Review Article

Efficacy and Safety of Re Du Ning Injection for Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Background. Re Du Ning, a traditional Chinese medicine injection, has been widely used for the treatment of chronic obstructive pulmonary disease, although without established systematic review evidence. This systematic review aimed to assess the efficacy and safety of Re Du Ning in the treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Methods. We searched seven databases (PubMed, Embase, the Cochrane Library, SinoMed, CNKI, WanFang, and the Chinese Clinical Trial Registry) up to November 1, 2021, to identify randomized controlled trials of Re Du Ning for AECOPD. Two researchers independently carried out literature screening and data extraction. Effects were measured by risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals (CIs). The meta-analysis was completed by RevMan 5.4 software. Results. Twenty-six studies met the eligibility criteria, with a total of 2284 patients. The findings of the meta-analysis indicated that the response rate of the experimental group was higher than that of the control group: RR = 1.14% and 95% CI: (1.09, 1.19). Significantly greater improvements in pulmonary function: FEV1: MD = 0.28 L, 95% CI: (0.20, 0.36); FEV1/FVC: MD = 0.63%, 95% CI: (4.68, 12.59); T-lymphocyte counts: CD4: MD = 6%, 95% CI: (2.44, 9.56); CD3: MD = 10.42%, 95% CI: (8.6, 12.24); CD4/CD8: MD = 0.38%, 95% CI: (0.32, 0.43); acid/base imbalance: PH: MD = 0.05, 95% CI: (0.01, 0.10); PaO2: MD = 9.02 mmHg, 95% CI: (11.11, 9.19); p = 0.005; C-reactive protein: MD = −6.65 mg/L, 95% CI: (−10.97, −2.34); and PCT: MD = −0.28 μg/L, 95% CI: (−0.41, −0.15) were observed in patients receiving Re Du Ning compared with those receiving the control treatment. Re Du Ning did not significantly change the carbon dioxide partial pressure. All reported adverse reactions were mild. Conclusion. Re Du Ning injection, as a complementary therapy to routine treatment, has better efficacy than Western medicine alone in relieving clinical symptoms, delaying pulmonary function decline, and improving inflammation indicators for AECOPD, with good safety. The evidence was limited by a lack of high-quality RCTs.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by continuous airflow limitation. COPD is related to the increased chronic inflammatory response of the respiratory tract and lungs to toxic particles or gases. According to the 2021 Global Initiative for Chronic Obstructive Lung Disease, COPD has become one of the top causes of death in the world [1]. An 8-year retrospective cohort study showed that the economic losses caused by COPD amount to 50 billion dollars per year in Europe [2]. The 2019 Asia-Pacific Respiratory Association’s position statement on COPD management in Asia pointed out the shortcomings of COPD prevention and treatment in underdeveloped regions, namely, insufficient awareness, insufficient diagnosis, and insufficient treatment [3].
2. Methods

2.1. Inclusion and Exclusion Criteria. The study population was set as adults who were diagnosed with COPD by any recognized international guidelines and developed acute exacerbations. The intervention in the experimental group was Re Du Ning combined with Western medicine, and the control group was treated with Western medicine alone. Eligible Western medicine included antibiotics, phlegm-reducing drugs, and bronchodilators. Only RCTs were included. The outcomes of interest included the response rate, pulmonary function, and inflammation indicators.

2.2. Search Strategy. We searched PubMed, Embase, the Cochrane Library, SinoMed, CNKI, WanFang, VIP, and the Chinese Clinical Trial Registry to find relevant RCTs. The search date was from the inception of these databases up to November 1, 2021. The search strategy in PubMed, for example, was as follows: ("Pulmonary Disease, Chronic Obstructive" [mh] OR "chronic obstructive pulmonary disease"[tiab] OR "COPD"[tiab]) AND ("re du ning" [tiab] OR "e du ning" [tiab]). All records yielded were imported into Endnote X9.3.3 for management.

2.3. Data Collection. Two team members independently screened the bibliography records according to the inclusion and exclusion criteria by reading the titles, abstracts, and full texts. They then extracted the data needed for this study, including authors, year of publication, sample size, course of disease, age, intervention and control measures, dose and course of treatment, and outcomes, and imported them into a pretested table. Any disagreements were resolved through consensus discussion.

2.4. Outcomes. The primary outcome was the response to treatment according to the "Guiding Principles for Clinical Research of New Chinese Medicines," which is generally indicated by the symptoms of AECOPD (such as cough, wheezing, chest tightness, and dyspnoea) being relieved by more than 30%. Secondary outcomes included changes in pulmonary function (FEV1 and FEV1/FVC); changes in counts of T-lymphocytes (CD3, CD4, CD8, and CD4/CD8); changes in blood gas indicators (PH) such as hydrogen ion concentration, partial pressure of carbon dioxide (PaCO2), and partial pressure of oxygen (PaO2); changes in inflammation indicators such as C-reactive protein (CRP), and procalcitonin (PCT), and the incidence of adverse reactions.

2.5. Risk of Bias Assessment. The risk of bias of the RCTs was assessed using the Cochrane Risk of Bias Assessment tool. This tool includes seven items, namely, random sequence generation method, allocation hiding, blinding of patients and clinicians, blinding of outcome evaluators, data completeness, selective reporting, and other bias. Each item was rated as “low risk,” “high risk,” or “uncertain risk.”

2.6. Data Analysis. RevMan 5.4 software was used to perform the meta-analyses. For dichotomous data, relative risks (RRs) and 95% confidence intervals (CIs) were used as the effect size, with the Mantel–Haenszel method (M–H method) being used for incorporating data. For continuous data, the mean differences (MDs) were pooled by the inverse variance method, and the 95% CIs were given. All meta-analyses were based on a random effects model. Statistical heterogeneity between studies was assessed by the chi-squared test and I² values, with significance levels of \( p < 0.10 \) and \( I^2 > 50\% \), respectively. We performed subgroup analyses stratified by different courses of treatment (≤7 days versus >7 days) to explain the source of heterogeneity. Funnel plots...
and Egger’s tests were used to detect publication bias for outcomes with at least 10 studies included.

3. Results

3.1. Results of the Search and Screening. A total of 704 records were identified, 350 of which remained after the exclusion of duplicates. After screening the titles, abstracts, and full texts, 26 RCTs [12–37] were included in our review. Figure 1 shows the process of literature screening.

3.2. Descriptive Characteristics. The included RCTs enrolled a total of 2284 patients with AECOPD, with a sample size in individual RCTs ranging from 30 to 226. The average age was 55−73 years in the experimental (Re Du Ning) group and 54−76 years in the control group. Re Du Ning was administered through intravenous infusion in all RCTs, with a frequency of once a day and a dose of 20 ml/day. Anti-infective treatments were administered in all trials. The course of treatment was ≤ 7 days in 12 studies and > 7 days in 16 studies. The detailed study characteristics are compiled in Table 1.

3.3. Results of Risk of Bias Assessment. All 26 included studies claimed that allocation was random, but only 10 of them described the process of random number generation [13, 21, 22, 24−27, 30, 31]. None of the studies reported the application of allocation concealment or the status of blinding. There was no suspicion of selective reporting in any of the included studies, and no missing data were found. In general, all RCTs had an overall moderate to high risk of bias (Figure 2).

3.4. Response to Treatment. Twenty-four studies [12−24, 26−28, 30−37] reported the response rate to treatment, involving 1962 patients with AECOPD. Their response rates were 92.8% and 79.6% in the experimental group and the control group, respectively. The pooled results demonstrated that the experimental group had a significantly better response rate than the control group (RR: 1.14%; 95% CI: (1.09, 1.19), p < 0.00001) (Figure 3), with low heterogeneity (I^2 = 34%).

3.5. FEV1. Three studies [17, 21, 27] (n = 314) reported on FEV1. Significantly more improvement in pulmonary function (FEV1) was obtained under with Re Du Ning injection (MD: 0.28 L; 95% CI: (0.20, 0.36), p < 0.00001) (Figure 4), with low heterogeneity (I^2 = 1%).

3.6. FEV1/FVC%. Six studies [13, 17, 21, 25, 27, 36] (n = 694) reported on FEV1/FVC%. The treatment effect was more obvious in the Re Du Ning group than in the control group (MD: 8.63%; 95% CI: (4.68, 12.59), p < 0.0001) (Figure 5), with substantial heterogeneity (I^2 = 92%).

3.7. pH, PaO2, and PaCO2. Four studies [16, 21, 26, 29] (n = 414) reported data on indicators of blood gas analysis. As shown in Figure 6, the Re Du Ning injection significantly increased pH (MD: 0.05; 95% CI: (0.01, 0.10), p = 0.03; I^2 = 85%) and PaO2 (MD: 9.02 mmHg; 95% CI: (2.73, 15.3), p = 0.005; I^2 = 93%) when compared with the control treatment but did not significantly change PaCO2 (MD: −7.75 mmHg; 95% CI: (−15.64, 0.15), p = 0.05; I^2 = 96%) (Figure 6).

3.8. CRP. Eight studies [14, 16, 19, 21, 24, 27, 29, 30] reported the level of CRP before and after treatment (n = 722). Meta-analysis suggested that the experimental group had a better change in CRP than the control group (MD: −6.65 mg/L; 95% CI: (−10.97, −2.34); p = 0.003) (Figure 7), with substantial heterogeneity (I^2 = 90%).

3.9. PCT. Five studies [12, 21, 27, 29, 31] reported on PCT (n = 456). Meta-analysis suggested that the experimental group had a better change in PCT than the control group (MD: −0.28 µg/L; 95% CI: (−0.41, −0.15); p < 0.00001) (Figure 8), with substantial heterogeneity (I^2 = 86%).

3.10. T-Lymphocytes. Only two trials [25, 26] (n = 336) reported on T-lymphocytes. As shown in Figure 9, compared with the control treatment, the Re Du Ning treatment significantly increased the CD4 count (MD: 6%; 95% CI: (2.44, 9.56)), p = 0.001), the CD3 count (MD: 10.42%, 95% CI: (8.6 to 12.24); p < 0.00001), and the ratio of CD4/CD8 (MD: 0.38%; 95% CI: (0.32 to 0.43); p < 0.00001) but did not significantly impact the CD8 count (MD: −0.15%; 95% CI: (−2.80 to 2.50); p = 0.91).

3.11. Subgroup Analyses. According to the study settings in the PROSPERO protocol, we performed a subgroup analysis of the treatment response group, the CRP group, and treatment duration ≤ 7 and > 7 days (details in Table 2).

3.12. Sensitivity Analysis. The sensitivity analyses changing the effect model to be fixed did not show any significant changes in the effect size for all outcomes.

3.13. Publication Bias. Publication bias was only available in the outcome of the response rate, which was included in at least ten studies. The funnel plot was asymmetrical (Figure 10), and the p value was < 0.001 in the Egger test, confirming the existence of significant publication bias in this outcome.

3.14. Safety. Four studies reported adverse events after Re Du Ning treatment, including four cases of chest tightness, four cases of dizziness, eight cases of rash, and nine cases of gastrointestinal reactions. No serious adverse events were reported.
Records identified from*: Databases (n = 704)
Records removed before screening: Duplicate records removed (n=350)
Records excluded: 155: NO-AECOPD studies. 28: Animal experiments. 18: Reviews
Record a/f_ter duplicates removed (n =354)
Records excluded:
155: NO-AECOPD studies.
28: Animal experiments.
18: Reviews
Full-text articles assessed for eligibility (n =153)
Report sex cluded:(n=125):
9: No definite diagnostic. 7: studying other diseases 35: Intervention was not meet the inclusion criteria. 48: Not RCT. 28: TCM was used in control group
Studies included in review (n = 26)

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Figure 1: Process of literature screening.

### Table 1: Studies characteristics.

| Author       | Sample size (EG/CG) | Mean age (EG/CG) | Experimental intervention | Cointerventions                                      | Course of treatment (days) | Outcomes |
|--------------|---------------------|------------------|----------------------------|------------------------------------------------------|----------------------------|----------|
| Zeng et al. 25 | 116/110             | —                | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM; AD                 | 10                         | C, D     |
| Chen et al. 21 | 77/77               | 64.7/65.8        | RDN 20 ml ivgtt qd         | Antibiotics; PRM; AD                                 | 7                          | A, B, C, E, F, G, H, I |
| Chen et al. 23 | 30/30               | —                | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM; AD; oxygen therapy | 10                         | A        |
| Dong et al. 22 | 30/30               | 62.3/61.3        | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM                     | 7                          | A        |
| Tian 2015 36   | 37/37               | 59.7/60.8        | RDN 20 ml ivgtt qd         | Antibiotics; PRM; AD                                 | 10                         | A, C     |
| Zhang et al. 24 | 45/41               | 55/57            | RDN 20 ml ivgtt qd         | Antibiotics; PRM; AD                                 | 3                          | A        |
| Liu et al. 34  | 80/80               | 68.2/66.8        | RDN 20 ml ivgtt qd         | Antibiotics; PRM; AD                                 | 14                         | A        |
| Yao [33]       | 50/50               | 62.1/62.4        | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM; AD; oxygen therapy | 7                          | A        |
| Weng et al. 32 | 40/40               | 57/58            | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator                          | 5                          | A        |
| Xu et al. 28   | 15/15               | —                | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM; AD; oxygen therapy | 7                          | A        |
| Gao et al. 30  | 38/39               | 66/63            | RDN 20 ml ivgtt qd         | Antibiotics; AD; oxygen therapy                      | 5                          | A, H     |
| Nie et al. 29  | 50/50               | 72.4/70.2        | RDN 20 ml ivgtt qd         | Antibiotics; oxygen therapy                          | 3                          | E, F, G, H, I |
| Tang [27]      | 45/45               | 63/63            | RDN 20 ml ivgtt qd         | Antibiotics; PRM; oxygen therapy                     | 14                         | A, B, C, H, I |
| Pang et al. 26 | 55/55               | 55/54            | RDN 20 ml ivgtt qd         | Antibiotics; PRM; AD; oxygen therapy                 | 14                         | A, B, D, E, F, G |
| Lu [20]        | 44/44               | 65.9/67.1        | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM                     | 7                          | A        |
| Wan [18]       | 48/48               | 58.9/59.5        | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM                     | 7                          | A        |
| Wei [17]       | 37/33               | —                | RDN 20 ml ivgtt qd         | Antibiotics; bronchodilator; PRM                     | 10                         | A, B, C  |
Table 1: Continued.

| Author          | Sample size (EG/CG) | Mean age (EG/CG) | Experimental intervention | Cointerventions                        | Course of treatment (days) | Outcomes |
|-----------------|--------------------|------------------|---------------------------|----------------------------------------|---------------------------|----------|
| Zhou 2014 [16]  | 30/30              | 72.6/73.1        | RDN 20 ml ivgtt qd        | Antibiotics; bronchodilator; PRM        | 7                         | A, E, F, G, H |
| Zhang [14]      | 45/44              | 66.2/65.7        | RDN 20 ml ivgtt qd        | Antibiotics; bronchodilator; PRM; AD    | 10                        | A, H     |
| Ye et al. [13]  | 40/40              | 62.8/62.4        | RDN 20 ml ivgtt qd        | Antibiotics; bronchodilator; PRM        | 28                        | A, C     |
| Yang et al. [12]| 30/30              | 64.5/64.2        | RDN 20 ml ivgtt qd        | Antibiotics; bronchodilator; PRM; AD    | 10                        | A, I     |
| Zhang et al. [35]| 45/42             | 66.2/65.7        | RDN 20 ml ivgtt qd        | Antibiotics; PRM; AD                    | 10                        | A, H     |
| Yue [19]        | 33/32              | 73/70            | RDN 20 ml ivgtt qd        | Antibiotics; AD                         | 14                        | A, H     |
| Peng et al. [15]| 26/26              | 65.0/62.9        | RDN 20 ml ivgtt qd        | Antibiotics; PRM; AD                    | 10                        | A        |
| Tong [37]       | 39/39              | 64.2/63.8        | RDN 20 ml ivgtt qd        | Antibiotics; AD                         | 10                        | A        |
| Xu et al. [31]  | 26/26              | 62.7/61.4        | RDN 20 ml ivgtt qd        | Antibiotics; PRM                        | 10                        | A, I     |

EG: experimental group; CG: control group; PRM: phlegm resolving medicine; AD: antiasthmatic drugs; RDN: Re Du Ning injection; ivgtt: intravenous drip; qd: once a day; A: response rate; B: FEV1; C: FEV1/FVC; D: T-lymphocyte E: PH; F: PaO2; G: PaCO2; H: C-reactive protein; I: procalcitonin.

Figure 2: Results of the risk of bias assessment.

Figure 3: Forest plot of the meta-analysis of response to treatment.

Table 2: Continued.

| Study or Subgroup | Experimental Events | Control Events | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------------|---------------|--------|-----------------------------|-------------------------------|
| Chen 2014         | 70                 | 77            | 4.5%   | 1.27 [1.09, 1.49]            |                               |
| Dong 2015         | 29                 | 30            | 4%     | 1.21 [1.00, 1.46]            |                               |
| Gao 2013          | 34                 | 38            | 3.9%   | 1.06 [0.89, 1.26]            |                               |
| Liu 2014          | 75                 | 80            | 8%     | 1.04 [0.95, 1.14]            |                               |
| Lu 2018           | 40                 | 44            | 3.8%   | 1.14 [0.96, 1.36]            |                               |
| Pang 2015         | 53                 | 55            | 8.2%   | 1.04 [0.95, 1.14]            |                               |
| Peng 2021         | 24                 | 26            | 1.8%   | 1.33 [1.01, 1.76]            |                               |
| Rao 2012          | 46                 | 50            | 4.9%   | 1.10 [0.95, 1.27]            |                               |
| Shen 2012         | 29                 | 30            | 6.4%   | 1.04 [0.92, 1.16]            |                               |
| Tang 2021         | 44                 | 45            | 4%     | 1.29 [1.09, 1.54]            |                               |
| Tian 2015         | 30                 | 37            | 1.4%   | 1.43 [1.04, 1.97]            |                               |
| Tong 2020         | 37                 | 39            | 3.8%   | 1.19 [1.00, 1.42]            |                               |
| Wan 2013          | 45                 | 48            | 3.7%   | 1.25 [1.05, 1.49]            |                               |
| Wei 2014          | 35                 | 37            | 3.0%   | 1.25 [1.01, 1.54]            |                               |
| Wen 2011          | 39                 | 40            | 5.2%   | 1.15 [1.00, 1.32]            |                               |
| Xu 2011           | 7                  | 15            | 0.2%   | 1.75 [0.64, 4.75]            |                               |
| Xu 2019           | 24                 | 26            | 1.8%   | 1.33 [1.01, 1.76]            |                               |
| Yang 2018         | 27                 | 30            | 2.3%   | 1.23 [0.96, 1.57]            |                               |
| Ye 2016           | 38                 | 40            | 3.7%   | 1.23 [1.02, 1.47]            |                               |
| Yue 2014          | 31                 | 33            | 3.5%   | 1.16 [0.96, 1.39]            |                               |
| Zhang 2011A       | 43                 | 45            | 5.7%   | 1.09 [0.96, 1.24]            |                               |
| Zhang 2011B       | 44                 | 45            | 6.8%   | 1.10 [0.98, 1.22]            |                               |
| Zhang 2012        | 44                 | 45            | 8.1%   | 1.05 [0.96, 1.15]            |                               |
| Zhou 2014         | 27                 | 30            | 1.8%   | 1.35 [1.02, 1.79]            |                               |

Total (95% CI): 985 [977, 100.0%] 1.14 [1.09, 1.19]

Heterogeneity: tau^2 = 0.00, chi^2 = 34.73, df = 23 (p = 0.006), I^2 = 34%

Test for overall effect: Z = 6.33 (p < 0.0001)
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Mean Difference | Mean Difference |
|------------------|------|----|-------|------|----|-------|-----------------|----------------|
| Chen 2014        | 20.36| 1.86| 116   | 19.4 | 1.86| 116   | 0.92            | 0.92           |
| Tian 2013        | 18.4 | 1.86| 116   | 19.4 | 1.86| 116   | 0.92            | 0.92           |
| Pang 2015        | 20.2 | 1.86| 116   | 19.4 | 1.86| 116   | 0.92            | 0.92           |
| Zhou 2014        | -21.1| 14.62| 30   | -16.85| 30| 30   | 5.26%           | 5.26%          |
| Tang 2021        | 4.8  | 8.1 | 33    | 13.5%| 8.1| 33    | -3.52           | -3.52          |
| Ye 2016          | 20.02| 12.67| 40   | 14.2%| 12.67| 40   | -3.37           | -3.37          |
| Zeng 2014        | 20.88| 1.86| 116   | 19.4%| 1.86| 116   | -11.93          | -11.93         |
| Nie 2013         | 25.16| 8.43| 77    | 13.8%| 8.43| 77    | -13.15          | -13.15         |
| Nee 2013         | 18.4 | 7.34| 77    | 13.8%| 7.34| 77    | -10.15          | -10.15         |
| Pang 2015        | 26.7 | 9.63| 77    | 13.8%| 9.63| 77    | -7.80           | -7.80          |
| Zhou 2014        | 24.2 | 9.56| 77    | 13.8%| 9.56| 77    | -6.46           | -6.46          |

**Figure 4:** Forest plot of the meta-analysis of FEV1.

**Figure 5:** Forest plot of the meta-analysis of FEV1/FVC%.
### Table 2: Results of subgroup analysis.

| Outcome                  | Course of treatment (days) | No. of studies | Effects within subgroups (95% CI) | Heterogeneity within subgroups | Interaction p value |
|--------------------------|---------------------------|----------------|----------------------------------|--------------------------------|-------------------|
| Response rate            | ≤7                        | 9              | RR 1.15 (1.09, 1.22)              | p = 0.53; I² = 0%               | p = 0.74          |
|                          | >7                        | 14             | RR 1.14 (1.07, 1.20)              | p = 0.02; I² = 36%              |                   |
| C-reactive protein (mg/L)| ≤7                        | 4              | MD −10.06 (−19.05, −1.07)         | p < 0.00001; I² = 94%           | p = 0.16          |
|                          | >7                        | 4              | MD −3.48 (−5.33, −1.63)           | p = 0.98; I² = 0%               |                   |

### 4. Discussion

With the ageing of the population, environmental pollution, and urbanization, COPD as a global challenge is becoming increasingly difficult. Traditional Chinese medicine injections composed of herbal extracts provide a new approach for the treatment of COPD. A total of 26 studies were included in this study, and the results of the meta-analysis showed that Re Du Ning injection had a significant adjuvant effect on the improvement of clinical symptoms and pulmonary function in patients with acute exacerbations of COPD, as well as reducing inflammatory factors and correcting the acid-base imbalance in the body.

AECOPD is mostly caused by respiratory infections. CRP and PCT have attracted attention as clinically sensitive indicators of inflammation and bacterial infection. According to the results of the meta-analysis, the Re Du Ning injection reduced the levels of CRP and PCT. Pharmacological analyses have shown that *Gardenia*, honeysuckle, and *Artemisia annua*, the components of Re Du Ning injection, have anti-inflammatory, antibacterial, and antiviral effects, and their active chemicals include iridoids, lignans, coumarins, sesquiterpenoids, flavonoids, caffeoylquinic acids, and phenolic acids [38, 39]. *Artemisia annua* is widely known as the source of artemisinin, discovered by academician Youyou Tu, and in addition to killing malaria parasites, its antibacterial activity against a variety of Gram-
negative bacteria/positive bacteria is outstanding [40]. Iridoids and flavonoids have antitussive, expectorant, antiasthmatic, and antibacterial activities. Geniposide (the main iridoid in Gardenia) and chlorogenic acid in honeysuckle can inhibit acute and chronic inflammatory disease-related macrophage responses, reduce the release of inflammatory factors, lower C-reactive protein, and suppress infection at the same time [41]. Pharmacological experiments also showed that geniposide can protect pulmonary artery smooth muscle from lipopolysaccharide damage by affecting the tlr-4/myd88 signalling pathway, improve pulmonary function, and avoid the formation of pulmonary hypertension [42]. These mechanisms confirm the authenticity of the results of this study on FEV1 and FEV1/FVC, suggesting that Re Du Ning may be a new approach for improving exercise tolerance and delaying pulmonary function decline in patients with COPD.

Acute exacerbations of COPD often lead to carbon dioxide retention and hypoxemia. Severe cases can be complicated by respiratory acidosis, resulting in respiratory depression, respiratory failure, pulmonary encephalopathy, and even death. The improvement in pulmonary function after the Re Du Ning treatment was also reflected in the results of blood gas analyses—the findings of the meta-analysis indicated that the hypoxemia and acid-base imbalance in the experimental group were improved, and the acidosis of the body was corrected. The results of PaCO2 were not statistically significant, which may be impacted by Nie et al.’s study [29] with a treatment course of only 3 days, which was much shorter than that of the other 3 studies. There is no evidence on the effect of Re Du Ning injection on direct airway expansion, and therefore its effects on pulmonary function and blood gas indicators may be associated with its efficacy on respiratory tract inflammation and infection.

Re Du Ning injection seemed to be well tolerated in patients with COPD, as indicated by only mild adverse reactions reported in four out of 26 RCTs. However, there is no lack of adverse reactions caused by Re Du Ning injection in previous reports. A survey on adverse reactions of Re Du Ning injection reported 1452 adverse reactions, of which 952 (65.9%) were reported by minors and were mostly immediate, occurred within 60 minutes of the first administration, and commonly manifested as local skin rashes; however, some adverse reactions may also be severe in a small proportion of patients [43]. The analysis by high-performance liquid chromatography on ultrafiltration of Re Du Ning injection suggested that allergic reactions may be associated with Tween-80 (made by the polymerization of dehydrated sorbitol monooleate and ethylene oxide, used as a solvent or emulsifier for injection and oral liquid) [44]. According to the “Basic Principles of Clinical Use of TCM Injections” issued by the Chinese government, the adverse reactions of this injection can be prevented to a certain extent by strengthening the safety monitoring of the first administration, avoiding combined administration with other injections, and controlling the drip rate [45].

There are some limitations in this study. First, the included RCTs did not mention the implementation process of blinding, which may cause performance bias. Second, the criteria of efficacy assessments were not entirely consistent across the RCTs, and the accuracy of effect estimates may thus be impacted. Third, the heterogeneity in the meta-analyses was high in some outcomes, and the subgroup analysis stratified by the length of treatment did not explain the source of heterogeneity.

5. Conclusion

The current RCT evidence shows that Re Du Ning injection is an effective and safe complementary therapy based on routine treatments for AECOPD, as indicated by improvements in the response rate, pulmonary function, acid-base imbalance, inflammatory indicators, and mild adverse reactions. The quality of evidence was impacted by the risk of bias and heterogeneity in the RCTs of the meta-analysis. More well-designed RCTs are warranted to further validate the efficacy and safety of Re Du Ning injection on AECOPD.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| RDN          | Re Du Ning injection |
| COPD         | Chronic obstructive pulmonary disease |
| AECOPD       | Acute exacerbation of chronic obstructive pulmonary disease |
| PRM          | Phlegm resolving medicine |
| AD           | Antiasthmatic drugs |
| Ivgtt        | Intravenous drip |
| qd           | Once a day |
| RR           | Relative risk |
| MD           | Mean difference |
| CI           | Confidence interval |

Data Availability

The data supporting this research article are available from the corresponding author on reasonable request.

Disclosure

Bofei Shu and Hong Li are co-first authors.
Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Liling Wan and Zhaohui Ding were responsible for the design and conception of the study; Bofei Shu conducted statistical analysis, graph drawing, and manuscript writing; Hong Li and Xu Zhou were responsible for searching databases, screening documents, extracting data, and evaluating methodological quality; and all authors critically revised the manuscript. Bofei Shu and Hong Li contributed equally.

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