REVIEW ARTICLE

Chinese Herbal Medicine for Idiopathic Pulmonary Fibrosis: An Overview of Systematic Review

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ABSTRACT

Objective • To summarize the use of Chinese Herbal Medicines (CHMs) for Idiopathic Pulmonary Fibrosis (IPF) and provide high-level evidence for clinical decisions.

Methods • We analyzed systematic reviews (SRs). Two English-language and three Chinese-language electronic databases were searched from inception to July 1, 2019. Published SRs and meta-analyses evaluating CHM use in IPF and reporting clinically-relevant outcomes such as lung function, PO_2, and quality of life were eligible for inclusion in this overview. The methodological qualities of the included SRs were assessed by AMSTAR and ROBIS tools.

Results • All reviews were published from 2008 to 2019. 15SRs were published in Chinese-language while 2 were in English. A total of 15550 participants were included. All intervention arms received CHM with or without conventional treatment and were compared with control arms with conventional treatment alone, or hormone therapy. Twelve SRs were assessed with low risk of bias while five were assessed high risk by ROBIS. The quality of evidence was assessed to be "moderate" or "low" or "very low" using GRADE.

Conclusions • CHM has potential benefits for patients with IPF especially in improving lung function (forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity of the lungs for carbon monoxide (DLCO)), PO_2 level, and the quality of life of patients. Due to the low methodological quality of reviews, our findings should be interpreted with caution. (*Altern Ther Health Med.* 2023;29(6):150-157).

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a very specific form of chronic, progressive fibro-proliferative interstitial pneumonia of unknown etiology limited to the lungs.[1] Genetic factors, environmental exposures, maladaptive repair process, [2] gastroesophageal reflux disease (GERD), and even some viral infections are considered to be the causative factors.[3] The incidence of IPF is gradually increasing each year. In Europe and North America, there are an estimated 2.8 to 18 per 100 000 people per year incidences of IPF. The incidence in Asia and South America is low, with an estimation of 0.5 to 4 per 100 000 people per year.[4]

According to the 2011 American Thoracic Society (ATS) guideline, there is no proven drug treatment for the treatment of pulmonary interstitial fibrosis. Although some studies have shown potential benefits for certain pharmaceutical preparations, the committee's recommendations for these drugs are "weak". In the 2015 ATS guideline, although there are no highly recommended drug treatments, the use of certain drugs has been recommended, such as pirfenidone and antacid therapy.[1] The main treatment options for patients with IPF are supportive care with or without pulmonary

rehabilitation, active disease-directed treatment: anti-fibrotic drugs, supplementary therapy, management of exacerbations, and lung transplantation.[5] Five non-drug therapies such as smoking cessation, oxygen therapy, mechanical ventilation, pulmonary rehabilitation, and lung transplantation have also been proposed in "The Consensus on the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis in China". It also proposed that Chinese medicine can be used to alleviate the symptoms of IPF in patients.[6]

Chinese herbal medicine (CHM) is widely used for symptoms of IPF in China, but evidence-based guidance on CHM's management of symptoms of IPF is lacking. Although randomized controlled trials (RCTs) have demonstrated the benefits of CHM for symptoms of IPF, it is important to summarize all available evidence on the potential benefits and risks. Based on the current situation of no specific treatment drugs and the lack of evidence-based medicine for the treatment using Chinese medicine, it is necessary to summarize the efficacy of CHM for the treatment of IPF and to provide high-level evidence for clinical decisions.

METHODS

This systematic overview was conducted following a predetermined written protocol registered on the PROSPERO database with registration number CRD42019137326.

Criteria for considering SRs for inclusion

Reviews were required to meet the following criteria to be considered eligible for this study.

Types of systematic reviews (SRs)

In this overview of SRs, all SRs were eligible if they contained at least one randomized controlled trial (RCT). Quasi-experimental studies are at a higher risk of bias due to the lack of random assignment. However, the quasi-experimental studies were included if the majority of the studies were RCTs that evaluated the use of CHM for IPF. All systematic reviews were included with or without a meta-analysis. Inclusion criteria of participants, interventions, comparisons, and outcomes reported in the SRs were as follows: (1) participants: SRs that included patients diagnosed with IPF using clear diagnostic criteria without restrictions in terms of age, gender, condition duration, or intensity; (2) intervention: SRs were accepted if they evaluated treatment groups using CHM with or without conventional treatment. Effects of any CHM therapy were included irrespective of the dosage form; (3) comparison: acceptable control groups included no treatment, placebo, and conventional treatment; (4) outcomes: according to the guideline for IPF, the primary outcomes were lung function while the secondary outcomes were scores of symptoms, oxygen partial pressure (PO_2), and effectiveness rate(The significant effectiveness was defined as the symptoms scores improvement rate ≥70% according to "the guide for clinical trials of new drugs"). Adverse events, if any, were also extracted as outcomes.

Search methods for identification of SRs

We searched two English-language electronic databases (PubMed, Cochrane Library) and four Chinese-language electronic databases (China Network Knowledge Infrastructure (CNKI), VIP Chinese Science and Technology Journal Database, Wanfang Data, and Chinese Biomedicine (CBM)) from inception to July 1, 2019. We used subject searches in CNKI, VIP, Wanfang, and CBM databases, and an abstract/title search in PubMed and the Cochrane Library. The search strategy was as follows: ("traditional Chinese medicine" or "herbal medicine" or "Chinese patent medicine") AND ("Idiopathic pulmonary fibrosis" or "IPF") AND ("Systematic review" or "meta-analysis" or "SR"). We also manually searched the reference lists of all full-text papers for additional relevant reports. No language restrictions were imposed.

Study screening and study selection

Only SRs that assessed the use of CHM for treating IPF were included in this overview of reviews. Two authors (RHW and SGL) independently screened the literature for eligibility of SRs, according to the criteria above. Any disagreements regarding eligibility were resolved by a third reviewer (HL).

Data extraction and management

Two authors (RHW and SGL) independently extracted study information and summarized the review in a characteristic table. Data was extracted from full-text reviews using a standardized data extraction form designed by the review group. Information was extracted such as author, date, list of studies included, intervention and comparator summary, number of participants, diagnosis criteria, meta-analysis results or summary of results, whether a sensitivity analysis was conducted, risk of bias assessment, and adverse events. We resolved discrepancies by consensus or by a discussion with a third overview author (HL).

Assessment of methodological quality of the included reviews

Two authors (RHW and ML) evaluated the methodological quality of the included SRs using two assessment tools: Assessment of Multiple Systematic Reviews (AMSTAR) and the Risk of Bias in Systematic Review (ROBIS).[7,8] AMSTAR is an assessment tool for assessing the quality of systematic reviews. The use of AMSTAR for the rigorous evaluation of articles of different quality has been widely recognized.[9] The AMSTAR tool consists of 11 items and has good face and content validity for measuring the methodological quality of SRs.[10] Each criterion was rated as "Yes" (done), "No" (not done), "Can't answer" (unclear), or "Not applicable."

ROBIS is a new tool for assessing the risk of bias in SRs, which was developed by reviewing existing tools and literature, then refined via a face-to-face meeting and Delphi process with a panel of experts, which could guide the

appraisal of the risk of bias within SRs (http://www.robis-tool.info/). The ROBIS tool has three phases: assessing relevance (optional), identifying concerns with the review process, and judging the risk of bias. Using ROBIS, the risk of bias in each SR was judged as low, high, or unclear.

Assessment of quality of evidence

The quality of evidence of the included SRs was assessed by Grading of Recommendations Assessment, Development, and Evaluation (GRADE). GRADE pro GDT is an easy-to-use all-in-one web solution for summarizing and presenting information for healthcare decision-making (https://gradepro.org/). Two authors (RHW and SGL) assessed the evidence and independently upgraded or downgraded the degree. Using GRADE, the quality of evidence was judged as high, moderate, low, or very low.

Data synthesis

Due to the expected overlap of studies and heterogeneity between reviews, we produced a summary of all the results reported in the included systematic reviews and presented a summary of the data. When meta-analysis was performed, we report pooled estimates using the models and measures of effect reported by systematic review authors, with 95% confidence intervals. Dichotomous data were summarized as odds ratios (OR) or risk ratios (RR), and continuous outcomes were described as standard/mean differences (SMD/MD).[11]

RESULTS

General description of overall studies

We initially identified 192 citations. After the removal of duplications, 159 articles remained. After screening for eligibility by reading the titles and abstracts, 140 articles were excluded and 19 full texts were assessed further. 17 SRs met the inclusion criteria and were included in this overview of SRs (Figure 1).

All reviews were published by research institutions in China between 2008 and 2019. 15 SRs were published in Chinese-language while 2 in English. A total of 15550 participants were included. All SRs used CHM dosages (including capsules, tablets, oral liquids, injections, and decoctions). The characteristics of the included studies are summarized in Table 1.

Methodological quality of the included SRs

Methodological quality of included SRs assessed by AMSTAR. The qualities of the included SRs were low to moderate as assessed by the AMSTAR tool (Table 2). All the included SRs didn't provide protocol but all SRs had clear inclusion criteria, so we assessed 'Yes' in the priori design provided. All 15 SRs had at least two independent data extractors and a consensus procedure for disagreements. All the searched words were appropriate but were not always mentioned. Thirteen SRs searched 4 Chinese databases and

Figure 1. Flow Diagram

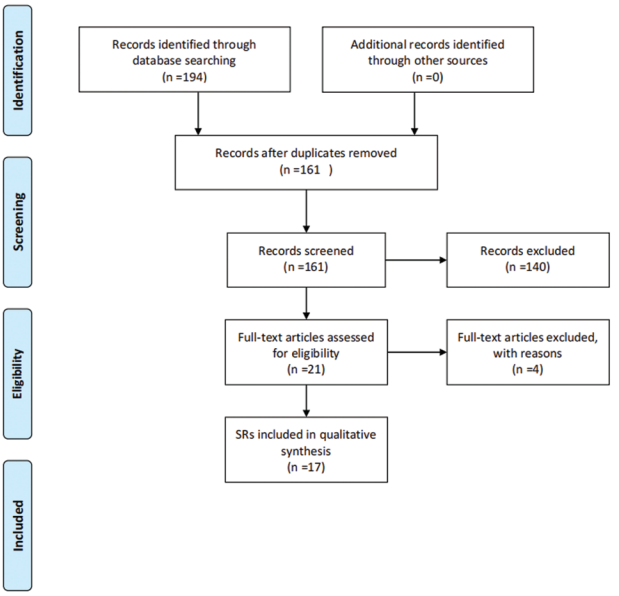

Table 1. Characteristics of Systematic Reviews Included in the Study

ID	Author (year) Date	Include trials	Participants	Treatment group	Control group	Outcomes
1	Wang YX 2019[12]	22	1380	CHM+CT±HT	CT ± HT	ER; SS
2	Guo J 2019[13]	13	733	CHM+CT	*N*-acetylcysteine+CT	LF; PO_2; 6min
3	Li GH 2018[14]	13	807	CHM+CT+HT	CT+HT	PO_2; 6min; ER
4	Liu M 2018[15]	17	1113	CHM+CT	CT	LF; PO_2; SGRQ; 6min; SS
5	Shi LT 2018[16]	7	332	CHM	HT or CT	PO_2; AE
6	Wang BB 2018[17]	24	1143	CHM	HT	LF; PO_2; ER
7	WU Qi 2018[18]	25	1471	CHM+CT	CT	Mortality; LF; SGRQ; 6min
8	Cui LF 2017[19]	33	1876	CHM+CT	CT	3 years survival rate
9	Yan QW 2017[20]	10	652	CHM+CT	HT	LF; PO_2; SS; ER; AE
10	Yang FD 2017[21]	17	1337	CHM+CT	HT	LF; PO_2; SS; ER; AE
11	Zang NZ 2017[22]	11	413	CMH	HT	LF; PO_2; SS; AE
12	Ji J 2016[23]	7	549	DHI+HT	HT	LF; PO_2; ER; AE
13	Xin LL 2016[24]	12	844	DHI	NR	LF; PO_2; ER; AE
14	Xu F 2016[25]	7	388	CXQI+HT	HT	PO_2; ER
15	Li HJ 2015[26]	22	1338	CHM	HT	LF; AE
16	Zheng WD 2015[27]	10	576	CMH	CT±HT	LF; SGRQ; ER
17	Yu H 2008[28]	9	598	CHM± HT	HT	LF

Abbreviations: CT: Conventional treatment; HT: Hormone therapy; ER: Effectiveness rate; SS: Scores of Symptoms; LF: Lung function; AE: Adverse events; DHI: *DanHong* Injection; NR: Not report; CXQI: *Chuanxiongqin* Injection; SGRQ: St George's Respiratory Questionnaire; PO_2: Partial pressure of Oxygen.

Table 2. Assessment of Methodological Quality—AMSTAR Tool

	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriate in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Wang YX 2019	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	Y
Guo J 2019	Y	Y	Y	Y	N[b]	Y	Y	Y	Y	Y	Y
Li GH 2018	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	Y[b]
Liu M 2018	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	N
Shi LT 2018	Y[a]	Y	N	N	N[b]	Y	Y	Y	Y	Y	Y[b]
Wang BB 2018	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	N
WU Qi 2018	Y[a]	Y	Y	Y	N[b]	Y	Y	Y	Y	Y	Y
Cui LF 2017	Y[a]	Y	Y	N	N[b]	Y	Y	N	N	Y	N
Yan QW 2017	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	Y
Yang FD 2017	Y[a]	Y	Y	N	N[b]	Y	Y	N	N	Y	N
Zang NZ 2017	Y[a]	Y	N	N	N[b]	Y	Y	Y	Y	Y	Y
Ji J 2016	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	N
Xin LL 2016	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	Y
Xu F 2016	Y[a]	Y	Y	Y	N[b]	Y	Y	Y	Y	Y	Y
Li HJ 2015	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	Y
Zheng WD 2015	Y[a]	Y	Y	N	N[b]	Y	Y	Y	Y	Y	N
Yu H 2008	Y[a]	Y	Y	N	N[b]	Y	Y	Y	NR	N	Y

[a]SR had no protocol but had clear inclusion criteria.
[b]SR listed the included studies but no excluded studies.

Abbreviations: NR, Not Reported; Y, Yes; N, No.

Table 3. Assessment of Methodological Quality—ROBIS Tool

	Phase 2				Phase 3
Review	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
Wang YX	☺	☹	☹	☹	☹
Guo J	☺	☺	☺	☺	☺
Li GH	☺	☹	?	☹	☹
Liu M	☹	☹	☺	☺	☹
Shi LT	☹	☹	☺	☺	☹
Wang BB	☹	☹	?	☹	☹
WU Qi	☺	☺	☺	☺	☺
Cui LF	☺	☹	☺	☺	☺
Yan QW	☹	☹	?	?	☹
Yang FD	?	?	☺	☹	☹
Zang NZ	☹	☹	?	☹	☹
Ji J	?	☹	☹	☹	☹
Xin LL	☺	☺	☺	☺	☺
Xu F	☺	?	☺	☺	☹
Li HJ	?	☹	☺	☺	☺
Zheng WD	☹	☹	?	?	☹
Yu H	☺	☺	☺	?	☺

Abbreviations: J, low risk; L, high risk; ?, unclear risk.

more than two English databases but 2 SRs[16,22] searched only Chinese databases. All SRs (except 2[13,25]), did not state that they searched for reports regardless of their publication type. All the authors did not state whether or not they excluded any reports based on their publication status or languages. All the SRs listed the included studies but none listed the studies that were excluded. All SRs reported the number of cases, interventions, and outcomes, and all the studies included in SRs were RCTs.

In respect of methodological and scientific quality, 6 SRs[14,16,17,21-23] used a jaded scale, while others used Risk of Bias (ROB). All SRs mentioned the random methods and blinds used. All 17 SRs except 1[21] used the appropriate analysis, while 1 SR used the fixed effects model when heterogeneity existed. 7 SRs [18-20, 22-24, 27] did not use subgroup analysis when there was a high heterogeneity. The conclusions and recommendations were based on scientific research methods. 13 SRs used funnel plots to assess the publication bias, 1 SR used Egger's test,[13] while 3 SRs[23,28] did not report.

Risk of bias assessed by ROBIS. Phase 1 was risk of bias assessment of the included SRs as assessed by ROBIS, which was displayed in Table 3. Phase 2 consists of four segments: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Phase 3 demonstrated the total risk of bias of these SRs. There were 12 SRs with a low risk of bias, and 5 SRs[20,22,25,27] with a high risk.

Judgments regarding each ROBIS item have been presented as percentages across all the included SRs in Figure 2.

Quality of evidence in the included SRs assessed by GRADE. The quality of evidence for 9 main outcomes in 17 SRs included and GRADE evidence is presented in Table 4 and Appendix 2. All the quality of evidence was "moderate" or "low" or "very low" by using GRADE. The reasons that the evidence was downgraded were as follows: (1) Quality of evidence was downgraded one level because of the risk of bias: inadequate methods of sequence generation, lack of allocation concealment, and/or lack of blinding of participants, (2) the heterogeneity of the study is large but not treated accordingly, (3) unstable confidence interval, and (4) publication bias.

Figure 2. ROBIS

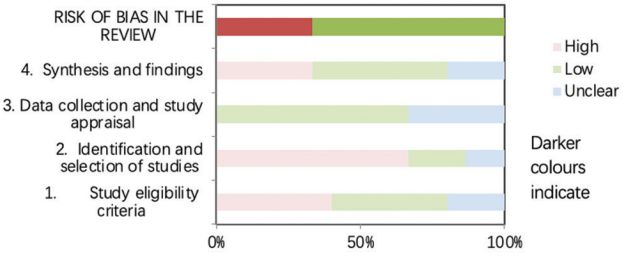

Table 4. GRADE Evidence Form

Quality assessment							Summary of findings				
							No of patients		Effect		
Study ID	No. of SRs	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chinese herbal medicine	control	Relative (95% CI)	Quality	Importance
Lung function –forced vital capacity (FVC)											
Liu M 2018	7	serious[a]	serious[d]	no serious indirectness[c]	serious[e]	none	278		MD 4.46 higher (1.87 to 7.04 higher)	⊕OOO Very Low	Important
Wang BB 2018	9	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	281	269	4.21 higher (2.91 to 5.52 higher)	⊕⊕⊕O Moderate	
Yang FD 2017	4	serious[a]	no serious inconsistency	no serious indirectness[c]	serious[e]	none	675	662	MD 5.18 higher (4.63 to 5.73 higher)	⊕⊕OO Low	
Li HJ 2015	5	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	177	171	SMD 0.37 higher (0.16 to 0.58 higher)	⊕⊕OO Low	
Yu H 2008	2	serious[a]	no serious inconsistency	no serious indirectness	serious[f]	reporting bias[f]	56	56	2.9 lower (4.02 to 1.78 lower)	⊕OOO Very Low	
Lung function – total lung capacity (TLC)											
Liu M 2018	6	serious[a]	no serious inconsistency	no serious indirectness[c]	serious[f]	none	293		MD 2.33 higher (0.54 to 4.12 higher)	⊕⊕OO Low	Important
Wang BB 2018	8	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	242	230	NR[7]	⊕⊕⊕O Moderate	
Yan QW 2017	5	serious[a]	serious[f]	no serious indirectness	serious[f]	reporting bias	169	160	SMD 0.47 higher (0.25 to 0.69 higher)	⊕OOO Very Low	
Yang FD 2017	4	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	124	115	MD 2.28 higher (0.33 lower to 4.9 higher)	⊕⊕⊕O Moderate	
Zang NZ 2017	16	serious[a]	serious[f]	no serious indirectness	serious[f]	none	265	252	SMD 0.04 lower (0.21 to 0.13 lower)	⊕OOO Very Low	
Li HJ 2015	13	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	382	361	SMD 0.1 lower (0.24 lower to 0.05 higher)	⊕⊕OO Low	
Lung function – Diffusing Capacity of Lung for Carbon Monoxide (DLCO)											
Wang YX 2019	11	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	reporting bias	627	586	MD 5.22 higher (4.29 to 6.15 higher)	⊕⊕OO Low	Critical
Liu M 2018	10	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	608		MD 3.90 higher (1.9 to 5.9 higher)	⊕⊕⊕O Moderate	
Wang BB 2018	8	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	196	193	5.34 higher (4.38 to 6.3 higher)	⊕⊕⊕O Moderate	
WU Qi 2018	9	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	259	243	SMD 0.40 higher (0.22 to 0.58 higher)	⊕⊕⊕O Moderate	
Yan QW 2017	5	serious[a]	serious[f]	no serious indirectness	serious[f]	reporting bias	156	129	SMD 0.90 higher (0.04 to 1.76 higher)	⊕OOO Very Low	
Yang FD 2017	5	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	173	171	MD 2.84 higher (0.16 to 5.51 higher)	⊕⊕⊕O Moderate	
Zang NZ 2017	16	serious[a]	serious[f]	no serious indirectness	serious[f]	none	265	252	SMD 0.03 higher (0.36 to 0.42 lower)	⊕OOO Very Low	
Ji J 2016	66	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	224	224	MD 3.23 higher (2.59 to 3.86 higher)	⊕⊕⊕O Moderate	
Xin LL 2016	116	serious[a]	serious[7]	no serious indirectness	no serious imprecision	reporting bias/ strong association[d]	383	380	MD 4.25 higher (3.32 to 5.18 higher)	⊕⊕OO Low	
Li HJ 2015	14	serious[a]	serious[g]	no serious indirectness	no serious imprecision	reporting bias	416	391	SMD 0.06 higher (0.36 to 0.48 lower)	⊕OOO Very Low	
Zheng WD 2015	4	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias/ strong association[d]	104	97	MD 6.28 higher (3.16 to 9.4 higher)	⊕⊕⊕O Moderate	
Yu H 2008	2	serious[a]	no serious inconsistency	no serious indirectness	serious[f]	reporting bias[f]	56	56	not pooled	⊕OOO Very Low	

Table 4. (continued)

Quality assessment							Summary of findings				
							No of patients		Effect		
Study ID	No. of SRs	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chinese herbal medicine	control	Relative (95% CI)	Quality	Importance
Partial Pressure of Oxygen (PO_2)											
Wang YX 2019	11	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	reporting bias	271	246	MD 4.35 higher (2.54 to 6.16 higher)	⊕⊕OO Low	Critical
Li GH 2018	4	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	128	127	MD 2.76 higher (0.83 to 4.68 higher)	⊕⊕⊕O Moderate	
Liu M 2018	10	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	608		MD 4.59 higher (2.63 to 6.55 higher)	⊕⊕⊕O Moderate	
Shi LT 2018	4	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	106	106	MD 3.27 higher (1.41 to 5.13 higher)	⊕⊕⊕O Moderate	
Wang BB 2018	7	serious[a]	serious[g]	no serious indirectness[c]	no serious imprecision	strong association[d]	217	205	5.56 higher (3.96 to 7.15 higher)	⊕⊕⊕O Moderate	
Yan QW 2017	6	serious[a]	serious[f]	no serious indirectness	no serious imprecision	reporting bias/ strong association[d]	189	162	MD 5.54 higher (2.4 to 8.69 higher)	⊕⊕OO Low	
Yang FD 2017	3	serious[a]	serious[g]	no serious indirectness	no serious imprecision	none	96	92	MD 0.78 higher (0.46 to 1.09 higher)	⊕⊕OO Low	
Zang NZ 2017	NR[g]	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	217	204	SMD 0.47 higher (0.28 to 0.67 higher)	⊕⊕⊕O Moderate	
Ji J 2016	66	serious[a]	serious[g]	no serious indirectness	no serious imprecision	very strong association[d]	224	224	MD 14.29 higher (12.11 to 16.47 higher)	⊕⊕⊕⊕ High	
Xin LL 2016	116	serious[a]	serious[g]	no serious indirectness	no serious imprecision	reporting bias/ very strong association[d]	383	380	MD 14.51 higher (12.35 to 16.68 higher)	⊕⊕⊕O Moderate	
Xu F 2016	26	serious[a]	serious[g]	no serious indirectness	no serious imprecision	reporting bias	36	36	MD 6.20 higher (0.45 to 11.59 higher)	⊕OOO Very Low	
Yu H 2008	2	serious	no serious inconsistency	no serious indirectness	serious	reporting bias	56	56	not pooled	⊕OOO Very Low	
Quality of life- St George's Respiratory Questionnaire (SGRQ)											
Wang YX 2019	3	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	74	68	MD 5.84 lower (10.74 to 1.21 lower)	⊕⊕OO Low	Not Important
Guo J 2019	3	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	66	MD 10.87 lower (14.30 to 7.44 lower)	⊕⊕⊕O Moderate	
Liu M 2018	3	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	160		MD 7.62 lower (11.21 to 4.03 lower)	⊕⊕⊕O Moderate	
WU Qi 2018	2	serious[a]	serious[e,g]	no serious indirectness	no serious imprecision	none	33	27	SMD 0.59 lower (1.14 to 0.05 lower)	⊕⊕OO Low	
Yan QW 2017	3	serious[a]	serious[f]	no serious indirectness	no serious imprecision	reporting bias	91	86	MD 4.74 lower (9.14 to 0.35 lower)	⊕OOO Very Low	
Zheng WD 2015	4	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	124	117	MD 2.17 higher (1.2 to 3.92 higher)	⊕⊕OO Low	
Quality of life-Six Minute Walk (6MW)											
Wang YX 2019	7	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	199	192	MD 41.42 higher (15.79 to 67.05 higher)	⊕OOO Very Low	Not Important
Guo J 2019	3	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92	79	MD 30.00 higher (26.22 to 33.77 higher)	⊕⊕⊕O Moderate	
Li GH 2018	2	serious[a]	no serious inconsistency	no serious indirectness	very serious[e]	none	41	41	MD 99.93 higher (97.06 to 102.88 higher)	⊕OOO Very Low	
Liu M 2018	2	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	74		MD 30.52 higher (8.8 lower to 69.83 higher)	⊕⊕⊕O Moderate	
WU Qi 2018	2	serious[a]	serious[e,g]	no serious indirectness	no serious imprecision	none	193	92	SMD 0.59 higher (0.34 to 0.84 higher)	⊕⊕OO Low	
Zang NZ 2017	1	serious[a]	serious[g]	no serious indirectness	no serious imprecision	none	56	51	SMD 0.47 higher (0.28 to 0.67 higher)	⊕⊕OO Low	
Scores of symptoms—cough											
Wang YX 2019	7	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	392	373	MD 0.9 lower (1.04 to 0.77 lower)	⊕⊕OO Low	Important
Liu M 2018	5	serious[a]	no serious inconsistency	no serious indirectness[c]	no serious imprecision	none	277		SMD 0.47 lower (0.88 to 0.05 lower)	⊕⊕⊕O Moderate	
Yan QW 2017	4	serious[a]	serious[f]	no serious indirectness	no serious imprecision	reporting bias	148	139	MD 0.72 lower (1.05 to 0.39 lower)	⊕OOO Very Low	
Yang FD 2017	3	serious[a]	serious[g]	no serious indirectness	no serious imprecision	none	104	97	SMD 0.68 lower (0.97 to 0.39 lower)	⊕⊕OO Low	
Zang NZ 2017	NR[g]	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	147	134	SMD 0.56 lower (0.80 to 0.32 lower)	⊕⊕⊕O Moderate	
Zheng WD 2015	6	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	190	181	MD 1.05 lower (1.27 to 0.83 lower)	⊕⊕OO Low	
Scores of symptoms—dyspnea											
Wang YX 2019	7	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	292	279	MD 1.05 lower (1.25 to 0.84lower)	⊕⊕⊕O Moderate	Important
Liu M 2018	3	serious[a]	serious[g]	no serious indirectness[c]	no serious imprecision	none	194		SMD 0.23 lower (1.24 lower to 0.78 higher)	⊕⊕OO Low	
Yang FD 2017	3	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	108	MD 1.00 lower (1.26 to 0.75 lower)	⊕⊕⊕O Moderate	
Li HJ 2015	6	serious[a]	serious[g]	no serious indirectness	no serious imprecision	reporting bias	176	174	MD 0.45 lower (0.65 to 0.25 lower)	⊕OOO Very Low	

Table 4. (continued)

Quality assessment							Summary of findings				
							No of patients		Effect		
Study ID	No. of SRs	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chinese herbal medicine	control	Relative (95% CI)	Quality	Importance
Effectiveness rate											
Li GH 2018	12	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	324/377 (85.9%)	252/370 (68.1%)	OR 2.86 (1.98 to 4.13)	⊕⊕⊕O Moderate	Critical
Wang BB 2018	13	serious[a]	no serious inconsistency	no serious indirectness[3]	no serious imprecision	none	332/406 (81.8%)	210/397 (52.9%)	OR 4.53 (3.22 to 6.37)	⊕⊕⊕O Moderate	
Yan QW 2017	9	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	225/290 (77.6%)	137/260 (52.7%)	RR 1.50 (1.31 to 1.70)	⊕⊕OO Low	
Yang FD 2017	14	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	439/513 (85.6%)	338/516 (65.5%)	RR 1.31 (1.22 to 1.40)	⊕⊕⊕O Moderate	
Ji J 2016	6	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	204/229 (89.1%)	151/230 (65.7%)	OR 4.30 (2.61 to 7.08)	⊕⊕⊕O Moderate	
Xin LL 2016	9	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	291/323 (90.1%)	212/321 (66%)	RR 1.36 (1.25 to 1.49)	⊕⊕OO Low	
Xu F 2016	6	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	168/207 (81.2%)	119/181 (65.7%)	RR 1.22 (1.08 to 1.39)	⊕⊕OO Low	
Zheng WD 2015	10	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias	227/269 (84.4%)	165/259 (63.7%)	OR 3.16 (2.07 to 4.82)	⊕⊕OO Low	

[a]Quality of evidence was downgraded one level because of the risk of bias: inadequate methods of sequence generation, lack of allocation concealment, and/or lack of blinding of participants.
[b]Heterogeneity was not significant.
[c]Although the composition of CHM in different RCTs is different, we believe that the studies reflected the overall effect of CHM.
[d]No explanation was provided.
[e]Significant differences in studies' confidence intervals.
[f]Unable to get information from SR.
[g]Heterogeneity was significant.

Effects of interventions

Primary outcomes. 5 SRs[15,17,21,26,28] reported the result of lung function FVC. The result showed an improvement in FVC in the treatment groups compared to the control groups. 6 SRs[15,17,20-22,26] reported the result of lung function TLC. The result showed an improvement in the TLC values in the treatment groups in comparison with the control groups. 12 SRs[12,15,17,18,20-24,26-28] reported the result of lung function DLCO.

Secondary outcomes. 13 SRs[12,14-17,20-26,28] reported the result of PO_2. All SRs showed an improvement in PO_2 of the IPF patients receiving the treatment compared to the control arm. 6 SRs[12,13,15,18,20,27] reported the result of SGRQ, of which 5 SRs showed a positive result while 1 SR[27] showed no significant difference between the treatment group and the control group. Positive results were also obtained in terms of 6MW,[12-15,18,22] scores of cough symptoms,[12,15,20-22,26,27] scores of dyspnea symptoms,[12, 15, 21, 26] and effectiveness rate.[14,17,20,21,23-25,27]

DISCUSSION

Summary of main results

This overview of reviews included 17 SRs comprising 15550 participants with IPF and provides a comprehensive analysis of CHM use for treating IPF. All researches included in the SRs were RCTs. The research designs of these SRs were different, and the risk of bias assessment methods used was different. Only 5 SRs were considered to have a low risk of bias by reviewers.[18,19,24,26,28] The quality of evidence was assessed as low to moderate. This overview identified 17 reviews assessing CHM interventions for IPF by the ROBIS tool. There were 52.94% of SRs with a low risk of bias from the overall ROB rating. The proportion with low risk for each item was as follows: 47.06% in study eligibility criteria, 23.53% in identification and selection of studies, 58.82% in data collection and study appraisal, and 47.05% in synthesis and findings.

This study suggested that CHM has reasonable effectiveness in treating symptoms of IPF, particularly in improving lung function, PO_2, and reducing the scores of symptoms of cough and dyspnea. CHM also appears to improve the effectiveness rate compared to conventional treatment.[29]

Overall completeness and applicability of evidence

The SRs included in this study used a wide range of CHM interventions. From the perspective of TCM, IPF belongs to the category of insufficiency and excess syndrome, in which qi deficiency and blood stasis and phlegm and blood stasis obstructing the lungs are the most common causes of the pathogenesis of IPF. Hence, supplementing qi, nourishing yin, and activating blood are the main therapies.[30,31] One study conducted a cluster analysis of 124 medical records of 60 doctors.[32] The results showed that a total of 263 drugs were used (5455 occurrences).[33] Medicines were divided into qi-tonifying, yin-tonifying, blood-activating, phlegm-resolving, cough-suppressing, panting-calming, and ten other major medicinal categories.[34]

Quality of the evidence

The quality of evidence in included reviews was rated according to the GRADE criteria. No outcomes were rated as having high-quality evidence in any of the included reviews.

The most common reason for downgrading the quality of evidence was the high risk of bias in the relevant trials. The main reason is that the original study included in SRs did not report the blinding of outcome assessment and allocation concealment.

Potential biases in the overview process

While we identified and listed all SRs, assessed the risk of bias, and also assessed the quality of evidence of the reviews, we did not assess the RCTs included in them individually. Since results from different reviews were included which might have had some overlap, there is a risk of double counting of results in this study, both for qualitative and quantitative reviews.[35] Despite trying to ensure that the evaluator's standards are consistent in our study, and trying to minimize the bias caused by the different levels of evaluation, there could be some compromise in the precision of the overview.

CONCLUSION

In summary, our overview of SRs found that CHM has potential benefits for patients with IPF especially in improving lung function (FVC, TLC, and DLCO), improving PO_2, and improving the quality of life of patients. However, because of the low methodological quality of SRs included, the evidence is of insufficient strength to make strong clinical recommendations. Future SRs should be designed with rigorous reporting to inform clinical guidance.

DATA AVAILABILITY

The data in this article can be obtained from the corresponding author under reasonable circumstances.

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AUTHOR CONTRIBUTIONS

Ming Li and Ruohan Wu contributed equally to the work.

AUTHOR DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest.

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