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Review Article

# Effectiveness and Safety of Suhuang Zhike Capsule for Acute Exacerbation of Chronic Bronchitis or Chronic Obstructive Pulmonary Disease in Adults: A Systematic Review and Meta-Analysis

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## Abstract

**Background:** Acute exacerbation is an important factor in the progression of chronic bronchitis (CB) and chronic obstructive pulmonary disease (COPD). Recently, many studies have suggested that Suhuang Zhike capsule (SZC) combined with western medicine can suppress the inflammatory response efficiently and quickly, and shorten the course of the disease. Therefore, the treatment with SZC has important implications for the prognosis of the patients. However, the effectiveness and safety of SZC in the treatment to acute exacerbations of CB or COPD have not been systematically reviewed. **Purpose:** In order to evaluate the effectiveness of Traditional Chinese Patent Medicine-SZC in the treatment of patients with CB or COPD. **Methods:** We searched and reviewed the relevant publications by August 2022, in the following databases: EMBASE, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Chinese Vip database, China Biomedical Literature Database, and Wanfang. The risk bias was assessed for the included studies according to the Cochrane Handbook. Lung function was used as the primary outcome indicator, including the ratio of exertional expiratory volume in one second to exertional spirometry (FEV1/FVC), exertional expiratory volume in one second (FEV1), exertional spirometry (FVC). The secondary outcomes included tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and adverse events (AEs). **Results:** A total of 20 randomized controlled trials (RCTs) meet the inclusion criteria (including 1956 patients) and the results of the meta-analysis showed that the treatment of SZC combined with western medicine routine significantly improved the lung function of patients with CB or COPD compared to the western medicine routine alone: (FEV1/FVC [MD = -7.18, 95%CI (5.43,8.95), P < 0.01], FEV1[ MD= 0.37, 95%CI (0.19, 0.54), P < 0.01] and FVC [MD= 0.59, 95%CI (0.31, 0.86), P < 0.01, I2 = 94%]), significantly reduced the levels of inflammatory factors: TNF-α [MD= -6.86, 95% CI (-9.73,-3.99), P < 0.01, I2 = 94%], IL-6 [MD= -1.77, 95%CI (-2.81, 39-0.73),P < 0.01, I2 = 86.7%], and IL-8 [MD= -1.50, 95% CI (-2.25, -0.76), P < 0.01, I2 = 92%], and shorten cough duration [MD = -1.51, 95%CI (-2.15, -0.86), P < 0.01, I2 = 86%].There was no significant difference in the incidence of adverse events between the two groups. There was no publication bias in the statistics, according to begge test (z = 0.34 (p = 0.732)) and egger tests (t =0.46 (p = 0.653)) respectively. **Conclusions:** The current review suggest that the adjunctive therapy with SZC can safely and effectively improve lung function, reduce the levels of inflammatory factors, and shorten the duration of symptoms for the patients with acute exacerbations of CB or COPD.

**Keywords:** Suhuang zhike capsule; COPD; CB; RCTs; Meta-analysis.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease associated with an increased chronic inflammatory response of the airways and lungs to toxic particles or gases, and characterized by persistent airflow limitation, meanwhile exacerbations and comorbidities always lead to overall more severe prognosis for individual patients [1].

COPD is currently one of the three leading causes of death worldwide, and 90% of these deaths occur in low- and middle-income countries. The acute exacerbation contributes significantly to this situation [2]. It is estimated that 2 million people die from the disease each year in Asia, accounting for 2/3 of global COPD deaths [3]. In China, more than 100 million people suffer from COPD [4]. Due to the high mortality and morbidity rates, there is worldwide concern about the high incidence of COPD as well as its severe economic and social burden.

For most patients, COPD develops from chronic bronchitis (CB) [5], defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years. CB has a high prevalence in COPD patients, and CB is a common but variable phenomenon in COPD. Acute exacerbation of CB will result in worsening airflow obstruction and progressive decline in lung function [5,6]. If the ratio of FEV1/FVC in Spirometry is lower than 0.70 after inhalation of bronchodilators, the criteria for airflow limitation are met and COPD can be diagnosed.

Acute exacerbations of CB or COPD can be characterized by worsening respiratory symptoms, dyspnea, and they will aggravate cough and sputum, leading to a decrease in lung function. Recurrent exacerbations are the major factors in disease progression.

CB can cause from COPD. They have similar pathological mechanisms and clinical symptoms, furthermore, their principles of treatment during acute exacerbations are essentially same. Although several effective treatment modalities, such as glucocorticoids, bronchodilators, and antibiotics have been developed for the therapy of COPD, the disease is still not well treated. Additionally, long-term use of these drugs leads to some significant side effects, such as elevated blood glucose and bacterial resistance.

Patients can benefit from other treatment options, such as traditional Chinese medicine. Suhuang Zhike Capsule (SZC) is a proprietary Chinese medicine summarized by Professor Enxiang

Chao of the Department of Traditional Chinese Medicine for Pulmonary Diseases, Center of Respiratory Medicine, China-Japan Friendship Hospital, based on long-term clinical application (Supplementary Material). This agent consists of Ephedra, Perilla leaf, Geosaurus, honeyed

Folium Eriobotryae, Stir-fried Perilla seed, Cicadae Periostracum, Peucedani Radix, Stir-fried Greater burdock, Schisandra chinensis [7]. SZC has been approved by the Chinese Food and Drug Administration in 2008 and is widely used for the treatment of respiratory diseases such as cough variant asthma [8], post-infection cough [9], COPD [10], etc. These results of clinical studies have suggested that SZC can improve the lung function index of patients and enhance the efficacy. Modern pharmacological studies have suggested that SZC has suppressant of cough, reduces sputum secretion, elimination of inflammation, decreases airway hyperresponsiveness and inhibits airway remodeling [11,12]. However, the evidence regarding its efficacy and safety in patients with CB or COPD is still rare. Therefore, the purpose of this study was to conduct a systematic review to investigate the efficacy and safety of SZC for CB or COPD exacerbations in adults.

## Method

This research was carried out following a pre-established protocol registered on INPLASY(INPLASY202280084) and we performed this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

### Literature searches

Two independent reviewers (Liu Y and Hong Z) systematically searched eight electronic databases, EMBASE, PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, VIP database, China Biomedical Literature Database, and Wan fang. Biomedical Literature Database, and Wan fang for relevant papers published by August 2022, regardless of geographic region and language. Search terms included " Suhuang Zhike Capsules", "chronic bronchitis", "chronic obstructive pulmonary disease", the Cochrane Handbook for Systematic Reviewers (version 5.1.0) was used as a guide.

### Eligibility Criteria

The studies that met the following markers should be included in the meta-analysis: 1) participants (P): participants who meet the diagnostic criteria of acute exacerbation of CB or COPD will be included; 2) I (interventions): combination of SZC on western medicine routine; 3) comparators (C): the conventional treatment used in both control and experimental groups; 4) outcomes(O): lung function (FEV1/FVC,FEV1,FVC), inflammatory factors (TNF-α, IL-6,IL-8); 5) studies(S): Clinical randomized controlled trials. The specific method of random assignment should be described, or the word "randomized" should be mentioned. Exclusion criteria: 1) duplicate publications; 2) clinical trials using the date of birth, date of admission, hospital number, or alternate assignment; 3) conference papers and animal studies; 4) lack of information on relevant outcome indicators.

### Data Extraction

Data extracted included PICOS details, authors, year of publication, sample size, sex ratio, and treatment duration. We used lung function (FEV1/FVC, FEV1, FVC) as the primary indicator, and secondary outcomes included tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and the presence of nausea and vomiting, diarrhea, constipation, and dry throat were considered as adverse effects. Two researchers (Liu Y and Hong Z) evaluated the study and extracted the data separately. In case of disagreement, a third researcher (Zhang HC) entered the discussion and made the final decision.

### Risk of Bias Assessment

With the help of the Cochrane Collaboration, two reviewers (Liu Y and Hong Z) conducted the risk of bias and quality assessment methods, and disagreements occurred and will be discussed with the third reviewer (Zhang HC) in seven areas, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

In addition, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has been used to assess the quality of the included evidence.

### Data Analysis

The meta-analysis was performed by using Review Manager 5.4 and the Stata software (Stata SE, version 16). For continuous variables, we calculated the pooled estimates with mean differences (MD) and 95% confidence intervals (CI); for dichotomous variables, we used the relative risk (RR) to calculate effect sizes; when meta-analysis revealed significant heterogeneity ($I2 \geq 50\%$), sensitivity analysis and meta-regression were used to identify possible causes, and when the effect of significant clinical heterogeneity was excluded, a random effects model was used; when heterogeneity was not significant ($I2 < 50\%$), a fixed effects model was used. In addition, Egger and Begg tests were performed to investigate the effect of publication bias.

## Results

### Study Selection

294 literatures were preliminarily identified through searching 8 databases, and then 108 literatures were left after removing duplicates. These left studies were further screened, and

56 studies were excluded based on title and abstract because they were either non-acute stage patients, conference papers, or case reports. After reading the remaining 52 full-text articles, 32 were excluded because they did not meet the inclusion criteria, 2 [14,15] were not RCT, 14 literatures [16-29] did not use a randomized allocation, and 16 [30-45] did not include the required outcome indicators. Finally, a total of 20 RCTs [46-65] were included in the meta-analysis, and the specific flow figure is shown below (Figure 1).

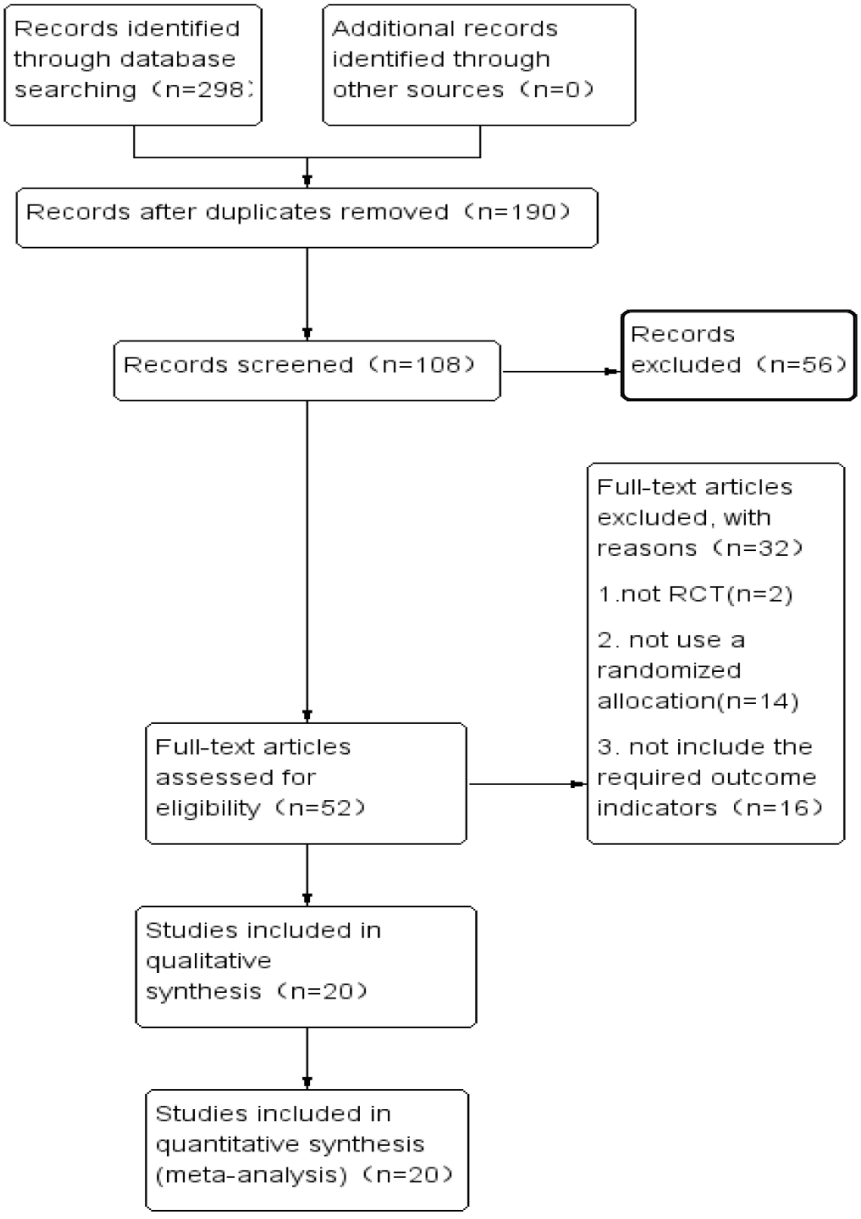


**Figure 1:** Flow diagram for study selection process.

### Study Characteristics

All of 20 clinical controlled trials were conducted in China and were single-center trials. A total of 1956 patients (988 in the trial group and 988 in the control group) were recruited. The mean age ranged from 57 to 75 years, with male patients predominating in most studies. 6 [46-51] studies included patients with acute exacerbations of CB and 14 [52-65] studies included patients with acute exacerbations of COPD.

The studies based on oral administration of SZC were set as in the trial group, in which no other proprietary Chinese medicines were used during the trial period. All studies used conventional western medicine under guidelines, and among the studies that described specific dosing regimens: seven chose to combine ICS + LABA on a conventional basis, six [52,53,56,59,63,65] of which chose salmeterol ticarbazone; while another [62] chose budesonide formoterol; and one [58] combined ICS and bronchodilator.

The duration of intervention ranged from 1 week to 8 weeks, 16 [46-48, 52-64] studies reported pulmonary function, 8 [47, 49-51, 56, 60, 62, 65] studies reported inflammatory indicators, 11 [50, 51, 53, 55, 56, 58, 59, 61, 62, 64, 65]studies did not report events related to adverse events, 3 [46, 57, 63] studies did not find adverse events, and the remaining 6 [47-49, 52, 54, 60] studies reported a total of 52 adverse events, as shown in the chart below(Table 1).

| Study ID | Participants | No. of | Age (years) | Male (%) | Interventions | Comparators | Duration |
|---|---|---|---|---|---|---|---|
| ZhuYaRui 2020 | CB | 70/70 | I:62.66±5.79<br>C:62.52±5.71 | I:38(54.3%)<br>C:39(55.7%) | RT+ Beclomethasone propionate; SZC | RT+ Beclomethasone propionate | 14D |
| ChenXI 2017 | CB | 46/46 | I:58.5 ± 6.3<br>C:57.3 ± 6.5 | I:32(69.6%)<br>C:30(65.2%) | RT; SZC | RT | 10D |
| ShenJun 2015 | CB | 45/45 | I:56.8 ± 6.8<br>C: 57.1± 6.9 | I:36(80%)<br>C:37(82.2%) | RT; SZC | RT | 10D |
| XuJianXin 2014 | CB | 60/60 | I:60.3 ± 8.2<br>C:60.7 ± 8.4 | I:37(61.7%)<br>C:35(58.3) | RT; SZC | RT | 10D |
| WangKeXiao 2016 | CB | 59/59 | I:60 ± 8<br>C:60 ± 8 | I:38(64.4%)<br>C:41(69.5%) | RT; SZC | RT | 14D |
| XuXingPing 2017 | CB | 46/46 | I:57.2 ± 7.6<br>C:57.6 ± 7.2 | I:25(54.3%)<br>C:27(58.7%) | RT; SZC | RT | 14D |
| LiWenJu 2022 | COPD | 35/35 | I:65.84 ± 5.24<br>C:65.9 ± 4.82 | I:14(40%)<br>C:17(48.6%) | Ceftazidime+ Budesonide + Ipratropium bromide+SZC | Ceftazidime+ Budesonide + Ipratropium bromide | 10D |
| LiHui 2021 | COPD | 40/40 | I:65.69 ± 9.14<br>C:65.41 ±7.86 | unclear | RT+ Seretide; SZC | RT+ Seretide | 14D |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ZhangYiXiu 2021 | COPD | 30/30 | I:58.56 ±10.26<br>C:58.58±10.24 | I:16(53.3%) | RT+ Seretide; SZC | RT+ Seretide | Unclear |
| LiuJian 2021 | COPD | 44/43 | I:59.27 ±15.44<br>C:58.93±15.62 | I:28(63.6%)<br>C:27(62.7%) | RT+ Symbicort Turbuhaler; SZC | RT+ Symbicort Turbuhaler | 30D |
| LiuHong 2021 | COPD | 31/31 | I:64.84±6.95<br>C:65.48±6.03 | I:22(71.0%)<br>C:18(58.1%) | RT; SZC | RT | 10D |
| ZhaoXia 2020 | COPD | 41/41 | I:57.42±1.38<br>C:57.69±1.53 | Unclear | RT+ Seretide; SZC | RT+ Seretide | 10D |
| PengGuangYao 2019 | COPD | 36/36 | I:65.41±5.79<br>C:64.29±5.76 | I:20(55.6%)<br>C:21(58.3%) | RT+ Seretide; SZC | RT+ Seretide | 30D |
| WangYiMin 2019 | COPD | 80/80 | I:61.8 ± 5.5<br>C:60.9 ± 5.9 | I:49(61.3%)<br>C:54(67.5%) | RT; SZC | RT | 10D |
| RenJunQing 2019 | COPD | 44/44 | I:75.5 ± 4.3<br>C:75.3 ±4.2 | I:39(88.6%)<br>C:40(90.9%) | RT; SZC | RT | 7D |
| OuCongLing 2018 | COPD | 60/60 | I:65.42 ±4.68<br>C:65.05 ±4.68 | I:29(48.3%)<br>C:31(51.7%) | RT; SZC | RT | 56D |
| ZouYanLi 2017 | COPD | 60/60 | I:68.4 ± 5.6<br>C:68.8 ± 6.2 | I:35(58.3%)<br>C:34(56.7%) | RT; SZC | RT | 7D |
| HuangYing Feng 2017 | COPD | 45/45 | I:67.67 ±5.17<br>C:68.05 ±5.57 | I:22(48.9%)<br>C:23(51.1%) | RT; SZC | RT | 56D |
| ZhaoNianKun 2017 | COPD | 53/54 | I:67.57 ±5.25<br>C:68.05±5. 57 | I:26(49.1%)<br>C:29(53.7%) | RT+ Seretide; SZC | RT+ Seretide | 28D |
| ZhaoXia 2020 | COPD | 53/53 | I:66.89 ±1.25<br>C:67.47 ±1.36 | Unclear | RT+ Seretide; SZC | RT+ Seretide | 10D |
| **I**: intervention; **C**: Control; **RT**: Routine Therapy; **D**: days; **SZC**: Suhuang Zhike Capsule | | | | | | | |

**Table 1:** Characteristics of the included RCTs and the detail of PICOS.

### Risk of Bias in Individual Studies

The risk of bias was assessed using the Cochrane Risk of Bias tool. In the included studies, 9 [48-51, 54, 57, 60, 61, 63] used the random number method, 1 study [46] used the random parity method, and 1 study [53] used envelopes, so these studies were flagged as low risk. Other studies claimed to have performed randomization grouping but did not report the specific randomization method, so these studies were treated as unclear risks.

Allocation concealment and blinding were not mentioned in all studies and all selective reporting bias had a low risk. The level of bias for the included studies is summarized in the figure below (Figure 2).

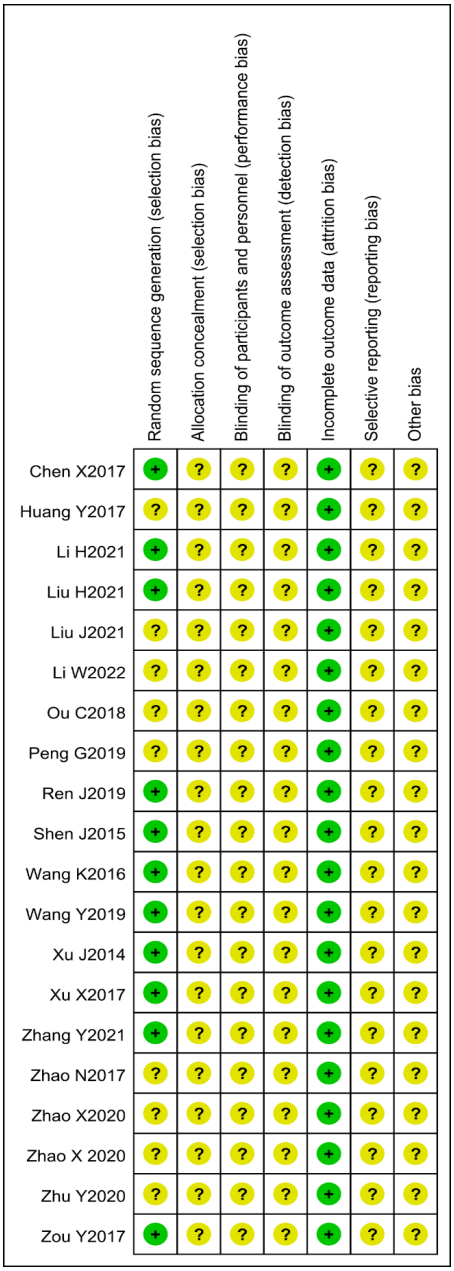


**Figure 2:** Risk of bias in the included studies.

## Overall Results of Meta-Analysis

### FEV1/FVC

The 12 [46, 48, 53-55, 57-60, 62-64] included studies used FEV1/FVC as the outcome index, and the heterogeneity of the results among the studies was high (P < 0.01, I2 = 78%), meta-regression results showed that year of publication (P = 0.423), difference between CB or COPD patients (P = 0.196), time on medication (P = 0.834) were not major factors contributing to high heterogeneity.so a random-effects model was used. the results of the Meta-analysis showed that the combination of conventional Western medicine with SZC further improved the expiratory volume per second and expiratory spirometry, i.e., FEV1/FVC.

Subgroup analysis: a total of 10 studies used conventional treatment combined with SZC to intervene in patients with acute exacerbations of COPD. The results of the random-effects model showed that the combination of SZC improved the one-second rate in a statistically significant way compared with conventional therapy with Western medicine [MD = 6.51, 95%CI (4.69, 8.34), P < 0.01], which means that SZC combined with conventional therapy better improved the FEV1/FVC levels in COPD patients compared with conventional therapy alone; using conventional therapy There were 2 studies of interventions using the combination of SZC in patients with acute exacerbations of chronic bronchitis. The results of the random-effects model showed a statistically significant difference in FEV1/FVC between conventional treatment with SZC and conventional treatment in the clinical trial for acute exacerbations of CB [MD= 10.24, 95% CI (8.45, 12.02), P < 0.01, Figure 3], indicating that the use of SZC also improved the FEV1/FVC levels in CB patients.

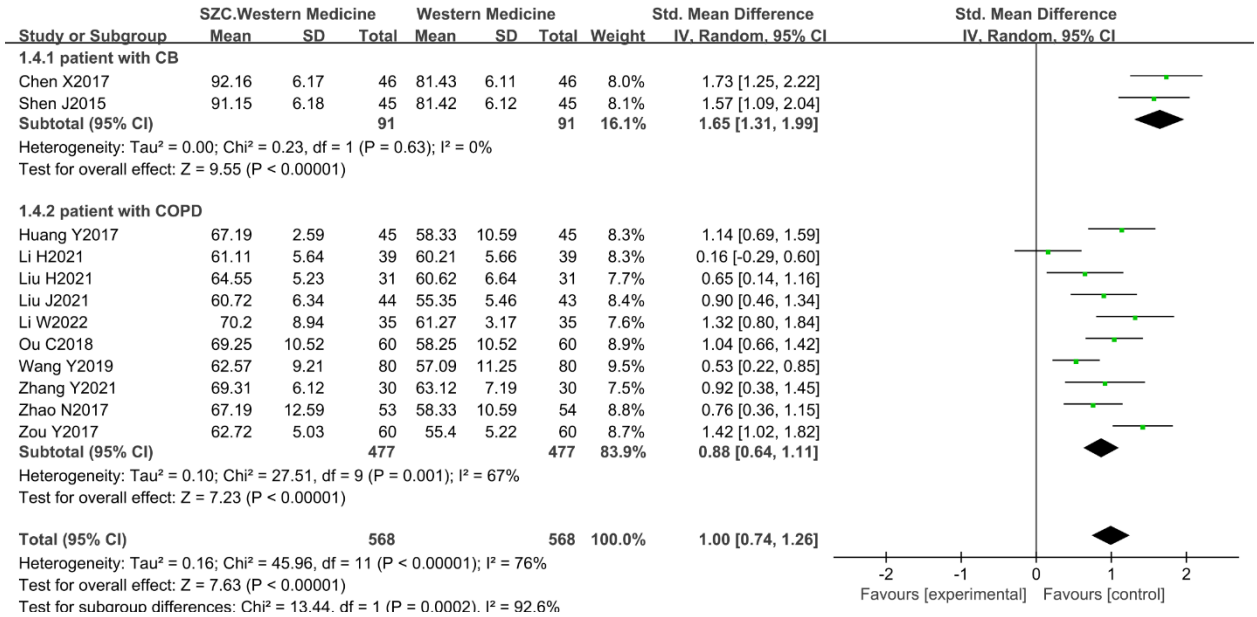


**Figure 3:** Comparison SZC combined with Western Medicine vs. Western Medicine in FEV1 FVC.

### FEV1

Pooled results from 7 randomized controlled trials [46-48, 52, 54, 61, 62] showed that SZC combined with western medicine routine significantly increased FEV1 levels [MD = 0.37, 95%CI (0.19, 0.54), P < 0.01, I2= 55.7%]. Subgroup analysis showed that SZC combined with western medicine routine significantly improved FEV1 levels during the intervention CB compared to the control group [MD = 0.23, 95%CI (0.15, 0.31), P < 0.01, I2 = 15%]; for COPD patients, too [MD= 0.44, 95%CI (0.18, 0.71), P< 0.01, I2 = 15%, Figure 4]; and because only a small number of studies were included, no meta-regression was performed.

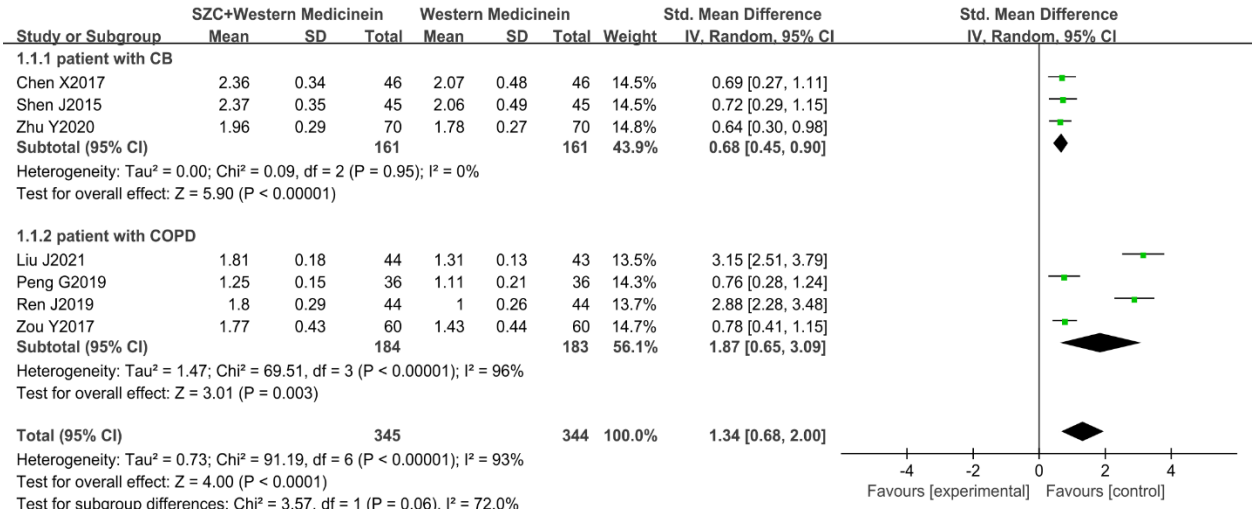


**Figure 4:** Comparison SZC combined with Western Medicine vs. Western Medicine in FEV1.

**FVC**

Pooled results from 9 randomized controlled trials [46, 48, 52, 54-56, 59, 62, 64] showed that SZC combined with western medicine routine significantly increased FVC levels [MD = 0.59, 95%CI (0.31, 0.86), P < 0.01, I2 = 94%], and no meta-regression was performed because only a small number of studies were included. Subgroup analysis showed that SZC combined with western medicine routine significantly improved FVC levels during intervention CB compared to controls [MD = 0.37,95%CI (0.20, 0.54), P < 0.01, I2 = 0%]; the same was true for COPD patients [MD = 0.65, 95%CI (0.31, 1.00), P < 0.01, I2 = 95%, Figure 5].

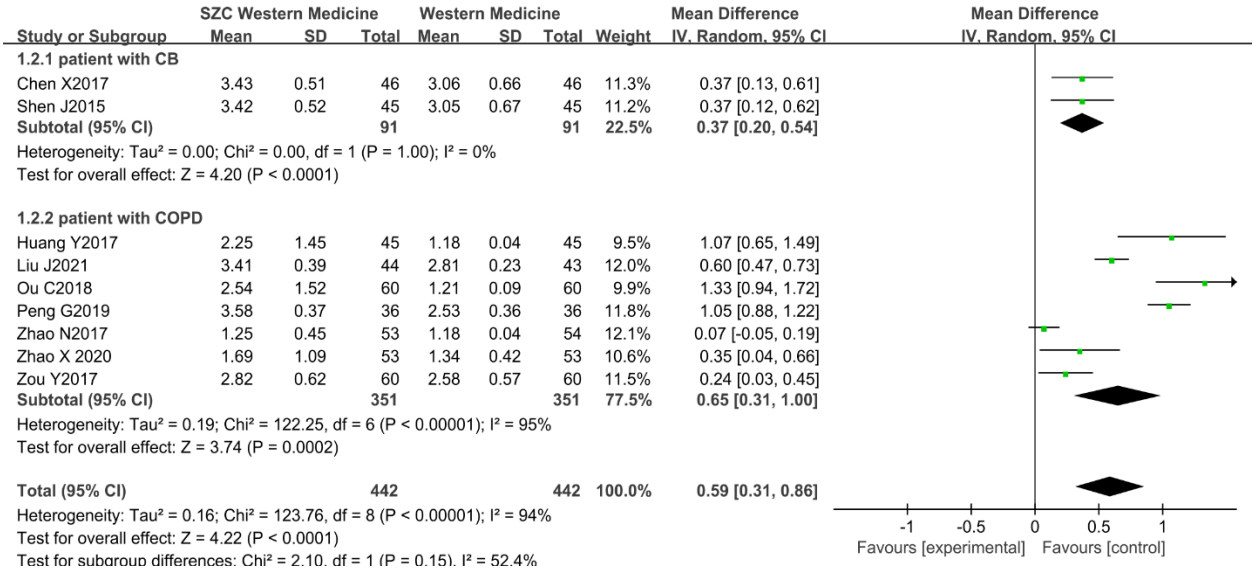


**Figure 5:** Comparison SZC combined with Western Medicine vs. Western Medicine in FVC.

### TNF-a

Pooled results from 9 randomized controlled trials [47, 49-51, 60, 62, 63, 65] showed that SZC combined with western medicine routine significantly reduced TNF-a levels [MD= -6.86, 95%CI (-9.73, -3.99), P < 0.01, I2 = 94%], no meta-regression was performed because only a small number of studies were included. Subgroup analysis showed that SZC combined with western medicine routinely significantly reduced TNF-a levels during the intervention CB compared to controls [MD = -8.41, 95%CI (-8.98, -7.83), P < 0.01, I2 = 0%]; the same was true for COPD patients [MD= 5.08,95%CI (-9.51, -0.65), P < 0.01, I2 = 95%, Figure 6].

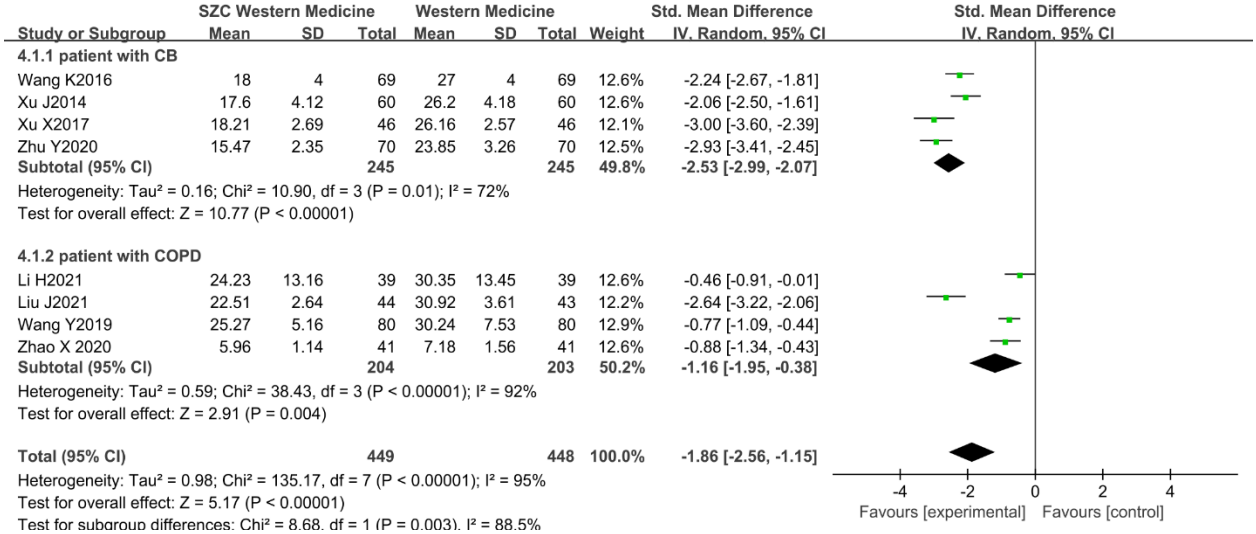


**Figure 6:** Comparison SZC combined with Western Medicine vs. Western Medicine in TNF-a.

### IL-6

Pooled results from 4 randomized controlled trials [49-51, 63] showed that SZC combined with western medicine routine significantly reduced IL-6 levels [MD = -1.77, 95%CI (-2.81, -0.73), P <0.01, I2 = 86.7%], and meta-regression was not performed because only a small number of studies were included. Subgroup analysis showed that SZC combined with western medicine routine significantly reduced IL-6 levels during the intervention CB compared to controls [MD = -2.20, 95%CI (-3.35, -1.06), P < 0.01, I2 = 94%]; the same was true for COPD patients [MD = 0.48, 95%CI (-0.93, -0.03), P = 0.04, Figure 7].

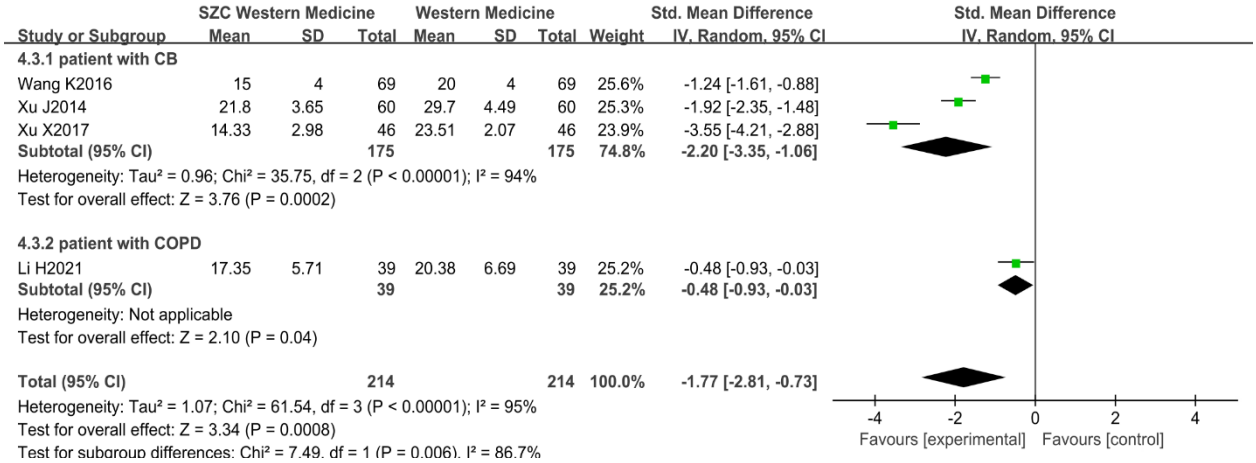


**Figure 7:** Comparison SZC combined with Western Medicine vs. Western Medicine in IL-6.

### IL-8

Pooled results from 4 randomized controlled trials [49-51, 63] showed that SZC combined with western medicine routine significantly reduced IL-8 levels [MD = -1.50, 95%CI (-2.25, -0.76), P < 0.01, I2 = 86.7%], and meta-regression was not performed because only a small number of studies were included. Subgroup analysis showed that SZC combined with western medicine routine significantly reduced IL-8 levels during the intervention CB compared to controls. [MD = -1.84, 95%CI ( -2.42, -1.25), P < 0.01, I2 = 84%]; the same was true for COPD patients [MD = -0.47, 95%CI (-0.92, -0.02), P = 0.04, Figure 8].

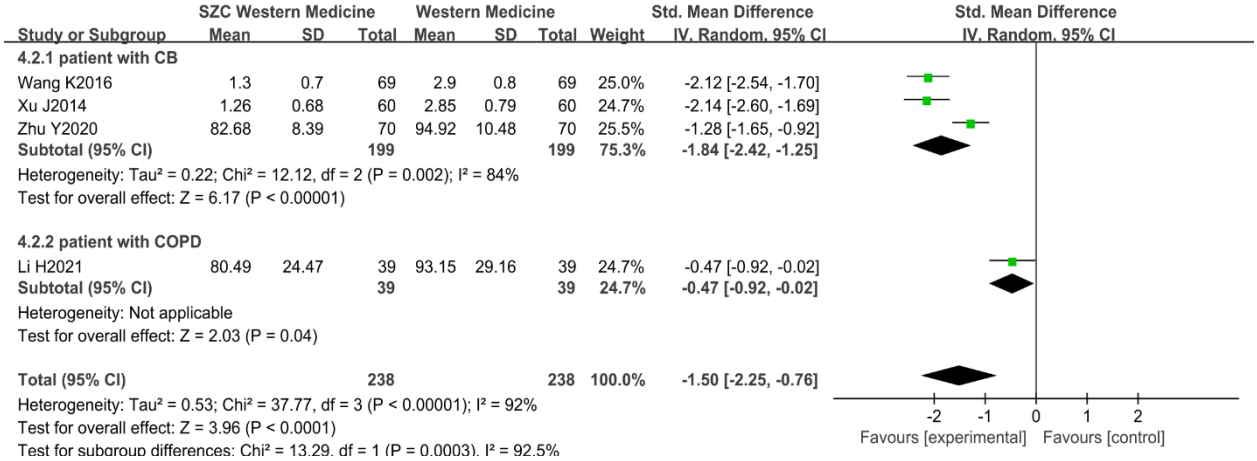


**Figure 8:** Comparison SZC combined with Western Medicine vs. Western Medicine in IL-8.

### Duration of cough

Pooled results from 4 randomized controlled trials [47, 50, 51, 60] showed that SZC combined with western medicine routine significantly reduced cough duration [MD = -1.51, 95%CI (-2.15, -0.86), P < 0.01, I2 = 86%] and meta-regression was not performed because only a small number of studies were included. Subgroup analysis showed that SZC combined with western medicine routine significantly reduced cough duration during intervention CB compared to controls [MD = -1.18,95%CI (-1.45, -0.91), P < 0.01, I2 = 0%]; the same was true for COPD patients [MD = -2.59,95%CI (-3.14, -2.04), P < 0.01, Figure 9].

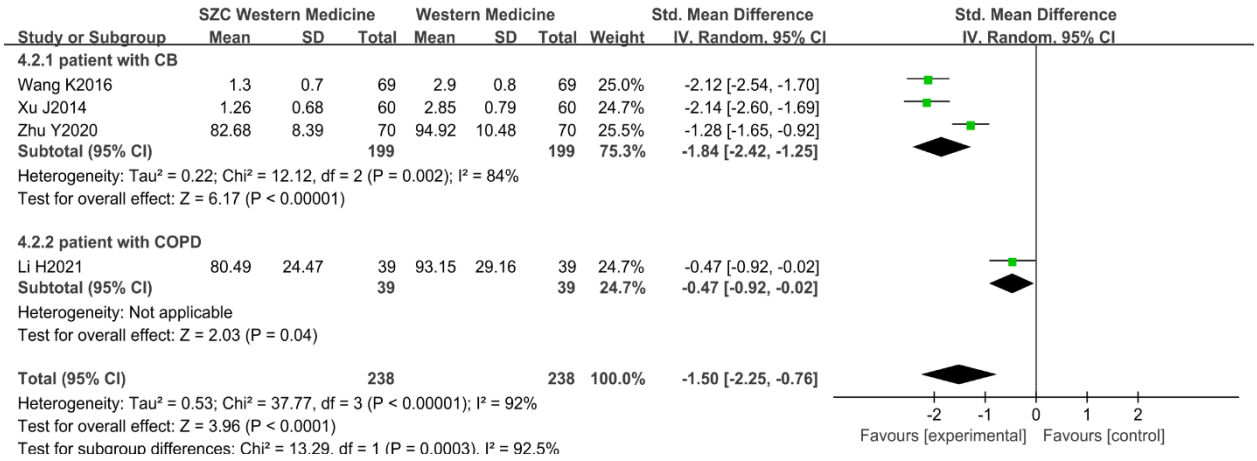


**Figure 9:** Comparison SZC combined with Western Medicine vs. Western Medicine in Duration of cough.

### Duration of coughing sputum

Pooled results from 4 randomized controlled trials [47, 50, 51, 60] showed that SZC combined with western medicine routine significantly reduced duration of coughing sputum [MD = -1.41, 95%CI (-1.78, -1.03), P < 0.01, I2 = 86%] and meta-regression was not performed because only a small number of studies were included. Subgroup analysis showed that SZC combined with western medicine routine significantly reduced cough duration during intervention CB compared to controls [MD = -1.23, 95%CI (-1.49, -0.98), P < 0.01, I2 = 0%]; for COPD patients, too [MD= -1.96, 95%CI (-2.40, -1.52), P < 0.01, Figure 10].

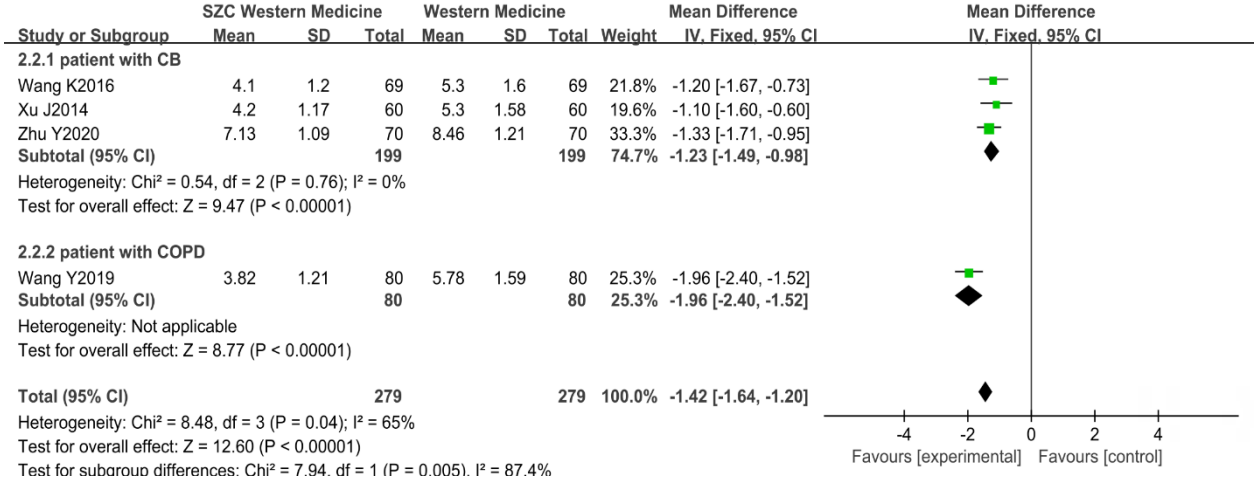


**Figure 10:** Comparison SZC combined with Western Medicine vs. Western Medicine in Duration of coughing sputum.

### AEs

Three randomized controlled trials [46, 57, 63] reported no adverse events at the end of the course of treatment. Heterogeneity between the results of the 6 RCTs [47-49, 52, 54, 60] reporting adverse events was low (P = 0.82, I2 = 0) using a fixed-effects model. Meta-analysis results showed no statistically significant difference (P > 0.05) (Figure 11) in the incidence of adverse reactions between conventional Western medical treatment combined with SZC and conventional Western medical treatment, suggesting that conventional Western medical treatment combined with SZC compared with conventional Western medical treatment. There was no significant difference in the incidence of adverse reactions, as shown in the figure below. 5 included trials [47, 48, 52, 54, 60] described different events with different symptoms during treatment, including gastrointestinal reactions (9 cases in the control group, 10 cases in the trial group), constipation (1 case in the control group, 3 cases in the trial group), dry mouth and throat (3 cases in the control group, 2 cases in the trial group), hoarseness (2 cases in the control group, 1 case in the trial group), dizziness (3 cases in the control group, 1 case in the trial group), and rash (3 cases in the control group, 2 cases in the test group), facial flushing (2 cases in the control group, 1 case in the test group), and no non-life-threatening adverse events were reported.

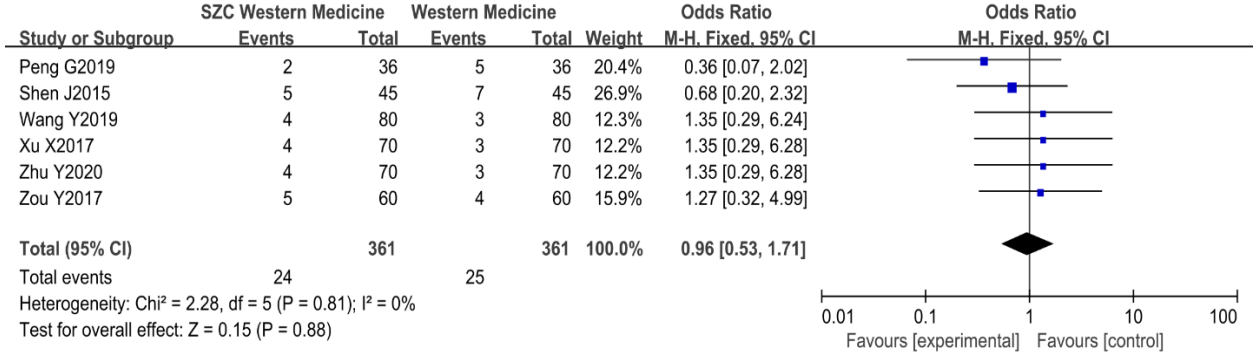


**Figure 11:** Forest plot of comparison SZC Western Medicine vs. Western Medicine in Duration of AEs.

### Publican bias

The following figure (Figure 12) shows the funnel plot of FEV1/FVC of SZC combined with conventional treatment with western drugs in CB or COPD patients, the distribution of each study in the funnel plot is approximately symmetrical but subjective bias exists. The begge and egger tests were performed on them and yielded z = 1.03 (P = 0.304) and t= 1.31 (P = 0.220), respectively, indicating the absence of publication bias in the statistics. However, considering that the published studies were in Chinese literature, positive results are more likely to be published and the results need to be interpreted with caution.

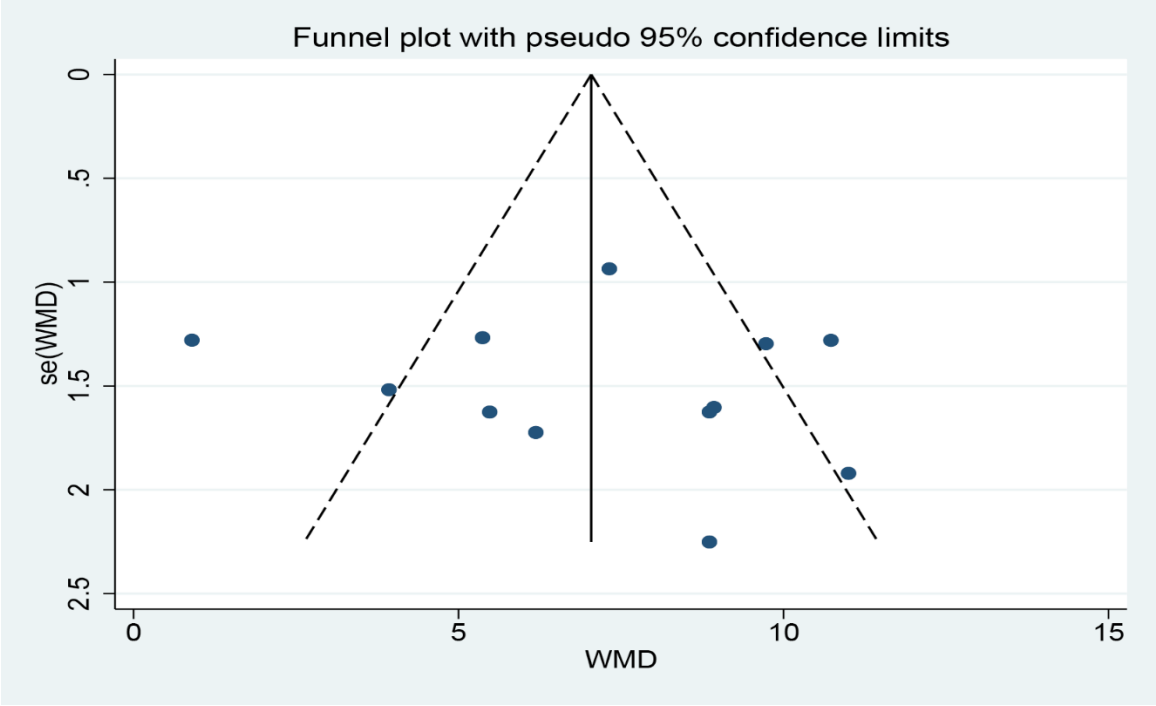


**Figure 12:** Funnel plot of the included studies.

### Sensitivity Analysis

The results, which were obtained by excluding studies from the analysis on a case-by-case basis to understand their effect on the results, showed that the combined effect of SZC on FEV1/FVC did not vary significantly (Figure 13).

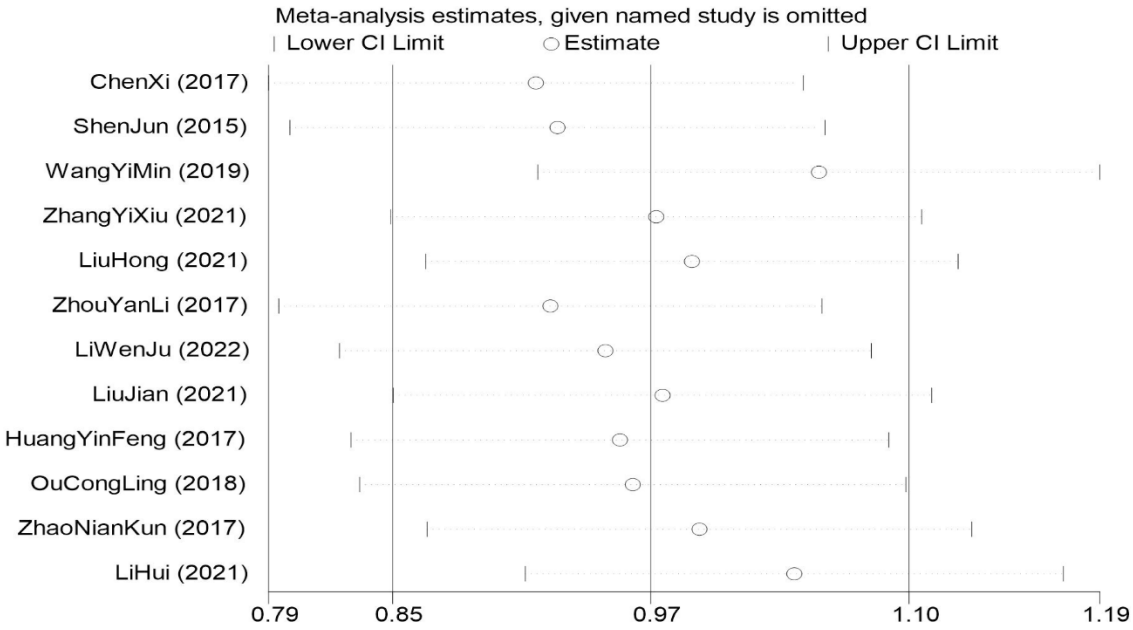


**Figure 13:** Sensitivity analysis.

## Discussion

In this review, 20 RCTs with a total of 1956 participants were included to assess the effect of SZC capsules on patients with acute exacerbations of CB or COPD. The results showed that SZC combined with conventional western medicine significantly improved lung function and reduced plasma inflammatory factor levels, Reduce the duration of symptoms such as coughing and phlegm; the results of subgroup analysis showed that SZC combined with conventional western medicine was superior to the conventional medicine alone group in both acutely exacerbated CB and COPD patients. In terms of adverse events, there was no significant difference between the experimental and control groups.

The exact pathogenesis of acute exacerbations of CB or COPD is still unclear, but there is consensus on the involvement of inflammatory factors [66-69], which not only disrupt capillary endothelial function, promote fibroblast proliferation, and lead to progressive airflow obstruction. How to quickly and effectively intervene and slow down the development is the focus of current research. Our findings show that the combination of SZC with western drugs can reduce the inflammatory response better and faster, shorten the course of the disease, reduce airway remodeling, and thus slow down the progression of the disease. Pulmonary function, as the gold standard for CB or COPD diagnosis, is mainly used to determine small airway lesions, and has an important role in assessing the severity and prognosis of the disease [70]. TNF-a [68], IL-6 [66, 67] and IL-8 [69], as important mediators of the inflammatory response, are positively correlated with the severity of disease and lung tissue damage in patients with acute exacerbations, and SZC combined with western medicine can significantly reduce the levels of TNF-a, IL-6 and IL-8 in patients.

With their multi-component and multi-target advantages, SZC play a unique role in the treatment of patients with acute exacerbations of CB or COPD. A basic study demonstrated that SZC inhibited NLRP3 inflammatory vesicle activation by disrupting NLRP3 inflammatory vesicle assembly and reducing cleaved caspase-1 expression as well as reducing IL-1β secretion, while improving NLRP3 inflammatory vesicle-mediated pulmonary dysfunction by modulating endoplasmic reticulum stress, contributing to reduced mucus hypersecretion, reduced cough frequency, and prolonged cough latency [71]; SZC ameliorates airway inflammation in mice by activating the AhR-Nrf2 pathway, thereby reducing the expression levels of secreted inflammatory mediators such as TNF-α, IL-1β and IL-6 to reduce airway inflammation damage to blood vessels and peribronchial connective tissue [72], which helps to improve alveolar wall edema and thickening in mice; SZC not only decreases lung dysfunction through EGFR-ERK signaling pathway to reduce airway inflammation, while promoting HGF secretion to improve sputum obstruction, while facilitating the promotion of tracheobronchial secretion [73]; SZC inhibits non-catabolic inflammation by

inhibiting NF-κB signaling and NLRP3 inflammatory vesicle activation to protect the stability of the mitochondrial endothelia [74], thus helping to improve lung parenchymal deformation, alveolar atrophy, severe edema and On the other hand, SZC inhibits the over-activation of p38MAPK signaling pathway, improves glucocorticoid sensitivity, and has a synergistic effect with budesonide combination therapy [75].

Only one previous meta-analysis has examined the evaluation of the effectiveness of SZC in COPD patients [10]; this review focuses for the first time on the effectiveness of SZC in patients with acute exacerbations of COPD, while including patients with CB, and for the first time evaluates safety. Although the results of the meta-analysis showed a favorable effect of SZC in patients with acute exacerbations of CB or COPD, the conclusions should be interpreted with caution. First, all 20 studies included RCTs were low-quality, single-center, small-sample clinical trials, and none of them were not registered in advance, and details about allocation concealment and blinding were not recorded; the methodological quality was insufficient such that it was difficult to make a clear judgment about the risk of bias; second, none of the 20 trials were registered in advance, the relevant trial protocols were not published, and the outcome indicators of treatment were different and prone to Second, none of the 20 trials were pre-registered, and the protocols of the trials were not published, and the outcome indicators of the treatments were not identical, making them prone to publication bias. Although we attempted to use meta-regression to explore potential sources of heterogeneity, it seemed to be ineffective, which made the results unconvincing.

## Conclusion

For patients with acute exacerbations of CB or COPD, SZC as an adjuvant therapy can significantly improve patients' lung function levels, reduce inflammatory factor levels, and decrease the duration of symptoms while balancing safety and efficacy; concern the low methodological quality of the included RCTs, more rigorous RCTs and real-world studies need to be designed in the future to confirm the efficacy and safety of SZC.

### Conflict of Interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### Author Contributions

YL, ZH, and HZ conceived and drafted this systematic review and registered the protocol at INPLASY. YL, ZH, HF and YM developed the search strategy and conducted the literature research, study selection, data extraction and risk of rias assessment, and contributed to manuscript drafting. YL, XC and HZ interpreted the evidence from methodological and clinical perspective. HZ and XC oversaw the conduct of the study.

All authors have read, critically reviewed, and approved the final manuscript.

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### Data Availability Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

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## Supplementary Material

**1.** Suhuang Zhike Capsule Prescription

Ephedra 556g; Perilla leaf 556g; Geosaurus 556g; Honeyed Folium Eriobotryae 556g; Stir-fried Perilla seed 332g; Cicadae Periostracum 444g; Peucedani Radix 444g; Stir-fried Greater burdock 556g; Schisandra chinensis 44g;

**2.** Preparation process

The above nine kinds of medicinal herbs, Perilla leaf and Peucedani Radix were soaked in water for one hour, and the volatile oil was extracted for eight hours. The volatile oil was collected, and the distilled water solution was collected in another device. The volatile oil was encapsulated with beta- cyclodextrin, dried under 40℃, and crushed into fine powder. Ephedra and Schisandra chinensis were extracted by reflux with 80% ethanol three times, 1.5 hours each time, after filtration, filtrate was combined, ethanol was recovered and concentrated into a thick paste with a relative density of 1.25-1.30 (50℃) for standby. The rest of the five kinds of medicinal herbs, such as Geosaurus, were boiled in water three times for 1 hour each time. After filtration, the filtrate was combined with the above distilled water solution and concentrated to a relative density of 1.10(50 ℃). Add ethanol to reach 70% alcohol content, refrigerate for 24 hours, filter, filtrate to recover ethanol, and concentrate to a thick paste with a relative density of 1.25~1.30(50℃). Combine with the thick paste above, dry into dry extract under pressure at 70℃, pulverize into fine powder, and combine with the fine powder above. Add appropriate amount of starch, mix well, granulate with 90%~95% ethanol in appropriateamount, dry, after 40 mesh sieve the whole grain, into the capsule, made of 1000 grains, ready.