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REVIEW ARTICLE

Clinical effectiveness of traditional Chinese medicine in modulating intestinal microbiota for pediatric *Mycoplasma pneumoniae* pneumonia: A systematic review and meta-analysis

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Abstract

This research aimed to perform a preliminary meta-analysis to comprehensively examine the effectiveness and safety of herbal medicines in modulating the intestinal microbiota of pediatric patients suffering from *Mycoplasma pneumoniae* pneumonia (MPP). A systematic search of seven databases was conducted in March 2024. The included randomized controlled trials were evaluated using the Risk of Bias (ROB) 2.0 tool, as recommended in the Cochrane Handbook. The analysis included a total of 11 studies, with a combined sample of 880 children. Traditional Chinese medicine (TCM) significantly enhanced the clinical outcomes of pediatric cases of MPP compared to Western medicine or symptomatic treatment. The meta-analysis results indicated that TCM significantly improved total clinical effectiveness (risk ratio = 1.19, 95% confidence interval [CI]: 1.13, 1.26), increased *Bifidobacterium bifidum* count (mean difference [MD] = 1.404, 95% CI: 1.180, 1.628), reduced serum interleukin-6 levels (MD = −4.665, 95% CI: −8.191, −1.139), and shortened the time required for rales to resolve (MD = −1.790, 95% CI: −1.951, −1.629) compared to the Western medicine group, with all differences being statistically significant at $p < 0.05$. Regarding safety, TCM modulation of the intestinal microbiota in treating pediatric mycoplasma pneumonia did not result in a higher incidence of adverse reactions, with the difference being statistically non-significant ($p > 0.05$). The ROB 2.0 assessment indicated potential bias, and the literature quality was moderate, necessitating future validation by higher-quality studies. The clinical effectiveness of intestinal microbiota-targeted TCM modulation in treating pediatric mycoplasma pneumonia was superior to Western medicine-only treatment, offering significant advantages in reducing inflammatory cell infiltration, shortening the time for rales to resolve, and demonstrating a better safety profile. However, future high-quality, large-scale clinical trials are needed to verify these findings.

Keywords: Intestinal microbiota; *Mycoplasma pneumoniae*; Traditional Chinese medicine; Systematic review; Meta-analysis; Clinical effectiveness of treatment

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1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a respiratory tract infection caused by *M. pneumoniae*. This bacterium induces an immune response that leads to lung damage

and can involve multiple organ systems, resulting in a wide range of extrapulmonary manifestations.[1-4] MPP is endemic worldwide, with regional pandemics occurring every 3 – 8 years.[5] In the past few years, there has been a trend of increased incidence, particularly among school-age children. For treatment, macrolides are the drugs of choice, but their widespread use has led to the development of genetic mutations in *M. pneumoniae*, resulting in drug resistance.[6] New tetracyclines are effective in improving symptoms but are prone to causing adverse reactions.[7] Antibiotic therapy can also lead to gastrointestinal and renal damage, as well as other adverse reactions in children.[8] Therefore, improving the safety and effectiveness of treatments for *M. pneumoniae* remains an important area for further exploration and research.

It has been found that[9] beneficial intestinal bacteria are effective in reducing pathogenic bacteria, restoring the gut mucosal barrier, and reducing the inflammatory response in children with MPP. Meanwhile, traditional Chinese medicine (TCM) has shown particular benefits in treating MPP and has yielded some positive outcomes[10,11]. However, it should be noted that the number of randomized controlled trials (RCTs) investigating the treatment of MPP from a gut flora perspective is still relatively small. In addition, some studies have issues, such as insufficient quality, and there is a lack of a comprehensive and objective systematic review and meta-analysis. Therefore, the aim of this study is to rigorously assess and validate the effectiveness and safety of TCM modulation of intestinal microbiota in treating MPP in children through high-quality clinical RCTs. We employ systematic review and meta-analysis to provide reliable, evidence-based medical support for clinical practice.

2. Materials and methods

This study has been registered with the International Prospective Register of Systematic Reviews, under registration number CRD42025632325. After registration, a meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[12] and the Cochrane Handbook for Systematic Reviews of Interventions.[13] The PRISMA checklist, which has been thoroughly completed, is appended in Table S1.

2.1. Eligibility criteria

Studies that met the following criteria were considered eligible for analysis:

(1). Research type: RCTs

(2). Participants: Participation must meet the diagnostic criteria for MPP in pediatric patients,[14,15] including patients with mild and severe pneumonia, with no restrictions on gender or case origin

(3). Intervention measures: Measures in the intervention group were focused on utilizing Chinese herbal medicine either solely or in conjunction with Western medicine

(4). Results: The main outcome was the overall clinical effectiveness rate. Secondary outcomes included changes in intestinal microbiota counts, time to resolution of rales, serum levels of the inflammatory cytokine interleukin (IL)-6, and adverse effects

(5). Criteria for clinical effectiveness: The clinical effectiveness was categorized as follows: disappearance of fever, cough, sputum, lung wet rales, and other symptoms; post-treatment was considered "markedly effective;" symptom improvement after treatment was classified as "effective;" lack of symptom relief after treatment was deemed "ineffective." The overall effectiveness rate was calculated as the sum of the markedly effective and effective rates.[16]

2.2. Search strategy

Comprehensive searches were conducted in several databases, including PubMed, Embase, Chinese Biomedical Literature Database (SinoMed), Cochrane Library, China National Knowledge Infrastructure, Wanfang, and VIP. Each database was searched for articles published from its inception until March 2024, including both English and Chinese-language articles. The retrieval strategy employed Medical Subject Headings and freeform terms. Detailed retrieval strategies for each database are provided in Table S2.

2.3. Research selection

The retrieved documents were imported into EndNote, a reference management tool, to eliminate duplicates. Subsequently, the remaining documents were read in full by two independent reviewers and re-screened based on the inclusion and exclusion criteria. Disagreements were resolved by a third party, and the final screening results were double-checked for accuracy.

Data pertinent to the literature were extracted using an Excel spreadsheet, encompassing: (i) fundamental details of the included studies, such as the principal author's name and publication year; (ii) primary characteristics of the study subjects, including age, gender, and the duration of illness; (iii) details of the interventions, including the specific implementation process, medications used, and treatment duration; (iv) key elements for assessing bias risks within the studies, such as the comparability of baseline characteristics, group randomization, and implementation of blinding; and (v) outcome data, including overall clinical effectiveness, time to resolution of rales, serum

inflammatory factor IL-6 levels, and changes in intestinal microbiota counts.

2.4. Risk of bias (ROB) in individual studies

The Cochrane Collaboration's ROB 2.0 tool was employed to evaluate the ROB in the literature that we reviewed. The evaluation covered six domains: (i) randomization bias; (ii) bias due to deviations from intended interventions; (iii) outcome measurement bias; (iv) bias caused by missing outcome data; (v) bias in the reporting of selected results; and (vi) overall bias. Based on these criteria, studies were classified as having a low, moderate, or high ROB.[17]

2.5. Statistical analysis

The statistical software Stata 12 was used to analyze the included studies. Given the study aimed to assess the effectiveness of TCM in treating MPP in pediatric patients, a random-effects model was applied when the study count was adequate. A fixed-effects model was used only when the sample size was small ($k < 5$). Heterogeneity was assessed using the I^2 test, with I^2 values interpreted as follows: <25% indicating low heterogeneity, $25\% \leq I^2 < 50\%$ indicating moderate heterogeneity, and ≥50% indicating high heterogeneity. Sensitivity analysis was carried out to evaluate the stability of results in the presence of heterogeneity. The risk ratio (RR) was used as the effect size measure for categorical outcomes, and the weighted mean difference (MD) was used for continuous outcomes, both accompanied by 95% confidence intervals (CIs). Differences were considered statistically significant at $p < 0.05$. In addition, when the number of studies exceeded 10, a funnel plot was generated to evaluate publication bias, where symmetry within the funnel plot indicated no bias. Egger's test was also performed for a quantitative analysis of publication bias.

3. Results

3.1. Database search

A total of 99 papers were initially screened, and 44 were identified as duplicates. Thirty-seven papers were excluded for non-compliance with the inclusion criteria: non-RCT studies, animal experimental studies, theoretical mechanism of action studies, mismatched interventions, outcome indicators, and inclusion/exclusion criteria. Ultimately, 11 papers[18-28] were selected for comprehensive analysis. The literature screening process is depicted in Figure 1.

3.2. Study characteristics

A total of 930 patients were initially considered, with 465 in the treatment group and 465 in the control group. Ultimately, 880 cases were included in the statistical analysis, comprising 455 in the experimental group and 457 in the control group. No statistically significant differences were observed when comparing the baseline characteristics of both groups (Table 1).

3.3. Results of literature quality evaluation

The risk assessment of the included literature is depicted in Figure 2. Regarding bias in the randomization process, all 11 studies employed the random number table method for random assignment and were rated as having a low ROB. However, none of the studies reported a concealed allocation sequence and were therefore being rated as having an unknown risk. Seven studies[18,21-25,28] had a single author, suggesting a higher likelihood that the trial intervention was administered by the same individual who evaluated the outcomes. This could potentially introduce bias due to the evaluator's awareness of the trial intervention, and these studies were rated as having a high ROB. In terms of missing data, ten studies[18,19,21-28] reported no cases of withdrawal, and the data were complete. The study by Li and Bai20 reported 10 dropouts in the experimental group and eight in the control group.

3.4. Meta-analysis

3.4.1. Clinical effectiveness

A total of 11 RCTs, comprising 880 patients, were included in the analysis of overall clinical effectiveness.18-28 The results of the heterogeneity test indicated significant heterogeneity ($\chi^2 = 27.93$, $p = 0.002$, $I^2 = 64.2\%$; Figure 3A). Consequently, a random-effects model was used for the meta-analysis. The analysis revealed a pooled RR of 1.19, 95% CI (1.13, 1.26), $p < 0.001$, indicating that the cure rate for children with MPP treated with TCM was 19% higher than that of the control group, and this difference was statistically significant.

3.4.2. Quantitative changes in Bifidobacterium counts

Regarding the change in *Bifidobacteria* count, four studies were included in this analysis.20,25,26,28 The heterogeneity test showed no significant heterogeneity ($p = 0.119$, $I^2 = 48.7\%$), so a fixed-effects model was applied (Figure 3B). The analysis revealed a significant difference in the change in *Bifidobacterium* counts between the two groups (MD = 1.404, 95% CI: 1.180, 1.628, Z = 12.30, $p < 0.05$), with the TCM group showing a significant increase in *Bifidobacteria* count compared to the control group.

3.4.3. Serum inflammatory factor IL-6 levels

Regarding serum IL-6 levels, four studies18,21-23 reported on this parameter. The analysis showed significant heterogeneity ($p = 0.00$, $I^2 = 93.3\%$), so a random-effects

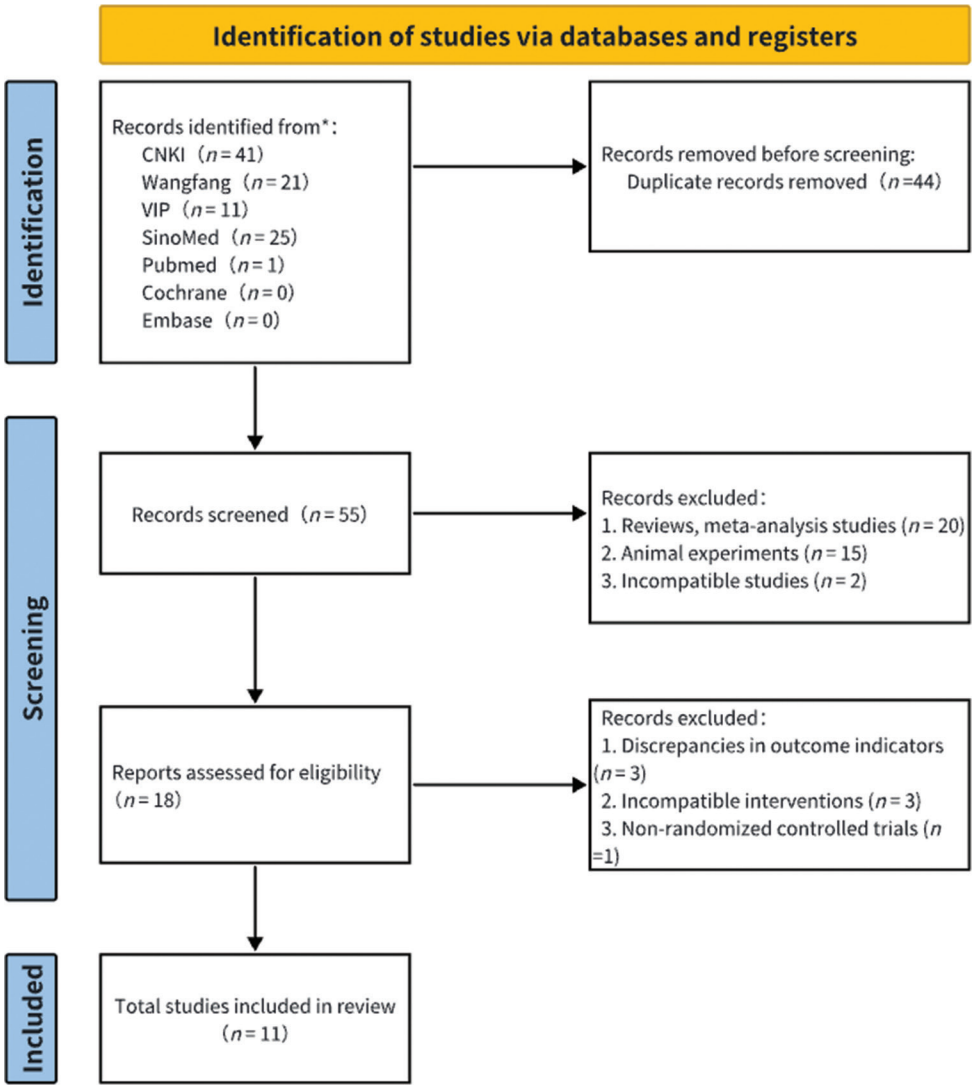


Figure 1. Flowchart of the literature screening process for the treatment of mycoplasma pneumonia with traditional Chinese medicine modulating intestinal microbiota
Abbreviation: CNKI: China National Knowledge Infrastructure

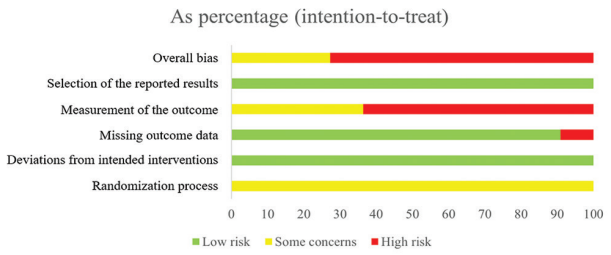


Figure 2. Bar chart of bias risk in relevant literature on the treatment of mycoplasma pneumonia based on intestinal microbiota using traditional Chinese medicine

model was used (Figure 3C). The results indicated that IL-6 levels were significantly lower in the TCM and Western medicine combined group compared to the Western medicine-only group. After excluding the study with high heterogeneity,18 the analysis showed no heterogeneity ($p = 0.535$, $I^2 = 0.0\%$). The MD was −5.803 (95% CI: −6.938, −4.668, Z = 10.02, $p < 0.05$), indicating a significant reduction in IL-6 levels.

3.4.4. Time to resolution of pulmonary rales

Regarding the time to rale resolution, four studies were involved.[19,20,22,28] Significant heterogeneity was observed among the studies ($p = 0.00$, $I^2 = 85.6\%$), so a random-effects model was used (Figure 3D). A significant difference was observed in the time for rales to resolve between the two groups (MD = −2.126, 95% CI: −2.718, −1.534,

Table 1. Baseline characteristics of the included studies

Study ID	Gender (male/female)	Sample size (I/C)	Age (mean or range, years)	Course (mean or range, days)	Intervention versus control	Therapy duration	Outcomes
Hua[28]	I, 19/24	I, 43	I, 5.22±1.90	I, 6.25±2.36	A versus G	5 days	(a) (b) (c)
	C, 21/22	C, 43	C, 5.16±1.83	C, 6.52±2.41			
Zhong[24]	I, 32/25	I, 62	I, 4.81±1.05	I, 9.53±1.74	E versus H	2 weeks	(a) (d) (e) (f)
	C, 41/21	C, 62	C, 4.76±1.01	C, 9.62±1.79			
Di *et al.*[27]	I, 26/19	I, 45	I, 7.09±2.43	I, 3.45±1.09	A versus G	2 weeks	(a) (d) (f) (g) (h) (i) (j)
	C, 24/21	C, 45	C, 7.14±2.38	C, 3.29±1.04			
Yang[23]	I, 17/15	I, 32	I, 6.59±1.62	I, 22.15±1.94	B versus J	20 days	(a) (d) (e) (g)
	C, 18/14	C, 32	C, 6.63±1.45	C, 22.63±1.88			
Bao and Jiang[26]	I, 14/16	I, 30	I, 4.63±1.16	I, NR	A versus H	5 days	(a) (b) (f) (g) (k)
	C, 16/14	C, 30	C, 4.63±1.13	C, NR			
Huang[18]	I, 16/14	I, 30	I, 4.70±2.37	I, 7.53±2.46	A versus H	1 week	(a) (d) (g)
	C, 12/18	C, 30	C, 5.17±2.93	C, 6.97±2.75			
Liu[21]	I, 31/25	I, 56	I, 7.91±1.05	I, 4.45±1.37	F versus K	21 days	(a) (d) (f) (h) (l) (m) (n)
	C, 32/24	C, 56	C, 7.97±1.09	C, 4.35±1.35			
Sha[22]	I, 19/15	I, 34	I, 6.53±1.34	I, 11.09±0.41	B versus J	14 days	(a) (d) (f) (h) (k)
	C, 18/16	C, 34	C, 6.50±1.32	C, 11.16±0.27			
Bao[25]	I, 14/16	I, 30	I, 4.63±1.16	I, NR	D versus L	5 days	(a) (b) (c) (f) (n)
	C, 17/13	C, 30	C, 4.47±1.14	C, NR			
Li and Bai[20]	I, 30/25	I, 55	I, 3.6±1.72	I, 5.5±1.9	A versus G	2 weeks	(a) (b) (d) (e) (k)
	C, 28/27	C, 55	C, 3.6±1.37	C, 5.8±1.2			
Ke[19]	I, 27/21	I, 48	I, 7.6±2.6	I, 6.5±3.5	D versus L	2 weeks	(a) (g) (o) (p)
	C, 26/22	C, 48	C, 7.5±2.4	C, 6.3±3.4			

Notes: "I" denotes the intervention group, and "C" denotes the control group. The "I/C" or "Intervention and Control" column outlines the specific definitions of all treatment interventions as follows: A, traditional Chinese medicine combined with conventional treatment; B, traditional Chinese medicine combined with conventional treatment and azithromycin; D, traditional Chinese medicine combined with azithromycin; E, traditional Chinese medicine acupressure combined with conventional treatment and budesonide; F, traditional Chinese medicine acupressure combined with a bacterial lysis product capsule; G, conventional treatment; H, conventional treatment and budesonide; J, conventional treatment and azithromycin; K, a bacterial lysis product capsule; L, azithromycin. The meanings of the "Outcomes" column are as follows: (a) indicates clinical efficacy; (b) indicates changes in intestinal microbiota; (c) denotes fecal sIgA levels; (d) denotes inflammatory markers; (e) refers to cellular immune function; (f) refers to adverse reactions; (g) indicates traditional Chinese medicine syndrome elements; (h) indicates pulmonary function indices; (i) denotes salivary sIgA levels; (j) denotes hBD2 levels and fecal CAL content; (k) refers to symptom resolution time; (l) refers to Toll-like receptor 4 levels; (m) indicates nuclear factor κB mRNA levels; (n) indicates immunoglobulin levels; (o) denotes clinical treatment outcomes; (p) denotes the comparison of CD4+CD25+Treg % and CD4+Foxp3+Treg % pre- and post-treatment. Abbreviations: CAL: Fecal calprotectin; CD: Cluster of differentiation; Foxp3: Forkhead box P3; hBD2: Human beta-defensin-2; mRNA: Messenger RNA; sIgA: Secretory immunoglobulin A; Treg: Regulatory T cell.

$Z = 7.04$, $p < 0.05$), with a shorter time for rales resolution in the TCM and Western medicine combined group compared to the Western medicine-only group. After excluding the study by Li and Bai,20 no heterogeneity was observed ($p = 0.916$, $I^2 = 0.0\%$, $Z = 21.8$, $p < 0.05$), further confirming the superiority of the combined treatment.

3.4.5. Adverse events

A total of five studies[19,21,22,27,28] were included in the analysis of reported adverse reactions and their incidence, which included loss of appetite, nausea, vomiting, abdominal discomfort, dizziness, headache, rash, and malaise. Four studies[19,21,22,28] found no significant difference in the incidence of adverse reactions between the two groups, while one study[27] reported a lower incidence in the TCM and Western medicine combined group. No serious adverse reactions were reported in either group across all studies. The meta-analysis revealed no significant difference in adverse reaction incidence between the groups (RR = 0.666, 95% CI: 0.364, 1.221, $p = 0.189$), indicating that TCM treatment does not increase the risk of adverse events during MPP treatment. The results are shown in Figure 4.

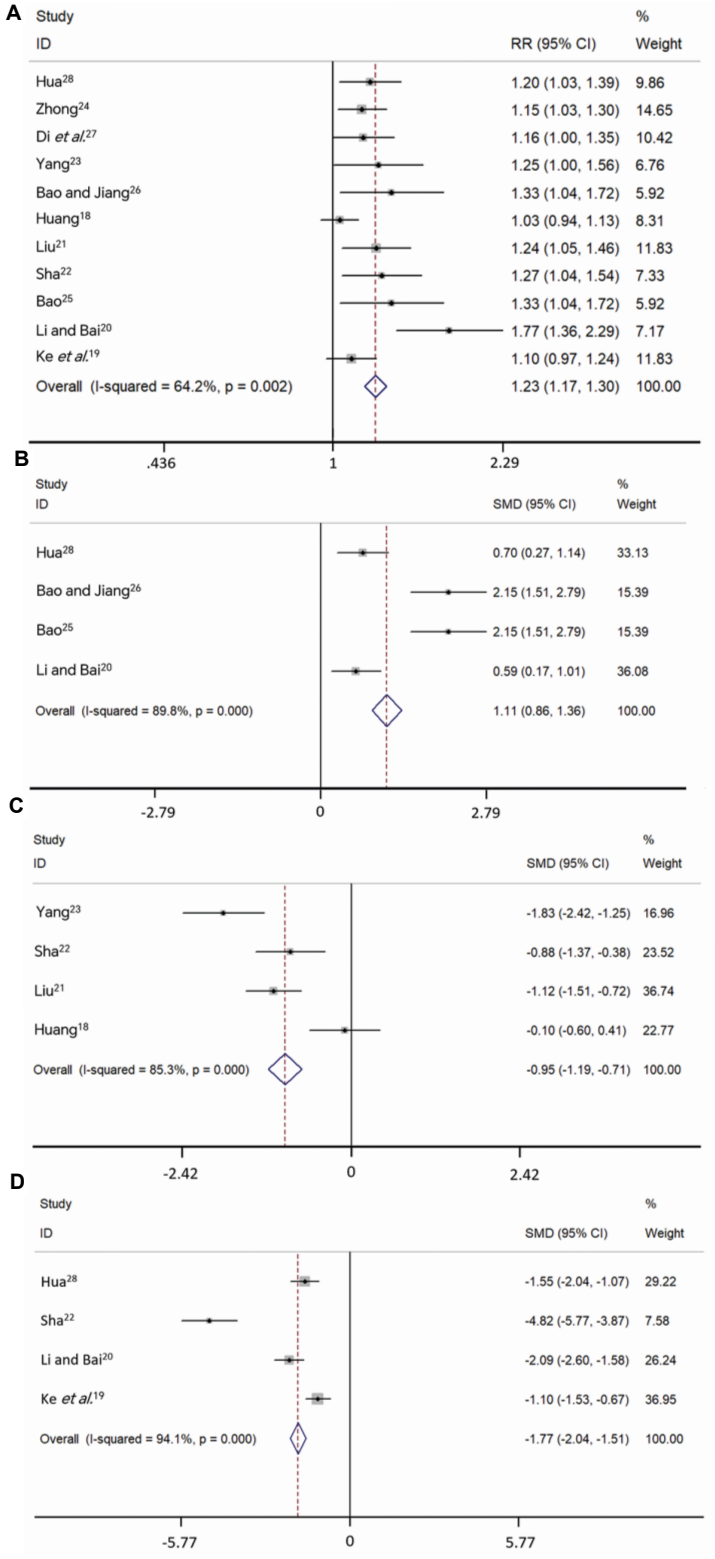


Figure 3. Forest plots of the meta-analyses. (A) Forest plot showing the total clinical effectiveness comparing patients treated for mycoplasma pneumonia with TCM, based on intestinal microbiota. (B) Forest plot depicting changes in *Bifidobacterium bifidum* counts. (C) Forest plot illustrating interleukin-6 levels. (D) Forest plot of the time to rhonchi resolution.
Notes: The effect size is presented as risk ratios (RRs) with 95% confidence intervals (CIs). The vertical line (RR=1) represents no effect
Abbreviation: SMD: Standardized mean difference.

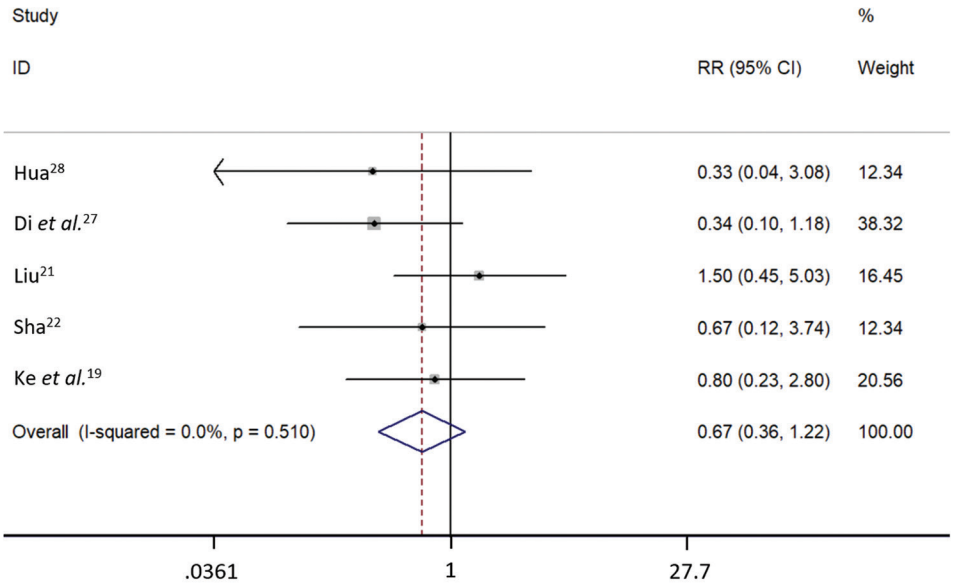


Figure 4. Meta-analysis of the incidence of adverse reactions
Notes: The effect size is presented as risk ratios (RRs) with 95% confidence intervals (CIs). The vertical line (RR=1) represents no effect.

3.5. Subgroup analyses

Subgroup analyses of total clinical effectiveness, stratified by different treatment types, are depicted in Figure 5. In terms of clinical effectiveness, all intervention groups showed significant statistical differences, except for the comparison between Western medicine and Chinese medicine acupressure (RR = 1.211, 95% CI: 1.116, 1.315, $p < 0.05$).

3.6. Sensitivity analysis and publication bias assessment

The meta-analysis, conducted using a random-effects model, revealed significant heterogeneity in the total clinical effectiveness ($p = 0.002$, $I^2 = 64.2\%$). The results of the publication bias assessment, shown in Figure 6, indicated asymmetry in the funnel plot, with the left and right sides not being balanced. In addition, a quantitative analysis using Egger's test yielded $p < 0.05$, suggesting the presence of publication bias. Potential reasons for this bias include the relatively low quality of the included studies, small sample sizes, varying severity of MPP in children, diverse interventions and treatment durations, as well as the challenges associated with publishing negative findings.

A sensitivity analysis was performed by sequentially removing individual studies, as depicted in Figure 7. Excluding the study by Li and Bai20 substantially reduced heterogeneity ($I^2 = 34.7\%$, $p = 0.131$), and the pooled results remained stable, indicating increased robustness of the findings, as shown in Figure 8.

3.7. Incorporation of analyses of TCM formulas

A total of 11 herbal formulations, comprising 40 traditional Chinese medicinal herbs, were identified across the 11 studies analyzed. The specific distribution of these herbs is shown in Figure 9. The names of the herbs are listed in Table 2, while the specific formulas are detailed in Table 3. Statistical analysis revealed that *Ephedra sinica* Stapf, *Amygdalus communis* L., *Gypsum fibrosum*, and *Glycyrrhiza uralensis* Fisch. were the most frequently used herbs, which correspond to the composition of Maxing Shigan Decoction, a classic TCM formula used to treat pneumonia associated with cough and dyspnea. Notably, the prescription used in the study by Sha[22] and Ke *et al.*[19] differed from those in other studies, likely due to the different stages of MPP that they were investigating. Maxing Shigan Decoction, first recorded in the *Treatise on Cold Damage Disorders*, consists of *E. sinica* Stapf, *A. communis* L., *G. fibrosum*, and *G. uralensis* Fisch. It is primarily used to treat symptoms such as fever, cough, and dyspnea caused by exterior "wind-cold" (a TCM concept referring to an external pathogenic factor that causes chills, nasal congestion, and respiratory discomfort) and interior heat accumulation. The formulation is believed to have the effects of dispersing "wind-heat" (a TCM concept referring to pathogenic heat accumulation in the body) to relieve fever and clearing the lungs to alleviate cough and dyspnea. In clinical practice, modifications to the basic formula can be made based on the specific symptoms of patients. For instance, *Morus alba* L. and *Draba nemorosa* L. may be added for patients with severe expectoration, whereas *Anemarrhena asphodeloides* Bge. and *Scutellaria baicalensis*

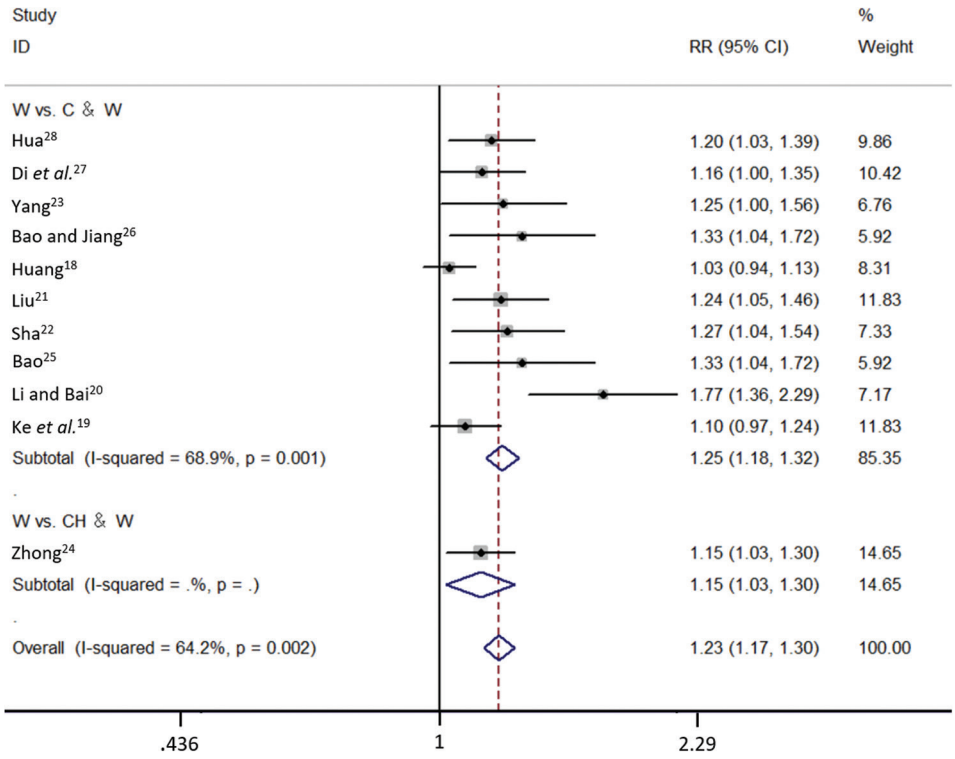


Figure 5. Subgroup analysis of total clinical effectiveness.
Notes: The effect size is presented as risk ratios (RRs) with 95% confidence intervals (CIs). The vertical line (RR=1) represents no effect. "W" stands for the Western medicine group; "CH" refers to the Chinese herbal medicine acupoint plaster therapy group; "C and W" denotes the group combining Western medicine and TCM; and "CH and W" indicates the group integrating Western medicine with Chinese herbal medicine acupoint plaster therapy.

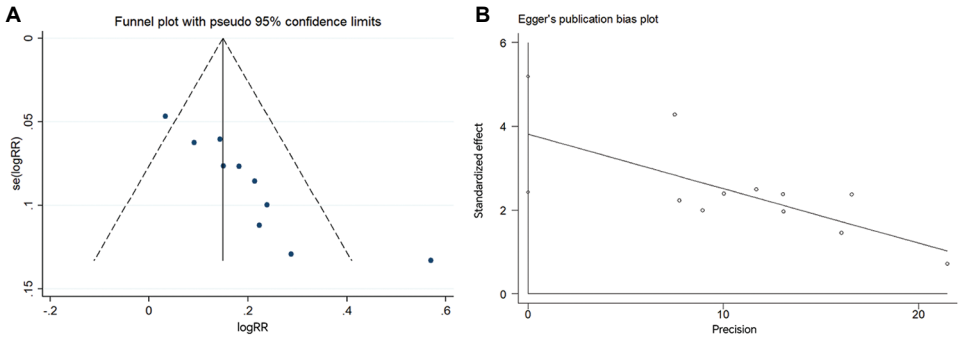


Figure 6. Funnel plot (A) and Egger's test plot (B) for the comparison of the total clinical effectiveness rate of traditional Chinese medicine based on intestinal microbiota in the treatment of mycoplasma pneumonia, as reported in the relevant literature
Abbreviation: RR: Risk ratio; SE: Standard error.

Georgi may be incorporated for those with severe fever. Maxing Shigan Decoction[29] is a commonly used formula in TCM for treating pneumonia-related diseases, and multiple studies[30,31] have demonstrated its favorable effectiveness and safety.

4. Discussion

This study aimed to further validate the potential effectiveness and safety of Chinese medicine modulated by intestinal microbiota in the treatment of MPP. Eleven RCTs involving 880 children with MPP were included, following a systematic review of seven national and multinational databases. These 11 RCTs encompassed treatments commonly used for MPP in both Chinese and Western medicine, including tonics such as Ma Xing Shi Gan Tang, antipyretic drugs combined with antibiotics, and symptomatic treatments. The meta-analysis confirmed that Chinese medicine modulated by the intestinal

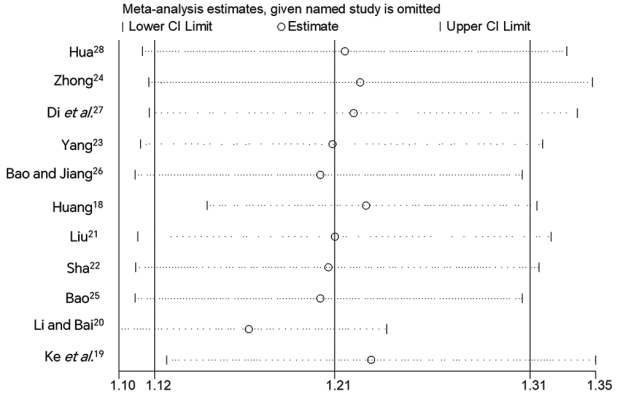


Figure 7. Sensitivity analysis of the total clinical effectiveness rate of traditional Chinese medicine based on intestinal microbiota in the treatment of *Mycoplasma pneumoniae* pneumonia
Abbreviation: CI: Confidence interval.

microbiota significantly improved the clinical effectiveness rate in children with MPP (RR = 1.19, 95% CI: 1.13, 1.26). Furthermore, the experimental group, as compared to the control group, accelerated the resolution of rales in children by 2.126 days and significantly influenced IL-6 levels and *Bifidobacterium* counts, indicating a clear treatment effect.

4.1. Significance of the study

This research aimed to confirm the potential effectiveness and safety of Chinese medicine, modulated by gut flora, in treating MPP. *M. pneumoniae* is a primary pathogen responsible for community-acquired pneumonia, accounting for approximately 8 – 40% of children hospitalized with community-acquired pneumonia. Studies have indicated a decrease in the age of onset in children with *M. pneumoniae*, accompanied by refractory and multisystem complications,[32] posing a significant threat to the life and health of children. In addition to common extrapulmonary complications, *M. pneumoniae* is emerging as a pathogen in acute pharyngitis in children, causing persistent paroxysmal coughing often associated with frequent pediatric pharyngitis,[33,34] although further verification through extensive clinical trials is required. At present, macrolides are commonly used as first-line drugs in Western medicine. However, Guo *et al.*[35] found that mutations in drug-resistant genes can prolong fever and cough duration in children with *M. pneumoniae*, necessitating the addition of tetracyclines to control further infection development[36]. Despite their use, antibiotics have several side effects, including abdominal pain, distension, nausea, vomiting, and other gastrointestinal symptoms.[37] Therefore, Western medicine alone cannot fully meet clinical needs. Chen[38] found that combining Western medicine with Chinese medicine soup therapy significantly improves cough duration, fever, and lung function indices in children while reducing the incidence of adverse reactions. The "lung-intestinal axis" in modern medicine aligns with the TCM concept of "the

Table 2. Names and sequential numbering of herbs

ID	Medicinal herb name
(1)	*Ephedra sinica* Stapf
(2)	*Amygdalus communis* L.
(3)	*Gypsum fibrosum*
(4)	*Glycyrrhiza uralensis* Fisch.
(5)	*Morus alba* L.
(6)	*Phragmites communis* Trin.
(7)	*Anemarrhena asphodeloides* Bge.
(8)	*Trichosanthes kirilowii* Maxim.
(9)	*Houttuynia cordata* Thunb.
(10)	*Draba nemorosa* L.
(11)	*Pheretima aspergillum*
(12)	*Lonicera japonica* Thunb.
(13)	*Curcuma aromatica* Salisb.
(14)	*Forsythia suspensa* (Thunb.) Vahl
(15)	*Bombyx mori* L.
(16)	*Bupleurum chinense* DC.
(17)	*Pueraria lobata* (Willd.) Ohwi
(18)	*Asarum sieboldii* Miq.
(19)	*Citrus aurantium* L.
(20)	*Paris polyphylla* Smith var. chinensis (Franch.) Hara
(21)	*Ilex pubescens* Hook. et Arn.
(22)	*Rheum palmatum* L.
(23)	*Fritillaria thunbergii* Miq.
(24)	*Ophiopogon japonicus* (L.f.) Ker-Gawl.
(25)	*Scrophularia ningpoensis* Hemsl.
(26)	*Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. et Mey.
(27)	*Paeonia lactiflora* Pall.
(28)	*Mentha haplocalyx* Briq.
(29)	*Stemona sessilifolia* (Miq.) Miq.
(30)	*Scutellaria baicalensis* Georgi
(31)	*Adenophora tetraphylla* (Thunb.) Fisch.
(32)	*Ginkgo biloba* L.
(33)	*Schisandra chinensis* (Turcz.) Baill.
(34)	*Trichosanthes kirilowii* Maxim.
(35)	*Ligusticum chuanxiong* Hort.
(36)	*Phragmites australis* (Cav.) Trin. ex Steud.
(37)	*Coix lacryma-jobi* L.
(38)	*Benincasa hispida* (Thunb.) Cogn.
(39)	*Prunus persica* (L.) Batsch
(40)	*Ziziphus jujuba* Mill.

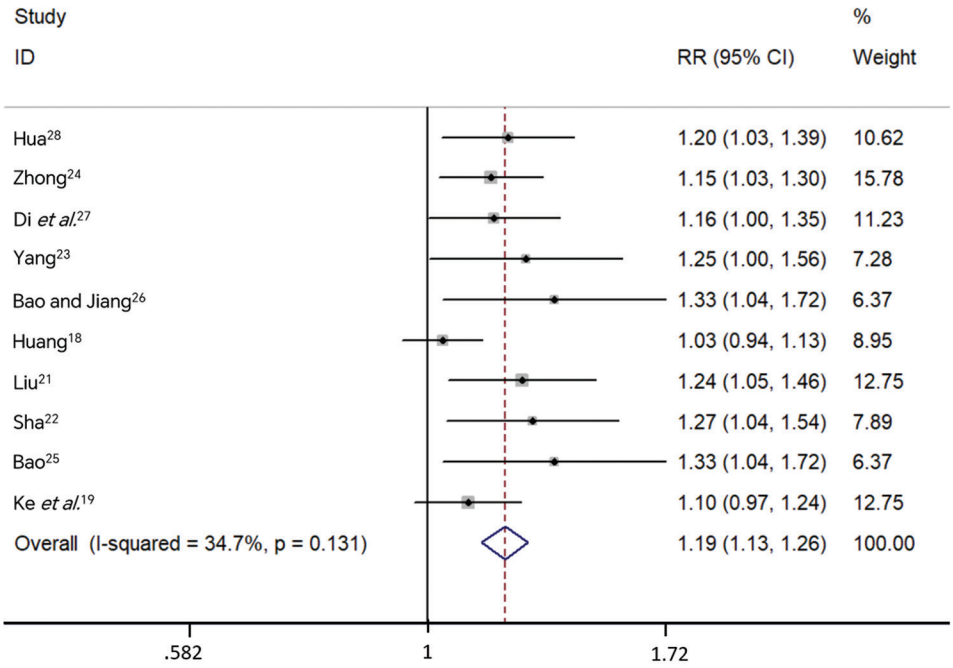


Figure 8. Forest plot comparing total clinical effectiveness of Chinese medicine based on gut flora in treatment of mycoplasma pneumonia post-sensitivity analysis
Notes: The effect size is presented as RRs with 95% CIs. The vertical line (RR=1) represents no effect
Abbreviations: CI: Confidence interval; RR: Risk ratio.

Table 3. Prescription and drug composition of Chinese medicines included in the study

Study ID	Herbal prescription	Herbal formula
Hua[28]	Maxing Shigan Tang	(1)(2)(3)(4)(5)(6)(7)(8)(9)
Zhong[24]	Chinese Herbal Plaster	(1)(2)(3)(10)(11)
Di *et al.*[27]	Xuanfei Tongluo Formula	(1)(2)(3)(4)(12)(13)(14)(15)(16)(17)
Yang[23]	Modified Wuhu Tang	(1)(2)(3)(4)(5)(18)(19)(20)(21)
Bao and Jiang[26]	Modified Xuanbai Chengqi Tang	(1)(2)(3)(4)(5)(8)(10)(19)(22)(23)
Huang[18]	Maxing Ganshi Tang	(1)(2)(3)(4)(22)
Liu[21]	Chinese Herbal Plaster	(1)(10)(18)(32)(33)
Sha[22]	Yangyin Qingfei Tang	(4)(8)(13)(23)(24)(25)(26)(27)(28)(29)(30)(31)
Bao[25]	Modified Xuanbai Chengqi Tang	(1)(2)(3)(4)(5)(10)(19)(22)(23)(34)
Li and Bai[20]	Modified Tingli Dazao Xiefei Tang	(1)(3)(5)(10)(30)(35)(40)
Ke *et al.*[19]	Modified Qianjin Weijing Tang	(3)(14)(16)(36)(37)(38)(39)

Note: The numbers in the parentheses can be referred to in Table 2.

lung and large intestine being mutually exclusive," and their combination can effectively improve the cure rate and safety of mycoplasma pneumonia. This offers a novel approach to the prevention and treatment of pediatric respiratory disorders.

The pathogenesis of MPP is primarily associated with immune evasion, adhesion, inflammatory damage, and cytotoxicity. *M. pneumoniae* colonizes the respiratory tract through specific adherence organelles. The bacterial components, metabolites, and toxins released by the organism induce inflammation and damage cells in various ways, ensuring pathogen survival through immune evasion.[39] Consequently, targeted therapy is particularly important for managing MPP.[40] Studies have shown that children with *M. pneumoniae* have significantly altered intestinal microbiota compared to healthy children.[41] T helper (Th) 1 and Th2 cells produce interferon-gamma (IFN-γ) and serum IL-4, respectively, and regulate each other to maintain normal immune status.[42] In contrast, pneumonia induces elevated levels of IFN-γ and IL-4, which kill inflammatory cells and affect the transcription and secretion of pro-inflammatory cytokines. Hu *et al.*[43] found that the serum levels of IFN-γ and IL-4 in pediatric patients with MPP increased as the abundance of intestinal microbiota decreased. *Bifidobacterium bifidum* in the intestinal microbiota can regulate Th1/Th2 and Th17/regulatory T (Treg) cell balance. By downregulating IL-4 levels, it prevents the activation of the STAT6 signaling pathway by JAK kinases, thereby enhancing

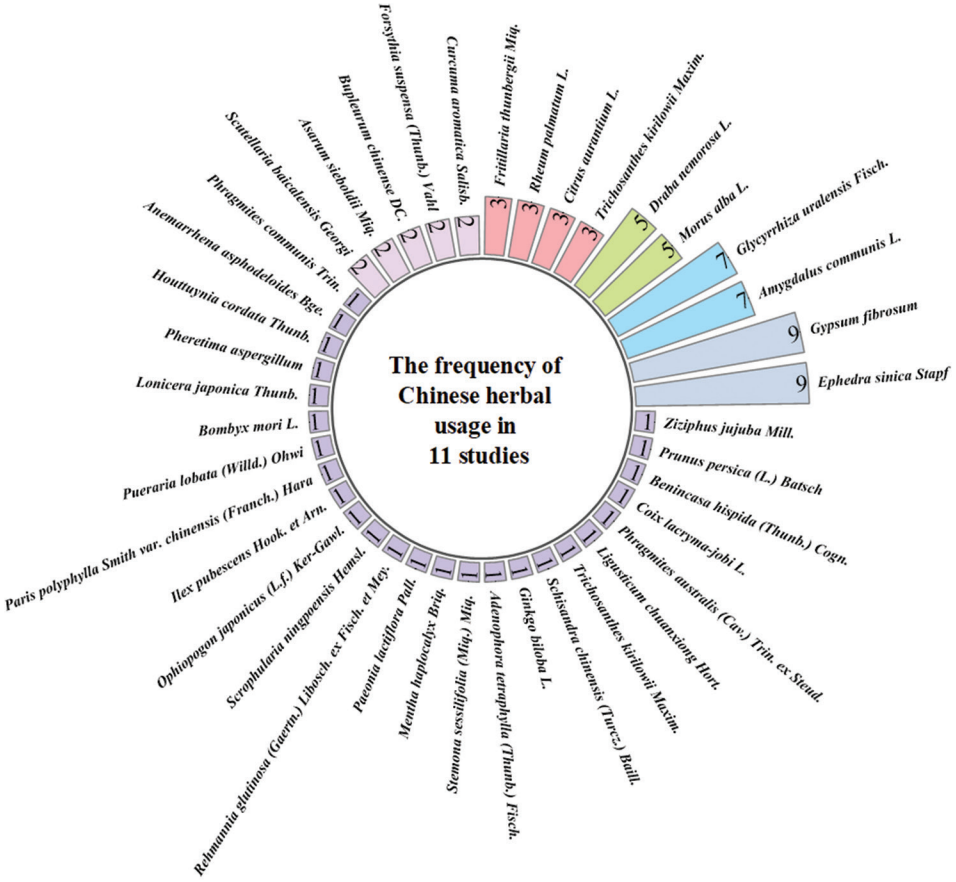


Figure 9. Radial bar chart depicting the frequency of each traditional Chinese medicinal herb. Each study utilized only one herb, and the frequency of an herb represents the number of studies in which it was included.

autoimmunity.[32] In addition, *B. bifidum* has been shown to effectively repair mucosal barriers. It also plays a crucial role in the repair of mucosal barriers by inhibiting the colonization and growth of harmful bacteria and promoting the proliferation of beneficial bacteria.

4.2. Analysis of potential mechanisms

The symptoms of MPP in TCM are categorized as "pneumonia with wheezing and coughing," a term first appearing in *The Ma Ke Living People Book*, which states: "wheezing without phlegm, and nasal instigators." TCM diagnoses and treatments are divided into various patterns, including wind-cold impeding the lung, wind-heat impeding the lung, phlegm-heat impeding the lung, toxic-heat impeding the lung, lung yin deficiency, and lung and spleen qi deficiency.[44] According to the TCM theory that "the lung and the large intestine are mutually exclusive," clinical treatments often aim to promote lung function and support the passage of internal organs, using methods such as the descending reverse cough technique. Commonly used formulas, such as Ma Xing Shi Gan Tang, Dabanxia, and Xuan Bai Cheng Qi Tang, have shown effectiveness.[40]

4.2.1. Immunomodulatory and anti-inflammatory effects of Chinese medicines

Cytokine levels of tumor necrosis factor (TNF) α, IL-6, IL-1β, IL-4, IFN-γ, and IL-10 were significantly elevated in both mild and severe cases of childhood MPP, particularly in those with severe disease.[45] This phenomenon is associated with the recognition of *M. pneumoniae* lipid-associated membrane proteins by Toll-like receptor 4 (TLR4), which triggers a myeloid differentiation primary response gene 88-dependent signaling pathway. This pathway further activates the phosphatidylinositol 3-kinase- protein kinase B (Akt), mitogen-activated protein kinase (MAPK), and nuclear factor kappa-B (NF-κB) signaling pathways, resulting in the release of inflammatory cytokines, including TNF-α and IL-6. TNF-α disrupts immune homeostasis by enhancing Th1 cell function while suppressing Th2 cell function.46 IL-647exacerbates inflammatory responses by promoting

cell differentiation and inhibiting Th2 cell function.[48] This immune imbalance significantly contributes to various inflammatory diseases; thus, modulating the levels of TNF-α and IL-6 and restoring the Th1/Th2 balance are crucial strategies for treating these conditions (Figure S1). The active ingredients of Ma Xing Shi Gan Tang target cytokines such as TNF, IL-6, and IL-1β through various signaling pathways, regulating the immune system and inhibiting the inflammatory response.49 For example, using the Network Pharmacology–TCM Target method, Wang *et al.*[50] identified 1604 effector targets (e.g., TNF) through which Ma Xing Shi Gan Tang exerts its therapeutic effects on pneumonia. These targets were significantly enriched in 19 pathways (e.g., the NF-κB pathway). These findings further support the notion that Ma Xing Shi Gan Tang treats pneumonia through its antiviral, anti-inflammatory, and immunomodulatory effects. In addition, a study by Wang and Tao[51] confirmed that Ma Xing Shi Gan Tang, with modifications, can regulate Th1/Th2 and Th17/Treg cytokine levels in children with MPP, significantly reducing serum IFN-γ and IL-17 levels.

The pathogenesis of MPP is complex and remains incompletely understood. By comparing the baseline characteristics of healthy children and those with MPP, it was found that serum NF-κB, CXC motif chemokine ligand 8 (CXCL8), and soluble B7-H3 (sB7-H3) are closely associated with disease severity and prognosis in children with MPP,[52] with all three significantly elevated in the MPP group. NF-κB, a key regulator of the inflammatory signaling pathway, modulates the expression of various chemokines and inflammatory factors, such as IL-8 (CXCL8). Its activation is closely associated with the persistent increase in inflammatory response.[53] CXCL8,[54] a key mediator of the host immune response, is activated at sites of infection and injury, mediating neutrophil migration and attracting various inflammatory cells to lung tissues, thereby inducing tissue immune injury. sB7-H3, an immune regulatory molecule of the B7 family, activates downstream signaling pathways (e.g., the NF-κB pathway) at high levels, leading to chemokine activation, enhanced pro-inflammatory cytokine production, and subsequent immune system damage.[55-57] Therefore, inhibiting the NF-κB signaling pathway is crucial for reducing pro-inflammatory factors. It is noteworthy that the main active ingredients of Ma Xing Shi Gan Tang include formononetin, kaempferol, luteolin, naringenin, and quercetin. Among these, kaempferol, luteolin, and quercetin[58] – common to several herbs – are flavonoid compounds. Flavonoids have been shown[59] to interact with various molecules involved in the inflammatory pathway by targeting the NF-κB, MAPK, extracellular signal-regulated kinase, and Akt pathways. These interactions reduce the activities of cytokines, chemokines, and inflammatory enzymes, thereby exerting antibacterial, antioxidant, and anti-inflammatory effects. For example, quercetin strongly inhibits pro-inflammatory cytokines by inhibiting the phosphorylation of NF-κB p[65] and Akt, thereby reducing the release of IL-1β, IL-6, and TNF-α and exerting anti-inflammatory effects.[60,61] High mobility group protein B1 (HMGB1) is closely related to both innate and adaptive immunity and acts as an upstream regulator of the NF-κB pathway. Naringenin reduces HMGB1 levels and inhibits the activation of the HMGB1/NF-κB signaling pathway by downregulating HMGB1, NF-κB mRNA, and protein expression.[62] Similarly, Sangbaekpi extract inhibits the HMGB1/TLR4 signaling pathway.[63] Both compounds downregulate pro-inflammatory factors and upregulate anti-inflammatory factors, thereby modulating excessive immune responses and alleviating lung tissue injury.

4.2.2. Regulation of microbiota balance by TCM

Modern medicine has proposed the concept of the "lung-gut axis," which highlights the strong correlation between the lungs and intestines in terms of tissue origin, mucosal immunity, and ecological changes.[64] Budden *et al.*[65] suggests that the lung-gut axis is closely related to the microbiota and that bidirectional regulation of the microbiota can modulate immune responses and influence distal immune responses. Specifically, the lung microbiota may influence or be influenced by the intestinal microbial immune response. Therefore, regulating the balance of the intestinal microbiota and maintaining the intestinal mucosal immune system may improve the prognosis and therapeutic outcomes in children with MPP. Research findings indicate that herbal interventions can treat pulmonary diseases by modulating inflammatory factors, mucosal immunity, protein expression, and maintaining the homeostatic balance of pulmonary and intestinal microbiota.[66] Short-chain fatty acids (SCFAs), produced by the fermentation of undigested carbohydrates by anaerobic bacteria in the colon, regulate epithelial barrier function as well as mucosal and systemic immunity.[67,68] TCM has been shown to effectively increase the abundance of beneficial intestinal bacteria and promote the production of SCFAs through active ingredients such as polysaccharides and flavonoids, along with the synergistic effects of compound formulations. *S. baicalensis* polysaccharide has been shown to alter the composition of the intestinal microbiota, reduce the expression levels of TLR4 and NF-κB p65, inhibit the activation of the TLR4/NF-κB signaling pathway, and decrease the production of inflammatory factors.[69] Dong's experiment[70] demonstrated that, in cases of antibiotic-induced intestinal dysbiosis, the abundance of *Bifidobacteria* and *Lactobacilli* increased significantly,

while *Enterobacteriaceae* decreased following intervention with Ginseng Ling Baijusan, which mitigated antibiotic-associated adverse reactions.

Pneumolysin, one of the major virulence factors of *Streptococcus pneumoniae*,[71] enhances bacterial colonization and drug resistance, helping *S. pneumoniae* evade immune clearance by suppressing the host immune response.[72] Studies have shown[73] that pneumolysin can activate inflammatory signaling pathways in intestinal epithelial cells (e.g., NOD-like receptor family pyrin domain containing 3 [NLRP3]) inflammasome, leading to the release of pro-inflammatory factors (e.g., IL-1β, and IL-18) and triggering intestinal inflammation. Moreover, pneumolysin can increase intestinal permeability and disrupt barrier function by disrupting tight junction proteins (e.g., zona occluden-1 and occludin) in intestinal epithelial cells, thereby promoting the infection and spread of pneumonia. In contrast, a study by *Guo et al.*[74] found that Ma Xing Shi Gan Tang not only affects the oligomeric state of pneumolysin, reducing its activity and protecting the intestinal barrier but also promotes the production of beneficial intestinal bacteria and SCFAs, thereby alleviating pneumonia exacerbated by immune dysregulation.[75,76] Experimental results showed that Ma Xing Shi Gan Tang significantly attenuated lung pathological damage and reduced mortality in mice infected with *S. pneumoniae*. Rhodopsin inhibits the NLRP3 inflammasome-mediated neutrophil recruitment and lysis signaling pathways, thereby ameliorating lipopolysaccharide-induced lung injury.[77] Thus, herbal interventions can treat pulmonary systemic diseases by modulating relevant inflammatory factors, mucosal immunity, protein expression, and maintaining the homeostatic balance of the pulmonary and intestinal microbiota.

In exploring effective treatment options for MPP in children, the combination of TCM and Western medicine therapies has demonstrated unique advantages. Clinical practice has shown that[78] the use of pediatric elimination of accumulation and relieving cough oral solution, combined with doxycycline, can significantly shorten the duration of symptoms such as fever, cough, and lung rales, while effectively reducing levels of inflammatory markers such as TNF-α and C-reactive protein, compared to the doxycycline-only treatment group. Furthermore, the combination of Xuanbai Chengqi Tang and azithromycin effectively regulates immune imbalances in children with MPP and alleviates acute-phase symptoms.[79] In clinical settings, antibiotics directly inhibit or kill *M. pneumoniae*, demonstrating rapid onset of action and significant pathogen inhibition and anti-inflammatory effects. The combined use of TCM and Western medicines can regulate the immune system, reduce adverse reactions, and provide anti-inflammatory and antiviral effects through a multi-target and multi-component mechanism of action, considering the child as a whole. In conclusion, the combined treatment of MPP in children using TCM and Western medicines is both effective and safe, warranting extensive attention and in-depth research in both academic and clinical settings.

During our review, we identified RCTs of TCM based on intestinal microbiota modulation for the treatment of children with MPP, starting with changes in intestinal microbiota modulation by TCM. We conducted a meta-analysis of the 11 included studies using Stata 12.0 software. The results revealed that the overall clinical effectiveness rate of combining Western medicine and TCM for treating MPP in children was higher compared to Western medicine alone. The analysis indicated that the treatment with TCM increased the number of probiotics, such as *Bifidobacteria* and *Lactobacilli*, and reduced the count of pathogenic bacteria like *Enterobacteriaceae*, thereby improving the inflammatory response. Concurrently, immune function showed improvements, with increased levels of cluster of differentiation (CD)4^+ and the $CD4^+$/$CD8^+$ ratio in children, as well as increased levels of secretory immunoglobulin A in saliva and feces. In terms of inflammation, the level of TNF-α significantly decreased. The study's results demonstrated that TCM treatment for MPP offers significant advantages in enhancing clinical effectiveness and modulating the systemic immune response by regulating intestinal microbiota and restoring homeostasis in children. In the authors' view, TCM can mitigate the inflammatory response in children, ameliorate immune imbalances, enhance immune capabilities, and repair lung and intestinal mucosal barrier damage by modulating the intestinal microbiota, thereby achieving the goal of treating MPP.

4.3. Limitations and shortcomings

This study has several limitations: (i) some of the included studies had small sample sizes, and specific blinding implementation protocols were not reported, potentially affecting the stability and authenticity of the results; (ii) several studies did not mention adverse reactions or safety evaluations, which limits the completeness and comprehensiveness of this study; (iii) the trial group involved Chinese medicine therapy, and due to the limited coverage of such studies in foreign journals, the included literature was all in Chinese, with China as the primary study area, which may introduce potential bias; (iv) most of the literature did not address the children's follow-up status, and the absence of long-term follow-up data makes the trial's long-term effectiveness unclear, rendering

conclusions potentially subjective; (v) the difficulty in publishing negative results suggests a potential publication bias; and (vi) the methodology and quality of many included studies were suboptimal, necessitating further improvements.

5. Conclusion

Treatment with Chinese medicine resulted in an increase in the number of *Bifidobacteria* and *Lactobacilli* in the intestines of children with MPP, while reducing the number of harmful bacteria, thereby improving the microecological environment of intestinal microbiota. Furthermore, the incidence of adverse reactions was lower. Therefore, in clinical practice, the intestinal microbiota of children with MPP can be regulated through the multifaceted effects of TCM to maintain immune homeostasis, especially when combined with Western medical treatments to enhance clinical effectiveness. However, this study has several limitations, and its results should be viewed as a reference for clinical treatment. Therefore, large-sample, high-quality RCTs are necessary to validate these findings and provide more reliable evidence for clinical practice.

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Conflict of interest

The authors declare that they have no relevant financial interests or personal relationships that could influence the objectivity of the research presented in this paper.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The article and accompanying supplementary material provide a comprehensive overview of the original findings from this study. Any questions or inquiries can be directed to the corresponding author.

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