REVIEW
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Meta-analysis of the efficacy and safety of Ding-Chuan Tang in the treatment of pediatric cough variant asthma

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Competing interests
The authors declare no conflicts of interest.
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Abstract
Objective: To systematically evaluate the clinical efficacy and safety of Ding-Chuan Tang in the treatment of pediatric cough variant asthma (CVA). **Methods**: Randomized controlled trials on the treatment of pediatric CVA with Ding-Chuan Tang were searched by computer through the China Journal Full Text Database (CNKI), WanFang Digital Journal Full Text Database (WanFang Data), Vipe Chinese Science and Technology Journal Database (VIP), Pubmed Database, Ovid Database, Embase Database, etc. The search time was from database establishment to April 1, 2021. Based on the inclusion and exclusion criteria,the two researchers independently screened the literature, extracted information, and assessed the methodological quality evaluation of the literature, and Meta-analysis was performed by RevMan 5.4 software. **Results**: The final number of RCTs was included 17, including cases of affected 1308 children. According to the results of the Meta-analysis: the test group was significantly better than the control group in terms of clinical efficiency, percentage of first second force expiratory volume (FEV1%), percentage of peak expiratory flow rate (PEF%), time to treatment onset, time to the disappearance of symptoms, Chinese medicine symptom score, and recurrence rate; the difference in the incidence of adverse reactions between the two groups was not statistically significant. **Conclusion**: The clinical treatment of pediatric CVA with Ding-Chuan Tang is effective and does not increase the incidence of adverse reactions. However, the methodological and reporting quality of existing small-sample randomized controlled trials (RCTs) is low, so evidence of efficacy must be confirmed by rigorously designed large-sample clinical trials.

Keywords: Ding-Chuan Tang; pediatric cough variant asthma; Meta-analysis; systematic evaluation; randomized controlled trial

Background

Cough variant asthma (CVA) is a specific type of asthma in which chronic cough is the main or only clinical manifestation [1]. CVA, also known as cough asthma, is often diagnosed by a combination of bronchodilator tests, bronchial excitation tests, and allergen tests. This leads to the existence of clinical misdiagnosis or underdiagnosis, and the application of antibiotics is not effective [2]. If inappropriate treatment delays the disease, it can easily develop into typical asthma, which will hurt the physical and mental health of children [3]. In this regard, Western medicine mostly adopts inhaled glucocorticosteroids or oral leukotriene receptor antagonists, but the long-term combination of drugs has certain adverse effects, and children often have poor compliance with treatment and are prone to relapse after stopping the drugs, resulting in unsatisfactory results [4, 5]. According to "Meta-analysis of Randomized Controlled Clinical Literature on the Treatment of Cough Variant Asthma in Children", CVA is one of the major diseases diagnosed and treated by Chinese medicine, and many people seek and receive treatment [6]. Many physicians use TCM evidence-based treatment in combination with the overall situation of children with CVA, which can effectively control clinical symptoms, improve the cure rate, reduce adverse effects and reduce recurrence. In recent years, a large number of clinical studies have shown that the treatment of pediatric CVA with Ding-Chuan Tang has great advantages over Western medicine, with fewer toxic side effects and is easily accepted by children and parents. However, it is not clear whether there is enough reliable evidence to support it [7-9].

This study adopts the Cochrane systematic evaluation method to conduct a comprehensive search of randomized controlled trials (RCTs) on the treatment of CVA with Ding-Chuan Tang at home and abroad and to comprehensively analyze its efficacy and safety, to provide an effective evidence-based medical basis for clinical treatment and rational drug use.

Information and Methods

Inclusion Criteria

Type of literature Randomized controlled trial (RCT), with or without blinding and with or without follow-up. The language was limited to Chinese and English.

Subjects Subjects Age ≤ 14 years; the diagnosis was by the revised diagnostic criteria for CVA related to the National Collaborative Group for the Prevention and Control of Pediatric Asthma in 2013 [1].

Interventions The control group was given conventional western medicine treatment, and the experimental group was given Ding-Chuan Tang or its combination with conventional western medical treatment.

Outcome indexes ① Main index: the efficacy standard is efficiency, and the clinical treatment effect usually includes "clinical control", "apparent effect", "effective", and "ineffective". The effective rate refers to the percentage of children who meet the criteria of "clinical control", "apparent effect" and "effective" in the total number. ② Secondary indicators: percentage of first second expiratory volume (FEV1%); percentage of peak expiratory flow rate (PEF%); time of treatment onset; time of symptom disappearance; Chinese medicine evidence score. ③ Safety indicators included recurrence rate and adverse reactions.

Exclusion criteria

① non-randomized controlled clinical trial studies; ② interventions including other therapies; ③ study subjects not children; ④ study indicators not related to the outcome indicators of this Meta-analysis; ⑤ studies for which data could not be extracted due to incomplete baseline data or unavailability of the full text; ⑥ literature with repeated reports of study data and literature with obvious statistical analysis of data.

Search strategy

Two evaluators independently searched China Journal Full Text Database (CNKI), WanFang Digital Journal Full Text Database (WanFang Data), VIP Chinese Science and Technology Journal Database (VIP), Pubmed Database, Ovid Database, and Embase Database to collect the RCTs related to Ding-Chuan Tang for pediatric CVA, and the search time was from the establishment of the database to April 1, 2021. There was no restriction on the type of publication, but only in English and Chinese. The Chinese search terms included "Ding-Chuan Tang", "cough variant asthma", "asthma", "croup", "children", etc. The search terms in English included "Ding Chuan Tang", "Ding Chuan Decoction", "cough variant asthma", "CVA ""cough""children", etc. The Chinese search strategy was based on CNKI: ① cough variant asthma OR asthma OR croup; ② Ding Chuan Tang; ③ children; ④ ①AND②AND③. English search strategy is based on Pubmed: ① (Cough variant asthma) OR (CVA) OR (cough); ② (Ding Chuan Decoction) OR (Ding Chuan Tang); ③ children; ④ ①AND ②AND ③."

Literature screening and data extraction2

The evaluators using the Excel sheet should independently screen the literature, extract relevant data and cross-check, and if they encounter disagreement, discuss and solve it or refer it to a third party to assist in solving it. Firstly, the preliminary selection was carried out by reading the title and abstract, further reading the full text after excluding irrelevant literature, and finally screening the relevant literature that met the criteria. The extracted data included: (1) basic information of the included literature (title, year of publication, first author, etc.); (2) baseline characteristics of the study subjects (sample size, age, and sex of the children, etc.); (3) interventions (name of the drugs used in the control and experimental groups, duration of treatment, etc.); (4) seven elements related to the quality evaluation of the literature; (5) outcome indicators.

Risk of bias assessment

Two researchers assessed the risk of bias in the included literature by referring to the "risk of bias assessment" tool recommended by the Cochrane Handbook. When evaluating the quality of the evidence, each investigator should conduct the evaluation independently and review the results with each other. Disagreements, if any, should be resolved through negotiation with a third party. The risk of bias was mapped by using Revman 5.4 software.

Statistical methods

Meta-analysis was performed using Revman 5.4 software. Heterogeneity was tested by using χ^2 test with $P > 0.1$ and $I^2 < 50\%$ considered multiple similar studies to be homogeneous, and a fixed-effects model is selected; if $P < 0.1$ and $I^2 \geq 50\%$ indicated greater heterogeneity among studies, a random-effects model is selected. Due to the different rubrics and measurement time between studies, standardized mean difference (SMD) was used as the effect size for measurement data, while ratio (OR) or relative risk ratio (RR) was used for count data, and each effect size was statistically significant at $P < 0.05$ with 95% confidence interval (CI). Funnel plots were used to determine the presence of publication bias.

Results

Literature search results and characteristics of included studies

Comprehensive computer search of various databases yielded relevant research literature117, including 35 articles in CNKI, 38 articles in VIP, 44 articles in WanFang Data, 0 articles in PubMed, 0 articles in Ovid, and 0 articles in Embase. After the initial screening, there48 was one article that might meet the inclusion criteria, and after reading the full text, duplicates and 31 articles that did not meet the inclusion criteria were excluded. A total of 1308 patients were finally included 17 in a randomized controlled trial for evaluation [10-26] (Figure 1, Table 1).

Risk of bias evaluation results of included studies

Randomization method: 12 studies [11, 12, 14-18, 20, 21, 23-25]

adopted the random number table method and rated Low risk; 4 studies [13, 19, 22, 26] were randomized into treatment and control groups with "order of consultation, order of admission, treatment plan, odd and even number of draws", with high-risk potential, rated high risk, and the rest did not specifically mention allocation concealment and rated Unclear risk; subject blinding: one study [11] mentioned subject blinding and rated Low risk, the rest were Unclear risk; outcome evaluator blinding: all studies did not mention outcome evaluator blinding and rated Unclear risk; data integrity assessment: one study [20] mentioned subject blinding and rated Low risk, the rest were Unclear risk. The remaining studies did not mention the presence of dislodged subjects, and all of them were rated as Low risk; selective reporting bias: all studies did not mention selective reporting of results and were rated as Unclear risk; other bias: all studies did not mention other sources of bias and were rated as Unclear risk (Figure 2).

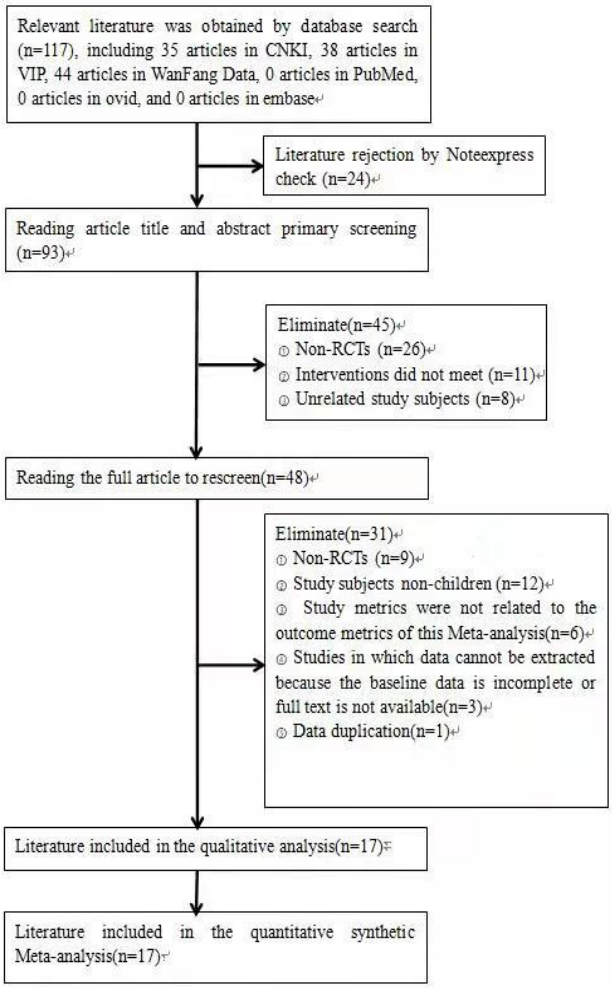

Figure 1 Literature selection and results

Table 1 General information characteristics of included trials

Included studies	Number of cases (T/C)	Mean age/year (T/C)	Clinical intervention		Course/d (T/C)	Patient reported outcomes
			T	C		
Yin Hongzhi	15/15	8.6 ± 3.3/8.5 ± 3.2	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	84	①②③④⑤⑦
Lv Tingting	13/13	≤ 14	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60/90	①④⑤⑦
Li Youzhi et al	39/39	8.92 + 2.71/8.27 + 2.63	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	56	②③

Table 1 General information characteristics of included trials (*Continued*)

Meng Yinhuan et al	20/20	7.0 ± 0.5/7.5 ± 0.6	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60	①②③
Jiang Nanfang	43/43	8.59 ± 1.48/8.17 ± 1.06	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60	①②③④⑤⑥
Zhang Tianying et al	42/42	7.5 ± 3.5/7.0 ± 3.7	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60	①②③④⑤⑥⑦⑧
Qin Ping	45/45	7.0 ± 3.7/7.5 ± 3.5	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60/90	①②③④⑤⑥⑦⑧
Jiang Xiumei	40/40	8.15 ± 1.29/8.09 ± 1.25	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60	①②③⑥⑦
Lv Denglei	50/50	7.48 ± 1.53/7.36 ± 1.24	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	14	①②③⑥⑧
Fang Shengmin et al	35/35	4.28 ± 1.42/4.59 ± 1.45	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	/	①④⑤
Zhang Xianzhi	49/49	8.25 ± 1.41/8.34 ± 1.46	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	60	①④⑤⑥
Li Jingjie	20/20	6.5 ± 3.0/6.55 ± 2.56	Ding-Chuan Tang plus reduction + Montelukast Sodium	Montelukast Sodium	28/30	①⑥
Zheng Zhiyong et al	71/71	10.3 ± 2.0/9.8 ± 2.3	Ding-Chuan Tang plus reduction + Western medicine treatment	Montelukast Sodium + Budesonide + Suhuangzhike cough capsule	56	①②③④⑤
Li Kegang	40/40	6.43 ± 0.51/6.67 ± 0.74	Ding-Chuan Tang plus reduction	Montelukast Sodium	28/30	①
Wang Huoyue	30/30	7.10 ± 2.482/7.17 ± 2.533	Ding-Chuan Tang plus reduction	Montelukast Sodium	14	①⑥
Du Rui et al	60/57	3～10	Ding-Chuan Tang plus reduction	Sustained-release theophylline + Ketotifen	14	①
Li li et al	40/47	3～10	Ding-Chuan Tang plus reduction	Aminophylline + Ketotifen	14	①

①Effective rate；②Percentage of forced expiratory volume in first second(FEV1%)；③Percentage of peak expiratory flow rate(PEF%)；④Effective time of treatment；⑤Symptom-free time；⑥TCM syndrome

Figure 2 Risk assessment of bias graph of included trials

Meta-analysis results

Efficiency analysis Sixteen papers [10-25] reported efficiency rates, including 1230 patients, including 613 in the trial group and 617 in the control group, and the heterogeneity test showed no significant heterogeneity among the studies (P = 1.00, I^2 = 0), using a fixed-effects model. The results of the meta-analysis showed that the clinical efficiency rate was higher in the trial group compared with the control group [OR = 4.89. 95% CI (3.34, 7.16), P < 0.00001] (Figure 3).

FEV1% analysis Nine papers [11-14, 16, 22, 24-26] measured the improvement of FEV1% before and after treatment in two groups of patients, including 871 patients, including 365 patients in the test group and 506 patients in the control group, and the results of the heterogeneity test showed a high degree of heterogeneity among the studies (P < 0.00001, I^2 = 90%), so the random-effects model was used. According to the sensitivity analysis, the data of the included literature were stable, which increased the confidence of the combined results; according to the results of the subgroup analysis, the high heterogeneity caused by the differences in Western medical interventions and the different treatment courses of the included studies could be excluded. the results of the meta-analysis showed that the improvement of FEV1% was significantly higher in the test group than in the control group, and the difference between the two groups was statistically significant [SMD = 1.30, 95% CI (0.78, 1.81), P < 0.00001] (Figure 4, Table 2, Figure 5, Figure 6).

PEF% analysis Six papers [12-14, 16, 22, 24] measured the improvement of PEF% before and after treatment in two groups, including 410 patients, including 205 patients in the test group and 205 patients in the control group, and the results of the heterogeneity test showed that there was no significant heterogeneity between the studies (P = 0.37, I^2 = 8%), and the fixed-effects model was used. the results of the meta-analysis showed that the patients in the test group had a significantly higher PEF% improvement was significantly higher than that of the control group, and the difference between the two groups was statistically significant [SMD = 1.16, 95% CI (0.95, 1.37), P < 0.00001] (Figure 7).

Analysis of treatment onset time Seven papers [10, 15-17, 22, 24, 25] reported on treatment onset time, including 596 patients, including 298 in the trial group and 298 in the control group, and the heterogeneity test showed a high degree of heterogeneity among the studies (P = 0.0009, I^2 = 74%), so the random-effects model was used. Further sensitivity analysis and subgroup analysis are now performed to address the sources of heterogeneity. According to the analysis, T.T. Lu's published literature had a large impact on the study results and lacked robustness. Combined with the subgroup analysis it is clear that differences in Western medical interventions were not a source of significant heterogeneity. the results of the Meta-analysis showed a shorter time to treatment onset in the trial group compared to the control group [SMD = -1.47, 95% CI (-1.84, -1.10), P < 0.00001] (Figure 8, Table 3, Figure 9).

Analysis of symptom disappearance time Seven papers [10, 15-17, 22, 24, 25] reported symptom disappearance time, including 596 patients, including 298 patients in the test group and 298 patients in the control group, and the results of heterogeneity test showed high heterogeneity among studies (P < 0.00001, I^2 = 87%), according to

sensitivity analysis and subgroup analysis to exclude high heterogeneity caused by different interventions. The results of the Meta-analysis showed a shorter time to symptom disappearance in the test group compared to the control group [SMD = -1.31, 95% CI (-1.82, -0.80), $P < 0.00001$] (Figure 10, Table 4, Figure 11).

Analysis of TCM evidence points Six papers [11, 12, 15, 20, 23, 24] measured the improvement of TCM evidence points before and after treatment in two groups, including 468 patients, 234 in the test group and 234 in the control group, and the heterogeneity test showed high heterogeneity among the studies ($P < 0.00001$, $I^2 = 94\%$), and the findings were robust according to sensitivity analysis. Subgroup analysis by different groupings of Western medical interventions and treatment courses revealed high heterogeneity before and after grouping, suggesting that differences in Western medical interventions and treatment courses were not a source of heterogeneity. Meta-analysis results showed that the improvement in TCM points was significantly higher in the test group than in the control group, and the difference between the two groups was statistically significant [SMD = 0.31, 95% CI (0.28, 1.88), $P = 0.008$] (Figure 12, Table 5, Figure 13, Figure 14).

Recurrence rate analysis The recurrence rate was reported in 5 papers [10, 12, 14, 16, 24], including 310 patients, including 155 in the trial group and 155 in the control group, and the heterogeneity test showed no significant heterogeneity among the studies ($P = 0.97$, $I^2 = 0$), using the fixed-effects model. the results of the Meta-analysis showed a higher clinical recurrence rate in the control group compared with the trial group [OR = 0.15, 95% CI (0.06, 0.34), $P < 0.00001$] (Figure 15).

Analysis of adverse reactions Four papers [11, 16, 24, 25] reported adverse reactions including 416 patients, including 208 in the trial group and 208 in the control group, and the heterogeneity test showed significant heterogeneity among the studies ($P = 0.05$, $I^2 = 61\%$), so the random-effects model was used. According to sensitivity analysis, the literature published by Z.Y. Zheng et al. was a reason for the non-robustness of the study results. Combined with the subgroup analysis it can be seen that differences in Western medical interventions and different treatment duration may be one of the sources of significant heterogeneity. the Meta-analysis showed that the difference between the two groups was not statistically significant [OR = 0.35, 95% CI (0.07, 1.78), $P = 0.21$] (Figure 16, Table 6, Figure 17, Figure 18).

Assessment of publication bias An inverted funnel plot was drawn based on the clinical efficiency rate of Ding-Chuan Tang for pediatric CVA (Figure 19), and the left-right distribution of the chart is symmetrical, which indicates the possibility of a small publication bias (Figure 19).

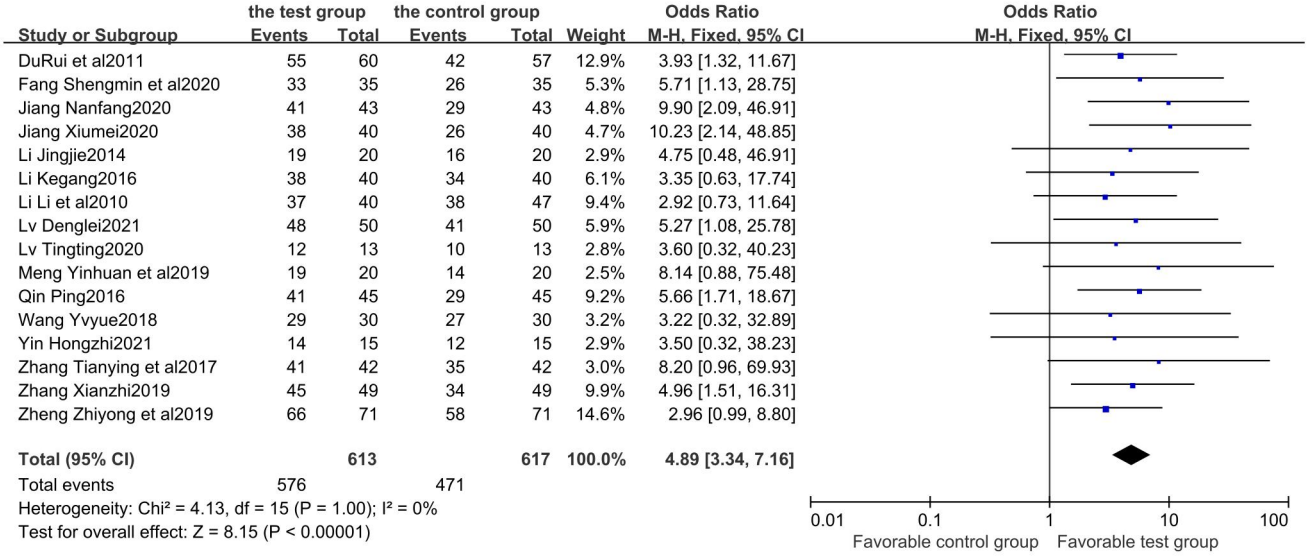

Figure 3 Meta-analysis of the efficiency of the included studies

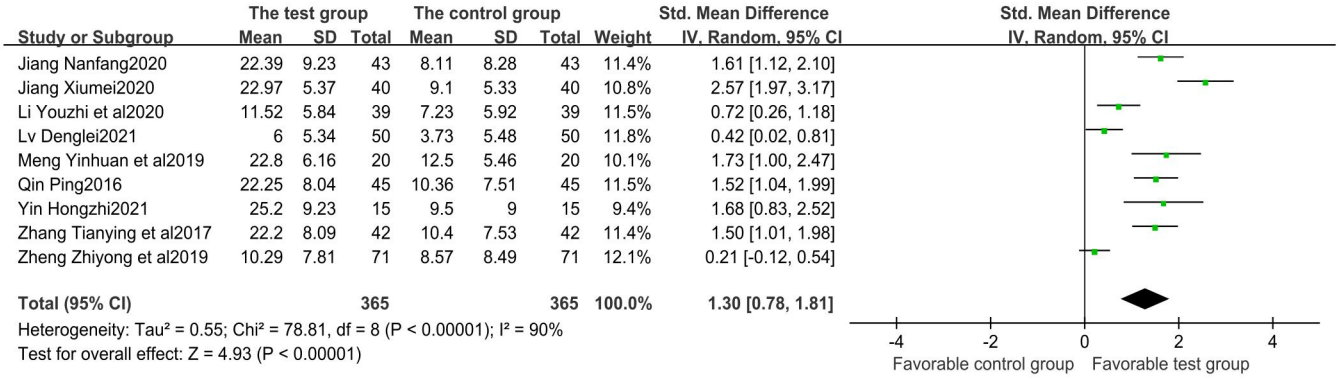

Figure 4 Meta-analysis of the percentage of the first second forceful expiratory volume (FEV1%) of the included studies

Table 2 Sensitivity analysis of the percentage of first second forceful expiratory volume (FEV1%) for the included studies

Eliminate the literature	*P*	I^2	SMD
0	<0.00001	90%	1.30[0.78，1.81]
Lv Denglei2021	<0.00001	90%	1.42[0.85，1.98]
Jiang Xiumei2020	<0.00001	86%	1.13[0.67，1.60]
Meng Yinhuan et al2019	<0.00001	91%	1.25[0.70，1.80]
Yin Hongzhi2021	<0.00001	91%	1.26[0.71，1.81]
Zhang Tianying et al2017	<0.0001	91%	1.27[0.70，1.85]
Li Youzhi et al2020	<0.00001	91%	1.38[0.79，1.96]
Jiang Nanfang2020	<0.0001	90%	1.26[0.69，1.82]
Qin Ping2016	<0.0001	91%	1.27[0.70，1.84]
Zheng Zhiyong et al2019	<0.00001	85%	1.44[0.95，1.93]

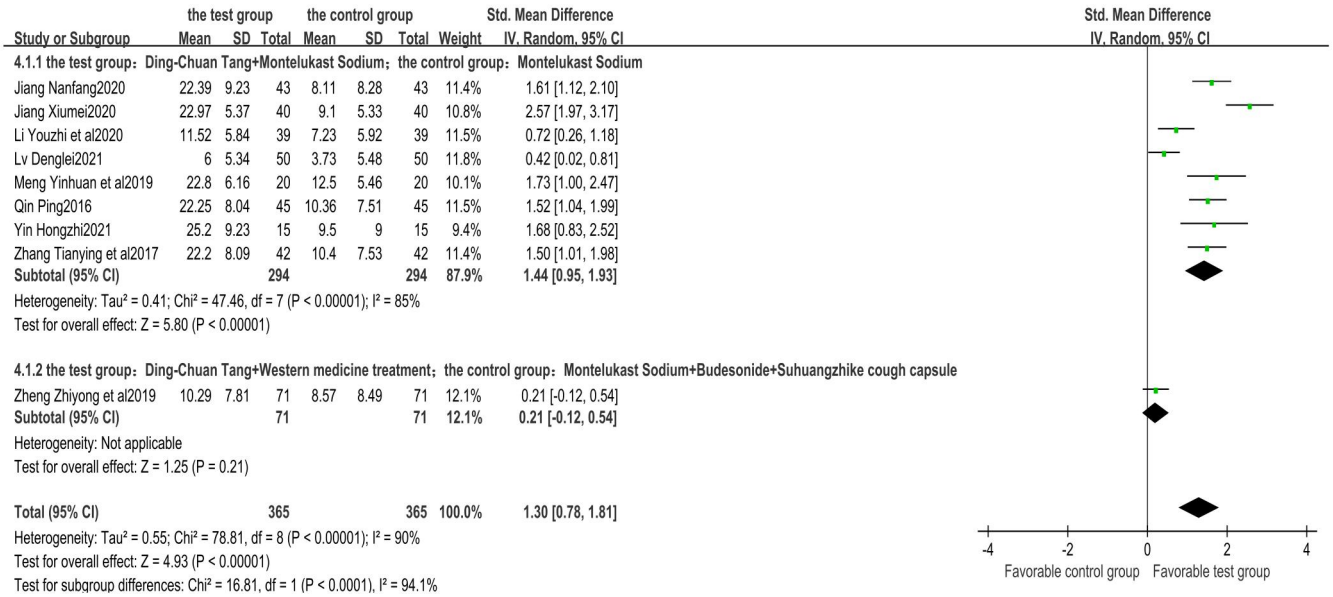

Figure 5 Subgroup analysis of the percentage of first second expiratory volume with force (FEV1%) for the included studies-Western medical interventions

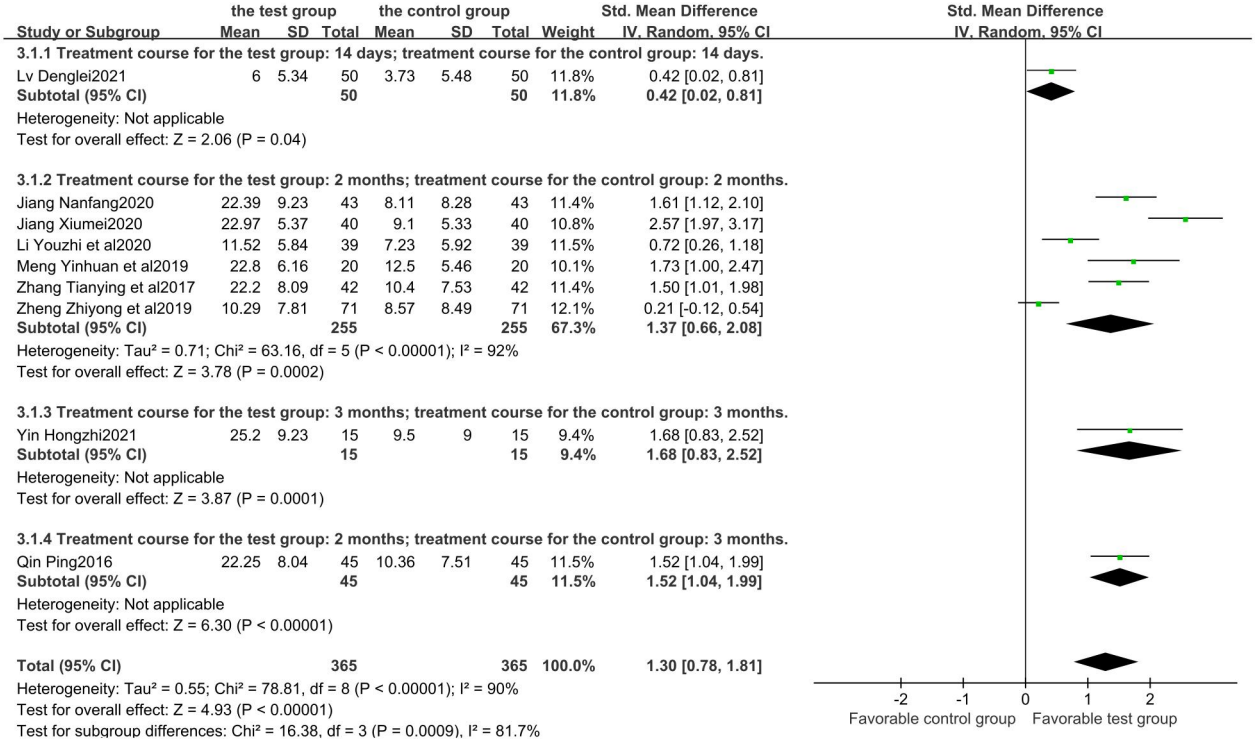

Figure 6 Subgroup analysis of the percentage of the first second expiratory volume exerted (FEV1%) for the included studies-sessions

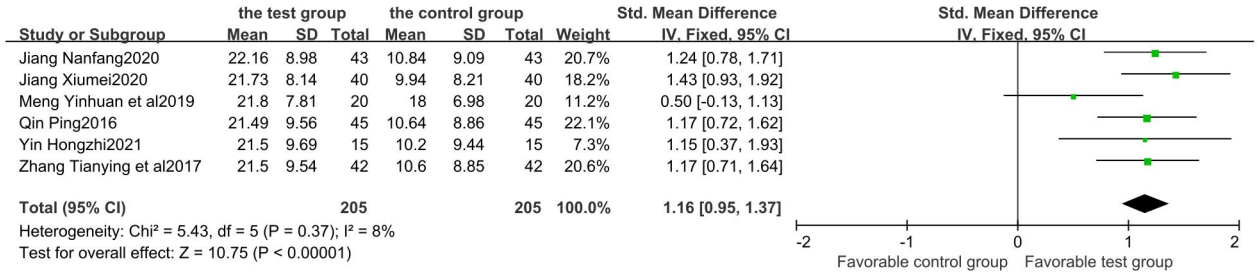

Figure 7 Meta-analysis of peak expiratory flow rate (PEF%) for included studies

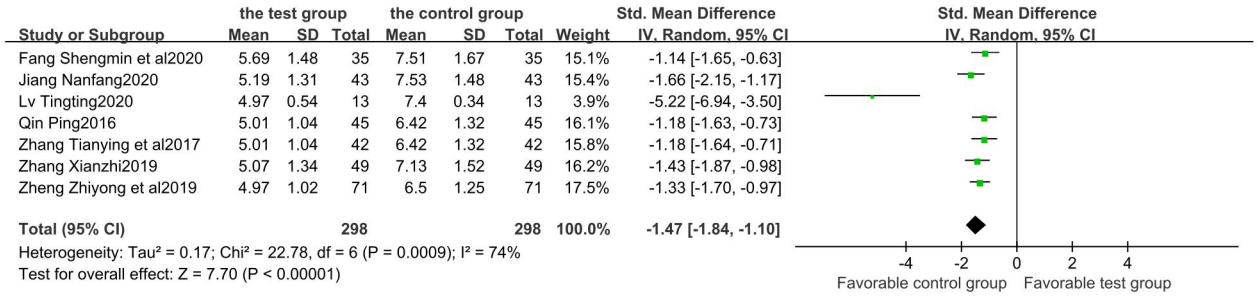

Figure 8 Meta-analysis of time to treatment onset in included studies

Table 3 Sensitivity analysis of the time to treatment onset in the included studies

Eliminate the literature	*P*	I^2	SMD
0	<0.00001	74%	—1.47[-1.84，-1.10]
Lv Tingting2020	<0.00001	0%	—1.32[-1.50，-1.14]
Zhang Xianzhi2019	<0.00001	78%	—1.51[-1.96，-1.05]
Zhang Tianying et al2017	<0.00001	77%	—1.55[-1.99，-1.10]
Fang Shengmin et al2020	<0.00001	77%	—1.55[-1.98，-1.11]
Jiang Nanfang2020	<0.00001	76%	—1.45[-1.88，-1.02]
Qin Ping2016	<0.00001	77%	—1.55[-2.00，-1.10]
Zheng Zhiyong et al2019	<0.00001	78%	—1.54[-2.01，-1.06]

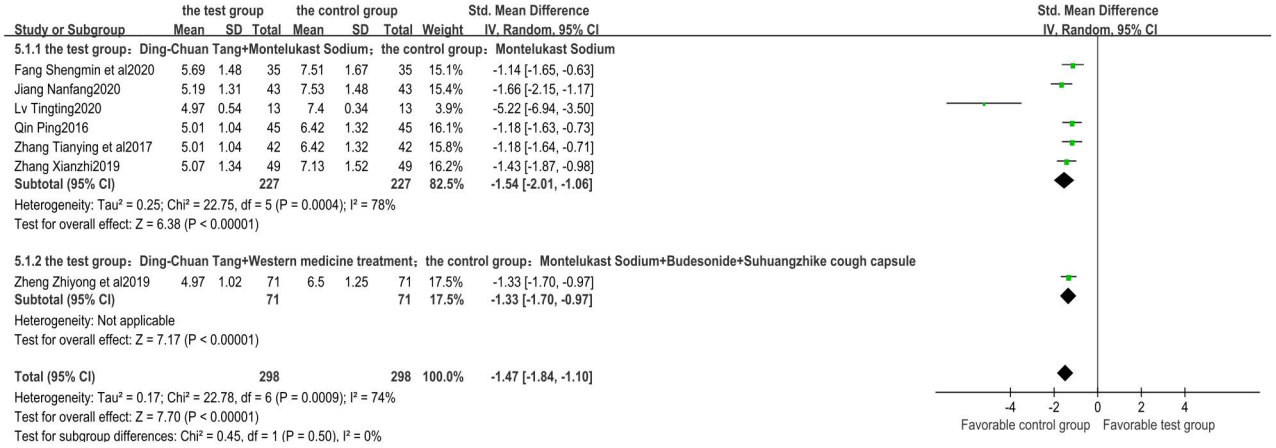

Figure 9 Subgroup analysis of time to treatment onset in included studies-Western medical interventions

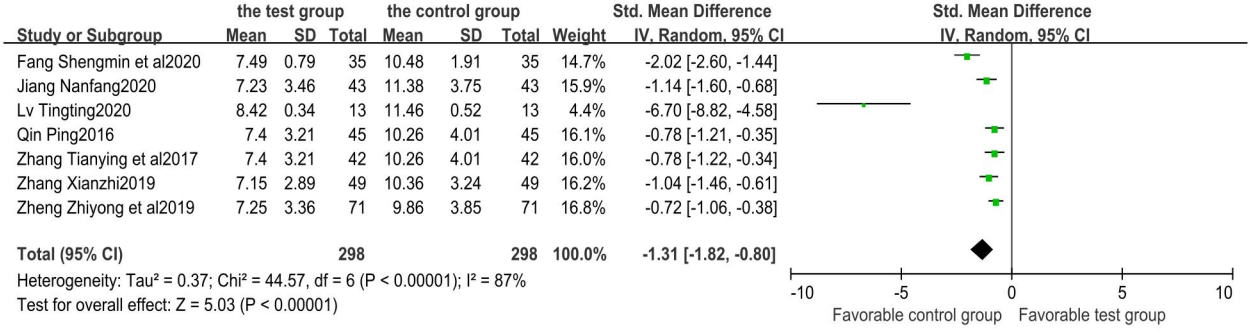

Figure 10 Meta-analysis of time to resolution of symptoms in included studies

Table 4 Sensitivity analysis of the time to the disappearance of symptoms in the included studies

Eliminate the literature	*P*	I^2	SMD
0	<0.00001	87%	—1.31[-1.82，-0.80]
Lv Tingting2020	<0.00001	70%	—1.04[-1.37，-0.71]
Zhang Xianzhi2019	<0.00001	89%	—1.42[-2.04，-0.79]
Zhang Tianying et al2017	<0.00001	88%	—1.45[-2.06，-0.84]
Fang Shengmin et al2020	<0.00001	84%	—1.15[-1.65，-0.65]
Jiang Nanfang2020	<0.00001	89%	—1.39[-2.00，-0.78]
Qin Ping2016	<0.00001	88%	—1.46[-2.07，-0.84]
Zheng Zhiyong et al2019	<0.00001	88%	—1.48[-2.11，-0.86]

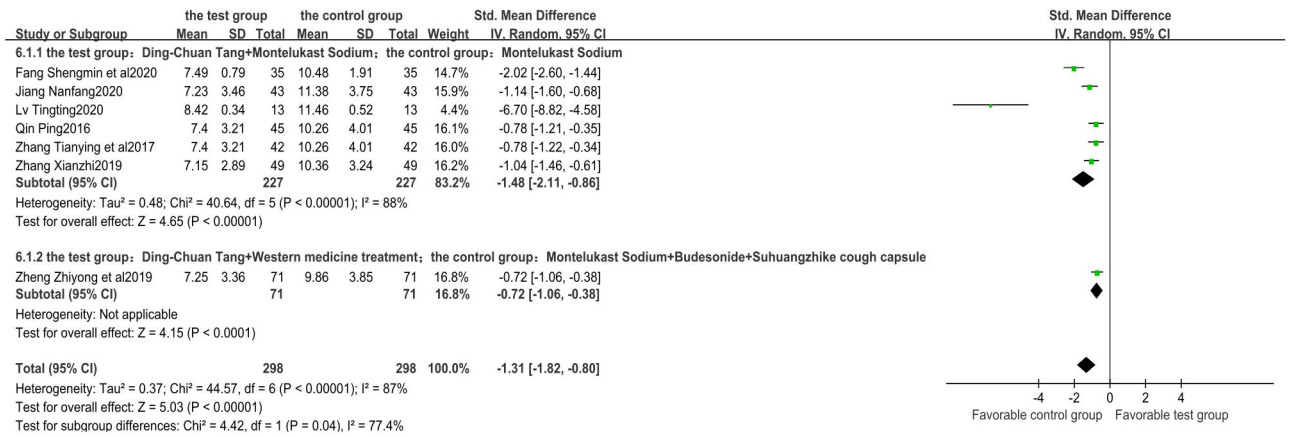

Figure 11 Subgroup analysis of time to symptom disappearance in included studies-Western medical interventions

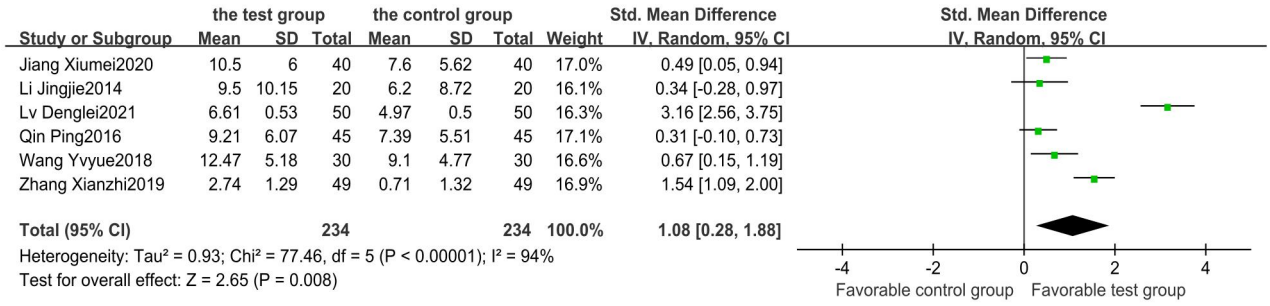

Figure 12 Meta-analysis of TCM symptom scores for the included studies

Table 5 Sensitivity analysis of TCM symptom scores for the included studies

Eliminate the literature	*P*	I^2	SMD
0	0.008	94%	1.08[0.28，1.88]
Lv Denglei2021	0.004	79%	0.68[0.21，1.15]
Jiang Xiumei2020	0.02	94%	1.20[0.23，2.17]
Zhang Xianzhi2019	0.04	94%	0.99[0.04，1.94]
Li Jingjie2014	0.009	95%	1.22[0.31，2.14]
Wang Yuyue2018	0.02	95%	1.16[0.20，2.12]
Qin Ping2016	0.009	94%	1.24[0.30，2.17]

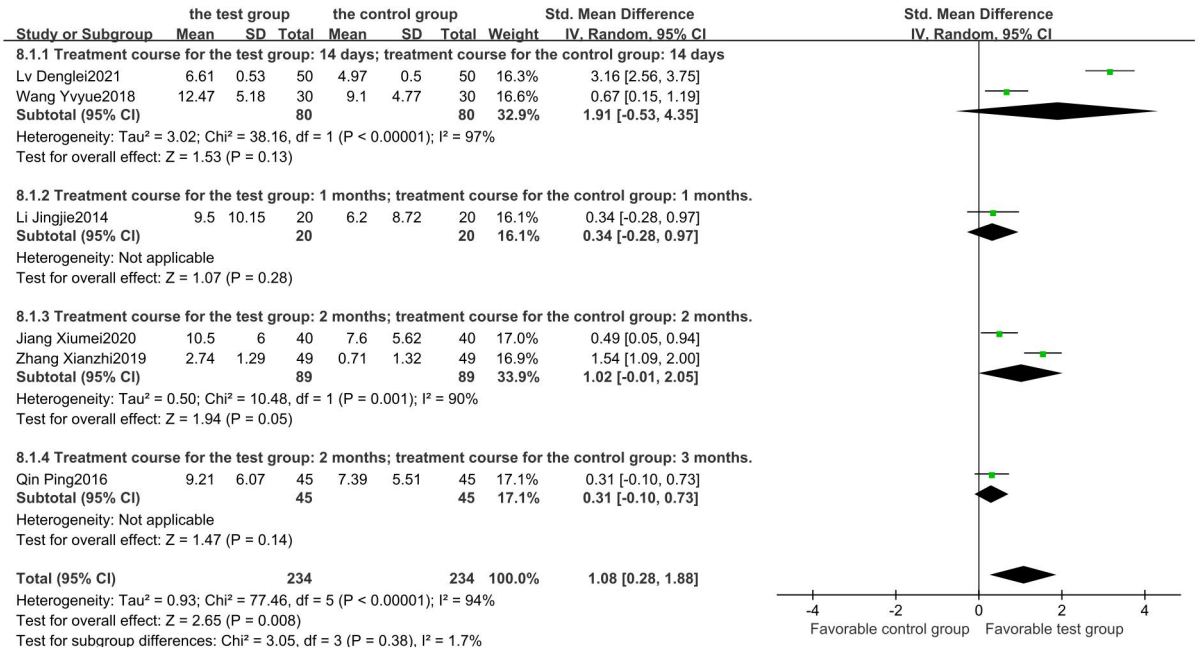

Figure 13 Subgroup analysis of TCM symptom scores for the included studies-Western interventions

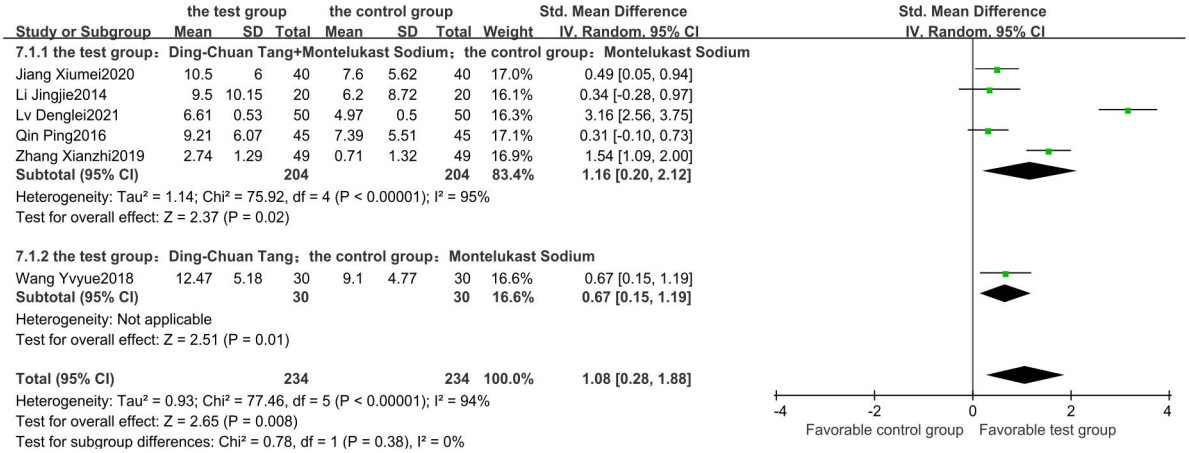

Figure 14 Subgroup analysis of TCM symptom scores for the included studies-therapy sessions

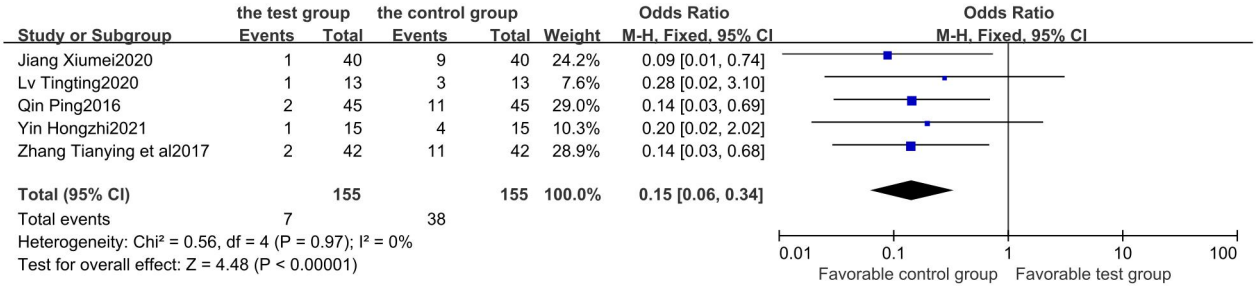

Figure 15 Meta-analysis of recurrence rates in included studies

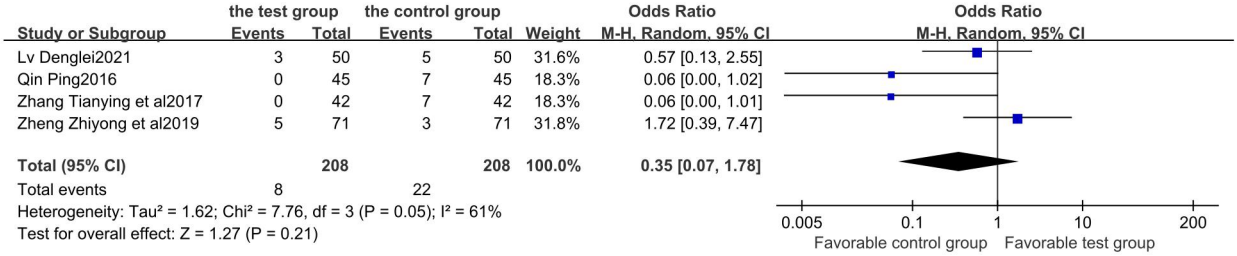

Figure 16 Meta-analysis of adverse reactions in included studies

Table 6 Sensitivity analysis of adverse reactions in the included studies

Eliminate the literature	*P*	I^2	SMD
0	0.21	61%	0.35[0.07，1.78]
Lv Denglei2021	0.28	74%	0.22[0.01，3.36]
Zhang Tianying et al2017	0.47	58%	0.55[0.11，2.81]
Qin Ping2016	0.47	58%	0.55[0.11，2.81]
Zheng Zhiyong et al2019	0.06	44%	0.18[0.03，1.07]

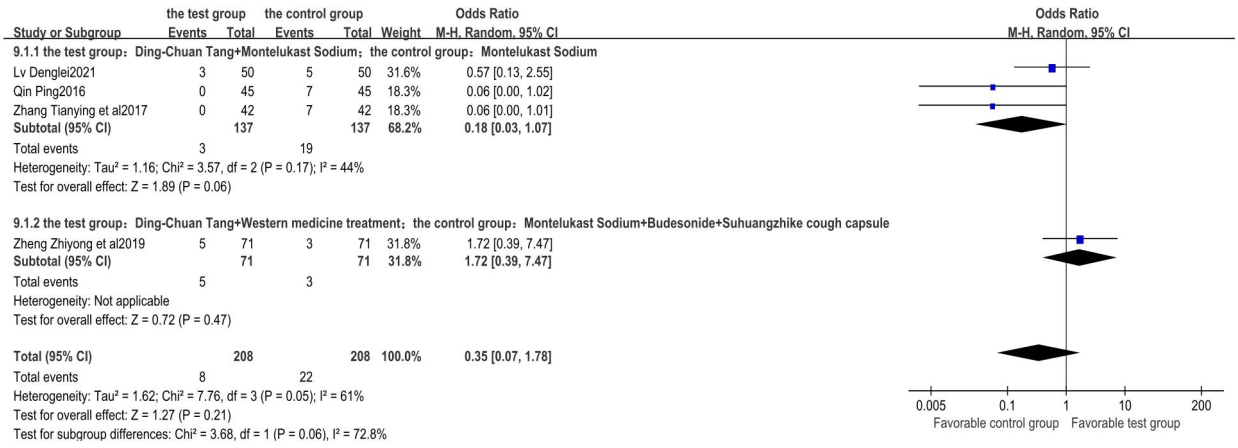

Figure 17 Subgroup analysis of adverse reactions in included studies-Western medical interventions

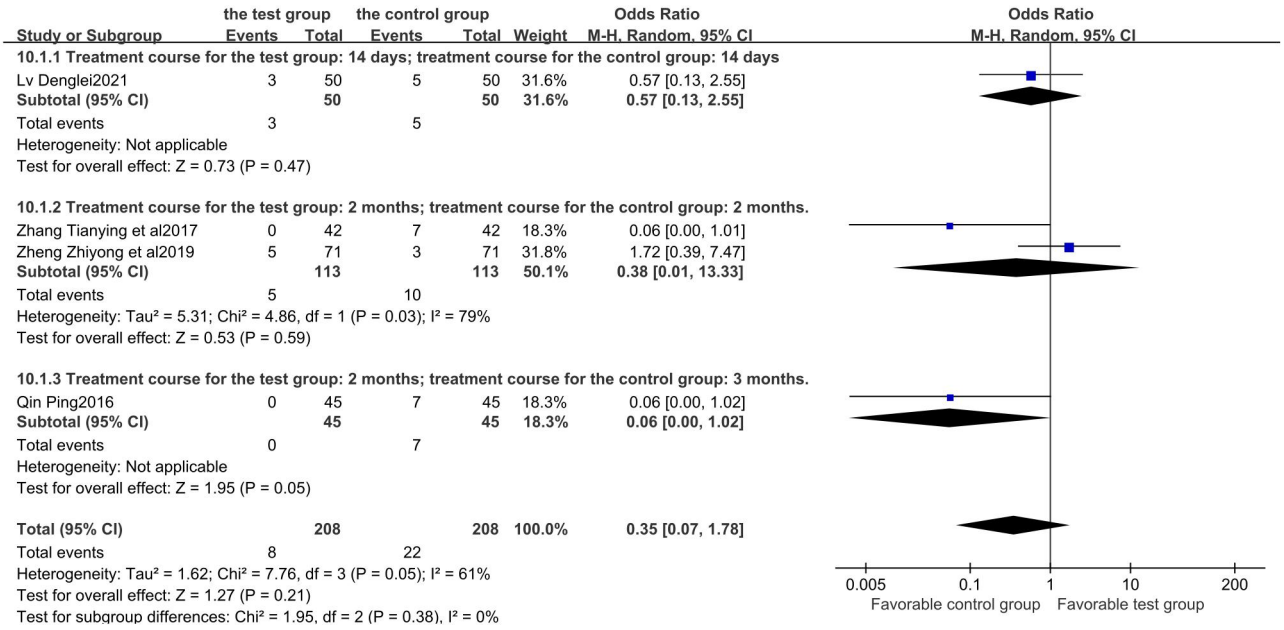

Figure 18 Subgroup analysis of adverse reactions in included studies - course of treatment

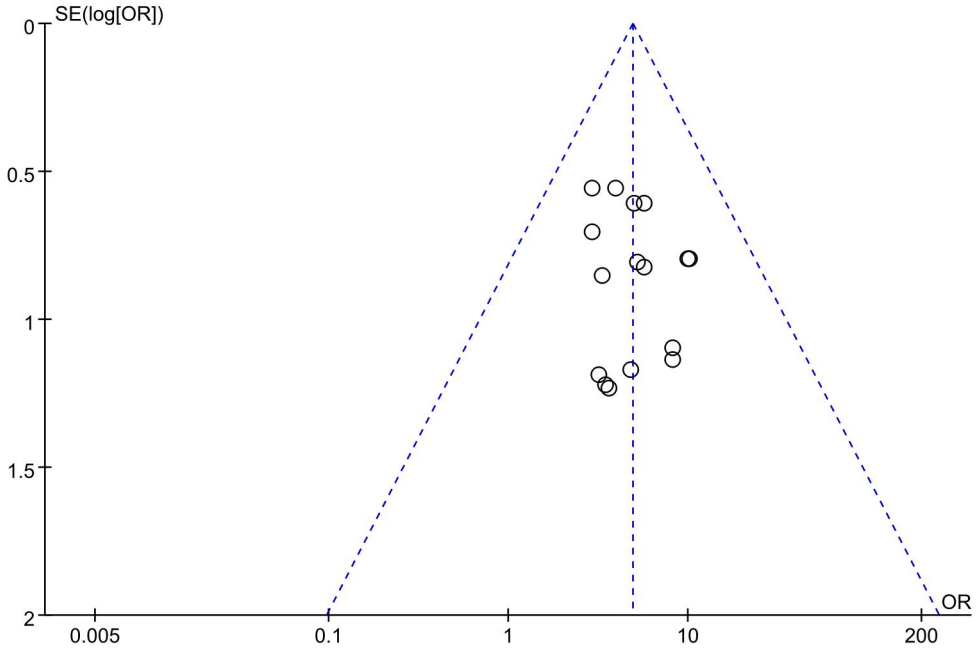

Figure 19 Funnel plot of Meta-analysis of clinical efficiency of two groups of patients

Discussion

Cough variant asthma (CVA) has become one of the main types of chronic cough [27, 28]. It was found that the prevalence of CVA in children is gradually increasing, and changes in the environment and climate may be an important reason for the increase in prevalence, and the statistics found that the prevalence is higher in preschool children [29]. Glauser [30] first named the disease "variant asthma". This particular type of bronchial asthma does not have symptoms and signs such as wheezing and shortness of breath, but rather the most important clinical manifestation is cough, which is often dry and irritating, and is often triggered by cold air, exercise, allergens, and other factors. Because of the single clinical manifestation of CVA, it is easy to be misdiagnosed and missed. If not detected and treated in time, some children may develop into typical bronchial asthma, which may have adverse effects on the physical and mental health of the children. The etiology of CVA has not been studied by modern medicine, but children with CVA also have chronic airway inflammation, airway remodeling, and airway hyperresponsiveness, so inhaled glucocorticoids, β2 receptor stimulants, and leukotriene receptor antagonists are the main drugs used in modern medical treatment of CVA. Parents and children are often unable to adhere to medical prescriptions, so it is difficult to promote the clinical application [31, 32]. The concept of TCM dialectic therapy has shown its superiority in the treatment of CVA. A large number of clinical studies have shown that the combination of TCM or Chinese and Western medicine has the characteristics of symptom improvement, radical treatment, drug safety, and few and mild adverse effects, which is important to improve the quality of life of children [7, 33].

Ding-Chuan Tang is a classic formula for preventing and treating pulmonary diseases in children, which is derived from the "Regimen of the Many Wonders of Life". It has the functions of promoting the lung and lowering Qi, clearing heat and removing phlegm, relieving asthma, and tranquilizing the surface. In this formula, ephedra is pungent and warm, promoting the lung to calm asthma, dispersing wind and dispersing cold; white fruit is sweet and astringent, astringent to the lung to calm asthma, expectorant to stop cough, the two drugs together, one dispersing and one collecting, can enhance the function of calming asthma, but also prevent ephedra from dispersing pungency too much to deplete lung qi, together as the ruling drug. Mulberry Bark is sweet and cold, dipping the lung qi and calming asthma; Scutellaria baicalensis is bitter and cold, clearing heat from the lung; the two are used together to clear the lung and subdue rebelliousness, which is the same subject medicine. Fructus perillae descends Qi and dissolves phlegm, relieves cough and asthma; Almond relieves cough and asthma; Pinellia ternata notoginseng dries up dampness and dissolves phlegm; Farfarae flos reduces Qi and relieves cough and dissolves phlegm; the four flavors together help the ruler and the minister to descend Qi and dispel phlegm, calm asthma and stop cough, all are adjuvants. Glabra is used in raw form to harmonize all medicines and stop coughing and is an adjuvant. The combination of these herbs can dispel wind and cold externally, clear phlegm and heat internally, and promote the lowering of lung qi so that all evidence of cough, phlegm, and asthma will be removed. In addition, modern pharmacological studies have shown that the Chinese herbal ingredients such as roasted ephedra, white fruits, and almonds in Ding-Chuan Tang have bronchodilator, anti-inflammatory, immune regulating, and anti-allergic effects, and can effectively remove CRP, leukotrienes, and other inflammatory mediators [34]. The principle of the formula of Ding-Chuan Tang reflects the understanding and treatment ideas of Chinese and Western medicine for cough variant asthma. The combination of the TCM dialectic method and modern Western medicine pharmacology is conducive to improving clinical efficacy. In the clinical study reports of many scholars so far, the treatment of pediatric CVA with Ding-Chuan Tang or combined with western medicine can effectively control clinical symptoms, improve the cure rate, reduce adverse reactions and reduce recurrence.

Therapeutic efficacy analysis

The results of the meta-analysis showed that the test group was significantly better than the control group in terms of clinical efficiency, percentage of the first second expiratory volume (FEV1%), percentage of peak expiratory flow rate (PEF%), treatment onset time, symptom disappearance time, Chinese medicine symptom score, and recurrence rate. The difference in the incidence of adverse reactions between the two groups was not statistically significant. Based on the results of the analysis, it can be concluded that Ding-Chuan Tang can improve the clinical efficacy of pediatric CVA without increasing the incidence of adverse reactions. However, due to the small number of included studies and the insufficient sample size included in each study, some bias may exist in the results.

Methodological quality of included studies

The methodological quality of the included studies in this systematic evaluation was not high: one study did not report a specific randomization method, and four studies were randomized into treatment and control groups according to "order of consultation, order of admission, treatment plan, and odd-even lottery", all of which had high-risk potential. All studies did not describe the concealment of the allocation scheme. Although most trials described the use of randomization groups, there was insufficient information to determine whether the trials were conducted correctly and there was the uncertainty of selective bias in all included studies. Only one literature mentioned subject blinding with the potential for measurement bias. In addition, this systematic evaluation included small literature with no English-language articles, studies in other languages, and a lack of evidence from gray literature, such as topical reports, unpublished materials, government reports, and other traditional or nontraditional literature sources. The sample sizes included in this study were all small, making it difficult to exclude the effect of chance. There was also variation in the Western medical interventions included in the study, with different durations of treatment and inconsistent outcome measures, which may be subject to large implementation bias and/or measurement bias.

Limitations

Of the 17 studies included in the systematic evaluation, all were of low methodological quality. The sample size of each study was small, and a multicenter, large sample and standardized RCT was lacking. the interventions of the included studies were also different, making a certain clinical heterogeneity among studies, which may affect the strength of the Meta-analysis and the extrapolation of the conclusions. Due to the lack of long-term follow-up data, this study is unable to answer the long-term efficacy and long-term safety of Ding-Chuan Tang. Therefore, the results of this study must be treated with caution when applied clinically.

In conclusion, Ding-Chuan Tang can significantly improve the clinical efficacy of pediatric CVA without increasing the incidence of adverse effects, thus providing a reliable therapeutic direction for the treatment of pediatric CVA. It is recommended that multicenter RCTs with large samples and rigorous designs be conducted in future studies; standardized randomized methods, blinded and concealed designs are used rationally, and sample sizes are pre-estimated before trials; the number of cases and causes of disenrollment and missed visits be recorded in detail, and long-term follow-up be conducted to reduce bias and provide more reliable evidence of evidence-based medicine for the clinical efficacy of Ding-Chuan Tang in the treatment of pediatric CVA.

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