The Q test and  $I^2$  test reported high heterogeneity ( $P < 0.00001$ ,  $I^2 = 98\%$ ), and the random effects model (REM) was applied to the combined analysis. Meta-analysis showed that EAP combined with control therapy was significantly more effective in treating AR than the control group in terms of nasal congestion symptoms, and the difference was statistically significant ( $MD = 0.63$ ,  $95\%CI (0.21, 1.05)$ ,  $Z = 2.97$ ,  $P = 0.003$ ). See Fig. 9.

2.3.7. Sensitivity analysis

The Meta-analysis was chosen to assess the sensitivity by manually excluding the literature one by one, observing the corresponding changes in RR and MD values after the exclusion of a literature to analyse its impact on the heterogeneity of the study. The

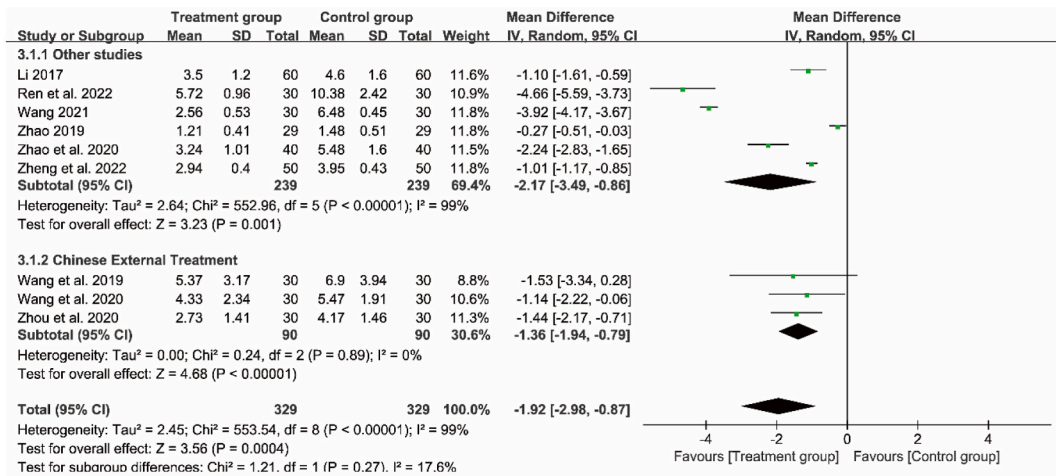


Fig. 5. Meta-analysis of nasal symptom scores.



Fig. 6. Meta-analysis of symptom scores for Nasal itch.

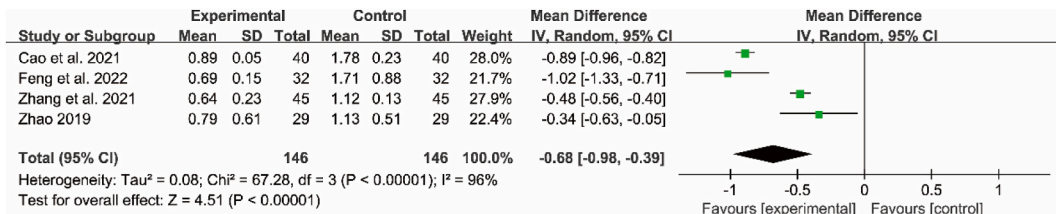


Fig. 7. Meta-analysis of symptom scores for Sneezing.

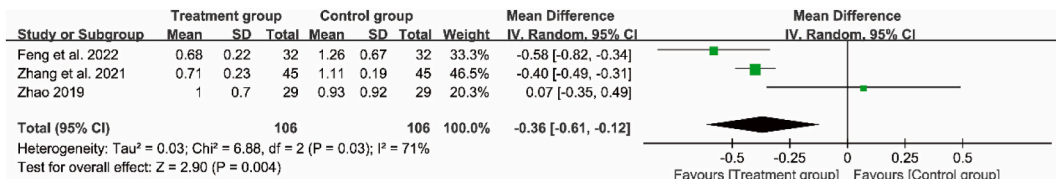


Fig. 8. Meta-analysis of symptom scores for runny nose.

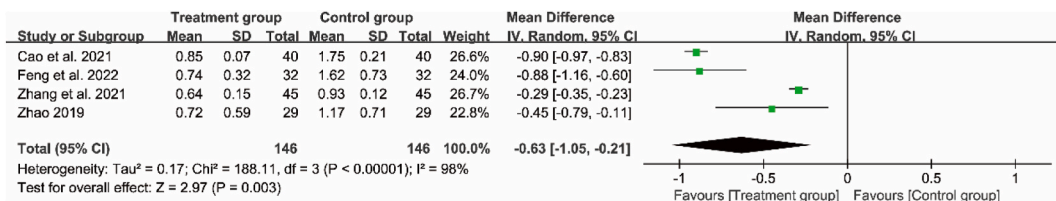


Fig. 9. Meta-analysis of symptom scores for nasal congestion.

results showed that for the Meta-analysis of clinical efficacy, there was no significant effect of a single study on heterogeneity. For the nasal symptom scores, the overall heterogeneity was large, and after subgroup analysis, the heterogeneity within the subgroup for the Chinese external treatment method [15,28,29] got lower ( $P = 0.29$ ,  $I^2 = 20\%$ ), but the heterogeneity within the subgroup composed of other studies was still large, and no significant change was seen for the overall heterogeneity after excluding the single study, considering that the heterogeneity may be related to the interventions; the remaining heterogeneity for Meta-analyses of nasal itching, sneezing, runny nose and nasal congestion symptom scores were not conducted for sensitivity analyses due to the small number of studies included in the study itself.

### 2.3.8. Publication bias analysis

The funnel plot analysis of this study, using the efficiency rate as an indicator, shows that the scatter is mostly concentrated in the middle and upper parts of the study, but there is no scatter distribution at the top, indicating that the sample size of the included studies is medium and there is a lack of studies with large sample sizes. The overall scatter is more uniform, with one scatter distributed outside the confidence interval, making it clear that this study is Zhang Xiaoyan's study [22], indicating that there may be heterogeneity in this literature compared to other literature. The bottom two scatters have a greater impact on the overall asymmetry, considering that the bias may be due to the small sample size. See Fig. 10.

### 2.3.9. Adverse reactions

3 studies [6,25,33] mentioned adverse reactions to medication, of which 1 study showed no adverse reactions and 2 studies had fewer adverse reactions in the treatment group than in the control group, so it is clear that EAP are safe to use.

## 3. Discussion

Of the 15 studies included, in addition to what has been reported above, there are a number of aspects worth mentioning: (1) Few studies were found during this search that examined the use of EAP alone in the treatment of AR, and future literature is still expected to validate the clinical efficacy of EAP alone as a treatment for AR. (2) 2 studies [16,24] used a probe to detect positive reaction points in the selection of auricular points, while the remaining studies selected among named auricular points, the most frequent of which were: lung 9 times, kidney 9 times, adrenal 9 times, external nose 9 times, internal nose 7 times, Shen Men 7 times and endocrine 5 times. (3) Magnetic beads are now used in the EAP but the 15 RCT studies included in this study all used Wang Bu Liuxing seeds. (4) One study [22] analysed changes in immune function before and after the study, but as this was the only study that compared this index, it was not compared in this analysis. In the future, if there are more relevant studies, a new comparative analysis can be conducted on the effect of EAP on immune function. (5) 6 of the 15 included studies [14–16,22,25,35] were conducted in children, but as Meta-analysis of the clinical efficacy of these six studies showed a large heterogeneity ( $P = 0.04$ ,  $I^2 = 57\%$ ), after analysis with a random effects model ( $RR = 1.15$ , 95%CI (1.05, 1.26),  $Z = 2.92$ ,  $P = 0.003$ ), but as it was not significantly specific, it will not be repeated in this analysis, but it does suggest that EAP do have merit over other therapies in the clinical management of AR in children.

However, there are still some limitations to this study: (1) The control group interventions varied across the 15 studies included, which has an impact on the results of this Meta-analysis and needs to be further confirmed by more studies with less variability. (2) The duration of treatment varied somewhat between studies, with the shortest duration being 12 days, the longest duration being 6 months and the most common duration being 4 weeks in 5 studies [9,10,12,30,33], which also had an impact on the results of this analysis. (3) Although the studies did not show that EAP caused significant adverse effects, only 3 of the studies [6,7,33] mentioned adverse effects, and this aspect needs to be strengthened. (4) Most of the 15 studies included in this study were small samples of RCTS, some did not mention “randomised” and only one mentioned “unblinded”, while the rest did not mention “blinded” and related words. “The above findings need to be further validated by more high-quality studies with large samples. (5) Only 4 studies [5,7,8,11] described follow-up, and this aspect needs to be strengthened in the subsequent literature to improve the quality of the literature. (6) No negative

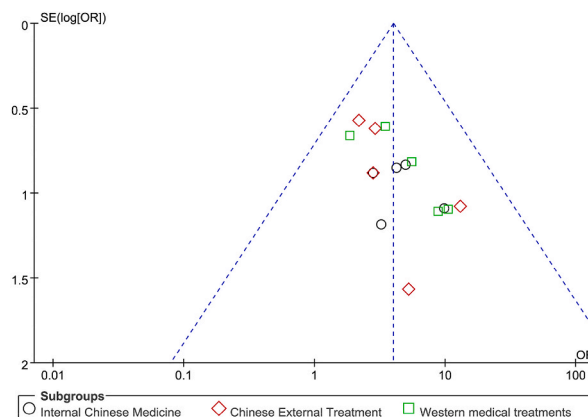


Fig. 10. Funnel chart of clinical efficiency.



results were seen in the included studies, indicating a possible publication bias. (7) There was subjective error in the assessment of study quality.

EAP, as a characteristic external treatment method of Chinese medicine, is widely used in clinical practice because it is simple, inexpensive, safe and non-invasive. The Yellow Emperor's Classic of Internal Medicine: "The twelve meridians belong to the internal organs and are externally connected to the limbs and joints." Ling Shu-Kou Wen: "The ear is also the place where the clan veins are gathered." [27] The human body is a unified whole, the ear for the hundred veins, blood convergence, All the meridians of the body are in the ears, the ear through the meridians and internal organs are also closely linked. The internal and external parts of the human body can be found in the ear on the corresponding parts of the body when other parts of the disease, corresponding to the auricle on the part of the reaction often occurs, these parts are the ear acupuncture points. 1957 French medical doctor P-Nogier found that the outer ear is not simply a curved cartilage, which has a close relationship with the internal organs, the internal organs when the disease in the auricle on the corresponding reaction occurs, put forward in the shape of an inverted auricular point, like the embryonic inverted auricle diagram. Auricular point is the whole body information in the auricle on the expression of a window, with the regulation of meridians and internal organs and the function of qi and blood, EAP is through the pinch pressure pasted on the auricular point of the Wang Bu Liuxing seeds and other medicinal beans, slow and continuous stimulation of the auricular point in order to pass the blood, dredge the meridians and regulate the operation of the internal organs and qi and blood, and to achieve the effect of the treatment of disease [23,26]. At present, there are many Chinese medical methods for the treatment of AR in clinical practice.

A multicentre randomised controlled trial confirmed that the use of auricular points with therapeutic effects on AR was more effective than other auricular points in patients with AR, and that the therapeutic effect of auricular points on AR is more than just placebo [4]. Although the treatment of EAP has not been mentioned in the Chinese guidelines for the diagnosis and treatment of AR, it has been recommended in the Chinese expert consensus on the combination of Chinese and Western medicine for other diseases such as polycystic ovary syndrome, eczema and acne [20,21,34]. Therefore more research is needed to explore the therapeutic effects of EAP in the treatment of allergic rhinitis.

This Meta-analysis was conducted to evaluate the therapeutic effects of combined EAP for the treatment of AR through a high angle comprehensive analysis and comparison with EAP for the treatment of AR, and to give reference to the application of EAP in clinical work for the treatment of AR. From the results of this Meta-analysis, it is suggested that EAP can be used as an adjunctive therapy for the treatment of AR and is recommended for clinical use.

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## CRedit authorship contribution statement

**Shihui Cheng:** Writing – review & editing, Writing – original draft, Data curation. **Kun Rong:** Writing – original draft, Software, Methodology, Data curation. **Jing Wu:** Software, Data curation. **Jing Zhou:** Supervision, Data curation. **Meijing Li:** Supervision, Software, Resources. **Chen Li:** Resources, Data curation. **Xiao Liang:** Writing – review & editing, Data curation. **Yu Zhang:** Writing – original draft, Supervision, Funding acquisition.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yu Zhang reports financial support was provided by China Academy of Chinese Medical Sciences Guang'anmen Hospital. Yu Zhang reports a relationship with China Academy of Chinese Medical Sciences Guang'anmen Hospital that includes: employment. Yu Zhang has patent pending to Yu Zhang. I have nothing to declare.

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