

Effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days, as the hottest days in summer, on the acute attack, the immunological response, and the pulmonary function in asthmatic children

A meta-analysis

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Abstract

Background: A meta-analysis was performed to evaluate the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days, as the hottest days in summer, on the acute attack, immunological response, and the pulmonary function in asthmatic children.

Methods: A systematic literature search up to July 2021 was performed and 13 studies included 1166 asthmatic children at the start of the study; 587 of them were using acupoint herbal patching as an add-on to asthma medication during Sanfu days and 579 were given asthma medication only.

Results: Acupoint herbal patching as add-on to asthma medication had significantly lower frequency of acute attack (mean difference [MD], -1.57 ; 95% confidence interval [CI], -2.28 to -0.85 , $P < .001$), lower asthma relapse (odds ratio, 0.13; 95% CI, 0.04–0.43, $P < .001$), and higher forced expiratory volume in 1 second (MD, 1.72; 95% CI, 0.89–2.65, $P < .001$), higher peak expiratory flow rate (MD, 1.15; 95% CI, 0.37–1.93, $P = .004$), lower immunoglobulin E after treatment (MD, -123.81 ; 95% CI, -185.60 to -62.02 , $P < .001$), and higher interferon-gamma after treatment (MD, 7.17; 95% CI, 2.42–11.92, $P = .003$) compared to asthma medication only in asthmatic children.

Conclusions: Acupoint herbal patching as an add-on to asthma medication during Sanfu days had a significantly lower frequency of acute attack, lower asthma relapse, higher forced expiratory volume in 1 second, higher peak expiratory flow rate, and higher interferon-gamma after treatment in asthmatic children compared to asthma medication only in asthmatic children.

Abbreviations: C = comparison, CI = confidence interval, I = intervention/exposure, MD = mean difference, O = outcomes, OR = odds ratio, P = populations.

Keywords: acupoint herbal patching, acute attack, and pulmonary function, asthma in children, immunological response, Sanfu days

1. Introduction

Asthma in children is the most frequent chronic disease.^[1] Up to 37% of children suffer from asthma worldwide.^[2] Asthma is moreover a chief reason for children's school days loss and hospital visits. Pharmacologic interventions for asthma comprise the use of controller and reliever medications. Even though the progress in medical care, asthma in children still causes mortality and recurrence in adulthood.^[3] Short-acting bronchodilators and inhaled corticosteroids are the most regularly used

treatment for children with asthma.^[4] However, growth suppression related to corticosteroid use remains a big alarm.^[5] Persistent childhood asthma can even cause a decline in pulmonary function at young ages.^[6] Consequently, novel treatment methods for asthma in children are required. Complementary medicine is progressively used in children with asthma.^[7] Acupoint herbal patching based on traditional Chinese medicine meridian principle has been used widely in China.^[8] This noninvasive pain-free method could be accepted by children. "Treating Winter diseases in Summer" is a definite technique

The authors have no conflicts of interest to disclose.

Data are available by the corresponding author upon reasonable request.

Ethical statement not needed as it is a meta-analysis study.

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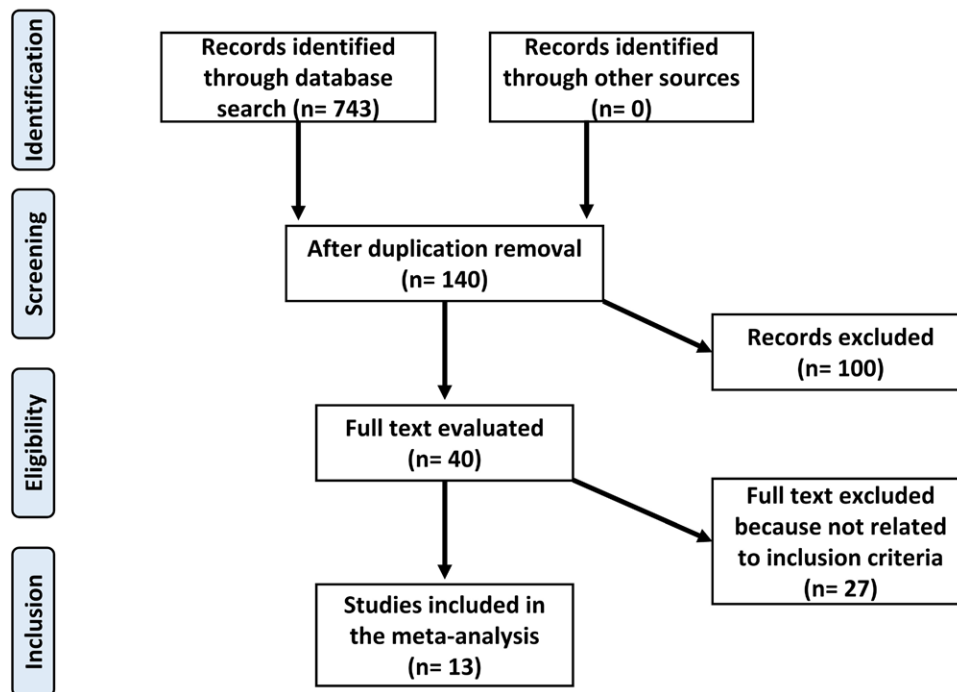


Figure 1. Schematic diagram of the study procedure.

of applying drugs on Sanfu days, as the hottest days in summer, to inhibit and manage disease attacks in winter.^[9] This method is initially presented in “Zhang’s Treatise on General Medicine.” Sanfu days (comprises 10 days) is the hottest time in the year based on the lunar calendar. Based on the principle of traditional Chinese medicine, Sanfu days are known as the irritating time for Yang-Qi. The use of acupoint herbal patching during Sanfu days produces therapeutic properties by the herbs’ transdermal absorption and acupoint stimulation. Several randomized clinical trials have assessed the supplementary advantageous properties of acupoint herbal patching through the Sanfu days for treating asthma in children.^[10–22] Though, the advantageous properties of acupoint herbal patching on the pulmonary functions are still conflicting. A previous meta-analysis showed that acupoint herbal patching had advantageous immunomodulatory properties for asthma in children.^[23] Though, clinical results and lung function were not assessed in this meta-analysis. An additional earlier meta-analysis examined only the properties of acupoint herbal patching during Sanfu days for stable asthma.^[24] Though their results are still conflicting. Hence, the present meta-analysis aimed to evaluate the effects of acupoint herbal patching during Sanfu days, as the hottest days in summer, on the acute attack and the pulmonary function in asthmatic children.

2. Materials and Methods

The present study followed the meta-analysis of studies in the epidemiology statement,^[25] which was performed following an established protocol. No ethical approval was needed as it is a meta-analysis study.

2.1. Study selection

The study parameters included statistical measures of association (odds ratio [OR], mean difference [MD], frequency rate ratio, or relative risk, with 95% confidence intervals [CIs]) between the effects of acupoint herbal patching as an add-on

to asthma medication during Sanfu days, as the hottest days in summer, on the acute attack, the immunological response, and the pulmonary function in asthmatic children.

Only those human studies in any language were considered. Inclusion was not restricted by study size or type. Publications excluded were review articles, commentaries, and studies that did not supply a degree of relationship. Figure 1 shows the whole study process.

The articles were integrated into the meta-analysis when the following inclusion criteria were met:

1. The study was a randomized control trials.
2. The target population includes asthmatic children.
3. The intervention program was acupoint herbal patching as an add-on to asthma medication during Sanfu days.
4. The study included comparisons between the acupoint herbal patching as an add-on to asthma medication during Sanfu days and asthma medication only.

The exclusion criteria for the intervention groups were:

1. Studies that did not determine the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu day on the acute attack, the immunological response, and the pulmonary function in asthmatic children.
2. Studies that included managements of acute attack, the immunological response, and the pulmonary function in asthmatic children other than acupoint herbal patching as an add-on to asthma medication during Sanfu days.
3. Studies that did not focus on the effect on comparative results.

2.2. Identification

A protocol of search strategies was prepared according to the PICOS principle,^[26] and we defined it as follow: P (population): asthmatic children; I (intervention/exposure): acupoint herbal patching as an add-on to asthma medication during Sanfu days; C (comparison): acupoint herbal patching as an

Table 1
Search strategy for each database.

Database	Search strategy
Pubmed	#1 "acupoint herbal patching"[MeSH Terms] OR "Sanfu days"[All Fields] OR "asthma in children"[All Fields] #2 "acute attack"[MeSH Terms] OR "acupoint herbal patching"[All Fields] OR "immunological response"[All Fields] OR "pulmonary function"[All Fields] #3 #1 AND #2
Embase	"acupoint herbal patching"/exp OR "Sanfu days"/exp OR "asthma in children"/exp #2 "acute attack"/exp OR "ICBG"/exp OR "immunological response"/exp OR "pulmonary function"/exp #3 #1 AND #2
Cochrane library	#1 (acupoint herbal patching):ti,ab,kw OR (Sanfu days):ti,ab,kw OR (asthma in children):ti,ab,kw (Word variations have been searched) #2 (acute attack):ti,ab,kw OR (immunological response):ti,ab,kw OR (pulmonary function):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

add-on to asthma medication during Sanfu days and asthma medication only; O (outcome): managements of acute attack, the immunological response and the pulmonary function; and S (study design): no restriction.^[27] First, we conducted a systematic search of Embase, PubMed, Cochrane Library, OVID, China National Knowledge Infrastructure, WanFang databases, Chinese Biomedical Literature Database and Google Scholar till July 2021, by using a blend of keywords and related words for the acupoint herbal patching, Sanfu days, asthma in children, acute attack, the immunological response, and pulmonary function as shown in Table 1. All detected studies were gathered in an EndNote file, duplicates were removed, and the title and abstracts were revised to eliminate studies that did not show any relationship between the effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days compared to asthma medication only on the acute attack, the immunological response, and the pulmonary function in asthmatic children. The remaining studies were examined for related information.

2.3. Screening

Data were abridged onto a standardized form on the following basis; study-related and subject-related characteristics as follows: last name of the primary author, period of study, year of publication, country, region of the studies, and study design; population type, the total number of subjects, demographic data and clinical and treatment characteristics; categories, qualitative and quantitative method of evaluation, information source, and outcome evaluation; and statistical analysis.^[28] If a study qualified for inclusion based upon the aforementioned principles, data were extracted independently by 2 authors. In case of disagreement, the corresponding author provided a final opinion. When the data from a particular study differed based on the assessment of the relationship between the effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days compared to asthma medication only on the acute attack, the immunological response, and the pulmonary function in asthmatic children, we extracted the data separately. There is a risk of bias in these studies; therefore, individual studies were evaluated using 2 authors who independently assessed the methodological quality of the selected studies. The "risk of bias tool" from the RoB 2: A revised Cochrane risk-of-bias tool for randomized trials was utilized to evaluate methodological quality.^[29] In terms of the evaluation criteria, each study was evaluated and allocated to one of the next 3 risks of bias-low: if all quality criteria were met, the study was considered to have a low risk of bias; unclear: if 1 or more of the quality criteria were partially met or unclear, the study was considered to have a moderate risk of bias; or high: if 1 or more of the criteria were not met, or not included, the study was considered to have a

high risk of bias. Any discrepancies were addressed by a reassessment of the original article.

2.4. Eligibility

The main result concentrated on the effectiveness of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the acute attack, immunological response, and the pulmonary function in asthmatic children. An assessment of these aforementioned effects was summarized.

2.5. Inclusion

Sensitivity analyses were limited to studies reporting the relationship between the effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days and asthma medication only on the acute attack, the immunological response, and the pulmonary function in asthmatic children. For subcategory and sensitivity analysis, we compared the acupoint herbal patching as an add-on to asthma medication during Sanfu days and asthma medication only.

2.6. Statistical analysis

We calculate the OR and the MD and 95% CI using the dichotomous and contentious method with a random or fixed-effect model. We calculated the I^2 index and the P index was ranging from 0% to 100%. When the I^2 index was approximately 0%, 25%, 50%, and 75% that specifies no, low, moderate, and high heterogeneity, respectively.^[26] If the I^2 was > 50%, we used the random-effect; if it was < 50%, we used the fixed-effect. We stratified the original assessment as per result categories as described previously to complete the subgroup analysis. Differences among the subcategories were considered statistically significant at a P value < .05. Publication bias was assessed quantitatively using the Egger regression test (publication bias is present if $P \geq .05$), and qualitatively, by visual inspection of funnel plots of the logarithm of ORs versus their standard errors.^[28] All the P values were calculated via 2-tailed tests. Reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to do all calculations and graphs.

3. Results

A total of 743 unique studies were identified, of which 13 randomized clinical studies (between 2003 and 2021) fulfilled the inclusion criteria and were included in this meta-analysis.^[10-22] The 13 studies included 1166 asthmatic children at the start of the study; 587 of them were using acupoint herbal patching as an add-on to asthma medication during Sanfu days and

Table 2

Characteristics of the selected studies for the meta-analysis.

Study	Total	Acupoint and medication	Asthma medication only	Age (yr)	Acupoint and medication treatment	Asthma medication only treatment
Deng and Zeng, 2003 ^[10]	160	80	80	4–6	Acupoint + inhale glucocorticoid	Inhale glucocorticoid
Cai et al, 2008 ^[11]	80	40	40	2–12	Acupoint + inhale glucocorticoid	Inhale glucocorticoid
Xiong, 2009 ^[12]	82	41	41	2–10	Acupoint + budesonide + salbutamol	Budesonide + salbutamol
Shi, 2011 ^[13]	80	40	40	3–12	Acupoint + inhale glucocorticoid	Inhale glucocorticoid
Chen et al, 2013 ^[14]	90	45	45	4–10	Acupoint + budesonide + salbutamol	Budesonide + salbutamol
Wu, 2014 ^[15]	86	43	43	5–14	Acupoint + inhale glucocorticoid	Inhale glucocorticoid
Zhao and Zhou ^[16]	40	20	20	2–12	Acupoint + inhale glucocorticoid	Inhale glucocorticoid
Wang and Wang, 2016 ^[17]	64	33	31	6–10	Acupoint + montelukast	Montelukast
Wu et al, 2016 ^[18]	56	31	25	5–14	Acupoint + montelukast	Montelukast
Fu et al, 2017 ^[19]	120	60	60	5–13	Acupoint + montelukast/seretide	Montelukast/seretide
Yin et al, 2017 ^[20]	80	40	40	5–12	Acupoint + inhale glucocorticoid	Inhale glucocorticoid
Shu et al, 2017 ^[21]	80	40	40	3–11	Acupoint + inhale budesonide	Inhale budesonide
Zhao et al, 2018 ^[22]	148	74	74	2–13	Acupoint + budesonide + salbutamol	Budesonide + salbutamol
Total	1166	587	579			

579 were given asthma medication only. All studies evaluated the effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days compared to asthma medication only on the acute attack, the immunological response, and the pulmonary function in asthmatic children.

The study size ranged from 40 to 148 asthmatic children at the start of the study. The details of the 13 studies are shown in Table 2.

3.1. Frequency of acute attack

Five studies^[10,13,15,16,19] including 486 subjects reported data stratified to the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the frequency of acute attack. Acupoint herbal patching as add-on to asthma medication during Sanfu days had significantly lower frequency of acute attack (MD, -1.57; 95% CI, -2.28

to -0.85, $P < .001$) with high heterogeneity ($I^2 = 86\%$). High heterogeneity level necessitate the need for further subgroup analysis (Fig. 2).

3.2. Asthma relapse

Two studies^[16,20] including 99 subjects reported data stratified to the effect on asthma relapse, and analysis of their findings reported lower asthma relapse (OR, 0.13; 95% CI, 0.04–0.43, $P < .001$) with low heterogeneity ($I^2 = 44\%$) in favor of interventional group receiving the add-on therapy (Fig. 3).

3.3. Forced expiratory volume in 1 second

Eight studies^[10,12,14,18–22] including 800 subjects reported data stratified to the effect on forced expiratory volume in 1 second, findings of this analysis as seen in Figure 4, showed a higher

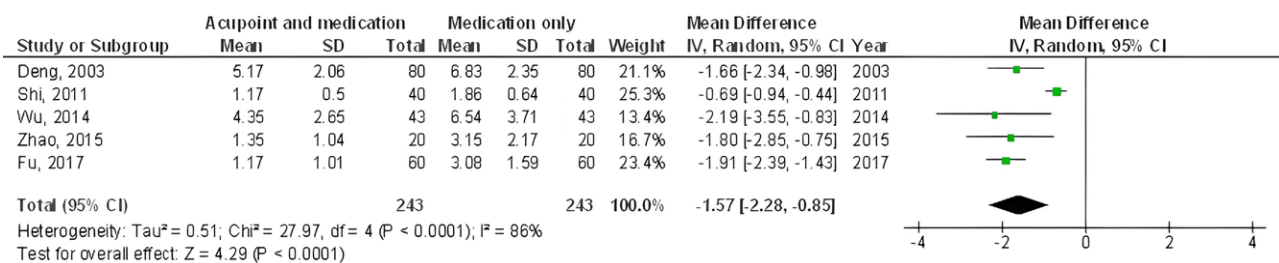


Figure 2. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the frequency of acute attack in asthmatic children compared to the asthma medication only group.

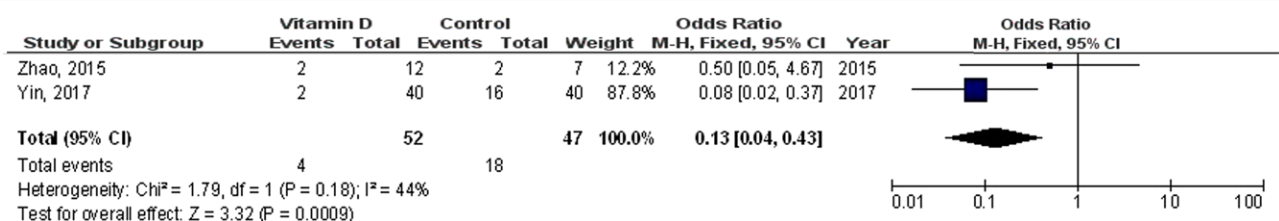


Figure 3. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the asthma relapse in asthmatic children compared to the asthma medication only group.

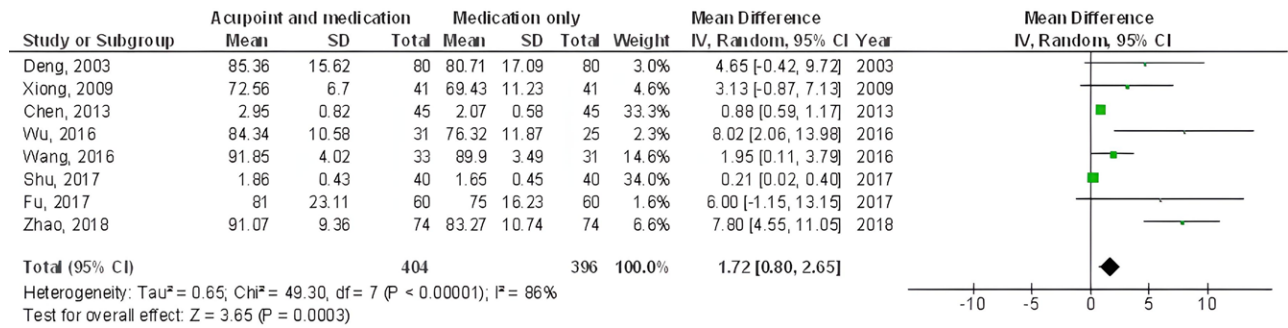


Figure 4. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the forced expiratory volume in 1 second in asthmatic children compared to the asthma medication only group.

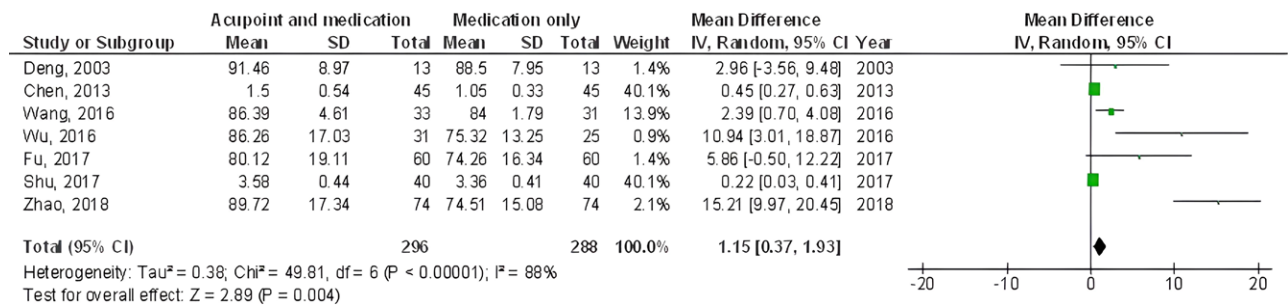


Figure 5. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the peak expiratory flow rate in asthmatic children compared to the asthma medication only group.

forced expiratory volume in 1 second (MD, 1.72; 95% CI, 0.89–2.65, *P* < .001) with high heterogeneity (*I*² = 86%) in favor of interventional group receiving the add-on therapy compared with control (Fig. 4).

3.4. Peak expiratory flow

Seven studies^[10,14,17–19,21,22] including 584 subjects reported data stratified to the effect on peak expiratory flow reflected higher peak expiratory flow rate (MD, 1.15; 95% CI, 0.37–1.93, *P* = .004) with high heterogeneity (*I*² = 88%) of interventional group compared with group receiving traditional asthma therapy only (Fig. 5).

3.5. Effect on immunoglobulin E

Two studies^[12,13] including 162 subjects reported data stratified to the effect on immunoglobulin E after treatment. Findings of this analysis showed lower immunoglobulin E after treatment (MD, –123.81; 95% CI, –185.60 to –62.02, *P* < .001) with high heterogeneity (*I*² = 82%) regarding the interventional group compared with higher levels for the control (Fig. 6).

3.6. Effect on interferon-gamma

Two studies^[11,13] including 160 subjects reported data stratified to the effect on interferon-gamma after treatment, results reflects a higher interferon-gamma after treatment (MD, 7.17; 95% CI, 2.42–11.92, *P* = .003) with no heterogeneity (*I*² = 0%) compared to asthma medication only in asthmatic children as shown in Figure 7.

3.7. Effect on interleukin-4

Two studies^[11,13] including 160 subjects reported data stratified to the effect on interleukin-4 after treatment compared to asthma medication only in asthmatic children. However, acupoint herbal patching as an add-on to asthma medication during Sanfu days had a significant effect regarding all previously measured parameters, there was no significant effect on interleukin-4 after treatment (MD, –3.67; 95% CI, –10.90 to 2.56, *P* = .32) with high heterogeneity (*I*² = 79%) compared to asthma medication only in asthmatic children as shown in Figure 8.

Selected studies stratified analysis adjusts for children age, gender, and ethnicity were not performed, since no studies reported or adjusted for these factors.

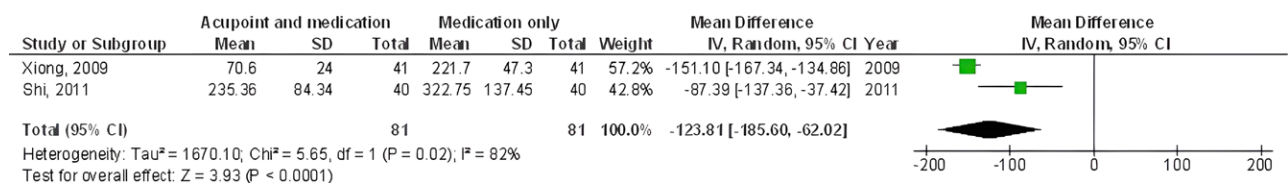


Figure 6. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the immunoglobulin E after treatment in asthmatic children compared to the asthma medication only group.

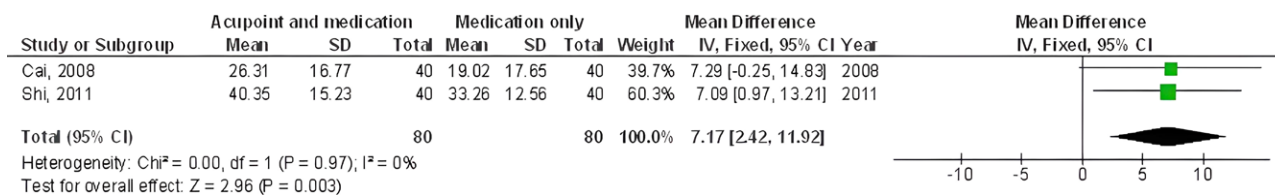


Figure 7. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the interferon-gamma after treatment in asthmatic children compared to the asthma medication only group.

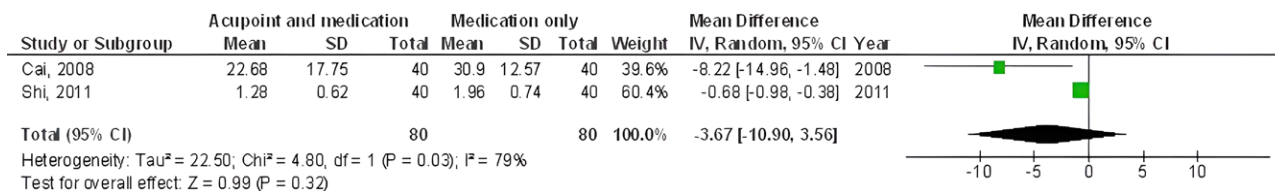


Figure 8. Forest plot of the effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days on the interleukin-4 in asthmatic children compared to the asthma medication only group.

Based on the visual inspection of the funnel plot as well as on quantitative measurement using the Egger regression test, there was no evidence of publication bias ($P = .84$). However, most of the included studies were assessed to be of low methodological quality due to their small sample size. All studies did not have selective reporting bias, and no articles had incomplete outcome data and selective reporting.

4. Discussion

This meta-analysis study based on 13 studies included 1166 asthmatic children at the start of the study; 587 of them were using acupoint herbal patching as an add-on to asthma medication during Sanfu days and 579 were given asthma medication only.^[10–22] Acupoint herbal patching as an add-on to asthma medication during Sanfu days had a significantly lower frequency of acute attack, lower asthma relapse, and higher forced expiratory volume in 1 second, higher peak expiratory flow rate, lower immunoglobulin E after treatment, and higher interferon-gamma after treatment in asthmatic children compared to asthma medication only in asthmatic children. However, acupoint herbal patching as an add-on to asthma medication during Sanfu days had no significant effect on interleukin-4 after treatment compared to asthma medication only in asthmatic children.^[10–22] However, the analysis of results should be done with carefulness due to the low number of studies for some drugs (<3), for example, for asthma relapse, and immunoglobulin E, interferon-gamma, and interleukin-4 after treatment and the low sample size in most of the included studies (10 studies ≤ 100 subjects) in the meta-analysis. Also, the level of heterogeneity was high in most of the parameters studied, which again for us to recommend that analysis of results should be done with carefulness; also recommending the requirement for more studies to confirm these findings or probably to significantly affect the confidence in the effect assessment especially for the interleukin-4 after treatment.

Our meta-analysis aim was to systematically gather the available studies' evidence and evaluate the possible efficiency of acupoint herbal patching as an add-on to asthma medication during Sanfu days in asthmatic children. Our findings are similar to the earlier meta-analysis.^[8,23,24,30–32] Acupoint herbal patching as an add-on to asthma medicine had extra advantages in improving pulmonary function, the prevalence of acute attack, and immunological response in asthmatic subjects and this difference could be related to large population samples as a result of including more recent studies that were not available for

the previous analysis. As shown in our results acupoint herbal patching can control serum levels of immunoglobulin A, E, G, and interferon-gamma.^[30] Though, the use of acupoint herbal patching should not be limited to Sanfu days.^[33] Assessment in Sanfu days and any time will be a meaningful topic for the upcoming trials. Acupoint herbal patching also controlled the serum levels of CD4⁺ T lymphocytes, CD8⁺ T lymphocytes, and eosinophil.^[34] Also, the immunomodulatory properties of acupoint herbal patching can decrease serum levels of tumor necrosis factor- α , and high-sensitivity C-reactive protein.^[12] Anti-inflammatory and immunomodulatory properties of acupoint herbal patching might partially account for its advantageous properties. A great concern was made to the skin reaction (e.g., burning, even cause blisters, itching, local skin redness, and pain). However, management-induced blisters seemed to show better healing outcomes.^[33] This phenomenon might be explained by local infiltrative results that make it easier for the body to absorb the herbs by the acupoints. Pediatrics with skin allergies or injured skin must be managed with carefulness. However, Previous studies indicated no association between age or gender with the clinical outcomes of the acupoint.^[33]

Radix Kansui, White Mustard Seed, and Rhizoma Corydalis are often chosen herbs in the acupoint. Upcoming trials must concentrate on the assessment of the effect of different herbal and various stimulating acupoints. Also, upcoming trials with longer follow-up periods are needed to assess properly the effect of acupoint herbal patching on asthma.

This meta-analysis showed the relationship between the effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days compared to asthma medication only on the acute attack, the immunological response, and the pulmonary function in asthmatic children. However, further studies are needed to validate these potential associations. Also, further studies are needed to deliver a clinically meaningful difference in the results. This was also suggested in another meta-analysis which showed a similar effect of acupoint herbal patching as an add-on to asthma medication during Sanfu days and asthma medication only in asthmatics children.^[8,23,24,30–32] This requires further investigation and explanation since no clear rationale was found to explain these results. Well-designed studies are also needed to assess these factors, including the combination of different children's age, gender, and ethnicity, because our meta-analysis study could not answer whether these factors are associated with the results. In summary, acupoint herbal patching as an add-on to asthma medication during Sanfu days had a significantly lower

frequency of acute attack, lower asthma relapse, and higher forced expiratory volume in 1 second, higher peak expiratory flow rate, lower immunoglobulin E after treatment, and higher interferon-gamma after treatment in asthmatic children compared to asthma medication only in asthmatic children. However, acupoint herbal patching as an add-on to asthma medication during Sanfu days had no significant effect on interleukin-4 after treatment compared to asthma medication only in asthmatic children. Further studies are required to validate these findings.

4.1. Limitations

There may be a selection bias in this study since so many of the studies found were excluded from the meta-analysis. However, the studies excluded did not satisfy the inclusion criteria of our meta-analysis. Moreover, we could not determine if the results were associated with children's age, gender, and ethnicity or not. The study designed to evaluate the association between the effects of acupoint herbal patching as an add-on to asthma medication during Sanfu days compared to asthma medication only was based on data from previous studies, which might cause bias induced by incomplete details. The meta-analysis was based on 13 studies with a low number of studies for some drugs (<3), for example, for asthma relapse, and immunoglobulin E, interferon-gamma, and interleukin-4 after treatment, and the low sample size in most of the selected studies (10 studies \leq 100 subjects). Factors including the children's age, gender, compliance, ethnicity, and nutritional status of patients were also possible bias-inducing factors. Some unpublished studies and missing data may cause a bias in the pooled effect. Patients were using different main pharmacological medicines, different management schedules, dosages, and health care systems.

5. Conclusions

Acupoint herbal patching as an add-on to asthma medication during Sanfu days had a significantly lower frequency of acute attack, lower asthma relapse, and higher forced expiratory volume in 1 second, higher peak expiratory flow rate, lower immunoglobulin E after treatment, and higher interferon-gamma after treatment in asthmatic children compared to asthma medication only in asthmatic children. However, acupoint herbal patching as an add-on to asthma medication during Sanfu days had no significant effect on interleukin-4 after treatment compared to asthma medication only in asthmatic children. Further studies are needed to confirm these findings. However, the analysis of results should be done with carefulness due to the low number of studies for some parameters studied and the low sample size in most of the included studies in the meta-analysis; recommending the requirement for more studies to confirm these findings or probably to significantly affect the confidence in the effect assessment.

Author contributions

Xinsheng Liu: search, analysis, writing.

Jing Li: search, analysis, reviewing.

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