THE USE OF *RHEUM PALMATUM L.* IN THE TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

Tie-zhu Yang[1], Yan Liu[2,3], Yue-Yun Liu[4], Xiu-Fang Ding[4], Jia-Xu Chen[3,4]*, Mei-Jing Kou[3], Xiao-Juan Zou[3]

[1]Luoyang Orthopedic Hospital of Henan Province, Orthopedic Hospital of Henan Province, Zhengzhou450000, China.; [2]Henan University of Traditional Chinese Medicine, Zhengzhou 450056, China; [3]Hubei University of Chinese Medicine, Wuhan 430061, China.; [4]Beijing University of Chinese Medicine, Beijing 100029, China.,

Corresponding Author E-mail: chenjiaxu@hotmail.com

Abstract

Background: Chinese medicine theory shows that "lung being connected with large intestine", and the modern western medicine also shows that the lung and intestinal tract affect each other in physiological and pathological conditions. If the lung ventilation dysfunction is caused by inflammatory exudate or secretions obstruction of the small airway ventilation, blood gas partial pressure is increased and intestinal gas absorption difficulty may lead to intestinal inflation and dysfunction (Wang N et al., 2011). *Rheum palmatum L.* can play the roles of anti-coagulation and anti-thrombosis, and improve microcirculation through lowering the endotoxin-induced permeability of microvascular tissue, reducing tissue oedema, decreasing inflammatory exudation and necrosis, and enhancing cyto-protection mechanism (Yang TZ et al., 2014). Therefore, systemic evaluation of the evidence pertaining to the usage of *Rheum palmatum L.* in treating acute lung injury and acute respiratory distress syndrome (ARDS) has significant clinical significance.

Materials and Methods: Various Electronic Databases CBM, CNKI, VIP, Wanfang, PubMed and Cochrane Library were searched until December 2015. Numerous randomized-controlled trials (RCTs) evaluating the efficacy of *Rheum palmatum L.* for the treatment of acute lung injury and acute respiratory distress syndrome were collected. The quality of the included studies was evaluated and a meta-analysis was performed using the RevMan5.0 software.

Results: Eight RCTs involving 489 patients were selected for this review. The results of the Meta-analysis revealed that *Rheum palmatum L.* therapy, combined with routine comprehensive treatment, was significantly superior to that of routine comprehensive treatment alone, in the areas of decreasing mortality, the mechanical ventilation time, the level of interleukin-6,8 and the untoward effect, and also in improving arterial blood gas (PaO_2/FiO_2, PaO_2) ($P<0.05$).

Conclusion: Compared with treatment with routine comprehensive alone, *Rheum palmatum L.* treatment combined with routine comprehensive, has been shown to effectively decrease the mortality, mechanical ventilation time and ameliorate the arterial blood gas, the cytokine levels, and the untoward effect. However, the evidence appears not to be very compelling due to the poor quality of the original studies.

Key Words: *Rheum palmatum L.*, Western medicine therapy, ALI/ARDS, Systematic Review, Meta-analysis

Introduction

Acute respiratory distress syndrome (ARDS) refers to the acute hypoxic respiratory failure, which is caused by alveolar damage induced by inflammatory injury of pulmonary capillary endothelial cells and alveolar epithelial cells in the process of severe infection, shock, trauma and burns, and with the pathological physiological characteristics of

fewer lung volume, lower lung compliance, serious imbalance of ventilation/blood flow ratio (Bernard et al., 1994). According to the ARDS diagnosis standards put forward by the medical conference in Berlin, Germany in October 2011, a draft definition proposed 3 mutually exclusive categories of ARDS, based on degree of hypoxemia: mild (200 mm Hg $<$ $PaO_2/FIO_2 \leq$ 300 mm Hg), moderate (100 mm Hg $<$ $PaO_2/FIO_2 \leq$ 200 mm Hg), and severe ($PaO_2/FIO_2 \leq$ 100 mm Hg), and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance ($\leq$40 mL/cm H_2O), positive end-expiratory pressure ($\geq$10 cm H_2O), and corrected expired volume per minute ($\geq$10 L/min) (ARDS Definition Task Force, 2012). Overall, it is a dangerous disease with a very poor prognosis and the mortality rate can reach as high as 40%-50% [Li et al., 2009]. According to the existing evidence, we can increase the intensity of treatment measures in accordance with the severity of ARDS [Liu et al., 2012]. Due to the heterogeneity of ARDS disease, however, treatment should be tailored according to the case of each patient. Therefore, in clinical decision making, we need to evaluate the benefit and risk of various treatment approaches based on the evidence-based medicine, in order to develop individualized treatment plans for each patient and ensure high clinical benefits for all. At present, many doctors act according to the theory of the interior-exterior relationship between the lung and the large intestine, and adopt a treatment methodology of combining *Rheum palmatum L.* with the routine comprehensive approach to treat ARDS, and procure a certain effect. Up to this day, a systematic evaluation about *Rheum palmatum L.* combined with routine comprehensive therapy for treating ARDS has not been reported. Therefore, it was deemed necessary to conduct a systematic review of the method of applying *Rheum palmatum L.* in combination with the routine comprehensive approach to treat ARDS, in order to provide solid scientific reference that would facilitate a reasonable individualized treatment plan for ARDS patients.

Methods and Materials

The supporting PRISMA checklist is available as supporting information; see Checklist Fig. S1.

Search strategies and study selection

Literature search was conducted in the National Knowledge Infrastructure (1999-2015), VIP Database for Chinese Technical Periodicals (1989-2015), PubMed (1950-2015), Chinese Bio-Medical Literature Database (1990-2015), and Cochrane Library (Issue 10 of 12, 2015). All of these searches ended at the end of December 2015. To search the databases, we used the terms "Acute respiratory distress syndrome", "Acute lung injury", "Western medicine", "*Rheum palmatum L.* combined with western medicine", and "TCM combined with Western medicine". These terms were combined variously and used according to the database searched. The bibliographies of the included trials were searched for additional references. The data of the included trials were extracted independently by two authors (Y. Liu and T. Z. Yang). The extracted data analyzed in this study mainly included paper authors, publication year, study size, details of methodological information, drug name and outcome indicators (for example, total effective rate). Disagreement between us was resolved by group discussion and reached consensus through a third party (J. X. Chen).

Inclusion Criteria

All the parallel-randomized controlled trials (RCTs) must be based on the principle of participants, interventions, comparisons, outcomes and study (PICOS) as follows: P: ARDS patients; I: comprehensive treatment with mechanical ventilation and traditional Chinese medicine treatment with *Rheum palmatum L.*; C: comprehensive treatment with mechanical ventilation combined with *Rheum palmatum L.* vs. comprehensive treatment with mechanical ventilation; O: Primary outcomes: mortality, mechanical ventilation time, oxygenation index (PaO_2/FiO_2), arterial partial pressure of oxygen (PaO_2) and untoward effect; Secondary outcomes: cytokine levels such as interleukin-6 (IL-6), interleukin-8

(IL-8). There were no restrictions on age, population characteristics, languages or publication types.

Trial quality assessment

The quality of included trials was evaluated by two authors (Y. Liu and T. Z. Yang) and assessed by using the 'risk of bias' assessment tool according to the 'Cochrance Handbook of Systematic Review of Interventions' (Chapter 8.5) with randomized controlled trials including: sequence generation, allocation concealment, blinding, incomplete outcome date, and selective outcome reporting. The quality of all the included trials was divided into 3 categories as low, unclear, and high risk of bias. Trials that met all the criteria were classified to low risk of bias, trials met none of the criteria were classified to high risk of bias, and other trials with insufficient information acquired to make judgment were classified to unclear risk of bias (Figure S2.1 and S2.2).

Data analysis

The data was analyzed by using the statistical package (RevMan 5.0) provided by the Cochrane Collaboration. Measurement data were summarized by using Mean Difference (MD) with 95% confidence interval (CI) for continuous outcomes. Fixed-effect or random-effect model used in the analysis depended on the absence or presence of significance heterogeneity which was evaluated by the Chi-square and I-square (I^2) tests. Measurement data with the same unit were summarized by using weight mean difference (WMD) with 95% CI, and the Measurement data with different unit were summarized by using standardized mean difference (SMD) with 95% CI (Altuntas et al., 2006).

Results

Description of included studies

The flow chart depicts the whole search process and study selection (Figure 1-X). After searching the six databases, 140 citations were screened. 54 articles were searched in the CBM database, 19 articles were retrieved from VIP, 49 articles were searched in CNKI and 4 articles were retrieved from PubMed. There was no related literature retrieved in the Cochrane Library. 83 papers were excluded due to duplicated publication. 22 of them were excluded on account of obvious ineligibility, which contained irrelevant titles and abstracts content. 27 articles were excluded by reason of non-RCTs, incomplete data, unqualified control, and so on. Finally, 8 RCTs (Ming et al., 2011; Song et al., 2004; Zhou et al., 2008; Yan et al., 2001; Feng J et al., 2012; Weng et al., 2008; Lu et al., 2009; Cui et al., 2001) were included and summarized in Tables 1 and 2.

A total of 489 participants with ALI/ARDS were involved in these studies, with the average number of 61 per trial, ranging from 31 to 100. All the included RCTs in this study were conducted in China and published in Chinese, no one published in English. The quality of the included studies was low, but the baseline of the experimental group and control group was good (Tables 1 and 2, Figure 2-X and Figure 3-X.).

PRISMA 2009 Flow Diagram

Identification

Records identified through database searching
(n =507)

Additional records identified through other sources
(n = 0)

Records after duplicates removed
(n =57)

Screening

Records screened
(n =57)

Records excluded: (n = 22)
Experiments (n=7)
Theory discussion (n=3)
Other treatment (n=10)
Case reports (n=2)

Included

Studies included in qualitative synthesis
(n =8)

Studies included in quantitative synthesis (meta-analysis)
(n =8)

Studies included in qualitative synthesis
(n =8)

Eligibility

Studies included in quantitative synthesis (meta-analysis)
(n =8)

Figure1-X. PRISMA 2009 Flow Diagram

Study ID	treatment cycle (d)	N (E/C)	Patient age	Comorbidity	Cause of ARDS
Ming et al.2011	5	50/50	43±25	Respiratory failure	primary diseases: Severe pulmonary infection, necrotic pancreatitis, bacterial encephalitis, cholecystitis, peritonitis
Song et al.2004	7	40/20	46±19	unstated	undefined
Zhou et al.2008	7	40/20	48.9±6.3	unstated	Trauma, necrotic pancreatitis, infection, suppurative cholangitis, DIC, post-renal transplantation
Yan et al.2001	7-10	16/15	46±12	unstated	Severe acute pancreatitis
Feng et al.2012	7	32/32	48.5±12.3	acute ulcer	General infection, necrotic pancreatitis, multiple trauma, organophosphorus intoxication, after cardiopulmonary resuscitation
Cui et al.2011	Unclear	20/20	44.3	Mediastinal tumors, esophagus cancer, lung cancer	Thoracic surgery, thoracic trauma
Weng et al. 2008	6	40/40	45.22±8.14	unstated	Thoracoabdominal trauma, maxilla-facial injury
Lu et al. 2009	7	27/27	48.1±6.8	unstated	Multiple injuries, chest and abdomen surgery, necrotic pancreatitis, organophosphorus intoxication, necrotizing intestinal obstruction, severe pneumonia with septic shock

Table 2: The basic features of included randomized controlled trials.

| Study ID	Treatment measures		Outcome Measures
	Experimental group	Control group	
Ming et al. 2011	0.1g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with mechanical ventilation	Mechanical ventilation	The comparison of baseline, mortality rate, the duration of hospitalization in ICU, Pplat, PIP, Mpaw, Raw, PaO_2, PaO_2/FiO2, $PaCO_2$, pH value, MAP, HR, CO, SVR
Song et al. 2004	0.03～0.06g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with mechanical ventilation	Mechanical ventilation	The comparison of baseline, PaO_2/FiO_2, mechanical ventilation time, the incidence of pressure ulcers, mortality rate
Zhou et al. 2008	0.6g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with mechanical ventilation	Mechanical ventilation	The comparison of baseline, mortality rate, the hospitalization time, mechanical ventilation time, PaO_2, PaO_2/FiO_2, IL-6, IL-8
Yan et al. 2001	0.1g/ml rhubarb decoction nasal feeding by stomach tube every 24 hours combined with mechanical ventilation, cure the primary disease, improve minicirculation and nutrition support	Mechanical ventilation, cure the primary disease, improve minicirculation and nutrition support	PEEP, the concentration of oxygen, MOF, mortality rate, PaO_2, SaO_2, DO_2, Qs/Qt, cardiac output, cardiac index, PAPm, PVR
Feng et al. 2012	0.3g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with mechanical ventilation	Mechanical ventilation	The comparison of baseline, PaO_2/FiO2, PaO_2, mechanical ventilation time, mortality rate, IL-6, IL-8, the incidence of stress ulcer
Cui et al. 2011	0.03～0.05g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with united injury treatment, antibiotic treatment, respiratory support and nutrition support	United injury treatment, antibiotic treatment, respiratory support and nutrition support	mortality rate, ventilator treatment time
Weng et al. 2008	0.03g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with cure the primary disease, mechanical ventilation, circulation and respiration supporting, oxygen therapy, hemostasis and blood transfusion, and antibiotic therapy	Mechanical ventilation, circulation and respiration supporting, oxygen therapy, hemostasis and blood transfusion, and antibiotic therapy	the duration of hospitalization in ICU, the hospitalization time, the incidence rate of ARDS, mortality rate, RR, $PaCO_2$, PaO_2/FiO_2, PaO_2, TNF-α, IL-6, IL-8, IL-2
Lu et al. 2009	0.3g/ml rhubarb decoction nasal feeding by stomach tube every 8 hours combined with mechanical ventilation	Mechanical ventilation	PaO_2/FiO_2、PaO_2、SaO_2、PIP、Raw、CL
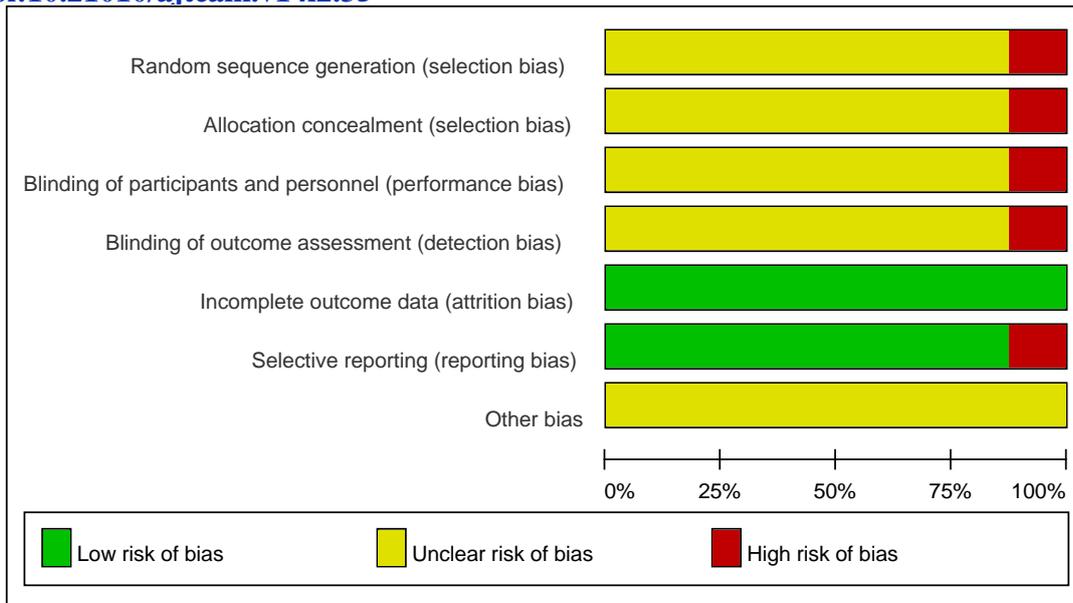
Figure 2-X: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3-X: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Comparison of clinical mortality rate

Seven out of eight RCTs (Ming et al., 2011; Song et al., 2004; Zhou et al., 2008; Yan et al., 2001; Feng et al., Weng et al., 2012; Cui et al., 2011) reported the comparison of clinical mortality rate between experimental group and control treatment group. There is no significant heterogeneity between the studies (I^2=0%), so we used the fixed effect

model for analysis. Meta-analysis results showed a significant difference in the mortality rate between the two treatments [RR=0.42, 95%CI (0.30, 0.60), Z=4.81, P<0.00001] (Figure 4-X). The clinical mortality rate of the *Rheum palmatum L.* therapy combined with routine comprehensive in the treatment of ARDS was lower than the routine comprehensive approach alone.
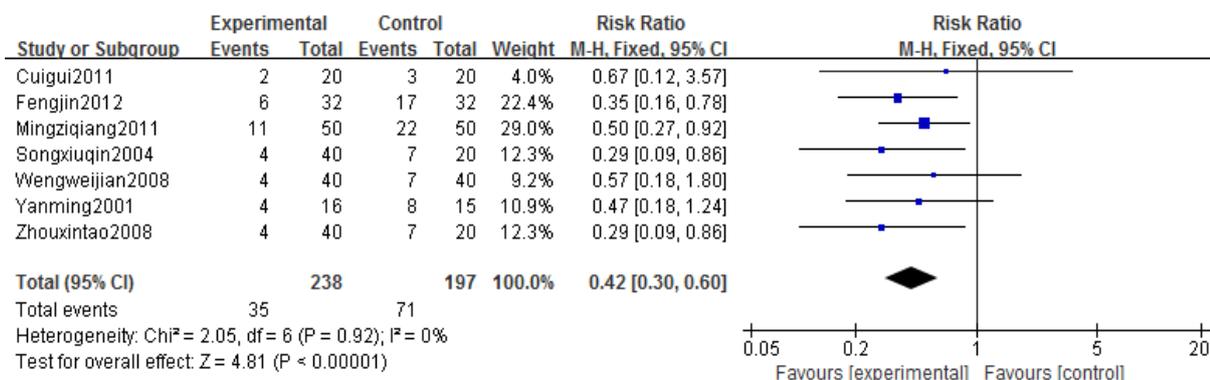

Figure 4-X. The forest plot of mortality rate

Comparison of mechanical ventilation time

3 trials [**Song XQ et al., Zhou XT et al., Feng J et al.**] made a comparison of the therapeutic effects on mechanical ventilation time. There were 184 patients, 112 cases in the *Rheum palmatum L.* group and 72 cases in the control group. Meta-analysis results showed a significant difference in reducing the mechanical ventilation time of patients [MD=-13.27, 95%CI (-18.08, -8.46), Z=5.41, P<0.00001] (Figure 5-X). More specifically, the therapeutic efficacy of *Rheum palmatum L.* combined with routine comprehensive therapy was superior to that of routine comprehensive approach alone, in reducing the mechanical ventilation time of ARDS patients.
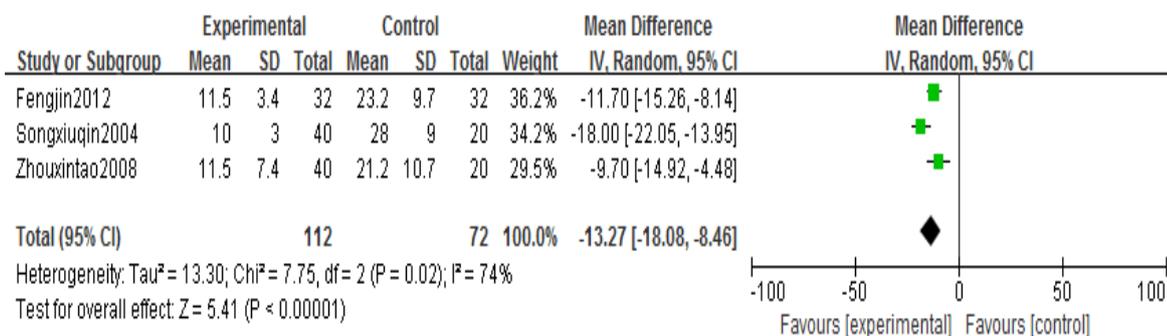

Figure 5-X. The forest plot of mechanical ventilation time

Comparison of arterial blood gas

PaO_2 : 5 trials (Ming et al., 2011; Zhou et al., 2008; Yan et al., 2001; Feng et al., 2012; Weng et al., 2008) made a comparison of two kinds of treatment on improving the PaO_2 levels of patients with ALI/ARDS. A total of 335 patients were involved, 178 cases in the experimental group and 157 cases in the control group. There was significant statistical heterogeneity in the researches (P=0.0001, I^2=83%). The results of meta-analysis showed that between the two different treatments, there was a significant difference in the level of PaO_2 [MD=8.44, 95%CI (4.22, 12.66), Z=3.92, P<0.0001] (Figure 6-X). The diamond on the right side of the invalid line, points out that the treatment of *Rheum palmatum L.* combined with routine comprehensive therapy was better than the routine comprehensive approach alone in promoting the level of PaO_2.
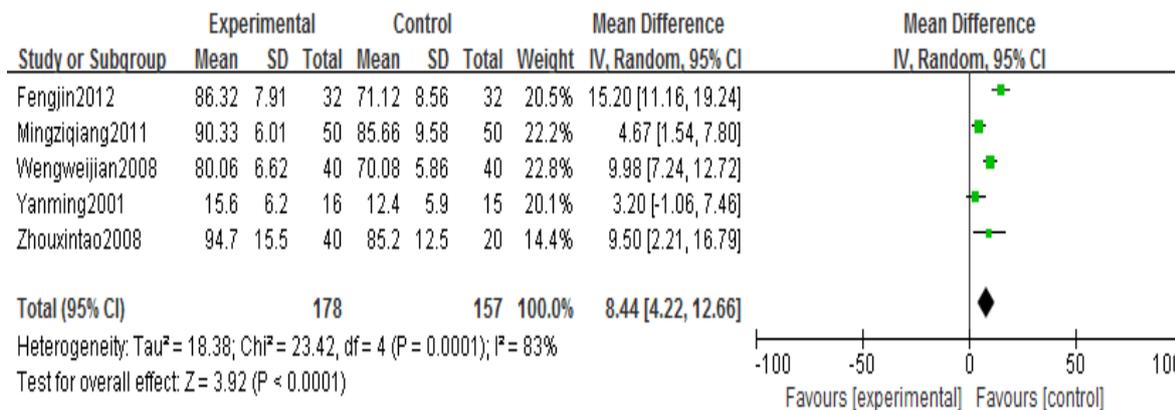
PaO_2/FiO_2: 5 out of 8 RCTs (Ming et al., 2011; Song et al., 2004; Zhou et al., 2008; Feng et al., 2012; Weng et al., 2008) made a comparison of the effects of the two kinds of treatment in patients with PaO_2/FiO_2. There were 364 patients included in the study of oxygenation index, and the number of patients in the control group and the experimental group were 162 and 202, respectively. There is statistical heterogeneity in the researches (P<0.000001，I^2=99%). According to meta-analysis, the results indicated that the treatment strategy using *Rheum palmatum L.* combined with routine comprehensive approach was superior to routine comprehensive therapy alone in improving the level of PaO_2/FiO_2 with ALI/ARDS patients [MD=76.12, 95%CI (34.92, 117.33), Z=3.62, P=0.0003] (Figure 7-X).
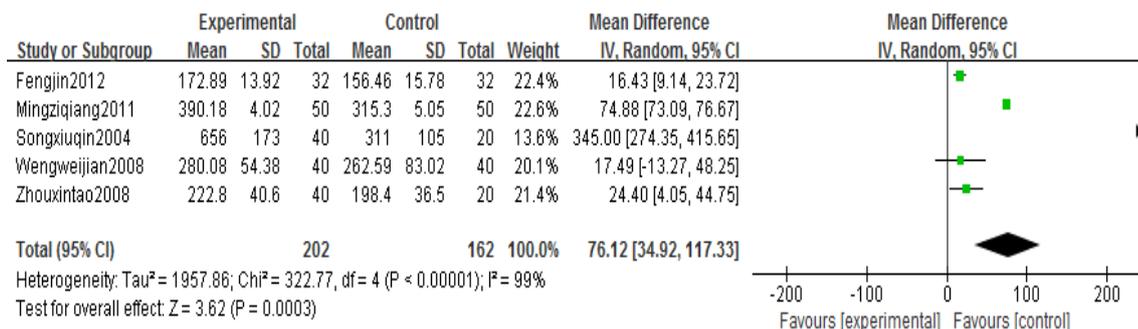

Figure 7-X: The forest plot of PaO_2/FiO_2

Comparison of cytokine levels (IL-6 and IL-8)

Three (Zhou et al., 2008; Feng et al., 2012; Weng et al., 2008) out of eight trials made simultaneous comparison of the effect of the two therapeutic modalities in ameliorating the levels of IL-6 and IL-8 with ALI/ARDS patients. There was no significant heterogeneity between the studies, IL-6 (P<0.0001，I^2=91%), IL-8 (P=0.99，I^2=0%). Meta-analysis results indicated that in lowering the level of IL-6 in patients with ARDS, the curative effect of experimental group was significantly better than that of the control group, and with statistically significant difference between the two groups [MD=-7.44, 95%CI (-12.48, -2.41), Z=2.90, P=0.004] (Figure 8-X). At the same time, when comparing the efficacy of the two therapeutic methods in reducing the levels of cytokines in patients with IL-8, the therapeutic effect of *Rheum palmatum L.* combined with routine comprehensive treatment remained significantly superior to that of routine comprehensive approach alone, and the difference was also statistically significant [MD=-7.7, 95%CI (-9.36, -6.04), Z=9.08, P<0.00001] (Figure 9-X).
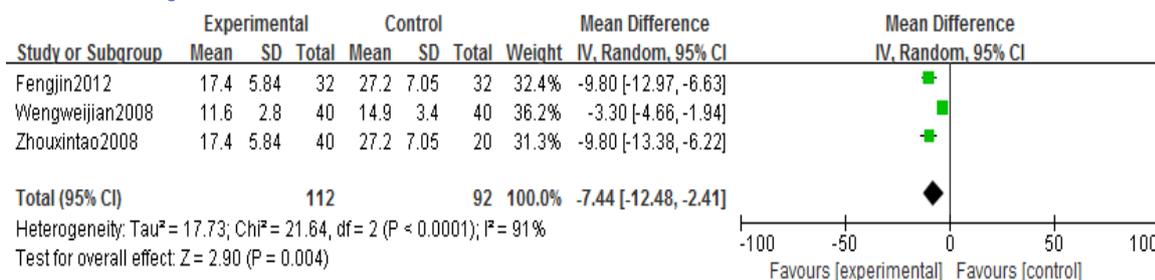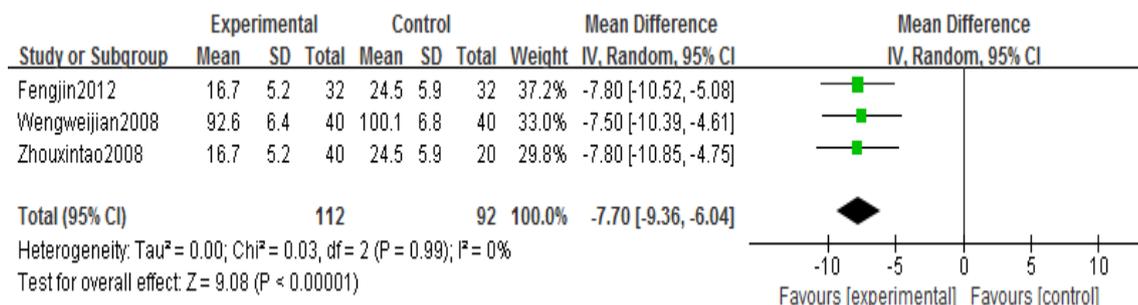
Figure 8-X. The forest plot of IL-6

Figure 9-X. The forest plot of IL-8

Untoward reaction

Two papers (Song et al., 2004; Feng et al., 2012) reported the incidence of stress ulcer after either therapeutic option. In total, there were 124 patients, with 72 cases belonging to the experimental group, and 52 cases in the control group. There was no significant heterogeneity between the studies (P=0.87，I^2=0%), so the fixed effect model was adopted to analyse the outcomes. The results have shown that the incidence of stress ulcer with the experimental group was significantly lower than that of control group, and with statistically significant difference [RR=0.58, 95%CI (0.38, 0.89), Z=2.49, P=0.01] (Figure 10-X).
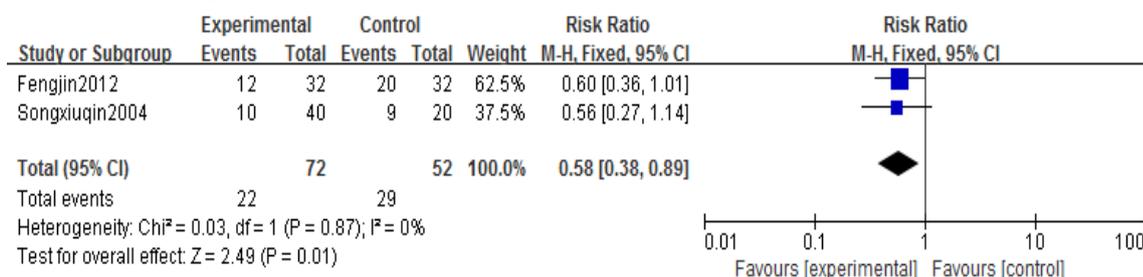

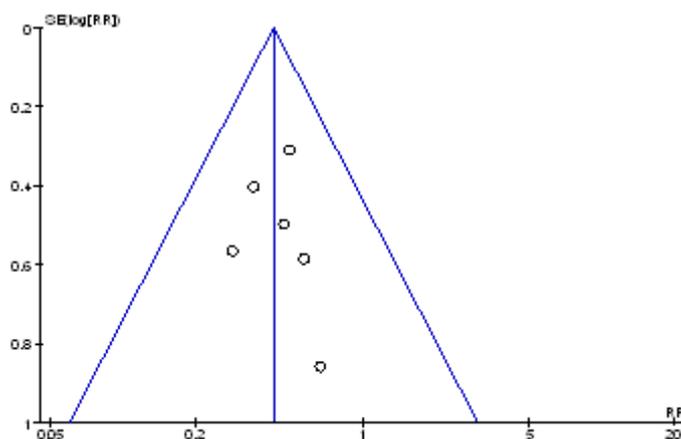**Figure 10-X:** The forest plot of the incidence of stress ulcer

Figure 11-X. The funnel plot

Publication bias

Seven trials compared the effect of the two therapeutic modalities in ameliorating the clinical mortality rates in ARDS patients. A funnel plot analysis showed a serious asymmetry in the general effective rate among the 7 trials (Figure 11-X). It indicated that the included literatures suffer from low quality and publication bias. Because of the limited number of papers, the result of this systematic review is deemed useful only for reference.

Discussion

There are more than 100 kinds of etiologic factors for ARDS. The various factors inducing ARDS differ in their pathological process and prognosis, and, therefore, the causes are divided into two main categories: direct lung injury and indirect lung injury. The former mainly includes severe pulmonary infection, aspiration, pulmonary contusion, drowning, pulmonary embolism and oxygen poisoning. The latter mainly involves severe sepsis and septic shock, severe non-pulmonary trauma, acute fatal pancreatitis, large area burns, and so on. The most common causes for ARDS are severe infection, shock, trauma and burn (He et al., 2011). Although the etiology of ARDS is complex, its pathogenesis is also not yet fully elucidated. However, it has been demonstrated that the common "central link" of the pathogenesis is the inflammatory process mediated by inflammatory mediators released by a variety of effector cells (Gu et al., 2007). In recent years, the role of inflammation mediators, especially the cytokines, has been gathering more attention for explaining the pathogenesis of ARDS.

Traditional Chinese Medicine believes that ARDS belongs to the pathology of "syndrome characterized by dyspnea", "sudden attack of wheezing and dyspnea" and "collapse syndrome caused by dyspnea". Severe pulmonary contusion leads to stagnancy of qi and blood, and impaired dispersion of the lung qi, and thus disturbing the physiological conditions of "the interior-exterior relationship of the lung and the large intestine". If the functional activities of the stomach and intestines qi are obstructed, the lung-qi becomes aggravated. *Rheum palmatum L.* has the effect of restoring normal bowel movement, clearing away heat and toxic materials, cooling the blood, and dissipating blood stasis. The "Shen Nong Ben Cao" states: "*Rheum palmatum L.* can clear the stomach and intestines, capture and purge fire, clear away heat and toxic materials, engender the new through the old and stabilize the five internal organs". Modern research confirms that *Rheum palmatum L.* can prevent the membrane flow of calcium ions, influence the content of the intracellular calcium and reduce the synthesis and release of inflammatory mediators (Hachida et al., 1998). *Rheum palmatum L.* can prevent neutrophil activation by inhibiting the production and release of TNF-α, IL-2, IL-6, IL-8 and other cytokines. It could effectively prevent the amplification of inflammatory mediators and the playing of biological effects. *Rheum palmatum L.* also can increase the intestinal peristalsis, relieve constipation by purgation, inhibit the translocation of intestinal bacterial and the absorption of endotoxin, and maintain the barrier function of intestines and stomach. These can prevent bacteria entering into the blood circulation, reduce endotoxemia, and eventually decrease the inflammation of lung tissue (Zhu et al., 2004). In recent years, *Rheum palmatum L.* is applied to salvage many kinds of severe cases, such as among other various types of shock, major multiple injuries, acute respiratory distress syndrome and multiple organ dysfunction syndrome (He et al., 2007).

Based on this paper and meta-analyses of outcomes on mortality, mechanical ventilation time, oxygenation index (PaO$_2$/FiO$_2$), arterial partial pressure of oxygen (PaO$_2$), untoward effect, cytokine levels such as interleukin-6 (IL-6), interleukin-8 (IL-8), *Rheum palmatum L.* combined with routine comprehensive therapy may have certain effect on patients with ARDS, and the curative effect is superior to routine comprehensive alone in the areas of reducing the clinical mortality rate, shortening the mechanical ventilation time and ameliorating the arterial blood gas and cytokine levels in patients with ARDS to some extent. According to the two trials, *Rheum palmatum L.* combined with routine comprehensive therapy has less adverse events, compared to routine comprehensive alone with significant difference,

and this shows that the safety of *Rheum palmatum L.* combined with routine comprehensive therapy is better than routine comprehensive therapy alone, to some extent. We also considered some limitations of this article before accepting the findings. Firstly, the obtained literatures of RCTs in treating ARDS by using *Rheum palmatum L.* combined with routine comprehensive therapy were originally published in Chinese, and no English translation exists. Secondly the methodologies of these clinical trials were generally of very poor quality, according to the quality assessment tool for quantitative studies, and it also indicated that there is unclear risk of bias in most of trials. The methods of randomization and allocation concealment in those trials were described inadequately or incompletely. Most randomized studies did not follow the established rules. For example, none of the included 8 trials mentioned any single blind without providing detailed information, and we understood that it was difficult to perform double-blinding or single-binding because of the peculiarity of ARDS and certain features associated with Chinese herbs, for example, aroma and appearance, while it could be feasible that binding to outcome assessor and data analyzer. None of the trials explained the concrete method of randomization, and the rest merely provided insufficient information for judging whether or not it was conducted properly. The lack of dropout or withdrawal and insufficient side-effect reports were some of the factors that negatively impacted the reliability of this review. Thirdly, there was lack of placebo control in the included RCTs. One trail claimed that they used placebo control. However, the placebo of these trial is ulinastatin (Weng et al., 2008), not Chinese herbs, and it is not an appropriate control for the estimation of the effect of Chinese herbs. Therefore, it should be made with caution, when interpreting the positive outcomes of treatment with Chinese medicine. To remedy this situation, we suggest using caution when referencing these studies in the future.

The quality of the clinical research methodology of using *Rheum palmatum L.* combined with routine comprehensive therapy in the treatment of ARDS should be improved. In addition, the following aspects should be emphasized. Firstly, the production of random allocation sequences and the hidden random schemes should be reported in detail. Secondly, double blind method and placebo control should be applied. Thirdly, the withdrawal and drop-out rate should be clearly described. Fourthly, the importance of clinical outcome in a long-term follow-up should be reported. The effect of the treatment of the ARDS with *Rheum palmatum L.* combined with routine comprehensive therapy should be improved by designing strict double blind, randomized, controlled trials.

We hope that future clinical research would be sufficiently designed to avoid the limitations of current research methodologies. A revised design should pay particular attention to the use of the final therapeutic effect index, which in the cases we examined was highly objective, and thus allow international recognition that would facilitate future exchanges.

Author Contributions

JXC conceived the experiments and gave final approval of the version to be published. YL wrote the paper and screened literatures according to inclusion and exclusion criteria. TZY collected the document from databases. XJZ analyzed the data. XFD participated in the revision of the paper. YYL participated in the design of the study. MJK participated in the collection of useful data from the included RCTs.

Conflict of Interest: The authors declare that there is no conflict of interest that would prejudice the impartiality.

Acknowledgements

References

1. **ARDS Definition Task Force**, Ranieri VM, Rubenfeid, Thompson BT, Ferquson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. (2012). Acute respiratory distress syndrome: the Berlin Definition. JAMA. 307:2526-2533.

2. **Altuntas CZ**, Johnson JM, Tuohy VK. (2006). Autoimmune targeted disruption of the pituitary-ovarian axis causes premature ovarian failure. J Immunol. 177: 1998-1996.

3. **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. (1994). The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 149: 818-824.

4. **Cui G**, Huang K, Jing K, Zhang DS, Zhang DY. (2011). The curative effect observation of combination of traditional Chinese and western medicine on ARDS after chest trauma. Liaoning journal of traditional Chinese medicine. 38: 1166-1167.

5. **Feng J**, Zhou M. (2012). Clinical observation on Rheum palmatum L. in the complex treatment for ARDS. Chinese archives of traditional Chinese medicine. 30: 1568-1569.

6. **Gu X**, Jin FG, Fu EQ, Li XY, Liu JL, Sun YN. (2007). Effect of cytokines in pathogenesis of acute respiratory distress syndrome. Progress in modern biomedicine. 7: 1383-1386.

7. **Hachida M**，Morton DL. (1998). The protection of is, chemic lung with vera-pamil and hydralazine. J Thorac Cardiovasc Surg. 95: 178-83.

8. **He TN**, Liu B. (2011). The application of continuous blood purification in the acute respiratory distress syndrome. The journal of practical medicine. 27: 706-708.

9. **He ZX**, Xin YQ, Chen M. (2007). The chemical constituents, pharmacological action and clinical application in emergency of Rheum palmatum L.. Journal of emergency in traditional Chinese medicine. 16: 227-228.

10. **Li A**, Wang HM, Yin ZH, Wang C, Duan ML, Zhang SW. (2009). Epidemiology of acute respiratory distress syndrome in the patients with multiple organ dysfunction syndrome in China Analysis of the 1087 MODS patients with the multi-centered, prospective method. Chinese journal of practical internal medicine. 29: 1036-1038.

11. **Liu C**, Li JG. (2012). Acute respiratory distress syndrome: new definition and progress. Practical journal of clinical medicine. 9:15-19.

12. **Lu HJ**, Sun XB. (2009). Effect of Rheum palmatum L. combined with mechanical ventilation on respiratory function with ARDS patients. Modern journal of integrated tradition Chinese medicine. 18: 1889-1890.

13. **Ming ZQ**, Yu LM, Lv YX, Wang LW. (2011). Clinical research of Rheum palmatum L. on lung protection in acute lung injury ventilation patients. Chinese archives of tradition Chinese medicine. 29: 919-921.

14. **Song XQ**, Xie WX, Shi J, Lu RG, Wang Y, Heng JF. (2004). Therapeutic value of Rheum palmatum L. on patients with acute respiratory distress syndrome. Modem diagnosis and treat. 15: 293-294.

15. **Weng JW**, Li XF, Mai HP, Yang YZ. (2008). A clinical study of combination of Rheum palmatum L. and ulinastatin in treatment of acute lung injury after severe thoracic and abdominal trauma. Chinese journal of integrated traditional and western medicine in intensive and critical care. 15: 272-275.

16. **Wang N,** Fu Q, Zhao EP. (2011). Research Progress of Integrative Chinese and Western Medicine of "lung being connected with large intestine". Liaoning Journal of Traditional Chinese Medicine.38: 566-569.

17. **Yan M**, Yang XY, Chen DC, Xu YH, Guo CX. (2001). The therapeutic effects of Rheum palmatum L. on severe acute pancreatitis complicated with acute respiratory distress syndrome. Chinese journal of gastroenterology. 6: 94-96.

18. **Yang TZ,** Li LY, Han LL, Wang FY. (2014). Influence of Tongfu Jinghua Decoction on hemodynamics and tissue oxygen metabolism of post – traumatic patients with septic shock. Chinese Journal of Integrated Traditional and Western Medicine. 34: 1453-1456.

19. **Zhao YS**, Yang SF, Zhang L. (2008). The diagnosis and treatment of acute respiratory distress syndrome (ARDS). Journal of north Sichuan medical college. 23: 301-304.

20. **Zhou XT**, Tang Y, Lei HM, Tian JF, Miao LX, Fu YY. (2008). Investigate the integrative therapy effect of Rheum palmatum L.

which used in patients with ARDS. Journal of clinical internal medicine. 25: 114-116.

21. **Zhu YY**, Jing BW, Lou YH. (2004). Mechanism of the prophylactic- therapeutic effects of Rheum palmatum L. on early lung injury on early lung injury caused by gut delved infection. Chinese journal of integrated traditional and western medicine in intensive and critical care. 11: 53-56.